NICE National Institute for Health and Care Excellence

Highly Specialised Technology Evaluation

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

Evaluation Report

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

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

Contents:

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

Pre-meeting briefing

Strimvelis for the treatment of adenosine deaminase deficiency-severe combined immunodeficiency [ID926]

This slide set is the pre-meeting briefing for this evaluation. It has been prepared by the technical team with input from the committee lead team and the committee chair. It is sent to the appraisal committee before the committee meeting as part of the committee papers. It summarises:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report

It highlights key issues for discussion at the first evaluation committee meeting and should be read with the full supporting documents for this evaluation

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies.

The lead team may use, or amend, some of these slides for their presentation at the Committee meeting

Key abbreviations			
ADA	Adenosine deaminase	IQ	Intelligence quotient
ADA-SCID	Adenosine deaminase-severe combined immunodeficiency	IVIG	Intravenous immunoglobulin
AE	Adverse event	LTFU	Long-term follow-up
BMT	Bone marrow transplant	LY	Life years
CUP	Compassionate use programme	MFD	Matched family donor
EBMT	European Society for Blood and Marrow Transplant	MRD	Matched related donor
EMA	European Medicines Agency	MSD	Matched sibling donor
ERT	Enzyme replacement therapy	MUD	Matched unrelated donor
ESID	European Society for Immunodeficiencies	NPP	Named Patient Programme
GOSH	Great Ormond Street Hospital	PedsQL	Paediatric Quality of Life Inventory
GvHD	Graft versus host disease	PEG-ADA	Polyethylene glycol-modified bovine adenosine deaminase
Haplo	Haploidentical donor	QALY	Quality-adjusted life years
HLA	Human leukocyte antigen	SAE	Serious adverse event
HRQoL	Health-related quality of life	SCID	Severe combined immunodeficiency
HSCT	Haematopoietic Stem Cell Transplantation	TREC	T cell receptor excision circles
HSR-TIGET	San Raffaele Telethon Institute for Gene Therapy	VCN	Vector copy number
ICER	Incremental cost-effectiveness ratio		2

Disease background

Adenosine deaminase deficiency-severe combined immunodeficiency (ADA-SCID)

- Autosomal recessive inherited immune disorder; ADA-SCID is chronically debilitating and life-threatening.
- ADA-SCID accounts for 10–15% of all severe combined immunodeficiency
- Ultra rare condition – The company assumes 3 people are born with ADA-SCID in England per year
- Faulty gene inherited from both parents impairs production of adenosine deaminase. This leads to systemic accumulation of deoxyadenosine, which impacts the formation of lymphocytes and a functioning immune system and also causes further non-immunological effects
- Majority of patients with ADA-SCID are diagnosed in the first year of life and rarely survive beyond 1 to 2 years unless immune function is restored.
- Approximately 10% to 15% of ADA-SCID cases have a delayed onset (6 to 24 months), and a smaller percentage are diagnosed after age 4 years (late/adult onset)

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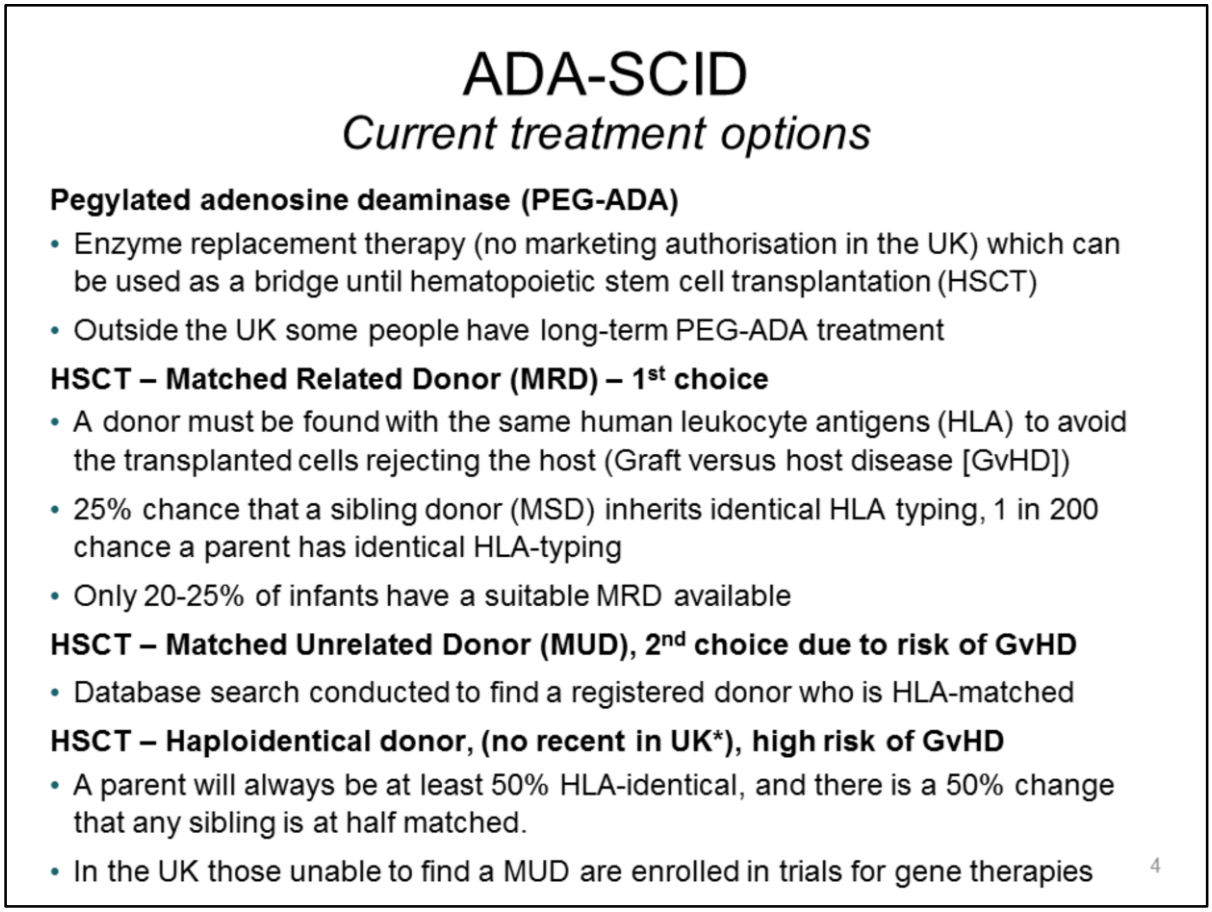
- The incidence of ADA-SCID varies widely by population, but is around 1 in 200,000 and 1 in 1,000,000 live births.
- Unlike other forms of SCID, non-immunological abnormalities can also occur due to the systemic metabolic defect



*HSCT from a haploidentical donor is an option considered in other countries, but has not been performed in England in a patient with ADA-SCID in the past 15 years according to external expert clinical advice.

- Patients are also managed with treatment for opportunistic infections whilst immunocompromised, including treatment with antibiotics, antiviral and antifungal medicines, intravenous immunoglobulins and prophylaxis for *Pneumocystis jiroveci* (a type of fungal pneumonia)

Graft versus host disease

- A primary cause of death after HSCT. For patients who survive, GvHD can affect health-related quality of life (HRQL).
- Acute GvHD may cause rash, nausea, vomiting, anorexia, profuse diarrhoea, ileus, and cholestatic hepatitis.
- Chronic GvHD can be limited to a single organ or could be more widespread. Chronic GvHD can lead to debilitating consequences, such as loss of sight, joint contractures, end-stage lung disease, or death

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ADA-SCID

Impact of the disease

- Quality of life is impacted by recurrent infections due to fungal, viral, and opportunistic agents. Without treatment, patients with ADA-SCID would die before school age.
- Children may have non-immunological manifestations of their disease as a consequence of the systemic metabolic defect. These may include hepatic, lung, and renal disease, lymphoma, skeletal alterations, neurological and cognitive/behavioural deficits.
- Neurological abnormalities, including cognitive deficits and hearing impairment, are common in patients with ADA-SCID. Treatment with HSCT is not thought to improve these aspects of the disease
- [redacted] can have a profound impact on both patient and carer quality of life [redacted]
- Quality of life for family members would be expected to be low - with increasing need for hospitalisations, more intensive caregiving requirements, and resulting emotional toll

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- Neurological events may be directly related to the underlying disease of ADA-SCID, comorbidities (e.g., Arnold Chiari malformation), to infections that patients may have experienced (e.g., meningitis, otitis media) or to other medications received (e.g., antibiotics such as gentamycin)

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ADA-SCID

Impact on families and carers – company survey

Redacted

Strimvelis

GlaxoSmithKline

Marketing authorisation	Indicated for treating 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
Mechanism of action	Gene therapy containing autologous $CD34^+$ cells transduced *ex vivo* with a replication-deficient retroviral vector containing the correct form of the human ADA gene in the DNA sequence
Administration & dose	• Must be administered in a specialist transplant centre* • 5 million purified CD34+ cells/kg required per patient# recommended that patients have pre-treatment with busulfan • Single intravenous infusion. Effects estimated to be lifelong
List price	List price: manufacture of Strimvelis = €594,000

*At present, treatment with Strimvelis can only be performed at HSR-TIGET, Milan, Italy due to the 6-hour shelf life of the manufactured cell therapy product and the location of the manufacturing site.
#4 million CD34+ required for Strimvelis manufacture, 1 million required for possible rescue treatment
Source: Strimvelis summary of product characteristics; Company submission

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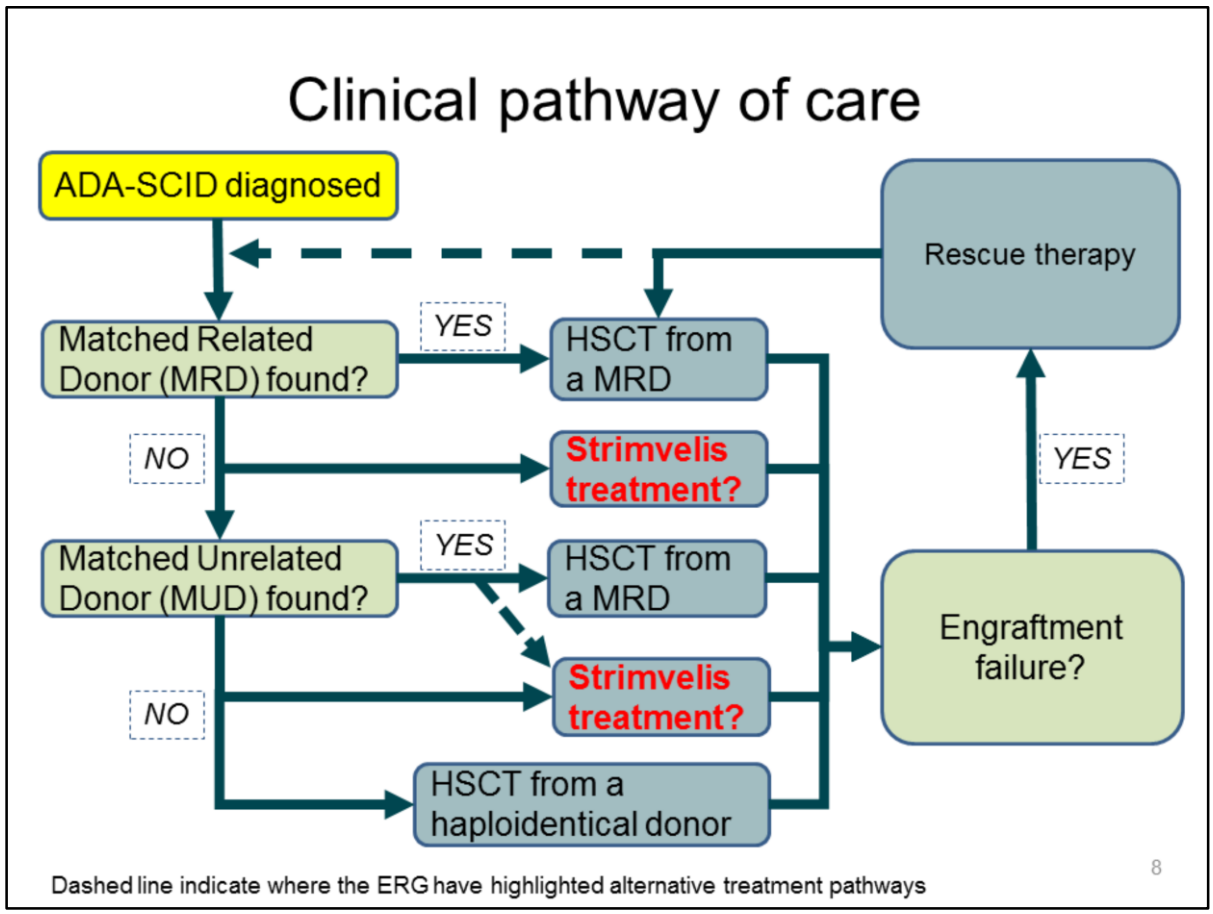
- Strimvelis is the transduced cell product and should not be confused with the gene therapy procedure, which encompasses all of the hospital-based procedures that take place as part of delivering Strimvelis to patients.



PEG-ADA treatment

- PEG-ADA treatment may not be started for people who have a matched related donor, as the time between diagnosis and HSCT is short. Treatment would be started for all people by the time a matched unrelated donor is searched for.
- PEG-ADA would be stopped following HSCT or shortly before gene therapy. After treatment people may be transiently treated with PEG-ADA during immune reconstitution, or restarted continuously if treatment fails.

Pre-treatment conditioning

- For matched related donors no chemotherapy conditioning is required prior to HSCT
- For HSCT from matched unrelated and haploidentical donors and Strimvelis treatment busulfan chemotherapy before treatment is recommended.
- Low-dose (non-myeloablative) busulfan is used as pre-treatment for Strimvelis instead of the full-dose chemotherapy regimens used in some HSCT protocols

Strimvelis treatment pathway

Stage	Details; average duration (range)
Screening	Includes clinical and laboratory tests and a bone marrow biopsy to determine adequate CD34+ cells. Biopsy is currently performed in Italy, but may be performed in England (24 days)
Baseline Patient Preparation	Includes in-patient stay for central venous catheter placement and obtaining bone marrow back-up 31 days (31-45 days), including a 3-day inpatient stay
Treatment	50 days in isolation room if no complication occur. Includes non-myeloablative dose of busulfan chemotherapy before cell reinfusion
Outpatient Follow-up in Milan	Generally includes clinics and laboratory tests, imaging, bone marrow biopsy and specific disease/gene therapy tests 60 days (60-90 days)
Outpatient Follow-up in England	4 months (3-4 months) Continued for lifetime as per routine care for all ADA-SCID patients

Source: adapted from table B1, page 40, company submission and response B5, page 23, company response to clarification

Decision problem

No inconsistency between the final scope and decision problem

	Final Scope
Population	People with ADA-SCID for whom no suitable HLA-matched related stem cell donor is available
Intervention	Strimvelis (retroviral-transduced autologous CD34+ cells)
Comparator	Bone marrow transplant (including HSCT from an HLA-MUD and HSCT from an HLA-haploidentical donor)
Outcomes	• Overall survival • Intervention-free survival • Immune function • Non-immunological aspects of ADA-SCID • Need for and duration of in-patient treatment • Adverse effects of treatment • Health-related quality of life (for patients and carers)

Source: Final scope 10

- Immune function includes rate of severe infection, lymphocyte counts, thymopoiesis, use of intravenous immunoglobulin, and vaccination response
- Non-immunological aspects of ADA-SCID includes neurological and developmental effects

Patient expert comments

Patient groups

- Babies with SCID may seem well at birth, but soon suffer infections more frequently and severely than other infants
- If there is no family history of ADA-SCID people can suffer delays to diagnosis due to the rarity of the condition and it not being recognised
- Prolonged hospitalisation, separation from extended family, blood tests and uncomfortable procedures will contribute to a great deal of stress and anxiety and even guilt for parents of a child with ADA- SCID.
- Strimvelis treatment involves travel to Milan. This would represent a huge upheaval for a family and may have cost implications in terms of family income and having on hand support from family and friends.
- Enrolling in a UK clinical trial may be more attractive for some people
- Based on current knowledge of incidence 6-10 children will present with ADA-SCID per annum, of these most will be eligible for Strimvelis

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- Other challenges identified for traveling to Milan include cultural differences such as language, approach to healthcare, different foods, and dealing with a new healthcare team. For some families this may not present a challenge and they may decide this route to a cure is in the best interest of the child.

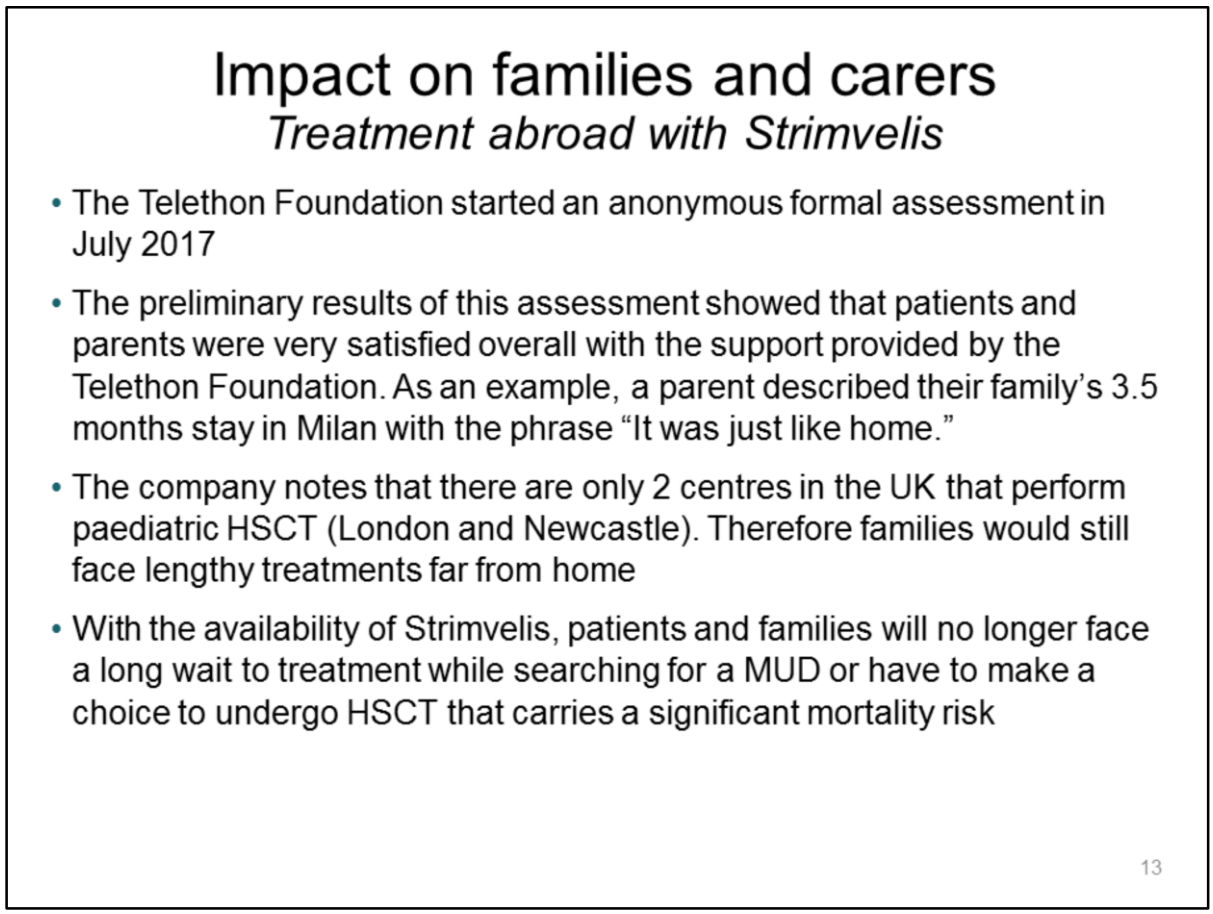
- One parent giving up work to become a fulltime carer is not uncommon. Loss of income in conjunction with paying for travel for hospital visits and or time off work puts a financial strain on the family. The psychological impact on the family of a diagnosis is profound and can often put a strain on a marriage.

- The UK Primary Immunodeficiency Network registry has 28 reported cases of ADA-SCID in England although this is known to be an underestimate due to underreporting.

Patient expert comments

Carers

- Delays in diagnosis occur due to lack of knowledge of this condition
- HSCT may not be a viable treatment option depending on other health issues
- All aspects of life for both child and family are impacted
- Anxiety is a huge emotion to have to deal with as a carer
  - Before diagnosis, you know something is wrong and have to watch your child suffer terribly with severe illnesses without knowing why
  - After diagnosis, there is a strain of having to think about what lies ahead in terms of treatment, life changes, possibility of giving up a job to be a carer
- This technology is a safer, less risky, less harsh. The benefits are life changing including everything from emotional wellbeing, physical appearance, quality of life etc.
- The financial and impact on family and work with this technology you would get from other treatments



Telethon Foundation - the charity responsible for providing the care services at Milan for patients who undergo gene therapy
Areas assessed include: patient/parent satisfaction and quality of care support provided, logistical and practical support services, travel and accommodations, emotional support and guidance provided by their care coordinator, clinical research nurses, clinicians and psychologists.

In addition to the formal assessment, the Telethon Foundation collects ongoing feedback from patients and relatives as part of a continual assessment to support performance. Spontaneous and unsolicited feedback contributes to the foundation's understanding of the kind of support that makes a difference in a family's experience in Milan. Here are some examples of the spontaneous feedback that was provided to GSK: "The biggest help was to find a babysitter for my daughter. It was a wonderful evening and we were really happy to go out together"; "We are so grateful for all that you did for us. We really felt welcomed by friends. We would never have imagined to receive all this. Now we only hope that all will be good for our son"; "Me and my family did not thank you enough for all the things you brought to us, it was too much and it helped us a lot, so thank you so much for everything."

Clinical expert comments

- Strimvelis could be offered to the large majority of ADA-SCID patients for whom a MSD is not available (up to 80% of the patients)
- In the UK, to my knowledge, patients without an HLA-identical sibling donor are usually enrolled in a clinical trial at Great Ormond Street Hospital (GOSH)
- For patients who are not suitable to receive Strimvelis or who have failed gene therapy, a matched unrelated donor (MUD) search is started while the patient is maintained on enzyme replacement therapy.
- Gene therapy could potentially benefit all subgroups, from early onset to late onset
- older patients usually have a lower cell content in the bone marrow, and may not produce enough cells for the Strimvelis procedure
- Usual complications of HSCT (including veno-occlusive hepatic disease, GvHD, and severe mucositis requiring parenteral nutrition) have not been observed with Strimvelis

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- Can be offered to a large majority of ADA-SCID patients because Strimvelis treatment requires only a low intensity conditioning and there is no need of immune suppression.

- Patients at GOSH have in the past have been offered compassionate use /hospital exemption with experimental lentiviral gene therapy.

NHS England comments

- All patients with ADA-SCID treated at Newcastle Children's hospital or Great Ormond Street hospital (GOSH). There is no variation in their clinical practice
- Where no suitable donor is available (~ 2 people a year) patients are treated under the gene therapy programme at GOSH*
- Strimvelis appears to offer an alternative treatment option
- Key additional resource would be the cost of treatment in Milan and the cost of travel for patient and parent(s) to Milan. Arrangements for follow up, after care and management of complications if any would also need to be explicit. NHS England would expect to pay for the service as a public sector commissioner and the contract would need to be managed within NHS England's usual financial processes.

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*GOSH gene therapy programme:

- Initial lentiviral vector trial was completed and recruited 20 patients (10 on trial and 10 off trial)
- New trial with a cryopreserved formulation (so as to allow access to patients in different locations) is in the process of being initiated (est. to open Oct 2017), In the meantime, 2 patients have been treated off trial with the cryopreserved formulation out of clinical need. A third is awaiting treatment.

Clinical effectiveness evidence

Company submission section C

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Clinical evidence

Summary of included evidence

Integrated population (n=18)

- AD1117054 (pilot 1); n=1 – *Complete*
- AD1117056 (pilot 2); n=2 – *Complete*
- AD1115611 (pivotal trial); n=12 – *Complete*
- AD1115611 (long-term follow-up [LTFU]); n=14 – *Ongoing,*
  - Patients eligible if they had received Strimvelis in any of the above studies
  - 14 patients at latest datacut (1 from pilot 1; 2 from pilot 2; 11 from pivotal trial)
- AD1117064 (Compassionate use programme [CUP]); n=3 – *Complete*
  - After 3 years of follow-up eligible to join the LTFU study

Supportive evidence

- Named Patient Programme; [redacted] – *Ongoing*
  - [redacted]

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- Latest data-cuts for the trials are:
  - Pilot 2: Feb 2005
  - Pivotal trial: July 2011
  - LTFU: May 2014
  - CUP: May 2014

- Comparative evidence for HSCT is obtained from the literature

Clinical evidence
Trial methodology

- Methodology consistent across studies

Design	Open-label; single-arm
Site	HSR-TIGET (Milan, Italy). [redacted]
Inclusion	• Aged <18 years with ADA-SCID and for whom an HLA-identical healthy sibling was not available as suitable bone marrow donor • Exhibited lack of efficacy (defined by immunological measurements) ≥6 months of treatment with PEG-ADA prior to enrolment; OR had PEG-ADA discontinued due to intolerance, allergic reaction, or autoimmunity, OR enzyme replacement therapy was not a lifelong therapeutic option
Exclusion	HIV; current or history of malignancy; received a previous gene therapy treatment in the 12 months
Intervention	Infusion of Strimvelis after busulfan non-myeloablative conditioning

Source: table C5 (page 52) of the company submission

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Clinical evidence

Patient baseline summary

		Integrated population (n=18)	Named Patient programme ([redacted])
Median age (range)		1.70 years (0.5 – 6.1 years)	[redacted]
Female (%)		7 (39%)	[redacted]
Male (%)		11 (61%)	[redacted]
Median height (range)		4th centile (<1st – 97th centile)	[redacted]
Median weight (range)		15th centile (<1st – 97th centile)	[redacted]
Ethnicity	Caucasian	10 (56%)	[redacted]
	Arabic	5 (28%)	[redacted]
	African American / African	2 (11%)	[redacted]
	Asian	1 (6%)	[redacted]

[redacted]

Source: adapted from EPAR page 46; table 1, page 3, company response to clarification

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Overall and intervention-free survival

Source	Overall survival	Intervention-free survival
Strimvelis		
Integrated population	18/18 (100%)	14/17 (82%)
Integrated population + named patient program	[redacted]	[redacted]
HSCT		
Matched unrelated donor Hassan 2012	10/15 (67%)	1/15 received 2nd HSCT after initial transplant
Haploidentical donor Hassan 2012 (full cohort)	13/30 (43%)	-
Haploidentical donor Hassan 2012 (2000-2009)	5/7 (71%)	2/7 did not engraft • 1 received gene therapy • 1 had 2 rescue HSCTs and then died

Source: adapted from page 94-95, Company submission

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- No data from patient 1 for intervention-free survival
- No reports of HSCT patients who required reintroduction of PEG-ADA

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Overall survival

Strimvelis

- 18/18 treated with Strimvelis in the trials remain alive
- All ([redacted]) patients from the Named Patient Programme remain alive

HSCT

- 29 references found reporting overall survival of matched unrelated and haploidentical donor hematopoietic stem cell transplantation
- Matched unrelated donor: 4 studies included 5 or more patients. Overall survival range was 60% to 71% (follow-up range: 1 year – 12.3 years)*
- Haploidentical donor: 5 studies included 5 or more patients. Overall survival range was 23% to 68% (follow-up range: 1 year – 25.8 years)*
- As survival has improved over time, most recent reference and time period has been used for comparison (Hassan 2012, 2000-2009 cohort)
- The majority of deaths reported in Hassan 2012 for all types of HSCT were in the first 100 days after transplantation (63%; 22/35)

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*follow-up was not consistent across the identified studies:
For MUD overall survival:

- 71%, follow-up: mean of 2.5 years (range of 1.1-12.3 years) for survivors
- 67%, follow-up: 6.5 years
- 67%, follow-up: 1 year
- 60%, follow-up not reported

For Haploidentical overall survival:

- 43%, follow-up: 6.5 years
- 68%, follow-up: 1.5-25.8 years
- 43%, follow-up: 1 year
- 23%, follow-up not reported
- 67%, follow-up: mean of 14.6 years (range of 4.6-22.2 years) for survivors

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Intervention-free survival

Strimvelis

Defined as no post-gene therapy PEG-ADA of ≥3 months, HSCT, or death

Integrated population

- 3/17 patients treated with Strimvelis required PEG-ADA reintroduction
- 2/3 of those that required reintroduction subsequently received a MSD HSCT. The other person remains on PEG-ADA in the LTFU

Named Patient Programme

- [redacted] required reintroduction of PEG-ADA
- [redacted]
- [redacted]
- [redacted]

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Intervention-free survival
HSCT

- Comprehensive reference data on intervention-free survival following HSCT are not available

Dvorak, 2014

- 0/7 received a second HSCT after initial MUD transplant (2 died)
- No data on PEG-ADA use

Hassan 2012

- MUD HSCT: 1/15 received a second HSCT after initial transplant (5 died)
- Haploidentical donor HSCT (2000-2009 cohort): 1/7 received gene therapy and 1 patient received long-term PEG-ADA, required a 2nd HSCT from a new matched sibling donor, and subsequently died (2 died in total)
- Of the 52 who received HSCT not from matched siblings or family members, 9 went on to receive at least 1 additional transplant (25 died)
- No report on patients who required reintroduction of PEG-ADA

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- New techniques have been explored, but outcomes reported in the literature since 2000 for patients with ADA-SCID have not been superior to normal transplant techniques.

Immune function
Strimvelis

Lymphocyte counts

- Lymphocytes in general and CD3+ T cell counts in particular increased compared to baseline

T cell receptor excision circles (TREC) - marker of thymic activity

- Increased from baseline Years 1-3 post treatment, declined years 5-8 but remained above baseline levels

Rates of metabolic detoxification

- Rates of metabolic detoxification were high, based on dAXP and dATP levels. lymphocyte ADA activity dropped at year 4, but was increased at other time points

Vaccination response

- Majority of patients had antibodies to a range of infectious antigens at one or more time points after IVIG had been stopped

IVIG discontinuation rate

- Total of 11/17 (65%) discontinued. 8/11 before 3 years and 3/11 after 3 years

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- Only evidence available is from the integrated population

- T cell receptor excision circles (TREC) are DNA fragments formed in T cells during the T cell receptor generation which occurs during the development of T cells in the thymus. They are non-replicative; thus, when immune cells divide in response to antigen the TREC do not. For this reason, their presence in peripheral blood T cells is a useful marker of thymic activity (i.e., production of newly formed naïve CD45RA+ T cells). The contribution of the thymus to immune development in adults has historically been unclear; however, an age-related decrease in thymus size and activity is expected as children approach adolescence and the thymus atrophies

Immune function
HSCT

Lymphocyte counts

- At last follow-up in Hassan 2012 cell counts for all donors were similar to those observed in the Strimvelis programme after a median follow-up of 6.9 years

T cell receptor excision circles (TREC) - marker of thymic activity

- Comparable data for either HSCT comparator was not identified

Rates of metabolic detoxification

- Rates of metabolic detoxification were high, based on dAXP and dATP levels. No comparable data of lymphocyte ADA activity for either HSCT comparator

Vaccination response

- Although data is limited, vaccination response appears comparable for patients receiving HSCT from a MUD. No data from haploidentical donors.

IVIG discontinuation rate

- Higher rate in Hassan 2012 for both MUD (5/7, 71%) and haploidentical (7/7, 100%) discontinuing IVIG treatment

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- Cell counts from the available literature in patients with ADA-SCID after HSCT from a MUD or haploidentical donor are presented in Table C 25.

- Interpretation of the literature search results is limited by differences in the method (cell counts versus number normal) and timing of reporting as well as whether data are reported for all patients or only survivors.

Non-Immunological aspects of ADA-SCID

Strimvelis

- All but 1 patient had events during treatment or post-treatment, and many patients reported events pre-treatment
- 9 patients reported 12 adverse events of hearing impairment, of which 2 patients reported deafness and 2 further reported bilateral deafness
- 5 patients and 3 reported cognitive disorders and psychomotor hyperactivity.
- People showed increases in height and weight, although they remained generally below the 50th percentile, most patients continued along their original percentiles for growth. Weight of 1 patient was below the third percentile for most of the LTFU period.

HSCT

- Very limited reporting, but a high incidence of non-immunological problems was also found for ADA-SCID patients following HSCT
- Strengths and Difficulties Questionnaire indicated IQ levels more than two standard deviations below the general population mean (100) and greater risk of behavioural problems

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- Fourteen of the 17 patients with neurologic, CNS, or hearing events on or after gene therapy had either relevant conditions ongoing at Screening or events during the pre-treatment phase. Nine of these 10 patients were on PEG-ADA prior to gene therapy. It is noteworthy that parental consanguinity was reported in 9 of 18 patients.

- Company notes neither HSCT or Strimvelis are expected to impact non-immunological events

Need and duration of in-patient treatment

Strimvelis

- Patients were hospitalised for a median of 45 days (range: 34 to 110 days) after receipt of gene therapy, and the company expect that patients who receive Strimvelis in the future will be hospitalised for a similar period (average 50 days)

HSCT

- The UK Stem Cell Strategy Oversight Committee guidelines on unrelated donor stem cell transplantation in the UK states that recovery from HSCT typically takes 4-8 weeks as an inpatient

Adverse events

- The safety of Strimvelis is in line with that expected in an ADA-SCID population that has undergone busulfan conditioning and undergoing immune reconstitution
- All adverse events were resolved
- No GvHD was observed – No immune rejection is expected as Strimvelis is an autologous treatment. Lack of GvHD expected to be a key benefit of Strimvelis treatment over HSCT
- Severe infections, (reported separately as a key secondary endpoint) were significantly reduced after gene therapy relative to baseline rates
- No events indicative of leukemic transformation or myelodysplasia were reported and no issues around immunogenicity were evident*

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*Since 2000, 40 patients with ADA-SCID have been treated with gamma retroviral vectors and 20 have been treated with lentiviral vectors. All 60 patients are alive with no reports of leukaemia. Retroviral insertion site and replication competent retrovirus testing would only be performed in the event of a leukemic adverse event.

- The long-term efficacy, tolerability, and safety outcomes will be monitored via the Strimvelis Patient Registry Study, a non-interventional, observational, prospective Post-Authorisation Safety Study of patients with ADA-SCID treated with Strimvelis. The primary objective of this study is to characterise the long-term safety and effectiveness of Strimvelis over a 15-year post-treatment period in up to 50 patients treated.

Adverse events

Rate of severe infections

		Pre-treatment*	Post-treatment[b]
	Patients with events, n (%)	14/17[a] (82)	10/17[a] (59)
Number of events, n	**Total**	**40**	**15**
	4 months to 3 years follow-up[b]		12
	4 to 8 years follow-up		3
Number per person, n (%)	1	4 (29)	7 (70)
	2	4 (29)	1 (10)
	≥3	6 (43)	2 (20)
Person-years of observation (free from infection)	**Total**	**34.3**	**89.23**
	4 months to 3 years follow-up[b]		45.81
	4 to 8 years follow-up		43.42
Rate of infection	**Total**	**1.17**	**0.17**
	4 months to 3 years follow-up[b]		0.26
	4 to 8 years follow-up		0.07

*patient history and screening (including carer-recalled infections) from birth up to the time of gene therapy
[a]patient excluded as data was not recorded, [b]Excludes planned 3-month hospitalisation period
Source: Adapted from table C23, page 96, company submission

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- Severe Infections defined as those that led to hospitalisation or prolonged hospitalisation
- Rate of infection estimated as number of infections over person-years of observation (free from infection)
- The most frequently reported severe infections were device-related infections (n=5) and gastroenteritis (n=3); the device-related infections were expected due to long-term placement of CVCs, and gastroenteritis is a common childhood illness. Of note, 2 patients reported Varicella infection and one patient had Staphylococcal sepsis. All severe infections in the Strimvelis programme were reported as resolved.
- Severe infections, defined as infections that led to or prolonged hospitalisation, were not clearly reported by that definition in the available literature for HSCT. However, infections that were reported in the literature for HSCT are discussed under adverse events and provided in Table C28. Several infections, including infections resulting in deaths, were reported but details were limited in many cases and not enough information was provided to determine a severe infection rate after HSCT.

Adverse events
EMA assessment report

- EMA notes the short term safety evaluation appears to be hampered by the busulfan conditioning, medium and longer term safety seem to be consistent with safety findings in ADA patients undergoing immune reconstitution
  - Company notes Strimvelis uses a low-dose busulfan conditioning regimen whereas some HSCT protocols use full-dose chemotherapy regimens and adverse events may be dose-dependent
- EMA notes that the use of gamma-retroviral vector mediated gene therapy has been associated with insertional mutagenesis in 3 different gene therapy trials – and the long-term carcinogenic potential of Stimvelis cannot be determined at the time of assessment.
- EMA assessment report contains greater detail of adverse events including,
  - Serious adverse events post-treatment
  - Adverse events which required intervention with PEG-ADA, high dose IVIG, high-dose steroids or additional cells
  - Adverse events potentially related to autoimmunity

Additional measures necessary to address issues related to safety in the EMA assessment report are:

- Non-interventional post-authorisation safety study: In order to investigate the long term safety and efficacy of Strimvelis gene therapy, the company should conduct and submit the results of a long term prospective, non-interventional follow up study using data from a registry of patients with adenosine deaminase severe combined immunodeficiency (ADA-SCID) treated with Strimvelis. The company will follow up on the risk of immunogenicity, insertional mutagenesis and oncogenesis as well as hepatic toxicity. The company will review the occurrence of angioedema, anaphylactic reactions, systemic allergic events and severe cutaneous adverse reactions during the FU period, particularly in those patients who had unsuccessful response and received ERT or SCT. The company will also evaluate intervention-free survival.
- The applicant will provide the final study report of the long term follow up study AD1115611 LTFU as an obligation. In this respect all 18 patients should be followed up for a period of 8 years,
- The applicant should provide more details regarding the survey (i.e. timelines, outcomes for success, follow up questionnaires) to evaluate effectiveness of risk minimisation. The applicant will commit to providing full details of this post-authorisation study at a later date as a post-approval commitment. The study is anticipated to start in 2Q 2017.

- The applicant will conduct a post approval methodology study to investigate the retroviral insertion site analysis.

Source: EMA assessment report, page 78

Adverse events
HSCT

- Adverse events after HSCT from a MUD or haploidentical donor for patients with ADA-SCID have not been systematically described
- Several cases of GvHD have been described following both HSCT from MUDs and haploidentical donors
- None of the literature reports of GvHD in patients with ADA-SCID identified in the literature search provided the definition used in reporting terms such as acute, chronic, severe, or specific grades.
- Several infections, including infections resulting in deaths, were reported but details were limited in many cases and not enough information was provided to determine a severe infection rate after HSCT

Health-related quality of life (HRQoL)

Strimvelis

- Paediatric Quality of Life Inventory (PedsQL) collected for 1 person in the LTFU study
- Lansky Performance status index was collected in the LTFU study. Initial response rate was n=8 (year 4) and dropped to n=1 (year 9 and year 13)
- All patients were reported as 'fully active, normal' during the LTFU, with 1 exception, who had minor restrictions in strenuous physical activity recorded at Year 7

HSCT

- 1 poster presentation of quality of life in SCID survivors treated with HSCT in Newcastle included 12 patients with ADA-SCID. Limited data, and no information on type of HSCT, but people had significantly lower quality of life (except for the emotional domain) compared with published UK norms.

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- Additional data (although not pre-specified) showed that most (12/14) Strimvelis patients reported on-time vaccinations, attendance at school or preschool as appropriate for their age. However, most patients reported not participating in sports. Company submission stated that this was mainly due to the wishes of parents however the ERG noted this may potentially be reflective of impairment of health.

- Response rate for Lansky Performance status was n=8 at Year 4; n=9 at Year 5; n=6 at Year 6; n=6 at Year 7; n=1 at Year 9; n=1 at Year 13

- Quality of life results reported in the company's response to clarification of query A8, page 8

ERG Comments

Generalisability of evidence to UK clinical practice

- The ERG noted the following concerns with generalisability:
  - Lack of clarity regarding numbers screened or excluded outside the pivotal trial, therefore unclear if selection biases occurred
  - No Strimvelis patients had viral infections at screening. Active viral infection is known to impact HSCT prognosis and it may be an important prognostic factor for Strimvelis treatment
  - Likely that duration of PEG-ADA use was longer than would be expected in UK practice
  - The age of people treated in the study is older than the expected age of people who are newly diagnosed with ADA-SCID
- The clinical advisor to the ERG confirmed that he would not expect differences in the efficacy of treatment due to patient ethnicity.

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Viral infection

- Most viral infections present with asymptomatic or subclinical manifestations, but viruses may result in fatal complications in severe immunocompromised recipients.
- Age of patient, which is known to impact HSCT outcomes, may be a proxy for the presence of active viral infection

ERG Comments
Summary

- The ERG considers all important studies have been included for evaluation
- Substantial uncertainty based on small number of patients treated with Strimvelis. Small number of deaths will substantially impact perceived efficacy of Strimvelis
- Named Patient Programme data should be included in synthesis of evidence
- Strimvelis benefit based on overall survival is likely to be overestimated, due to the concomitant use of PEG-ADA and rescue therapy. Intervention-free survival is a more relevant outcome
- HSCT comparison is with historical controls, and overall survival from HSCT has improved substantially over time
- Variable reporting or lack of comparable data in the literature for many key outcomes
- Given the small sample size of patients who have received Strimvelis, the risk of leukaemia cannot yet be ruled out as an important potential risk.

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- Data is based on small open label single arm trials that are inherently at a high risk of bias and lack precision. Therefore all survival estimates are highly uncertain and future data could substantially change conclusions.

Key issues for consideration

Clinical evidence

- Where will the technology be used in the treatment pathway?
- Will people whose initial treatment failed have similar outcomes to people who are treatment-naïve?
- Is the Strimvelis clinical evidence generalisable to:
  - English clinical practice?
  - All ages of people with ADA-SCID?
- Should the Named Patient Programme be included in the evidence synthesis?
- What are the most relevant outcome measures to inform decision-making?
- Is the technology clinically effective:
  - Versus a matched unrelated donor HSCT?
  - Versus a haploidentical donor HSCT?
- How does the committee view the long-term risks of Strimvelis treatment?

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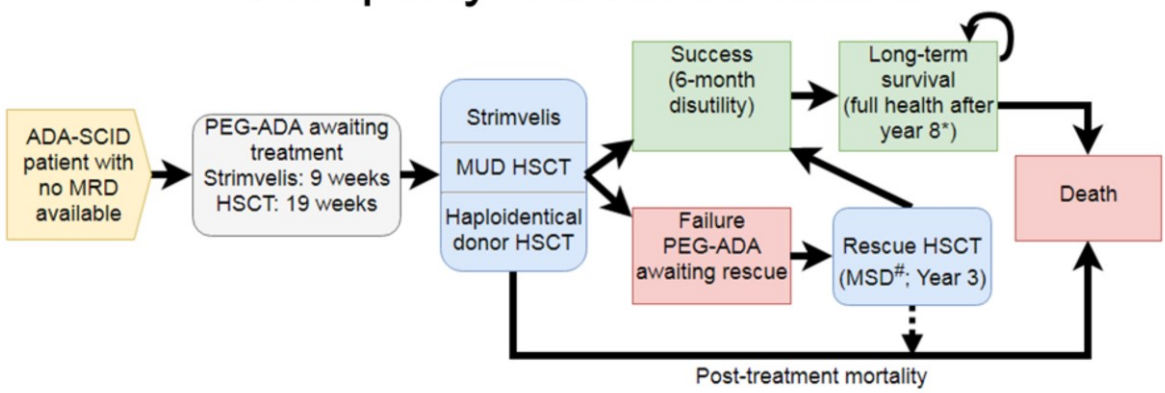
Cost effectiveness evidence

Company submission section D

Company model structure



*A proportion in year 1-8 use IVIG and are at risk of GvHD, and severe infection
#Rescue HSCT assumed from MSD, with 100% success rate and no post-treatment mortality, serious infection or GVHD. 66% mortality explored in scenario analysis

Time horizon: lifetime (100 years)
Discount rate: 1.5%
Perspective: NHS
Cycle length: 2 cycles of 6 months, 1 year thereafter
Modelled population: aged 1; 50% male and 50% female

Source: Adapted from figure 5, page 139, company submission

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- The company model specifies that a haploidentical donor is only chosen if no MUD is found, however Strimvelis is compared to each HSCT separately rather than a weighted average based on the probability of a successful MUD search.

Key company assumptions (I)

Assumption	Source / Justification
Survival	
100% survival from diagnosis to initial treatment	78% at 20 years with half of the deaths on ERT occurring within the first 6 months of treatment. Conservatively[a] assumed that survival is 100% for simplicity
100% survival for people waiting for rescue transplant	No patients died waiting for rescue transplant in Strimvelis trials. No data from Hassan 2012. Conservatively[a] assumed that all survive until transplant
Life expectancy equal to general population after 6 months	Data from Hassan 2012 do not show deaths after ~1 year. Clinical advice confirmed that this life expectancy assumption is reasonable
Post-transplant outcomes	
Rate of severe infections is equal for all treatments	No available data for MUD or haploidentical donor

[a]Lower survival rate would increase relative cost-effectiveness of Stimvelis, as the company assume a shorter wait-time for people who are treated with Strimvelis

Key company assumptions (II)

Assumption	Source / Justification
Treatment failure	
PEG-ADA restarts 3 months after treatment failure	~4 months earliest restart to PEG-ADA in Strimvelis trials. Based on expert clinical advice
Rescue transplant occurs in year 3	Based on expert clinical advice.
Rescue transplant from matched sibling donor – with 100% success and survival	Rescue transplants from Strimvelis and Hassan 2012 were all from newly born siblings. For simplicity rescue is assumed to be successful with no adverse events (i.e. GvHD or severe infection)
Other	
1.5% discount rate for costs and outcomes	Strimvelis meets the criteria for a 1.5% discount rate as treatment leads to long and sustained benefit and people regain normal life expectancy
Average weight is the 25th percentile of an average child	Patients continued to track along their original percentiles but remained below the 50th percentile

Source: Table D2 and D4, page 142-145 and 149, Company submission

Discount rate

- The company have applied a discount rate of 1.5% to both costs and outcomes on this basis. Patients treated with Strimvelis are expected to have a long and sustained benefit and regain normal life expectancy. Given the minimal budget impact of Strimvelis, the introduction of the technology would not commit the NHS to significant irrecoverable costs.
- 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 public health programmes. The NICE Appraisal Committee accepted this same rationale as justification for using a 1.5% discount rate in the cost-consequence analyses for eculizumab for treating atypical haemolytic uraemic syndrome and mifamurtide for the treatment of osteosarcoma.

Key company clinical variables

Variable	Strimvelis	MUD	Haploidentical
6-month overall survival	100% (18/18)[a]	67% (10/15)[b]	71% (5/7)[b]
>6-month overall survival	Assumed equal to general population, independent of treatment success		
Severe infections	26% for first 3 years, 7% for Years 4-8	Assumed equal to Strimvelis	
Rescue HSCT	17.6% (3/17)[a]	6.7% (1/15)[b]	28.6% (2/7)[b]
IVIG use	Year 1: 100% (18/18)[a] Year 3: 58.8% (10/17)[a] Year 8: 0% (0/4)[a]	Assumed equal to Strimvelis	
Grade I/II GvHD	0%	17.9% (5/28)[c]	22.2% (2/9)[c]
Grade III/IV Acute GvHD	0%	10.7% (3/28)[c]	11.1% (1/9)[c]
Grade III/IV Chronic GvHD	0%	3.6% (1/28)[c]	0% (0/9)[c]

[a]Does not included NPP population; [b]based on Hassan 2012 data; [c]based on pooled incidence of GvHD from the literature (see Table C28, page 114-117, company submission)
Source: Table D5, page 158-167, Company submission

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Key timings and durations

Variable		Company value	Source / Justification
PEG-ADA duration before treatment	Strimvelis	9 weeks	Clinical schedule
	MUD	19 weeks	Gaspar 2013
	Haplo	19 weeks	Assumes MUD searched initially
Timing of rescue transplant		In Year 3	Based on clinical expert advice
Duration of PEG-ADA in bridge to rescue transplant		1.75 years	Continuous PEG-ADA minus initial 3 months after treatment
Duration of acute GvHD		8 months	Based on clinical advice
Duration of chronic GvHD		3 years	Clinical advice suggests few months to several years, but would normally be resolved by the time of a rescue transplant. Assumed 3 years.

Source: Table D5, page 158-167, Company submission

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- Donor availability can differ based on ethnicity, with non-Whites having a more difficult time finding a suitable donor and a longer wait for an available donor

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Treatment cost

Variable	Strimvelis	MUD	Haploidentical
Initial PEG-ADA[a]	£124,254	£262,314	£262,314
Cost of screening for donor[b]	N/A[c]	£45,127	£45,127
Price of technology	£505,000[d]	N/A	N/A
Confirmation of eligibility	[redacted]	N/A	N/A
Hospitalisation cost	[redacted][d]	£95,516	£108,760
Follow-up costs[e]	[redacted]	£59,541	£59,541
Total cost per treatment/patient	[redacted]	**£462,444**	**£475,742**

[a]Cost per week is £13,500 (1.5 vials; clinical expert advice) + £306 administration (NHS reference costs)
[b]Source: Van Agthoven 2002 in euros. Inflated to 2016 value conversion of 1€ = £0.85 on 08 May 2017
[c]Not applicable as UK ESID and EBMT clinical guidelines recommend gene therapy after no MRD available
[d]Cost to be paid in euros. Conversion 1€ = £0.85 on 08 May 2017; includes 2 months follow-up
[e]per living patient; does not include long-term costs such as IVIG, PEG-ADA, and VCN monitoring costs;
Source: Adapted from Tables D8 – D10, page 172-175, Company submission

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Further treatment costs

- Some costs due to travel may not reimbursed by the NHS, but the patients and carers would likely incur these costs regardless of the treatment selected.

[redacted]

- Any additional procedures, treatment failure, or extended hospitalisation in Italy beyond the assumed clinical schedule (i.e. over 55/days standard stay) would incur additional costs. These would depend on the commissioning route of the patient
  - With S2 form – charged as Italian statutory patient
  - Without S2 form – charged per procedure conducted during that period
- See company response to clarification query B6 (page 26-27) for circumstances where the costs differ by commissioning route

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- Under the S2 route, a patient applies for authorisation for pre-planned treatment in another EEA country. If approved, NHS England provides the patient with an S2 as a guarantee of payment on behalf of the Secretary of State.

- Under the Directive route, for most treatments the individual seeks the healthcare they require in another EEA country, pays for the treatment directly and then may apply for reimbursement of eligible costs from the NHS. However, some specified treatments require the patient to obtain authorisation before receiving treatment. NHS England is responsible for reimbursing patients under the Directive route in line with the legislation, and in turn, the responsible commissioner in each case is required to refund NHS England for the reimbursements it has made to individual patients . Reimbursements will generally not exceed NHS tariff levels for the equivalent treatment.

Utilities

Variable	Company value	Source / Justification
Pre-treatment	0.98	For simplicity, assumed no disutility whilst waiting for treatment on PEG-ADA[a]
IVIG disutility	No disutility	Likely to have little impact as assumed the rates are equal
Severe infection	No disutility	
0-6 months post-treatment[b]	0.57 utility decrement	Value from study of patients with acute myeloid leukaemia after HSCT (Sung 2003)
>6 month post-treatment	Age-adjusted general population	No literature on non-immune related disutility.
Acute GvHD	One-off loss of 0.41	Values calculated from GvHD of lymphoma patients[c] (Swinburn, 2015), adjusted by assumed durations
Chronic GvHD	One-off loss of 1.44	

[a]Lower pre-treatment utility value would increase relative cost-effectiveness of Stimvelis, as a shorter wait-time to initial treatment is assumed for people who are treated with Strimvelis
[b]Treatment includes Strimvelis, HSCT from a MUD or haploidentical donor, or rescue transplant
[c]relapsed/refractory Hodgkin lymphoma or systemic anaplastic large cell lymphoma
Source: Table D5, page 158-167, Company submission

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- 1 article identified which investigated the cost-effectiveness of newborn screening for ADA-SCID (Ding, 2016). The Ding model referenced an article [McGhee, 2005] that used a utility value for survivors of ADA-SCID treatment based on health preference scores estimated by investigators after successful BMT for chronic myelogenous leukaemia. The same article [Ding, 2016] also used a utility value for patients receiving IVIG based on values for patients with chronic lymphocytic leukaemia [Weeks, 1991]. These utility values were not specific to patients with ADA-SCID, but they were identified as possibly useful for inclusion in a sensitivity analysis

Base case results

	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Company – base case					
Strimvelis	£1,059,425	41.4	-	-	-
MUD	£565,170	27.8	£494,255	13.6	**£36,360**
Haplo	£888,757	29.7	£170,668	11.7	**£14,645**

ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; MUD, Matched unrelated donor; Haplo, Haploidentical donor

Source: Table D14, page 189, company submission; company response to clarification query B20, page 44

- As the decision model is linear, the probabilistic ICER is almost identical to the deterministic ICER. The ERG believe the deterministic ICERs are suitable for decision-making

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Disaggregated results

Costs

Variable	Strimvelis	MUD	Haploidentical
Screening pre-procedure	£0	£45,127	£45,127
Confirmation of eligibility for Strimvelis treatment	[redacted]	£0	£0
PEG-ADA pre-procedure	£124,254	£262,314	£262,314
Product price	£505,000	£0	£0
Severe infection cost	£13,103	£8,735	£9,359
Rescue transplant cost	£16,119	£6,090	£26,098
Rescue PEG-ADA cost	£217,055	£81,999	£351,423
Hospitalisation cost	[redacted]	£95,516	£108,760
Follow-up cost[a]	[redacted]	£43,027	£58,259
GvHD	£0	£7,834	£8,354
IVIG cost	£23,041	£14,529	£19,063
Total	**£1,059,425**	**£565,170**	**£888,757**

[a]cost per patient; include long-term costs such as IVIG, PEG-ADA, and VCN monitoring costs
Source: Adapted from Tables D22-23, page 200-201, Company submission

Disaggregated results

Life years and QALYs

Outcome	Strimvelis		MUD		Haploidentical	
	LYs	QALYs	LYs	QALYs	LYs	QALYs
Pre-procedure (PEG-ADA)	0.2	0.2	0.4	0.4	0.4	0.4
Post-procedure, successful	37.8	34.0	27.6	24.7	19.7	17.7
Failure to engraft, PEG-ADA	0.3	0.3	0.1	0.1	0.6	0.4
Rescue transplant and post-transplant	7.8	6.9	2.9	2.6	12.6	11.2
Total	**46.1**	**41.4**	**31.0**	**27.8**	**33.2**	**29.7**

Source: Adapted from Tables D17, page 194, Company submission

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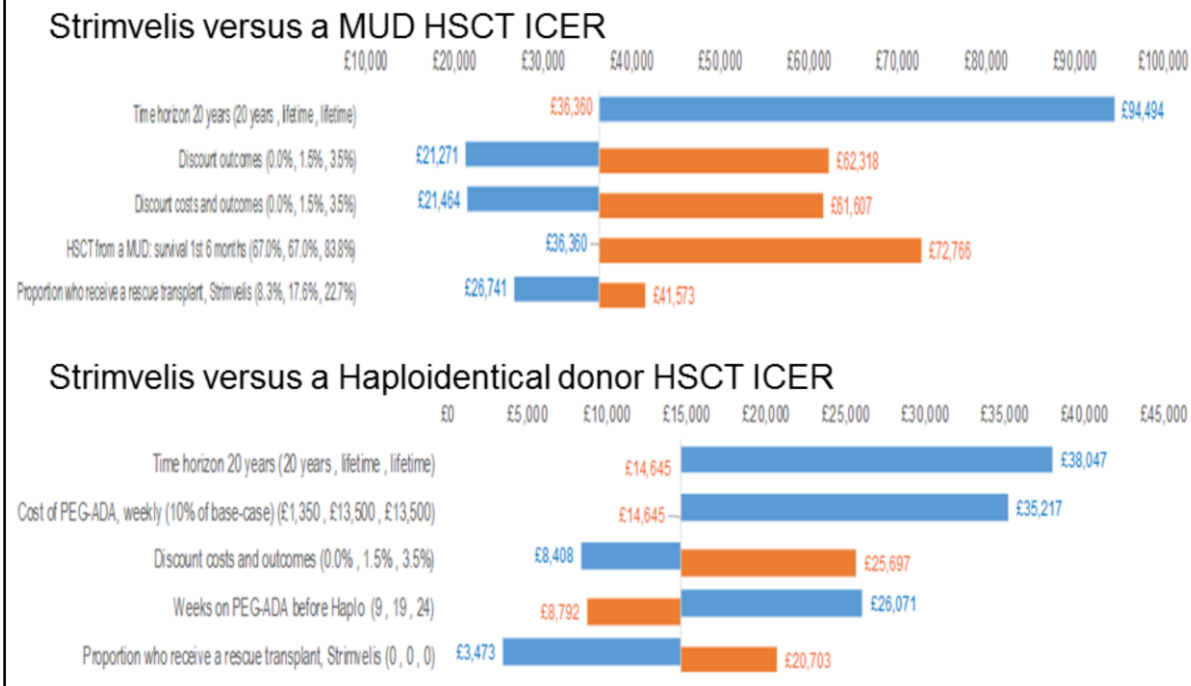
Sensitivity analysis

One-way sensitivity analysis (top 5)



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Source: Figure 1 and 2, page 48 and 49, Company response to clarification

- GSK did not wish to include further assumptions around Strimvelis or HSCT survival in the tornado diagram. The rationale is provided in clarification response B24.

Sensitivity analysis

Multi-way scenario-based sensitivity analysis

- Company explored the joint uncertainties in long-term utility scores and mean life-expectancy for survivors (MLS)

	MLS*1 (79.9 yrs)	MLS*0.9 (71.9 yrs)	MLS*0.8 (63.9 yrs)
Strimvelis vs HSCT from a MUD			
Utility Score by Age * 1	**£36,360**	£38,375	£40,987
Utility Score by Age * 0.9	£40,410	£42,650	£45,554
Utility Score by Age * 0.8	£45,475	£47,997	£51,266
Strimvelis vs HSCT from a Haploidentical donor			
Utility Score by Age * 1	**£14,645**	£15,456	£16,508
Utility Score by Age * 0.9	£16,290	£17,194	£18,366
Utility Score by Age * 0.8	£18,352	£19,371	£20,694

Source: Table D26, page 214, company submission; base case is bold and underlined

Scenario analysis

- Company also investigated some alternative scenarios

Key scenarios		Strimvelis versus HSCT			
		Inc. costs	Inc. QALY	ICER	Δ ICER
Company base case	MUD	**£494,255**	**13.6**	**£36,360**	**-**
	Haplo	**£170,668**	**11.7**	**£14,645**	**-**
0.75 IVIG utility weight	MUD	£494,255	13.3	£37,158	+£798
	Haplo	£170,668	11.5	£14,865	+£220
Carer's QALY loss due to death of child[a]	MUD	£494,255	14.9	£33,201	-£3,159
	Haplo	£170,668	12.8	£13,373	-£1,272
MUD rescue treatment mortality (66%)	MUD	£491,122	12.2	£40,413	+£4,053
	Haplo	£173,785	13.1	£13,279	-£1,366

Source: Adapted from table D24 and D25, page 203-213, Company submission

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[a]Following Christensen et al (2014), the additional quality of life-related QALY loss experienced by a bereaved family was assumed to be 9% of the child's QALY loss. The child is assumed to die in the first half year cycle (Year 0.5), and the discounted QALY loss of the child was calculated as the difference between the general population survival and the HSCT survival, integrated from Year 1 to Year 100. The child's discounted QALY losses are 23 and 20 QALY for HSCT from a MUD or from a Haplo, respectively. The additional QALY loss experienced by the bereaved family is 9% of the child's loss: 2.1 and 1.8 QALYs for HSCT from a MUD or from a Haplo, respectively.

Scenario analysis

Secondary analysis in response to clarification

Variable	Company value	Rationale
Weekly cost of PEG-ADA	£9,000 (1 vial) previous value £13,500 (1.5 vials)	Estimated on patient's body weight, dose per kg/per week and vials needed. Conservative assumption as some patients will require 2 vials per week
IVIG administration	£216 (£108 x 2 hours) previous value £306	Re-estimated based on the hospital nurse time (PSSRU 2016) and estimated time needed to deliver IVIG
PEG-ADA administration	£54 (£108 x 0.5 hour) previous value £306	Assumed 30 min Band 6 nurse time required (PSSRU 2016) for injection
Air travel to clinic in Italy	£600	Assumed £200 per person (£200 x 3 for family) round trip from London to Milan.
To and from UK airport	£472	UK ambulance cost (1-way). Note only 1 patient needed ambulance transportation
To and from Italy airport	£340	Italian ambulance cost (1-way). Note only 1 patient needed ambulance transportation

Source: Table 12, page 60, Company response to clarification 51

- Following a teleconference with the NICE technical team and the Evidence Review Group, it was noted there would be an interest in testing how eventual individual changes responding to the issues brought up at the clarification stage would impact the results when taken together. The company therefore decided to run a scenario analysis and to explore that scenario further with the respective sensitivity analyses. The company note they do not necessarily agree with all of the assumptions tested and that the inputs used in this analysis were taken from the most conservative spectrum of the possible range. This scenario analysis should therefore not be perceived as a new base case.

- The ERG believes this additional scenario analysis as a more appropriate account of the dosing and costs of administration and travel likely to occur in practice, and incorporate these assumptions into its preferred base case

Scenario analyses

Secondary analysis - combined impact of changes

Scenario		Strimvelis versus HSCT			
		Inc. costs	Inc. QALY	ICER	Δ ICER
Company base case	MUD	**£494,255**	**13.6**	**£36,360**	-
	Haplo	**£170,668**	**11.7**	**£14,645**	-
PEG-ADA cost @ £9000	MUD	£495,234	13.6	£36,432	+£72
	Haplo	£259,465	11.7	£22,264	+£7,619
Administration of IVIG @ £216	MUD	£492,722	13.6	£36,247	-£113
	Haplo	£170,001	11.7	£14,587	-£57
Administration of PEG-ADA @ £54	MUD	£494,310	13.6	£36,364	+£4
	Haplo	£175,641	11.7	£15,071	+£427
Inclusion of cost of travel to Milan	MUD	£495,667	13.6	£36,464	+£104
	Haplo	£172,080	11.7	£14,766	+£121
Combined secondary analysis	**MUD**	**£495,167**	**13.6**	**£36,427**	**+£67**
	Haplo	**£265,182**	**11.7**	**£22,755**	**+£8,110**

Source: table 30, page 117-120, ERG report

Budget impact (undiscounted)

- Budget impact is highly sensitive to expected patient numbers
- The company assumes that per year in England:
  - 3 people are diagnosed with ADA-SCID
  - 1/3 patients will have a matched related donor HSCT
  - Only 1/2 patients will choose to have Strimvelis, given the travel requirements

	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Cost per patient						
Strimvelis	£870,399	£150,112	£34,075	£6,202	£2,629	**£1,063,417**
MUD	£484,638	£62,861	£13,964	£3,218	£1,611	**£566,292**
Haplo	£619,058	£221,495	£46,181	£7,302	£2,323	**£896,358**
Incremental budget impact assuming 1 patient per year						
Vs. MUD	£385,761	£473,012	£493,123	£496,107	£497,125	**£2,345,128**
Vs. Haplo	£251,341	£179,958	£167,852	£166,752	£167,058	**£932,960**

Source: Adapted from table D30 – D3, page 231-238, Company submission

ERG Comments

Key concerns

1. **Treatment costs are overestimated for HSCT and underestimated for Strimvelis**
   - Not all relevant costs have been included
   - Assumed additional wait time before treatment overestimates HSCT costs
   - No additional costs incurred by people who have complications in Italy
   - Treatment failure with Strimvelis is only assumed to occur during follow-up

2. **Position of Strimvelis in the treatment pathway**
   - Strimvelis is assumed not to include search for a MUD
   - Other alternative treatment pathways have not been explored

3. **Overestimation of health gains with Strimvelis**
   - NPP data not included, which would reduce intervention-free survival
   - Plausible that overall survival benefit could be overestimated
   - Assuming people regain full health is contradicted by the evidence

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1. Treatment costs
PEG-ADA treatment

- ERG noted uncertainty regarding the duration and rate of PEG-ADA use

Variable		Company value	Source / Justification
PEG-ADA duration before treatment	Strimvelis	9 weeks	Clinical schedule
	MUD	19 weeks	Gaspar 2013
	Haplo	19 weeks	Assumes MUD searched initially

- Many patients with ADA-SCID did not receive ERT prior to HSCT, including 83/106 (78%) of those reported in Hassan 2012. In contrast the majority of patients did receive ERT prior to gene therapy (15/18; 83%)
- The 9 week PEG-ADA duration for Strimvelis differs from the length of the 'pre-treatment phase' observed for patients recruited to the Strimvelis pivotal study (average 5.7 months, equivalent to 25 weeks)
- ERG prefers to use equal PEG-ADA duration for all treatments

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- Although Hassan 2012 shows less PEG-ADA use in people who have HSCT, Clinical advice to the ERG indicated that most patients in the UK would be expected to receive PEG-ADA while awaiting transplant. However simplifying this assumption likely overestimates any savings from reducing the duration of time between diagnosis and transplant procedure

- The company note that PEG-ADA '*is usually stopped 20 days before infusion of Strimvelis*' and that they have overlooked this in the model for the sake of simplicity (company response to clarification B1). The ERG is also aware that PEG-ADA may be stopped to allow cellular immunity to wane in preparation to receive HSCT, in order to reduce the risk of graft rejection

- The ERG notes that the company's preference for using the clinical schedule of the San Raffaele Telethon Institute for Gene Therapy (SR-TIGET) to determine the wait time to Strimvelis in preference to observed wait times could be considered inconsistent with the preference to use observed wait times for HSCT and not the UK Stem Cell Forums recommendations of 6-8 weeks wait to HSCT (company response to clarification B1)

1. Treatment costs

Graft versus host disease duration

- In the company base case the duration of chronic GvHD (3 years) exceeds the assumed time to rescue transplant (in year 3 – therefore 2 years)
- Clinical advice is rescue transplant is only performed once GVHD is resolved. Company note that as Strimvelis does not cause GvHD rescue may occur earlier
- Company supplied at clarification a sensitivity analysis for time to rescue transplant, but the ERG could not implement this in their model. Therefore ERG prefer reducing the duration of chronic GvHD to 2 years, although note that the impact on the ICER is much smaller than delaying rescue transplant.

Variable	Year	-1 years	Base case	+1 years	+ 2 years
Rescue transplant	MUD	£30,699	**£36,360**	£41,971	£47,456
	Haplo	£20,822	**£14,645**	£8,414	£2,147
Chronic GvHD	MUD	£36,421	**£36,360**	-	-
	Haplo	£14,645	**£14,645**	-	-

Source: adapted from page 46, company response to clarification

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1. Treatment costs

Resources and costs

- ERG concerned that applying only the standard hospitalisation charge to patients for Strimvelis the company model underestimates the potential costs to the NHS. The ERG explored additional costs in a sensitivity analysis.
- ERG identified several alternative unit costs to the company:

Variable	Company base case	ERG preferred assumption
HSCT costs	£95,516 NHS reference cost HSCT from cord blood	£81,973 Weighted average including transplants undertaking using bone marrow (£79,199)
GvHD costs	£29,420 cost of severe (Grade III/IV) GvHD	£17,089 Inflated difference of any GvHD event (£28,860) and the mean cost of readmission without GvHD (£13,405)
Eligibility cost	[redacted] Includes outpatient tests and bone marrow test	[redacted] Assumes 1/18 people will not be eligible (but will incur testing cost)

Source: Section 6.2.7 and 6.2.8, page 116-117, ERG report

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- The rate of umbilical cord blood transplant observed in Hassan 2012 is 88/106, 83% and the national schedule of reference costs is 51/62, 82%. The NHS reference cost of bone marrow transplant, allogeneic graft, is £95,517

- ERG believe a more appropriate unit cost per GvHD event would be calculated by the difference between the mean readmission cost of any GvHD event (£28,860) and the mean cost of readmission for patients without GvHD (£13,405). After inflating the difference of £15,455 to 2016 prices, the resultant unit cost applied in the ERG's preferred analysis is £17,089.

2. Position in pathway

Alternative treatment pathways

- Strimvelis is assumed not to include search for MUD, however the comparator should then be a weighted average of possible HSCT options
- ERG considers some people would have Strimvelis after search for a MUD
- The model does not incorporate a pathway for patients unable to donate adequate CD34+ cells for Strimvelis treatment
- Alternative rescue therapy pathways are not explored, including:
  - People who have initial HSCT could have subsequent Strimvelis therapy
  - People who have had failed initial MUD HSCT may be less likely to have subsequent MUD HSCT, possibly increasing duration of PEG-ADA treatment
  - People with Strimvelis are not at risk of chronic GvHD, potentially shortening duration until rescue transplant
  - Rescue transplant could differ between people who fail gene therapy without completing search for MUD versus those who have completed a search

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- ERG note that the ICER for Strimvelis compared to a weighted combination of HSCT from a MUD and HSCT from a haploidentical donor would be lower than that estimated for Strimvelis compared to HSCT from a MUD only

- The ERG therefore note that the expected wait time, and the potential difference in wait time between gene therapy, HSCT from a MUD and HSCT from a haploidentical donor may be predictable by, and differ according to, known patient characteristics. If a reduction in wait time is an important factor in either the choice of treatment or in establishing the value for money of Strimvelis, then these factors could have been reflected in the model structure, for example by including branches with different expected wait times (e.g.to indicate the existence of a cord blood match in the bone marrow registry), or with the use of subgroups (e.g. to indicate longer expected wait times in certain ethnic groups).

- If rescue transplantation is earlier following Strimvelis, this would be expected to reduce the ICER for Strimvelis compared to HSCT from a MUD

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3. Overestimation of health gains

Treatment effectiveness – Survival

- ERG prefer to include the NPP data where possible. This would decrease the intervention-free survival from 82.4% to [redacted]
- Survival after transplant from a MUD is lower than that from a haploidentical donor, which lacks face validity.
- The absolute difference in overall survival between Strimvelis and HSCT may be overestimated in the company model because:
  - It is not implausible overall survival is less that 100% for Strimvelis given the severe nature of ADA-SCID
  - HSCT overall survival may now be higher than that reported in Hassan 2012
- ERG believe that the assumption that people return to full health after the initial treatment, regardless of treatment success is overly optimistic. They note:
  - Patients are modelled requiring IVIG for up to 8 years
  - People continue to be underweight
  - Strimvelis and HSCT is thought to have no impact on some adverse events

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- In general being underweight may compromise health, and is associated with increased all-cause mortality. The Royal College of Paediatrics and Child Health BMI centile charts indicate that children on the 25th percentile have a BMI of approximately 15, increasing slowly over time to a BMI of approximately 20 at age 19. BMI of less than 20 is associated with increased hazard ratio for all-cause mortality in adults compared to those with a BMI between 22.5 and 24.9.

- Individuals who have ADA-SCID are more likely to experience hearing loss, respiratory complications and neurologic abnormalities compared to the general population. Fourteen (78%) patients in the Strimvelis Integrated Population had ongoing neurological impairments at baseline and 10 of these experienced further events after gene therapy (56%). [45] These factors all indicate that ADA-SCID patients with successful engraftment may not be entirely comparable with the general population after a period of three years.

- Many long-term adverse events and the systemic sequelae of ADA-SCID consequences are assumed not to differ between gene therapy with Strimvelis and HSCT from a MUD or haploidentical donor, omitting these from the model risks overestimating the QALY gain from any deaths avoided and underestimates the health care resource use of survivors. This would be expected to overestimate the cost-

effectiveness of treatment strategies that reduce initial procedural mortality.

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3. Overestimation of health gains

Rescue therapy (I)

- The calculation of rescue therapy rates conducted by the company are not conditional on survival following the initial procedure
  - Transplant related mortality (death within 100 days of transplant) was reported in Hassan 2012, but not for the 2000-2009 haploidentical cohort
- Highly uncertain whether there is any difference in the rate of rescue therapy between Strimvelis and HSCT

	Strimvelis integrated population	Strimvelis integrated population + NPP	MUD	Haplo
Patients	17	[redacted]	15	7
Rescue transplant	3	[redacted]	1	2
Died	0	[redacted]	5	2
Survived	17	[redacted]	10	5
Non-conditional rescue rates	3/17 (17.6%)	[redacted]	1/15 (6.7%)	2/7 (28.6%)
Conditional rescue rates	3/17 (17.6%)	[redacted]	1/10 (10.0%)	2/5 (40%)

Source: table 26, page 113, ERG report

- The use of overall survival rather than transplant related mortality means that deaths from all causes, including rescue treatment attempts, are applied at the point of the initial procedure in the model
- Using the ERG's preferred assumption using transplant from a MUD with 66.67% survival, the failure to use transplant related mortality and conditional probabilities of rescue transplant is particularly problematic, as it may double count fatal events.
- Rescue rates are somewhat higher than those applied in the company model (6.7% for MUD and 28.6% for haploidentical)

3. Overestimation of health gains

Rescue therapy (II)

- Rescue transplant was assumed to come from MSD donor, with 100% success and survival, and no risk of GvHD or severe infection – which is not clinically plausible
- The company included a sensitivity analysis in which the survival rate from a rescue transplant is taken from a MUD procedure, but this did not include the risk of GvHD nor severe infections post-procedure.
- The ERG believes that the company base case that explores mortality associated with rescue transplant is favourable to Strimvelis by overestimating mortality in patients assigned to HSCT.
- ERG preferred assumption is that people would receive a MUD transplant, and incur chance of GvHD, severe infections, and further failure to engraft

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- Alternative ERG rescue transplant scenario incorporates:
  - The survival rate from a MUD transplant (66.6%)
  - The expected cost and QALY impacts of GvHD from a MUD donor
  - The expected cost of severe infections from a MUD donor
  - Patients who subsequently fail to engraft following rescue transplant go on to receive long term PEG-ADA (≥0.3% of modelled patient cohort)
- The ERG thinks that it is reasonable to assume that there will be similar mortality rates from a given rescue transplant procedure among patients who have failed to engraft following gene therapy as for those who fail to engraft following HSCT

3. Overestimation of health gains

Health-related quality of life (I)

- Model assumes no disutility in relation to severe infections, IVIG administration or central venous catheter placement
- The ERG considers that prior to transplantation the HRQL of patients awaiting treatment may be lower than that of the general population
- The company omit a cost-effectiveness study that estimated a mean health utility of 0.66 associated with use of IVIG. The justification is inconsistent with company acceptance of physician survey as a source of the health-related quality of life value for HSCT
- Evidence supports company assumption that there is a 6-month HRQoL decrement, but contradicts the assumption that people return to full health after
- ERG prefer to include the 0.75 weight for IVIG disutility included in the company sensitivity analysis

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- Justification for omitting IVIG disutility was due to the age of the study and the fact that health utility value was based on a small sample of physicians (company submission p130)

- The ERG note that where the company submission applies absolute health utility values taken from source studies in different disease areas it would have been preferable to calculate the decrement from the reference population in the respective studies. This would suggest utility weights of 0.43 (0.39/0.91) for acute GvHD, 0.57 (0.52/0.91) for chronic GvHD and 0.76 (0.66/0.87) for IVIG.

- Patients with ADA-SCID have been reported to have a high incidence of bilateral sensorineural deafness (58%). A pragmatic search by the ERG identified a study that used the HUI Mark 3 to estimate a mean health-related quality of life decrement for bilateral permanent hearing impairment of -0.294 ($p<0.01$) compared to children with normal hearing. Children with SCID exhibit worse emotional and behavioural outcomes compared to population norms as measured by the strengths and difficulties questionnaire (SDQ), and ADA-SCID is predictive of a worse SDQ score compared to other SCIDs[7] The SDQ score has been linked directly to a preference based measure of health-related quality of life

3. Overestimation of health gains

Health-related quality of life (II)

- The ERG identified the following disutilities associated with adverse events

	Decrement in HRQoL	Cost	Rates	Expected Value	
Condition	Value			HRQoL	Cost
Bilateral permanent hearing impairment	-0.294	£2,095.82	58.3%	-0.172	£1221.86
Emotional and behavioural dysfunction	-0.14	None found	15%	-0.021	None found

Source: adapted from table 28, page 115, ERG report

- Emotional and behavioural dysfunction is based is based on a mapping algorithm to predict preference-based utility scores based on clinical bandings of the Strengths and Difficulties Questionnaire
- Given uncertainties surrounding mapping, the ERG prefer to include the impacts from bilateral permanent hearing impairment only

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- Titman et al reported that 25% of SCID patients who survive HSCT experience higher levels of difficulties in emotional and behavioural function, as defined by a total difficulties score ≥17 on the SDQ. This was compared to 10% in the general population. Using a mapping algorithm to predict preference-based utility scores based on clinical bandings of the SDQ, the ERG estimate a decrement of 0.14 for difficulties in emotional and behavioural function among SCID patients.

ERG comments

Key changes to company model

- Using alternative assumptions from the company's secondary analysis
- Inclusion of Named Patient Programme data
- Assuming equal wait time and pre-procedure PEG-ADA use across treatment arms
- Assuming rescue therapy has cost and health outcomes of initial MUD HSCT
- Including ongoing healthcare costs and morbidity associated with systemic sequelae of ADA-SCID
- Adjusting unit costs for:
  - HSCT from a MUD to reflect the proportion sourced from bone marrow
  - GvHD events to make the cost per event consistent with severity
- Incorporating cost of baseline screening of patients ineligible for Strimvelis

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- In addition the ERG identified and corrected minor errors in the company model for the cost applied to the first six months' follow up after Strimvelis and the cost per test for vector copy number

ERG comments

Combined impact of changes (I)

Scenario		Strimvelis versus HSCT			
		Inc. costs	Inc. QALY	ICER	Δ ICER
Company base case	MUD	**£494,255**	**13.6**	**£36,360**	**-**
	Haplo	**£170,668**	**11.7**	**£14,645**	
Company secondary analysis	MUD	£495,167	13.6	£36,427	+£67
	Haplo	£265,182	11.7	£22,755	+£8,110
Company's IVIG scenario (utility = 0.75)	MUD	£494,255	13.3	£37,158	+£799
	Haplo	£170,668	11.5	£14,865	+£221
NPP patients included	MUD	£596,613	13.6	£43,950	+£7,590
	Haplo	£273,026	11.6	£23,465	+£8,820
Change to rescue therapy and minor corrections	MUD	£447,732	13.6	£32,917	-£3,443
	Haplo	£11,267	11.7	£964	-£13,680
Equal initial PEG-ADA durations	MUD	£632,315	13.8	£45,881	+£9,522
	Haplo	£308,728	11.8	£26,071	+£11,426

Source: table 30, page 117-120, ERG report

ERG comments

Combined impact of changes (II)

Scenario		Strimvelis versus HSCT			
		Inc. costs	Inc. QALY	ICER	Δ ICER
Rescue therapy from a MUD	MUD	£610,306	12.1	£50,246	+£13,886
	Haplo	£55,209	13.1	£4,216	-£10,428
Utilities for permanent hearing impairment	MUD	£494,255	11.0	£44,913	+£8,553
	Haplo	£170,667	9.4	£18,121	+£3,476
Costs for permanent hearing impairment	MUD	£512,977	13.6	£37,737	+£1,377
	Haplo	£186,716	11.7	£16,022	+£1,377
Updated unit costs for HSCT	MUD	£509,659	13.6	£37,493	+£1,133
	Haplo	£175,584	11.7	£15,067	+£422
Cost of ineligibility for Strimvelis	MUD	[redacted]	13.6	[redacted]	[redacted]
	Haplo	[redacted]	11.7	[redacted]	[redacted]
ERG preferred analysis	**MUD**	**£811,195**	**9.3**	**£86,815**	**+£50,455**
	Haplo	**£184,686**	**11.1**	**£16,704**	**+£2,060**

Source: table 30, page 117-120, ERG report

ERG Comments

Sensitivity to overall survival

- The difference in mortality between Strimvelis and a MUD HSCT is a key driver of the ICER. Reducing the difference increases the ICER.
- Reducing the difference in survival also impacts the adjusted QALY weighting
- Strimvelis must reduce mortality by over 25 percentage points compared to a MUD for the ICER to be below the adjusted threshold

MUD OS	Strimvelis vs MUD ICER	Adjusted threshold*
ICERs below the £100,000 QALY threshold		
0.667	**£86,856**	**£159,000**
0.70	£97,699	£140,000
ICERs above the £100,000 QALY threshold, but below the adjusted threshold		
0.71	£101,549	£135,000
0.74	£115,277	£118,000
ICERs above the £100,000 QALY threshold and the adjusted threshold		
0.75	£120,759	£112,000
0.78	£141,027	£100,000 (no adjustment)

Source: adapted from table 32, page 120-121, ERG report; ERG preferred analysis bolded and underlined

*adjusted threshold based on the QALY weighting applied to the undiscounted QALY gain

- The Strimvelis versus haploidentical ICER reduces when the difference in mortality between Strimvelis and a haploidentical donor HSCT is reduced. The underlying reason for this is the high rates of rescue therapy following HSCT from a haploidentical donor. Increasing survival following HSCT increases QALYs but is associated with large increases in the costs of PEG-ADA when awaiting rescue therapy and the cost and mortality risks of the rescue transplant. Given the very small numbers that inform the rates of rescue therapy the results should be taken with caution.

ERG Comments

Sensitivity to discount rate

- A discount rate of 1.5% may be considered if it is highly likely that, on the basis of the evidence presented, the long-term health benefits are likely to be achieved.
- Company considers Strimvelis meets this criteria as treatment leads to long and sustained benefit and people regain normal life expectancy
- The ERG is concerned that many patients will not return to full health, but the 1.5% discount rate applied may be reasonable according to NICE guidance
- The ICERs are sensitive to the discount rate, but remains below the respective adjusted thresholds

Scenario		Strimvelis versus HSCT			
		Inc. costs	Inc. QALY	ICER	Δ ICER
ERG preferred assumptions (1.5%)	MUD	£811,195	9.3	£86,815	-
	Haplo	£184,686	11.1	£16,704	
ERG preferred assumptions (3.5%)	MUD	£740,930	5.5	£135,028	+£48,213
	Haplo	£238,681	6.5	£36,837	+£20,133

Source: Table 1, page 1-2, ERG addendum

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- HST interim methods state: “A discount rate of 1.5% for costs and benefits may be considered by the Evaluation Committee if it is highly likely that, on the basis of the evidence presented, the long-term health benefits are likely to be achieved. Further, the Evaluation Committee will need to be satisfied that the introduction of the technology does not commit the NHS to significant irrecoverable costs.”

ERG Comments

Sensitivity to product price

- Product cost of Strimvelis is uncertain due to potential fluctuations in the exchange rate and the associated hospitalisation charge is still under negotiation between NHS England and the company
- ICER for Strimvelis compared to MUD is sensitive to both overall survival and the product cost

		Strimvelis product price						
Strimvelis survival (adjusted threshold)		+30%	+20%	+10%	0%	-10%	-20%	-30%
	1.00 (159K)	£103K	£98K	£92K	**£87K**	£81K	£76K	£71K
	0.95 (133K)	£119K	£112K	£106K	£99K	£93K	£87K	£80K
	0.90 (108K)	£142K	£134K	£126K	£118K	£110K	£102K	£94K

Source: adapted from figure 5, page 122, ERG report; ERG preferred analysis bolded and underlined 69

- The ERG identified a number of treatment relevant costs that were omitted from the company model, including additional costs for hospital stays in Milan that exceed 55 days and the costs of back up bone marrow administration. These uncertainties could increase the total cost the NHS must pay for the Strimvelis procedure

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ERG Comments

Sensitivity to rates of rescue therapy

- Highly uncertain whether there is any difference in the rate of rescue therapy between Strimvelis and HSCT
- Equalling rates of rescue therapy to the Strimvelis rescue rate would increase MUD rate from 10% and decrease haploidentical rate from 40%
- The ICER is sensitive to this change, which is driven by the assumed PEG-ADA costs required to bridge patients to rescue therapies

Scenario		Strimvelis versus HSCT			
		Inc. costs	Inc. QALY	ICER	Δ ICER
ERG preferred analysis	MUD	£811,195	9.3	£86,815	-
	Haplo	£184,686	11.1	£16,704	-
Equal rescue rates of [redacted]	MUD	£514,931	11.0	£46,849	-£39,965
	Haplo	£480,950	9.4	£51,116	+£34,412

Source: adapted from table 34, page 126, ERG report

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- Assumptions that improve the anticipated outcomes of rescue transplant after Strimvelis, for example if rescue transplantation is earlier following Strimvelis due to the avoidance of chronic GvHD or because MUD options have not yet been exhausted, this would be expected to reduce the ICER for Strimvelis compared to HSCT from a MUD.

ERG Comments

Alternative treatment pathway scenario

- ERG highlight there are alterative pathways to Strimvelis treatment
  - People may explore the potential for a MUD before deciding to use Strimvelis
  - People may have Strimvelis as a rescue therapy after HSCT
- For both these scenarios cost of searching for a MUD would be included
- ERG note that the ICER for Strimvelis compared to a weighted combination of HSCT from a MUD and HSCT from a haploidentical donor would be lower than that estimated for Strimvelis compared to HSCT from a MUD only

Scenario		Strimvelis versus HSCT			
		Inc. costs	Inc. QALY	ICER	Δ ICER
ERG preferred analysis	MUD	£811,195	9.3	£86,815	-
	Haplo	£184,686	11.1	£16,704	-
Cost of screening for a MUD	MUD	£856,322	9.3	£91,644	+£4,830
	Haplo	£229,913	11.1	£20,786	+£4,082

Source: table 33, page 125, ERG report

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- In the absence of evidence regarding the proportion of ADA-SCID patients for whom no appropriate MUD can be found, it is not possible to estimate a weighted combination of HSCT from a MUD or haploidentical donor to represent the costs and health outcomes that would be expected from HSCT prior to completion of a donor search.

- The ERG note that the ICER for Strimvelis compared to a weighted combination of HSCT from a MUD and HSCT from a haploidentical donor would be lower than that estimated for Strimvelis compared to HSCT from a MUD only.

ERG Comments
Conclusions

- ERG had concerns that:
  - Treatment costs are overestimated for HSCT and underestimated for Strimvelis
  - Position of Strimvelis in the treatment pathway has not been fully explored
  - There is an overestimation of health gains with Strimvelis
- Stimvelis is cost-effective versus HSCT from a haploidentical donor
- The results for Strimvelis versus HSCT from a MUD are very sensitive to the assumed reduction in mortality for Strimvelis
- Using the ERG's model, if Strimvelis does not improve mortality by more than 25 percentage points, it would not be cost-effective versus a matched unrelated donor HSCT under an adjusted threshold

Innovation

The company considers Strimvelis is an innovative treatment because:

- To date, Strimvelis is the only *ex vivo* gene therapy to gain marketing authorisation from the EMA
- Strimvelis is a step-change in the management of ADA-SCID because it corrects the underlying cause of the disease using the patients' own cells circumventing the need for a stem cell donor search and the risk of immune rejection (GvHD)
- Advanced therapies form an important part of the UK Life Sciences strategy. The UK aspires to position itself as a global hub for researching, developing, manufacturing, and adopting advanced therapies

Managed Access Agreement

- Given the low ICERs and budget impact, the company does not believe that a managed access arrangement (MAA) is required. Moreover, elements often observed in MAAs are already naturally in place for Strimvelis.
  - Strimvelis is only indicated for patients with ADA-SCID without an MRD; therefore, eligibility is already restricted to those patients that can benefit the most.
  - In addition, The company will only expect referrals from 2 specialist hospitals that are the major paediatric immune disease centres in the UK, which further ensures that Strimvelis will only be given to patients for whom the treatment is fully appropriate.
  - Data collection to monitor outcomes is already in place through the Strimvelis registry, and these data can be shared with the NHS as they become available.

QALY weighting

- For ICERs above £100,000 per QALY, recommendations must take into account the magnitude of the QALY gain and the additional QALY weight that would be needed to fall below £100,000 per QALY
- To apply the QALY weight, there must be compelling evidence that the treatment offers significant QALY gains

Lifetime incr QALYs gained	Weight
Less than or equal to 10	1
11–29	Between 1 and 3 (using equal incr)
Greater than or equal to 30	3

Strimvelis QALY gains

	Incr. QALYs (undiscounted)	
	Company	ERG
Strimvelis vs		
MUD-HSCT	23.2	15.9
Haploidentical HSCT	19.9	18.8

Source: Adapted from table D20, page 197, Company submission; table 31, page 120, ERG report

Factors affecting the guidance

- In forming the guidance, committee will take account of the following factors:

Nature of the condition	Clinical effectiveness
• Extent of disease morbidity and patient clinical disability with current care • Impact of disease on carers' QoL • Extent and nature of current treatment options	• Magnitude of health benefits to patients and carers • Heterogeneity of health benefits • Robustness of the evidence and the how the guidance might strengthen it • Treatment continuation rules
Value for money	**Impact beyond direct health benefits**
• Cost effectiveness using incremental cost per QALY • Patient access schemes and other commercial agreements • The nature and extent of the resources needed to enable the new technology to be used	• Non-health benefits • Costs (savings) or benefits incurred outside of the NHS and personal and social services • Long-term benefits to the NHS of research and innovation • The impact of the technology on the delivery of the specialised service • Staffing and infrastructure requirements, including training and planning for expertise

Equality

- In England ADA-SCID is most common in people from Irish Traveller and Somalian family origins
- Company have noted donor availability for HSCT can differ based on ethnicity, with people from non-Caucasian backgrounds having a more difficult time finding a suitable donor and a longer wait for an available donor
- Using gene therapy treatments such as Strimvelis will avoid the longer wait for these patients
- Due to low patient numbers the company model has not explored subgroup analysis by ethnicity
- The company does not explore alternative treatment pathways based on longer treatment durations for some people

Key issues for consideration
Cost-effectiveness evidence (I)

Overall modelling approach

- Is the company model appropriate for decision-making?
  - Should alternative treatment pathways be considered in the model?
- Should data from the Named Patient Program be included?
- Is it appropriate that a 1.5% discount rate is used?

Overall and intervention-free survival

- What is the most plausible difference in overall survival for Strimvelis and HSCT?
- What are the most plausible rates of intervention-free survival for the treatments?
- Will life expectancy following treatment be equal to the general population?

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Key issues for consideration

Cost-effectiveness evidence (II)

Assumptions in the model: costs, utilities and rescue therapy

- What are the most plausible pre-treatment PEG-ADA durations?
- What uncertainties around the product price need to be taken into account?
- Are the assumptions around utilities appropriate?
  - Will long-term utilities following treatment be equal to the general population?
  - What utilities should be included in the modelling?
- Are the assumptions around rescue therapy appropriate?
  - What form of rescue treatment will people whose treatment has failed have?
  - Do rescue rates differ systematically between different groups?

Conclusions

- What QALY weighting should be used in decision-making?
- What factors affecting the guidance need to be taken into account?
- What are the most plausible ICERs?

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technologies Evaluation

Strimvelis for treating severe combined immunodeficiency caused by adenosine deaminase deficiency

Final scope

Remit/evaluation objective

To evaluate the benefits and costs of Strimvelis within its licensed indication for treating severe combined immunodeficiency caused by adenosine deaminase deficiency for national commissioning by NHS England.

Background

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

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

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

considered in clinical practice as a short-term option before a bone marrow transplant.

The technology

Strimvelis (GlaxoSmithKline) is a gene therapy containing autologous $CD34^+$ cells transduced ex vivo with a replication-deficient retroviral vector containing the correct form of the human ADA gene in the DNA sequence. The patient's haematopoietic progenitor and stem cells are harvested from the bone marrow and purified. These are then modified using a viral vector to insert one or more copies of the ADA gene into the cells. When sufficient transduced cells are produced, the patient has pre-treatment with busulfan and the transduced cells are reintroduced into the patient.

Strimvelis has a marketing authorisation for treating severe combined immunodeficiency caused by adenosine deaminase deficiency (ADA-SCID), in people for whom no suitable human leukocyte antigen (HLA)-matched related stem cell donor is available.

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

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

Other considerations	If the evidence allows, subgroups based on the degree of HLA matching for HSCT (that is, people for whom matched unrelated or haploidentical HSCT is available) will be considered. The analysis will include consideration of the duration of enzyme replacement therapy with pegylated adenosine deaminase in people treated with the intervention or comparator, and should include any relevant differences in costs or outcomes associated with this. Guidance will only be issued in accordance with the marketing authorisation Guidance will take into account any Managed Access Arrangements
Related NICE recommendations and NICE Pathways	None
Related National Policy	NHS England (2016) Manual for prescribed specialised services 2016/17. Chapter 100: Severe combined immunodeficiency and related disorders service (children) NHS England (2013) NHS standard contract for severe immunodeficiency and related disorders service (children) Department of Health (2014) NHS Outcomes Framework 2015-2016. Domains 1, 2, 4 and 5.

References

1. Orphanet (2012) Severe combined immunodeficiency due to adenosine deaminase deficiency. Accessed April 2017.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technologies Evaluation (HST)

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

Matrix of consultees and commentators

Consultees	Commentators (no right to submit or appeal)
Company • GlaxoSmithKline (Strimvelis) Patient/carer groups • Action for Sick Children • Anthony Nolan • Climb (Children Living with Inherited Metabolic Diseases) • Friends, Families and Travellers • Genetic Alliance UK • Genetic Disorders UK • Jnetics • Midaye • Muslim Council of Britain • National Children's Bureau • Ocean Somali Community Association • Paveepoint Traveller and Roma Centre • Primary Immunodeficiency UK • Purine Metabolic Patients' Association • South Asian Health Foundation • Specialised Healthcare Alliance • The National Federation of Gypsy Liaison Groups • The Travellers Movement • Together for Short Lives • UK Primary Immunodeficiency Network • UK Primary Immune-deficiency Patient Support Professional groups • Association of Genetic Nurses & Counsellors • Association of Paediatric Emergency Medicine • British Inherited Metabolic Disease	General • All Wales Therapeutics and Toxicology Centre • Allied Health Professionals Federation • Board of Community Health Councils in Wales • British Society of Blood and Marrow Transplantation • British National Formulary • Care Quality Commission • Department of Health, Social Services and Public Safety for Northern Ireland • Healthcare Improvement Scotland • Medicines and Healthcare Products Regulatory Agency • National Association of Primary Care • National Pharmacy Association • NHS Alliance • NHS Blood and Transplant • NHS Commercial Medicines Unit • NHS Confederation • Scottish Medicines Consortium • United Kingdom National Screening Committee • Welsh Blood Service • Welsh Health Specialised Services Committee Comparator companies • Orchard Therapeutics (ex-vivo autologous gene therapy) • Sigma-Tau Pharmaceuticals (pegylated adenosine deaminase enzyme) Relevant research groups • Cell and Gene Therapy Catapult • Cochrane Cystic Fibrosis and Genetic

Consultees	Commentators (no right to submit or appeal)
Group • British Society for Gene and Cell Therapy • British Society for Genetic Medicine • British Society for Human Genetics • British Transplantation Society • Genomics England • Royal College of General Practitioners • Royal College of Nursing • Royal College of Paediatrics & Child Health • Royal College of Pathologists • Royal College of Physicians • Royal Pharmaceutical Society • Royal Society of Medicine • Society for the Study of Inborn Errors of Metabolism • UK Clinical Pharmacy Association • UK Genetic Testing Network <u>Others</u> • Department of Health • Great Ormond Street Hospital – Immunology Department • Newcastle upon Tyne Hospitals NHS Foundation Trust • NHS England • Welsh Government	Disorders Group • Gene and Cell Therapy Group - UCL • Medical Research Council - Human Genetics Unit • MRC Clinical Trials Unit • National Institute for Health Research <u>Associated Public Health Groups</u> • Public Health England • Public Health Wales

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people who share a protected characteristic and those who do not. Please let us know if we have missed any important organisations from the lists in the matrix, and which organisations we should include that have a particular focus on relevant equality issues.

PTO FOR DEFINITIONS OF CONSULTEES AND COMMENTATORS

Definitions:

Consultees

Organisations that accept an invitation to participate in the evaluation; the company that markets the technology; national professional organisations; national patient organisations; the Department of Health and the Welsh Government and relevant NHS organisations in England.

The company that markets the technology is invited to make an evidence submission, respond to consultations, nominate clinical specialists and has the right to appeal against the Final Evaluation Determination (FED).

All non-company consultees are invited to submit a statement[1], respond to consultations, nominate clinical specialists or patient experts and have the right to appeal against the Final Evaluation Determination (FED).

Commentators

Organisations that engage in the evaluation process but that are not asked to prepare an evidence submission or statement, are able to respond to consultations and they receive the FED for information only, without right of appeal. These organisations are: companies that market comparator technologies;
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 [MRC], National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Alliance and NHS Commercial Medicines Unit, and the British National Formulary.

All non-company commentators are invited to nominate clinical specialists or patient experts

[1]Non-company consultees are invited to submit statements relevant to the group they are representing.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technologies Evaluation Programme

Strimvelis for the treatment of ADA-SCID

Specification for company submission of evidence

June 2017

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Glossary of terms

Term	Definition
ADA	Adenosine deaminase
ADA-SCID	Adenosine deaminase-severe combined immunodeficiency
ADR	Adverse drug reaction
AE	Adverse event
AST	Aspartate aminotransferase
ATMP	Advanced therapeutic medicinal product
BMT	Bone marrow transplant
cDNA	Complementary deoxyribonucleic acid
CEAC	Cost Effectiveness Acceptability Curve
CI	Confidence interval
CMV	Cytomegalovirus
CNS	Central nervous system
cpm	Counts per minute
CRF	Case report form
CSR	Clinical study report
CUP	Compassionate use programme
CVC	Central venous catheter
dATP	Deoxyadenosine triphosphate
dAXP	Deoxyadenosine nucleotides
EBMT	European Society for Blood and Marrow Transplant
EBV	Epstein-Barr virus
EMA	European Medicines Agency
ERT	Enzyme replacement therapy
ESID	European Society for Immunodeficiencies
EU	European Union
GCP	Good Clinical Practice
GOSH	Great Ormond Street Hospital
GSK	GlaxoSmithKline
GvHD	Graft versus host disease
HLA	Human leukocyte antigen
HPV	Human papillomavirus
HRQL	Health-related quality of life
HSR-TIGET	San Raffaele Telethon Institute for Gene Therapy Ospedale San Raffaele s.r.l. (formerly Fondazione Centro San Raffaele del Monte
HSCT	Haematopoietic Stem Cell Transplantation

ICER	Incremental cost-effectiveness ratio
ICH	International Conference on Harmonisation
IEWP	Inborn Errors Working Party
IQ	Intelligence quotient
ISS	Integrated summary of safety
ITT	Intent-to-treat
IV	Intravenous
IVIG	Intravenous immunoglobulin
LTFU	Long-term follow-up
LY	Life years
MAA	Managed access arrangement
MedDRA	Medical Dictionary for Regulatory Activities
MFD	Matched family donor
MLS	Mean life expectancy
MMR	Measles mumps rubella
MMRM	Mixed model repeated measures
MMUD	Mismatched unrelated donor
MRD	Matched related donor (includes matched sibling donor and matched family donor)
MSD	Matched sibling donor
MUD	Matched unrelated donor
NA	Not applicable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NK	Natural Killer cells
NPP	Named Patient Programme
OMIM	Online Mendelian Inheritance in Man
ONS	Office for National Statistics
PASS	Post-Authorisation Safety Study
PedsQL	Paediatric Quality of Life Inventory
PEG-ADA	Polyethylene glycol-modified bovine adenosine deaminase
PSA	Probabilistic sensitivity analysis
PSS	Prescribed Specialised Services
QALY	Quality-adjusted life years
RBCs	Red blood cells
SAE	Serious adverse event

SCID	Severe combined immunodeficiency
SOC	System Organ Class
TREC	T cell receptor excision circles
UK	United Kingdom
US	United States
VCN	Vector copy number

Executive Summary

Summary

- Adenosine deaminase-severe combined immunodeficiency (ADA-SCID) is an ultra-rare and fatal autosomal recessive monogenic inherited immune disorder. The majority of patients with ADA-SCID are diagnosed in the first year of life and rarely survive beyond 1 to 2 years unless immune function is restored. ADA-SCID can have a devastating effect on quality of life for the patient and family members due to the need for isolation and continuous care.

- Strimvelis is the first approved ex-vivo gene therapy product for paediatric patients in the European Union (EU). No other ex-vivo gene therapy product has been approved for paediatric patients anywhere in the world.

- Strimvelis is a one-time gene therapy treatment that corrects the underlying cause of the disease using the patient's own cells, circumventing the need for a lengthy and expensive stem cell donor search and the risk of immune rejection (graft versus host disease [GvHD]) after haematopoietic stem cell transplantation (HSCT).

- Strimvelis treatment has resulted in 100% long-term survival for patients with ADA-SCID in the clinical programme (median and maximum follow-up durations of approximately 6.9 years and 13 years, respectively), which is a marked improvement in survival compared with HSCT in patients without a matched related donor (MRD) (reported as 67-71% for patients without an MRD, depending upon donor source). Intervention-free survival was 82% in the Strimvelis clinical programme. Following successful engraftment in the patient, the effects of single-dose treatment with Strimvelis are expected to be lifelong.

- European Society for Blood and Marrow Transplant/ European Society for Immunodeficiencies (EBMT/ESID) guidelines recommend that patients with ADA-SCID without an MRD available should receive a gene therapy product, such as Strimvelis, as first-line therapy.

- Strimvelis is estimated to be highly cost-effective with incremental cost-effectiveness ratios (ICERs) considerably below the Highly Specialised Technology programme threshold.

- With an estimated 1 patient per year receiving Strimvelis in England, the budget impact will be significantly below the £20 million budget impact threshold in any year.

The Technology

Strimvelis is the first approved ex-vivo gene therapy product for paediatric patients in the EU. No other ex-vivo gene therapy product has been approved for paediatric patients anywhere in the world. Strimvelis is indicated for the treatment of patients with severe combined immunodeficiency (SCID) due to adenosine deaminase (ADA) deficiency (ADA-SCID) for whom no suitable human leukocyte antigen (HLA)-matched related stem cell donor (MRD) is available.

Strimvelis is used as part of a one-time gene therapy treatment that corrects the underlying immunologic cause of the disease using the patient's own cells, circumventing the need for a lengthy and expensive stem cell donor search and the risk of immune rejection (graft versus host disease [GvHD]), which has a significant effect on survival. Strimvelis is the transduced cell product and should not be confused with the gene therapy procedure, which encompasses all of the hospital-based procedures that take place as part of delivering Strimvelis to patients. Strimvelis is registered as an advanced therapeutic medicinal product (ATMP) and was granted marketing authorisation by the European Medicines Agency (EMA).

Strimvelis must be administered in a specialist transplant centre, by a physician with previous experience in the treatment and management of patients with ADA-SCID and in the use of autologous CD34+ ex vivo gene therapy products. At present, treatment with Strimvelis can only be performed at HSR-TIGET, Milan, Italy due to the 6-hour shelf life of the manufactured cell therapy product and the location of the manufacturing site. Following successful engraftment in the patient, the effects of single-dose treatment with Strimvelis are expected to be lifelong.

Nature of the condition

ADA-SCID is a fatal autosomal recessive monogenic inherited immune disorder. The majority of patients with ADA-SCID are diagnosed in the first year of life (early onset) and rarely survive beyond 1 to 2 years unless immune function is restored [Hershfield, 2017]. The main features of ADA-SCID are failure to thrive and recurrent infections due to profound lymphopenia, impaired differentiation and function of T cells, B cells, and natural killer (NK) cells. ADA-SCID is different from other forms of SCID in that ADA-SCID is a systemic metabolic disorder [Hassan, 2012]. Non-immunological abnormalities may also occur as a consequence of the systemic metabolic defect and include hepatic, lung, and renal disease, lymphoma, often associated with cells bearing Epstein-Barr virus (EBV) genomes, skeletal alterations, neurological deficits affecting motor function and hearing, and cognitive/behavioural deficits.

In GlaxoSmithKline (GSK) research conducted through telephone interviews of carers of patients with ADA-SCID who were not treated with GSK gene therapy, frequently reported [redacted]. Aspects that most affected carer quality of life included [redacted] can have a profound impact on both patient and carer quality of life [redacted] [Data on file].

Current treatment options

Current treatment options remain suboptimal prior to the availability of Strimvelis. If a patient is diagnosed with ADA-SCID in England, the child is maintained in isolation and their siblings and parents are immediately screened to determine a matched related donor (MRD) is available for HSCT. Unfortunately, only 20-25% of infants have a suitable HLA-MRD available [Ferrua, 2010; Hirschorn, 2014]. If a suitable MRD is not identified, the patient begins stabilizing therapy with supportive enzyme replacement therapy (ERT) and the search for an alternative donor begins. Outcomes are less favourable for patients for whom MRDs are not available.

Besides HSCT from a MRD, current treatment options for ADA-SCID include:

- HSCT from a matched unrelated donor (MUD)
- HSCT from a haploidentical donor
- Long term enzyme replacement therapy (ERT)

HSCT from a MUD is the preferred treatment option in England for patients without an MRD based on external expert clinical advice. In an analysis of survival from 1995 to 2009, survival was reported to be 67% after HSCT from a MUD. The primary causes of death after HSCT include pneumonitis/respiratory failure, sepsis, GvHD, and fungal infections [Hassan, 2012]. For patients who survive HSCT from a MUD, GvHD can affect health-related quality of life (HRQL). Acute GvHD may cause rash, nausea, vomiting, anorexia, profuse diarrhoea, ileus, and cholestatic hepatitis. Chronic GvHD can be limited to a single organ or could be more widespread. Chronic GvHD can lead to debilitating consequences, such as loss of sight, joint contractures, end-stage lung disease, or death [Filipovich, 2005]. HSCT from a MUD requires a search for a donor, which can be lengthy, expensive, and a source of anxiety for patients' families. Donor availability can differ based on ethnicity, with non-Whites having a more difficult time finding a suitable donor and a longer wait for an available donor [Majhail, 2012; Lown, 2013; Pidala, 2013].

HSCT from a haploidentical donor is an option considered in other countries, but has not been performed in England in a patient with ADA-SCID in the past 15 years according to external expert clinical advice. In an analysis of survival from 1981 to 2009, survival was reported to be 43% overall after HSCT from a haploidentical donor. Survival has improved over time (71% for procedures from a haploidentical donor performed from 2000-2009) but remains suboptimal. As with HSCT from a MUD, GvHD may occur after HSCT from a haploidentical donor.

Supportive ERT, specifically polyethylene glycol-modified bovine adenosine deaminase (PEG-ADA), can also be used to manage the disease in the short term. However, there are several drawbacks to this product, which is not licensed in the United Kingdom (UK), such as availability, cost, the need for frequent

(weekly or bi-weekly) lifelong injections, the potential development of antibodies, and evidence of decreased efficacy over time [Chan, 2005]. PEG-ADA is not used as a long-term treatment option in England according to expert clinical advice. It was therefore excluded from the scope of this appraisal by the National Institute for Health and Care Excellence (NICE).

In summary, for those patients with ADA-SCID for whom no suitable HLA-MRD is available, the current treatment options are suboptimal. There is a high unmet need for a new treatment option such as Strimvelis. Following successful engraftment, Strimvelis provides long-term corrective therapy with an improved probability of survival and without additional complications associated with GvHD.

Impact of the new technology

Strimvelis is a one-time treatment, intended to provide lifelong benefit for this population with a high unmet need. This innovation is a step-change to the current clinical pathway recognised by EBMT/ESID guidelines, which have recently been updated to recommend gene therapy, using a product such as Strimvelis, as the treatment of choice for patients with ADA-SCID without an MRD (described as matched sibling donor [MSD]/matched family donor [MFD] in the guidelines) [EBMT/ESID Guidelines, 2017].

The safety and efficacy of Strimvelis have been evaluated in a programme comprising 2 pilot studies, 1 pivotal study, a compassionate use programme (CUP), and a long-term follow-up (LTFU) study. In total, 18 patients across all studies and the CUP were treated with Strimvelis and included in the Integrated Population that formed the basis of the regulatory submission.

Survival was the primary efficacy endpoint assessed. Gene therapy with Strimvelis has resulted in 100% long-term survival for patients in the programme (median and maximum follow-up durations of approximately 6.9 years and 13 years, respectively), which is a marked improvement in survival compared with available survival data for HSCT for ADA-SCID patients without an MRD. Intervention-free survival, defined as the proportion of patients surviving without further intervention (PEG-ADA use for a continuous period of ≥3 months or HSCT) after Strimvelis therapy, was 82% (14/17) in the Integrated Population. The majority of patients demonstrated evidence of engrafted gene-modified cells, sustained increases in functional gene-modified lymphocytes, maintenance of a robust immune reconstitution, significantly fewer severe infections over time, and continued physical growth.

Although patients in the Strimvelis clinical programme generally remained below the 50th growth percentile for a normal, age-matched population, most continued to track along their original percentiles for growth. At the time of the marketing application submission, 12 out of 14 patients (86%) surveyed were attending preschool/school as appropriate for their age. A remaining unmet need is treatment for central nervous system (CNS) abnormalities, which are frequent manifestations of ADA-SCID in long-term survivors of bone marrow transplant

(BMT) [Rogers, 2001; Booth, 2007]. Like HSCT, Strimvelis has not yet shown an impact on the non-immunological CNS defects associated with ADA-SCID. However, Lansky performance status index was queried in 14 patients, and all patients were reported as 'fully active, normal' during LTFU, with one exception who had minor restrictions in strenuous physical activity recorded at Year 7 [Cicalese, 2016].

Overall, the safety findings of Strimvelis are in line with those expected in an ADA-SCID population that has undergone busulfan conditioning and is undergoing immune reconstitution [Cicalese, 2016]. Low-dose busulfan is used as pre-treatment for Strimvelis instead of the full-dose chemotherapy regimens used in some HSCT protocols [Hassan, 2012]. As expected, given that Strimvelis is an autologous therapy, no GvHD was observed in the clinical programme [Cicalese, 2016]. The absence of GvHD after Strimvelis treatment is the key difference in adverse events (AEs) compared with HSCT. Otherwise, AEs were comparable to those expected after HSCT from a MUD or haploidentical donor.

The Strimvelis clinical programme has shown that Strimvelis is an innovative treatment option for patients with ADA-SCID that provides 100% survival and 82% intervention-free survival for this ultra-rare condition. The long-term efficacy, tolerability, and safety outcomes will be monitored via the Strimvelis Patient Registry Study, a non-interventional, observational, prospective Post-Authorisation Safety Study of patients with ADA-SCID treated with Strimvelis. The primary objective of this study is to characterise the long-term safety and effectiveness of Strimvelis over a 15-year post-treatment period in up to 50 patients treated.

Value for money

The acquisition cost of the Strimvelis product is £505,000. A cohort model was used to model the pathway of care and compare the costs and outcomes of Strimvelis treatment with that of the HSCT comparators over a lifetime horizon. Strimvelis is estimated to provide large quality-adjusted life year (QALY) gains: 13.6 QALYs when compared to HSCT from a MUD and 11.7 QALYs when compared to HSCT from a haploidentical donor.

As a result, although, lifetime costs for Strimvelis are higher than the lifetime costs for either HSCT procedure, the incremental cost-effectiveness ratios (ICERs) for Strimvelis versus HSCT procedures are quite low: the ICER for Strimvelis versus an HSCT from a MUD is £36,360/QALY gained and the ICER for Strimvelis versus an HSCT from a haploidentical donor is £14,645/QALY gained. The analysis assumes a 1.5% discounting rate for costs and outcomes, consistent with the latest NICE guidance for technology treatments that restore people who would otherwise die or have a very severely impaired life to full or near-full health and sustain gains over a very long period [NICE, 2017a].

These base-case ICERs are considerably below the recently introduced thresholds of £100,000/QALY gained and up to £140,000/QALY gained given the magnitude of QALY gains provided by Strimvelis, which would guarantee

automatic funding, from routine commissioning budgets, for treatments of very rare conditions (highly specialised technologies).

Uncertainty in these cost-effectiveness estimates has been explored through extensive deterministic and probabilistic sensitivity analyses. The deterministic analysis shows that, in all cases, the ICERs for Strimvelis versus either HSCT procedure remain below the recently introduced threshold criteria. The probabilistic sensitivity analysis indicates a 97% likelihood that the ICERs for Strimvelis versus either HSCT procedure are below £100,000/QALY gained.

Based on literature guidance [Ferrua, 2010; Hirschorn, 2014], it is expected that 2 patients per year in England will be eligible for Strimvelis. As uptake of the new technology is not expected to be 100% given the travel requirements and need to live in Milan for 4.5 months, approximately 1 patient per year would be expected to receive Strimvelis. Over the first year of uptake, the budget increase that results from treating 1 patient with Strimvelis (rather than HSCT from a MUD) is £385,761. Over 5 years, the cumulative budget impact of treating 1 patient with Strimvelis each year (rather than 1 patient with HSCT from a MUD each year) is £2,345,128.

Given the low ICERs and budget impact, GSK does not believe that a managed access arrangement (MAA) is required. Moreover, elements often observed in MAAs are already naturally in place for Strimvelis.

- Strimvelis is only indicated for patients with ADA-SCID without an MRD; therefore, eligibility is already restricted to those patients that can benefit the most.
- In addition, GSK will only expect referrals from 2 specialist hospitals that are the major paediatric immune disease centres in the UK, which further ensures that Strimvelis will only be given to patients for whom the treatment is fully appropriate.
- Data collection to monitor outcomes is already in place through the Strimvelis registry, and these data can be shared with the NHS as they become available.

In summary, the base-case and sensitivity analyses presented in this report show that Strimvelis provides a significant survival and quality of life benefit at an acceptable cost when compared against HSCT from a MUD or HSCT from a haploidentical donor, and is, therefore, estimated to be a highly cost-effective option for patients with ADA-SCID.

Impact of the technology beyond direct health benefits

The benefits of treating patients with ADA-SCID extend beyond improved health or value for money. ADA-SCID is a fatal disease that takes a toll on the quality of life of not only the patient but also the patient's carers and family.

The impact on family can be extreme and devastating, particularly whilst the search for a donor is ongoing, the child is kept in isolation, and the outcome of a HSCT procedure is unknown. In addition, GSK research telephone interviews of

carers of patients with ADA-SCID found that having a child with ADA-SCID [redacted] Successful treatment with Strimvelis would be expected to eliminate some of these concerns and improve key factors that contribute to carer quality of life, such as frequent infections and the resulting need for hospitalisation and isolation.

The impact of the technology on the delivery of the specialised service

No additional infrastructure will be required to ensure the appropriate use of Strimvelis. Patients will be diagnosed and initially assessed by doctors at specialist centres in England. If an HLA-matched related bone marrow donor is not available, the doctor may discuss the option of Strimvelis gene therapy with the family. Screening for eligibility will be conducted by doctors at specialist centres in England. HSR-TIGET will liaise with the clinical team and determine that Strimvelis is appropriate for the particular patient (patient has ADA-SCID without a suitable MRD and is able to donate adequate CD34+ cells). As treatment itself will only occur in Italy, expertise in administering gene therapy is not required. However, specialists may require access to gene therapy-specific diagnostic tests for long-term monitoring.

Conclusion

Strimvelis, the first ex-vivo gene therapy product approved for paediatric patients, represents a step-change in the management of ADA-SCID. Strimvelis provides important clinical benefits compared with HSCT from a MUD or haploidentical donor, including a significant improvement in survival, avoidance of expensive and burdensome GvHD, and reduction of the financial and emotional costs of screening. EBMT/ESID guidelines recognise these clinical improvements by positioning gene therapy, using a product such as Strimvelis, as first-line therapy for patients without an MRD. These clinical benefits have changed the paradigm for how ADA-SCID is treated and are offered at a cost that generates ICERs well below the £100,000/QALY threshold. **Strimvelis delivers significantly improved survival compared with HSCT from a MUD or haploidentical donor at a highly cost-effective price.**

Section A – Decision problem

1 Statement of the decision problem

Table A1 Statement of the decision problem

	Final scope issued by NICE	Variation from scope in the submission	Rationale for variation from scope
Population	People with ADA-SCID for whom no suitable HLA-matched related stem cell donor is available	None	Not applicable
Intervention	Strimvelis (retroviral-transduced autologous CD34+ cells)	None	Not applicable
Comparator(s)	Bone marrow transplant (including HSCT from an HLA-MUD and HSCT from an HLA-haploidentical donor)	None	Not applicable

	Final scope issued by NICE	Variation from scope in the submission	Rationale for variation from scope
Outcomes	The outcome measures to be considered include: •overall survival •intervention-free survival •immune function (including rate of severe infections, lymphocyte counts, thymopoiesis, use of IVIG, and vaccination response) •non-immunological aspects of ADA-SCID (including neurological and developmental effects) •need and duration of in-patient treatment •adverse effects of treatment •health-related quality of life (for patients and carers)	None	Not applicable
Subgroups to be considered	Not applicable	None	Not applicable
Nature of the condition	•disease morbidity and patient clinical disability with current standard of care •impact of the disease on carer's quality of life •extent and nature of current treatment options	None	Not applicable

	Final scope issued by NICE	Variation from scope in the submission	Rationale for variation from scope
Clinical Effectiveness	•overall magnitude of health benefits to patients and, when relevant, carers •heterogeneity of health benefits within the population •robustness of current evidence and the contribution the guidance might make to strength it •treatment continuation rules (if relevant)	None	Not applicable
Value for Money	•cost effectiveness using incremental cost per quality-adjusted life year •patient access schemes and other commercial agreements •the nature and extent of the resources needed to enable the new technology to be used	None	Not applicable

	Final scope issued by NICE	Variation from scope in the submission	Rationale for variation from scope
Impact of the technology beyond direct health benefits,	•whether there are significant benefits other than health •whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal and social services •the potential for long-term benefits to the NHS of research and innovation •the impact of the technology on the overall delivery of the specialised service •staffing and infrastructure requirements, including training and planning for expertise	None	Not applicable

Abbreviations: HLA-human leukocyte antigen; HSCT=haematopoietic stem cell transplantation; IVIG=intravenous immunoglobulin; MUD=matched unrelated donor; NA=not applicable; NHS=National Health Service; PSS= Prescribed Specialised Services; SCID-ADA=severe combined immunodeficiency due to adenosine deaminase deficiency (also referred to as ADA-SCID).

2 Description of technology under assessment

2.1 Give the brand name, approved name and when appropriate, therapeutic class.

Brand name: STRIMVELIS®

Approved name: STRIMVELIS® (autologous CD34+ cells transduced to express ADA)

Therapeutic class: Immunostimulants, other immunostimulants.

2.2 What is the principal mechanism of action of the technology?

Strimvelis® is a one-time gene therapy treatment in which autologous bone marrow-derived cells are transduced to express ADA. After infusion, CD34+ cells engraft in the bone marrow, where they repopulate the haematopoietic system with a proportion of cells that express pharmacologically active levels of the ADA enzyme.

The mechanism of action was established through assessment of several endpoints. The stable presence of gene-modified cells was demonstrated through measurement of vector copy number for the transduced gene in bone marrow and peripheral blood cell lineages. For cell lineages that are affected by the disease, such as CD3+ T cells, the level of gene marking was approximately 70% or higher from Year 1 and onwards of follow-up. This observation confirms the hypothesis of a survival advantage for the cells predicted from early clinical observations.

ADA gene activity was demonstrated in bone marrow and peripheral blood lymphocytes. Within 1 year of treatment, lymphocyte ADA activity showed increased levels relative to baseline that were maintained for the duration of follow-up to Year 8. The suppressive effect of ADA expression on toxic adenosine metabolite concentration levels was established by measurement of deoxyadenosine nucleotides (dAXP) in red blood cells (RBCs) from bone marrow and peripheral blood.

Following successful engraftment in the patient, the effects of single-dose treatment with Strimvelis are expected to be lifelong.

2.3 Please complete the table below.

Table A2 Dosing Information of technology being evaluated

Pharmaceutical formulation	Dispersion for infusion
Method of administration	Intravenous infusion, the period of administration is approximately 20 minutes
Doses	One or more EVA bags which contain an autologous CD34+ enriched cell fraction (CD34+ cells transduced with retroviral vector that encodes for the human ADA cDNA sequence). Concentration of 2 and 20 million CD34+ cells/kg
Dosing frequency	Once per lifetime
Average length of a course of treatment	One-time treatment, which includes an average hospital stay of 50 days (may be longer if complications occur) and an average 60-day (60-90 day) outpatient follow-up in Italy
Anticipated average interval between courses of treatments	Not applicable
Anticipated number of repeat courses of treatments	Not applicable
Dose adjustments	None

Abbreviations: EVA=ethyl vinyl acetate.

Strimvelis must be administered in a specialist transplant centre, by a physician with previous experience in treatment and management of patients with ADA-SCID and in the use of autologous CD34+ ex vivo gene therapy products.

The patient must be able to donate adequate CD34+ cells to deliver a minimum of 4 million purified CD34+ cells/kg required for the manufacture of Strimvelis.

A CD34+ stem cell back-up containing at least 1 million CD34+ cells per kg is required. This should be harvested from the patient at least 3 weeks prior to treatment with Strimvelis. The stem cell back-up is collected for use as rescue treatment should there be a failure during product manufacture, transplant failure, or prolonged bone marrow aplasia after treatment with Strimvelis.

3 Regulatory information

3.1 Does the technology have a UK marketing authorisation for the indication detailed in the submission? If so, give the date on which authorisation was received. If not, state the currently regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

The EU marketing authorisation application for Strimvelis was approved on 26 May 2016. Strimvelis is the first approved ex-vivo gene therapy for paediatric patients in the EU. No other ex-vivo gene therapy has been approved for paediatric patients anywhere in the world.

3.2 If the technology has not been launched, please supply the anticipated date of availability in the UK.

Strimvelis is currently only available at Hospital San Raffaele Telethon Institute for Gene Therapy, Italy (HSR-TIGET) in Milan, Italy. MolMed is the only approved manufacturing centre for Strimvelis. HSR-TIGET is co-located with MolMed, and transfer of biological materials between the sites is well validated. Strimvelis is available to UK patients at HSR-TIGET in Milan.

In the future, a cryopreserved formulation may become available, enabling treatment closer to the patients' home such as specialist UK hospitals. At this point there is no anticipated date of availability of the potential cryopreserved formulation.

3.3 Does the technology have regulatory approval outside the UK? If so, please provide details.

The EU approval of the marketing authorisation application for Strimvelis is valid in 28 EU Member States, 27 outside of the UK, plus Norway, Iceland, and Lichtenstein. No application for regulatory approval other than the original marketing authorisation application has been filed to date.

3.4 If the technology has been launched in the UK provide information on the use in England.

The technology is available to UK patients at HSR-TIGET in Milan, Italy. To date, no UK patients have been treated.

4 Ongoing studies

4.1 Provide details of all completed and ongoing studies on the technology from which additional evidence relevant to the decision problem is likely to be available in the next 12 months.

The use of Strimvelis in patients with ADA-SCID is supported by a primary data package comprising 18 patients: 15 patients treated in clinical studies, including a pivotal study (n=12) and 3 patients treated via early pilot studies, conducted over a treatment and maximum follow-up period of approximately 13 years, and 3 patients who received Strimvelis gene therapy under compassionate use.

These studies were as follows: 1 single arm, open-label, historically controlled pivotal trial (AD1115611; n=12) with a long-term follow-up (LTFU), 2 early open-label uncontrolled pilot studies (AD1117054/AD1117056; n=3), and a compassionate use programme (CUP) (AD1117064; n=3). Though the LTFU was a component of the pivotal study protocol, it was amended to permit enrolment of patients from the pilot studies and the CUP to participate in long-term assessments beyond the initial follow-up period of each study. In total, 18 patients across all studies and the CUP were treated with Strimvelis at the time of the data cut-off for the marketing authorisation application, and these 18 patients were included in the Integrated Population. Data for the first 10 patients enrolled in these studies with clinical follow-up ranging from 1.8 to 8 years have been published [Aiuti, 2002a; Aiuti, 2009b; Selleri, 2011], and a manuscript that expands on those data with long-term (2.3 to 13.4 years, median 6.9 years) safety and efficacy results in those and 8 additional patients has recently been published [Cicalese, 2016] (see Section 9.3).

Table A 3 provides a summary of the studies providing evidence to support the decision problem.

Table A 3 Summary of studies contributing evidence of efficacy and safety to support the decision problem

Study ID	**AD1115611[a]** **Pivotal**	**AD1117056** **Pilot 2**	**AD1117054** **Pilot 1**	**AD1117064** **CUP**	**AD1115611** **LTFU**
Level of Evidence	Pivotal	Supportive	Supportive	Supportive	Pivotal[b]
Number of Patients	12	2	1[c]	3	17

Study ID	AD1115611[a] Pivotal	AD1117056 Pilot 2	AD1117054 Pilot 1	AD1117064 CUP	AD1115611 LTFU
Site (Location)	HSR-TIGET (Milan, Italy)	HSR-TIGET (Milan, Italy)	[redacted]	HSR-TIGET (Milan, Italy)	HSR-TIGET (Milan, Italy) and Hadassah University Hospital (Jerusalem, Israel)
Critical Design Features	Phase 1/2, open-label, non-randomised, historical control, single arm	Phase 1/2, open-label	Phase 1, open-label[d]	Compassionate use programme (CUP)	LTFU of pivotal study[e]
Primary Endpoint	3-year survival	Not defined[f]	Not defined[f]	NA	Survival
Study Population	Paediatric patients with ADA-SCID lacking an HLA-identical sibling who had received ≥6 months PEG-ADA with demonstrated failure to PEG-ADA therapy (except in cases where PEG-ADA therapy was contraindicated or unavailable)				
Treatment Regimen	Non-myeloablative pre-conditioning with busulfan followed by gene therapy with Strimvelis, defined as transfusion of autologous CD34+ enriched cell fraction that contains CD34+ cells transduced with a retroviral vector that encodes for the human ADA cDNA sequence				
Study Status[g]	Complete	Complete	Complete	Complete[i]	Ongoing
Report data cut-off	06 Jul 2011	24 Feb 2005	25 Nov 2013[d]	08 May 2014	08 May 2014
Source	AD1115611 CSR	AD1117056 abbreviated CSR	AD1117054 CSR	AD1117064 CSR	AD1115611 LTFU interim CSR
Module Location	m5.3.5.1	m5.3.5.2	m5.3.5.4	m5.3.5.4	m5.3.5.2

Abbreviations: ADA-SCID = adenosine deaminase severe combined immunodeficiency; cDNA = complementary deoxyribonucleic acid; CSR = clinical study report; CUP = compassionate use programme; HLA = human leukocyte antigen; HSR= Ospedale San Raffaele; LTFU = long-term follow-up; NA = not applicable; PEG-ADA = polyethylene glycol modified bovine adenosine deaminase; wks = weeks.

a. Pivotal study (AD1115611) initiated with HSR-TIGET and transferred to GSK upon 2010 in-licensing.
b. LTFU data from Patients [redacted] (originally enrolled in the pivotal study, AD1115611) are considered as pivotal evidence of efficacy in this application. LTFU data from other patients are considered supportive.
c. Data for [redacted] from Years 0 to [redacted] were not integrated, except for the date of gene therapy used to determine duration of follow-up and survival. Data for [redacted] from Years 0 to 12 are not included in the integrated safety data,

Study ID	AD1115611[a] Pivotal	AD1117056 Pilot 2	AD1117054 Pilot 1	AD1117064 CUP	AD1115611 LTFU

with the exception of the date of gene therapy which was used to determine duration of follow-up. Safety data collected as part of Study AD1115611 LTFU (Year [redacted] onward) are included in the integrated safety data.

d. No study protocol is available but study design [redacted] are summarized in 2 primary publications [redacted] [Aiuti, 2002a; Aiuti, 2009b; GSK data on file].

e. Patients in the pilot studies and CUP who completed 3 years of follow-up were eligible to enrol in the LTFU.

f. Efficacy endpoints were not prospectively defined in the pilot studies.

g. Study status reflects completion of the interim clinical study report that supported the marketing application.

Final clinical study reports (CSRs) are available for AD1115611 (0 to 3 years), both pilot studies (AD1117054/AD1117056), and the CUP (AD1117064); an interim CSR is available for the AD1115611 LTFU study. A final CSR for the LTFU study will be available in 2019, as a post-authorisation measure following the transition of patients to the registry programme. The AD1115611 LTFU final CSR has been included as an additional pharmacovigilance activity (Category 3) in the updated EU risk management plan.

An investigator-initiated named patient programme (NPP 200893) that enrolled patients to allow compassionate use of Strimvelis is not included in the evidence to support the decision problem. Data collection from the NPP is currently in progress. Patients will continue to be followed in the NPP for 3 years before transitioning into the patient registry. As GSK is not the sponsor of this programme, available data are extremely limited. GSK does not have ongoing access to data with the exception of biannual data cuts to support safety reporting for the periodic benefit risk evaluation reports sent to the EMA as mandated by the license. For full transparency, available information on the NPP that has been reported to GSK is provided in Appendix 6.

The long-term efficacy, tolerability, and safety outcomes will continue to be monitored and assessed via the ongoing Strimvelis Patient Registry Study, a non-interventional, prospective Post-Authorisation Safety Study (PASS) of patients with ADA-SCID treated with Strimvelis. The primary objective of this study is to characterise the long-term safety and effectiveness of Strimvelis over a 15-year post treatment period in up to 50 patients treated. This registry as well as existing registries from established communities (e.g. European Society for Blood and Marrow Transplant [EBMT] and European Society for Immunodeficiencies [ESID]) will provide more information to strengthen the evidence available for this disease and associated treatments. GSK is actively exploring opportunities to collaborate with the community to strengthen the evidence of treatments for ADA-SCID.

4.2 If the technology is, or is planned to be, subject to any other form of assessment in the UK, please give details of the assessment, organisation and expected timescale.

No other UK assessments are planned or ongoing.

5 Equality

5.1 Please let us know if you think that this evaluation:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;

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

- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

One of the main comparators under consideration in this evaluation is haematopoietic stem cell transplantation (HSCT) from a human leukocyte antigen (HLA)-matched unrelated donor (MUD). Donor availability can differ based on ethnicity, with non-Whites having a more difficult time finding a suitable donor and a longer wait for an available donor [Majhail, 2012; Lown, 2013; Pidala, 2013]. This issue is significant because a large portion of patients with ADA-SCID in the UK are of Black African (mainly Somalian) ethnicity [Adams, 2015], and ADA-SCID is more common in people of Somali heritage [Sanchez, 2007]. Other ethnic minorities included in the ADA-SCID population in the UK include Pakistani, Bangladeshi, and Turkish patients [Adams, 2015]. A long wait for an available donor could mean leaving patients at risk for complications, such as infections, and result in potentially higher interim treatment costs.

Clinical data for Strimvelis are available for 18 treated patients. No specific analyses by subpopulation by race of patients treated with Strimvelis have been performed as there are too few patients to be able to draw meaningful conclusions. The current clinical data includes patients of Caucasian (n=10), Arabic (n=5), African American (n=2), and Asian (n=1) origins.

5.2 How will the submission address these issues and any equality issues raised in the scope?

GSK recommends that NICE take into consideration the availability of donors by ethnicity while evaluating the comparison of Strimvelis to HSCT from a MUD. Equality issues can be addressed by following the EBMT/ESID guidelines that recommend patients with no matched related donor should be considered for gene therapy, such a Strimvelis, as first-line therapy. This avoids the wait to find a MUD, which can be longer in patients from ethnic minorities.

Section B – Nature of the condition

6 Disease morbidity

Summary

- If immune function is not restored, patients with ADA-SCID rarely survive beyond 1 to 2 years.
- Approximately 75-80% of patients with ADA-SCID do not have a suitable HLA-Matched Related Donor and mortality after HSCT from a MUD or haploidentical donor is reported to be significant (33% and 29-59%, respectively).
- Current treatment options are suboptimal. For those patients with ADA-SCID for whom no suitable HLA-MRD is available, there is a high unmet need for new treatment options that provide long-term corrective therapy with substantially improved survival and without additional complications associated with GvHD.

6.1 Provide a brief overview of the disease or condition for which the technology is being considered in the scope issued by NICE. Include details of the underlying course of the disease, the disease morbidity and mortality, and the specific patients' need the technology addresses.

Severe combined immunodeficiency (SCID) due to ADA deficiency is a fatal autosomal recessive monogenic inherited immune disorder. The majority of patients with ADA-SCID are diagnosed in the first year of life (early onset) and rarely survive beyond 1 to 2 years unless immune function is restored [Hershfield, 2017]. ADA-SCID is different from other forms of SCID in that ADA-SCID is a systemic metabolic disorder; it is perceived in the clinical community to be more difficult to treat than other forms of SCID [Hassan, 2012]. The main features of ADA-SCID are profound lymphopenia, impaired differentiation and function of T cells, B cells, and natural killer (NK) cells; recurrent infections; and failure to thrive. Non-immunological abnormalities may also occur as a consequence of the systemic metabolic defect and include hepatic, lung, and renal disease, lymphoma, often associated with cells bearing Epstein-Barr virus (EBV) genomes, skeletal alterations, and neurological deficits affecting motor function and hearing, and cognitive/behavioural deficits, indicating that ADA-SCID is more complex than other forms of SCID. Patients experience developmental delay, chronic diarrhoea, failure to thrive, and recurrent infections due to fungal, viral, and opportunistic agents [Hirschhorn, 2014]. Frequent infections lead to hospitalisations and the need for isolation, which affects patients' quality of life both emotionally and socially as discussed in Section 7.

Current treatment options remain sub-optimal. One treatment option for ADA-SCID is haematopoietic stem cell transplant (HSCT). Survival for patients with a matched sibling donor (MSD) or matched family donor (MFD) in an analysis of survival in patients with ADA-SCID treated between 1981 and 2009 was 86% and 83%, respectively [Hassan, 2012]. Unfortunately, only 20-25% of infants have a suitable HLA-matched related donor (MRD, either an MSD or MFD) available [Ferrua, 2010; Hirschorn, 2014]. Outcomes are less favourable for the majority of patients for whom MRDs are not available. Survival in the same analysis was 67% after HSCT from a MUD (procedures performed since 1995) and 43% overall after HSCT from a haploidentical donor. Survival has improved over time (71% for procedures from a haploidentical donor performed from 2000-2009) but remains suboptimal [Hassan, 2012]. In the UK, HSCT from a MUD is preferred over HSCT from a haploidentical donor when an MRD is not available. According to external expert clinical advice, HSCT from a haploidentical donor has not been performed in England in a patient with ADA-SCID in the past 15 years. Accounting for 15% of deaths in patients with ADA-SCID treated with HSCT, graft versus host disease (GvHD) is a dangerous complication of HSCT that can lead to significant morbidity and mortality in some treated patients [Hassan, 2012]. Acute GvHD may cause rash, nausea, vomiting, anorexia, profuse diarrhoea, ileus, and cholestatic hepatitis. Chronic GvHD could be limited to a single organ or could be more widespread. Chronic GvHD can lead to debilitating consequences, such as loss of sight, joint contractures, end-stage lung disease, or death [Filipovich, 2005]. A remaining unmet need is treatment for CNS abnormalities, which are frequent manifestations of ADA-SCID in long-term survivors of bone marrow transplant (BMT) [Rogers, 2001; Booth, 2007].

Another treatment option for ADA-SCID is supportive enzyme replacement therapy (ERT), specifically PEG-ADA. There are several drawbacks to this product, which is not licensed in the UK. PEG-ADA requires frequent injections (weekly or bi-weekly) and regular monitoring of deoxyadenosine triphosphate (dATP) metabolite levels and antibody formation against PEG-ADA. A retrospective study of the long-term effects of PEG-ADA treatment for 5 to 12 years found that, despite initial improvements, lymphocyte counts were below the lower limit of normal for all patients and progressively worsened over time. There was also a gradual reduction in thymic function and a decline in mitogenic proliferative responses over time, demonstrating reduced T cell function. It is thought that metabolic reconstitution in the thymus is incomplete, and this leads to the gradual loss of immune function [Chan, 2005]. PEG-ADA is an expensive treatment that is not used as a long-term treatment option in England according to expert clinical advice.

For those patients with ADA-SCID for whom no suitable HLA-MRD is available, there is a high unmet need for new treatment options that provide long-term corrective therapy with an improved probability of survival and without additional complications associated with GvHD.

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Strimvelis is a one-time treatment, intended to provide lifelong benefit for this population with a high unmet need. It provides a step change in the management of ADA-SCID because it corrects the underlying cause of the disease using the patient's own cells circumventing the need for a stem cell donor search and the risk of immune rejection (Graft versus Host Disease [GvHD]).This is recognised by EBMT/ESID guidelines, which have recently been updated to recommend gene therapy, using a product such as Strimvelis, as the treatment of choice for patients with ADA-SCID without an MRD (described as MSD/MFD in the guidelines) [EBMT/ESID Guidelines, 2017].

6.2 Please provide the number of patients in England who will be covered by this particular therapeutic indication in the marketing authorisation each year, and provide the source of data.

The incidence of ADA-SCID in the UK has not been specifically studied, but this information can be extrapolated from available data. According to the 2012 Screening for Severe Combined Immunodeficiency: External Review Against Programme Appraisal Criteria for the UK National Screening Committee, 20 children per year presented with SCID to the 2 UK centres for care (Great Ormond Street Hospital and Newcastle Great North Children's Hospital), which suggests an incidence for SCID of approximately 2.86 infants per 100,000 [UK National Screening Committee, 2012]. Using an estimate quoted in that report that ADA-SCID accounts for 14.8% of all patients with SCID yields an incidence of ADA-SCID in the UK of approximately 3 patients per year. In another study, the percent of patients with SCID in the UK with ADA-SCID has been reported to be as high as 20% [Adams, 2015], which would yield an incidence of 4 patients per year in the UK. The number of patients diagnosed with the condition per year in England would be a portion of the patients diagnosed per year in the UK. The exact proportion is unknown, but 3 or fewer patients per year in England would be expected. Approximately 20% of patients with ADA-SCID have an MRD available, so approximately 3 patients per year in the UK and no more than 2 patients per year in England would be eligible for Strimvelis. Uptake of Strimvelis is not expected to be 100% given the travel requirements and need to live in Milan for 4.5 months.

6.3 Please provide information about the life expectancy of people with the disease in England and provide the source of data.

If immune function is not restored, children rarely survive beyond 2 years [Hershfield, 2017]. There are no data available on life expectancy after HSCT except for survival data after the procedure itself, which are provided in Section 9.8.

7 Impact of the disease on quality of life

7.1 Describe the impact of the condition on the quality of life of patients, their families and carers. This should include any information on the impact of the condition on physical health, emotional wellbeing and everyday life (including ability to work, schooling, relationships and social functioning).

Quality of life is impacted by developmental delay, chronic diarrhoea, failure to thrive, and recurrent infections due to fungal, viral, and opportunistic agents [Hirschhorn, 2014]. Patients with ADA-SCID may also develop neurological abnormalities, including behavioural impairment [Rogers, 2001; Hirschhorn, 2014] and sensorineural deafness [Tanaka, 1996; Albuquerque, 2004; Hirschhorn, 2014]. [redacted] can have a profound impact on both patient and carer quality of life [redacted] [Data on file].

A study of patients with SCID who survived HSCT (median 11 years post-transplant) evaluated patients using the Paediatric Quality of Life Inventory (PedsQL), which has 6 domains (physical, emotional, social, school, psychosocial, and total). This study found that patients with ADA-SCID had a significantly lower quality of life than the UK normal on all components except emotional. A diagnosis of ADA-SCID was a risk factor for poorer quality of life than patients with other types of SCID [Hamid, 2016]. This could be because ADA is expressed systemically and children with ADA-SCID may also have non-immunological manifestations of their disease, including cognitive, behavioural, and neurological defects and a decreased intelligence quotient (IQ) [Titman, 2008].

In an effort to better understand the family impact of ADA-SCID, GSK conducted research through telephone interviews of carers of patients with ADA-SCID. Carers were identified through patient associations and direct referral from healthcare providers. To be included in the study, the carer's child must have had a diagnosis of ADA-SCID with onset within the first year of life and must not have been involved in GSK gene therapy studies (including siblings). Patients were treated with ERT, HSCT, and gene therapy other than Strimvelis. Objectives of the study included exploring the emotional, physical, and social impact of the disease on patients' and carers' lives and evaluating patient and carer needs and preferences for current and future treatment of ADA-SCID. Carers' answers to questions included information at the time of diagnosis and time to treatment and also lasting effects on quality of life. [redacted] Frequently reported concerns that had an impact on quality of life included [redacted] Some carers reported that [redacted] Carers reported that their children with ADA-SCID [redacted] All carers reported feeling [redacted] Carers reported that having a child with ADA-SCID had an impact on [redacted] [Data on file].

Without treatment, patients with ADA-SCID would die before school age. Successful treatment is needed for patients to be able to attend school or work. Health-related quality of life (HRQL) would be expected to decline as overall health declines and infections become more frequent and severe.

In addition, quality of life for family members would be expected to decline as well with increasing need for hospitalisations, more intensive caregiving requirements, and resulting emotional toll. Choosing treatment with HSCT can lead to stress and anxiety for carers during the wait for a match and the wait to see if their child survives the procedure. Carer quality of life could decrease from potential feelings of guilt and depression if the child dies from a treatment-related complication.

7.2 Describe the impact that the technology will have on patients, their families and carers. This should include both short-term and long-term effects and any wider societal benefits (including productivity and contribution to society). Please also include any available information on a potential disproportionate impact on the quality or quantity of life of particular group(s) of patients, and their families or carers.

Strimvelis is expected to have a profound impact on patients, their families, and carers because Strimvelis is a step-change in the management of patients with ADA-SCID with no MRD due to its major impact on survival and lack of GvHD. This is reflected in EBMT/ESID guidelines that now recommend gene therapy, using a product such as Strimvelis, as the first -line therapy for patients without an MRD [EBMT/ESID Guidelines, 2017]. With the availability of Strimvelis, patients will no longer face a long wait to treatment while searching for a MUD or have to make a choice to undergo suboptimal treatment that still carries a significant mortality risk.

Based on the experience with the technology throughout follow-up of up to 13 years, overall quality of life for patients is expected to improve following the one-time treatment. Children are anticipated to show growth and weight gain, progressing within the anticipated range (per appropriate height and weight charts), and enter and maintain regular school attendance. These qualitative outcomes are consistent with the totality of evidence of long-term clinical benefit. The effects of Strimvelis into adulthood have not been studied as all patients treated with Strimvelis are still minors, but it is expected that children who are able to attend school will become adults who are able to work and contribute to society.

Recurrent infections, social isolation, hospital visits, antibiotic therapy, and time away from work to care for the patient with ADA-SCID have a significant impact on the daily lives of the family and carers. The improvement anticipated following Strimvelis therapy will greatly reduce this burden on the carers.

8 Extent and nature of current treatment options

Summary

- Based on external expert clinical advice, HSCT from a MUD is the current standard of care in England for patients with ADA-SCID who do not have an MRD. PEG-ADA is used as a supportive treatment only. HSCT from a haploidentical has not been performed in a patient with ADA-SCID in England in the last 15 years.

8.1 Give details of any relevant NICE, NHS England or other national guidance or expert guidelines for the condition for which the technology is being used. Specify whether the guidance identifies any subgroups and make any recommendations for their treatment.

There are currently no NICE guidelines or NHS England commissioning policy documents for ADA-SCID. However, with the availability of gene therapy, the EBMT has recently updated the guidelines for the treatment of patients with ADA-SCID in March 2017. The guidelines recommend gene therapy, using a product such as Strimvelis, as the first-line treatment for patients with ADA-SCID who do not have an MRD available before considering other types of HSCT, including from a MUD or haploidentical donor [EBMT/ESID Guidelines, 2017]. This is a paradigm shift in the management of ADA-SCID and, according to external clinical advice, expected to be followed in England.

8.2 Describe the clinical pathway of care that includes the proposed use of the technology.

Diagnosis in England usually occurs at centres known to have specialists for SCID, such as the Great Ormond Street Hospital in London and Great North Children's Hospital in Newcastle. The majority of patients with ADA-SCID are diagnosed in the first year of life (early onset) [Hershfield, 2017]. Approximately 10% to 15% of ADA-SCID cases have a delayed onset (6 to 24 months), and a smaller percentage are diagnosed after age 4 years (late/adult onset) [OMIM, 2013].

The immediate priorities are to provide a protective environment to reduce infection risk, conduct appropriate tests and assessments, and provide supportive care.

Patients are screened for a suitable MRD. Currently, patients with ADA-SCID without an MRD are screened for HSCT from a MUD. The search for a donor can be lengthy (19 weeks on average) [Gaspar, 2013]. Patients receive expensive, unlicensed supportive PEG-ADA while awaiting a match. Survival in an analysis of patients with ADA-SCID was 67% for HSCT from a MUD [Hassan, 2012].

HSCT from a haploidentical donor and long-term PEG-ADA are other treatment options, but they are currently not used in England based on external expert clinical advice. HSCT from a haploidentical donor using new techniques explored in other diseases is not considered for patients with ADA-SCID in England based on external expert clinical advice.

8.3 Describe any issues relating to current clinical practice, including any uncertainty about best practice.

Patients with ADA-SCID can be effectively treated with HSCT from allogeneic donors, but the best outcomes for this intervention are only achieved when an HLA-MRD is available, which makes it a viable option for 20-25% of patients with ADA-SCID [Hirschorn, 2014]. Stem cells from HLA-MRDs are usually given without chemotherapeutic conditioning to reduce the risk of chemotherapy-associated toxicity.

For the majority of patients, MRDs are not available. Therefore, alternative sources of stem cells are frequently used for transplantation, which may require chemotherapeutic preconditioning and are associated with increased morbidity and mortality primarily related to inadequate immune reconstitution and graft versus host disease (GvHD). Significantly decreased survival (compared with MRD) has been observed with less well-matched donor sources of stem cells, such as MUD or haploidentical donors.

For transplant from a MUD, donor availability can differ based on ethnicity, with non-Whites having a more difficult time finding a suitable donor and a longer wait for an available donor [Majhail, 2012; Lown, 2013; Pidala, 2013].

A non-transplant treatment option, for patients who are not suitable or do not have an HLA-matched donor for HSCT is ERT in the form of PEG-ADA. PEG-ADA is a non-curative therapy given in frequent injections that externally corrects the metabolic defect, and is used as a stabilising treatment; it is approved in the United States (US) and has been in use for nearly 20 years in over 150 patients in numerous countries with orphan drug designation [Booth, 2007; Gaspar, 2010]. This therapy is not currently approved in the EU, but it is made available via expanded access and compassionate use programs. Short-term treatment with PEG-ADA is often used to stabilise patients awaiting HSCT or gene therapy [EBMT/ESID Guidelines, 2017]. Long-term efficacy of PEG-ADA treatment is limited for some patients due to incomplete immune reconstitution and the development of antibodies. About 50-60% of the children with ADA-SCID treated with PEG-ADA develop anti-ADA antibodies. In approximately 10% of treated children (i.e., in approximately 20% of the children that develop antibodies), anti-ADA antibodies lead to neutralisation of ADA activity, which requires an increase in dosage, administration of corticosteroids, or cessation of therapy [Lainka, 2005; Chaffee, 1992; Chun, 1993].

ERT requires frequent monitoring of plasma levels and its long-term efficacy is limited for some patients. PEG-ADA, the only currently available ERT, is a

significant long-term cost commitment and has limited availability in some countries [Chan, 2005] (including the UK), while decreasing lymphocyte counts and functionality (possibly because of the development of anti-ADA neutralising antibodies [Gaspar, 2009]) over time leave patients susceptible to infection, autoimmunity, and malignancy [Chan, 2005; Baffelli, 2015]. As a result, long-term ERT is not seen as a preferred treatment option in England.

The Inborn Errors Working Party (IEWP) of EBMT is responsible for creating guidelines on the treatment of ADA-SCID. The updated EBMT/ESID guidelines (March 2017) for the treatment of ADA-SCID reflect the scientific advances that have been achieved for patients with ADA-SCID who have no suitable MRD available. The IEWP critically appraised the scientific evidence of all treatments for ADA-SCID, and their conclusions are reflected in the updated guidelines that position gene therapy, using a product such as Strimvelis, as the treatment of choice for patients with ADA-SCID without an MRD.

8.4 Describe the new pathway of care incorporating the new technology that would exist following national commissioning by NHS England.

Strimvelis represents a step-change in the clinical pathway of care for patients with ADA-SCID without an MRD. Overall survival in the Integrated Population for Strimvelis was 100%. EBMT/ESID guidelines recommend gene therapy, using a product such as Strimvelis, as first-line therapy for patients with ADA-SCID who do not have an MRD [EBMT/ESID Guidelines, 2017].

Patients will be diagnosed and initially assessed by doctors at specialist centres in England. If an HLA-matched related bone marrow donor is not available, the doctor may discuss the option of Strimvelis gene therapy with the patient and carers. Screening for eligibility will be conducted by doctors at specialist centres in England.

Strimvelis will be manufactured and administered at a single centre (HSR-TIGET, Italy). HSR-TIGET will liaise with the clinical team and determine that Strimvelis is appropriate for the particular patient (patient has ADA-SCID without a suitable MRD and is able to donate adequate CD34+ cells). In preparation for the single treatment, patients will be seen at HSR-TIGET slightly longer than 1 month (range: 31 to 45 days) before Strimvelis treatment to obtain a bone marrow back-up sample and undergo other relevant procedures, including insertion of a CVC. At least 1 family member will remain in Italy with the patient. For the period of treatment with Strimvelis, patients will be hospitalized at HSR-TIGET for approximately 50 days. This time includes bone marrow extraction for product manufacture, infusion of Strimvelis, and inpatient clinical monitoring after therapy. The actual length of hospitalisation may vary according to the patient's clinical condition. Patients will then be seen as an outpatient for a minimum period of 2 months and an estimated maximum of 3 months, depending on the clinical course, to monitor progress. The UK Stem Cell Strategy Oversight Committee guidelines on Unrelated Donor Stem Cell Transplantation in the UK states that recovery from HSCT typically takes 4-8 weeks as an inpatient [NHS, 2014],

which is comparable to Strimvelis. It should be noted that complications associated with HSCT (e.g. rejection and acute and chronic GvHD) can significantly prolong the inpatient period for this treatment option. Strimvelis is made from the patient's own cells; therefore, there is no risk of GvHD.

After the outpatient period in Italy, the patient would return to the UK and receive follow-up outpatient care by the patient's referring physician with specific guidance and recommendations, including recommendations for specialist blood tests, from the treating physicians at HSR-TIGET. Consenting families will be included in an observational registry to help determine long-term effectiveness and safety.

GlaxoSmithKline has had several discussions with NHS England that confirmed they would put an active commissioning policy in place were Strimvelis to be approved by NICE. This would involve contracting directly with the San Raffaele Hospital in Milan for the costs incurred whilst the patient is in Italy.

Table B 1 Clinical pathway showing time in Italy

Stage	Average Duration (Range)
Screening	Performed in England (24 days), 0 days in Italy
Baseline Patient Preparation (CVC placement, obtain bone marrow back-up)	31 days (31-45 days), including a 3-day inpatient stay
Treatment	50 days in isolation room (may be longer if complications occur)
Outpatient Follow-up in Milan	60 days (60-90 days)
Outpatient Follow-up in England	4 months (3-4 months) and then continued for lifetime as per routine care for all patients with ADA-SCID

Abbreviations: CVC=central venous catheter, UK=United Kingdom

8.5 Discuss whether and how you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits, and whether and how the technology is a 'step-change' in the management of the condition.

Strimvelis is an innovative treatment and represents a step-change for this fatal disease because:

- It is the first approved gene therapy for ADA-SCID.
- It is the first approved ex-vivo gene therapy for paediatric patients in the EU. No other ex-vivo gene therapy has been approved for paediatric patients anywhere in the world.
- It is a life-saving treatment with a 100% survival rate and highly successful engraftment rate.
- For the first time, patients with ADA-SCID without an MRD can have a one-time treatment with significantly better overall survival than the current standard of care (HSCT from a MUD).
- It is a one-time, single-dose therapy with the potential for long term or permanent benefit of immunological manifestations of ADA-SCID
- It is an autologous therapy, so there is no risk of GvHD or rejection due to HLA mismatching or minor antigen incompatibility [Aiuti, 2009a]

Strimvelis is a significant step-change as recognised by an update to the EBMT guidelines. The IEWP has critically appraised the scientific advice for all treatments for ADA-SCID, and their conclusions are reflected in the updated guidelines that position gene therapy, such a Strimvelis, as the treatment of choice for patients with ADA-SCID without an MRD.

8.6 Describe any changes to the way current services are organised or delivered as a result of introducing the technology.

Strimvelis must be administered in a specialist transplant centre, by a physician with previous experience in the treatment and management of patients with ADA-SCID and in the use of autologous CD34+ ex vivo gene therapy products. At present, treatment with Strimvelis can only be performed at HSR-TIGET, Milan, Italy due to the 6-hour shelf life of the manufactured cell therapy product and the location of the manufacturing site. In view of this, a specific cross-border treatment pathway has been established. Once eligibility for treatment with Strimvelis has been confirmed, the patient and their family will travel to Milan for their treatment and immediate follow-up period, in coordination with the clinical team and a care coordinator who will help facilitate any required cultural or linguistic support.

Upon discharge from hospital, and depending on the clinical course of recovery, the patient will be seen as an outpatient at the paediatric department to monitor progress. In uncomplicated cases, the child and family could return to the UK after a minimum of 2 months of outpatient monitoring. More complicated cases could need an additional month of outpatient follow-up in Milan.

As a result of this cross-border treatment process, clinical care of an eligible child will transition to the treating physicians at HSR-TIGET for a minimum of

approximately 3.7 months. After treatment and repatriation, clinical care will transition to the UK referring physician, who may discuss individual follow-up assessments and plans (including specialist blood tests) with HSR-TIGET's clinical team. Follow-up after the initial period in Italy will occur within the patient's home country and observational data from this will be recorded in a patient registry (for those choosing to participate) to monitor the effectiveness and safety of Strimvelis.

8.7 Describe any additional tests or investigations needed for selecting or monitoring patients, or particular administration requirements, associated with using this technology that are over and above usual clinical practice.

The tests and investigations needed for selecting patients for Strimvelis are similar to those for HSCT except that there is no need to screen for a donor for Strimvelis. Additionally, the patient must be able to donate adequate CD34+ cells to deliver a minimum of 4 million purified CD34+ cells/kg, required for the manufacture of Strimvelis. The recommended dose range of Strimvelis is between 2 and 20 million CD34+ cells/kg and it is intended to be administered as an intravenous infusion once only.

Monitoring will also be similar to HSCT. The only additional test required for Strimvelis is the vector copy number. Retroviral insertion site and replication competent retrovirus testing would only be performed in the event of a leukemic adverse event; no patients in the Strimvelis clinical programme experienced such an event.

GSK has set up a registry as a means to collate routine standard of care data to better characterise the outcomes of patients after Strimvelis use.

Strimvelis must be administered in a specialist transplant centre, by a physician with previous experience in the treatment and management of patients with ADA-SCID and in the use of autologous CD34+ ex vivo gene therapy products. Currently, due to the manufacturing timelines, Strimvelis can only be administered at HSR-TIGET.

8.8 Describe any additional facilities, technologies or infrastructure that need to be used alongside the technology under evaluation for the claimed benefits to be realised.

From a patient management and hospital infrastructure perspective, Strimvelis is very similar to bone marrow transplants. No significant additional facilities, technologies, or infrastructure are required to support the use of Strimvelis beyond those routinely available to currently well-equipped transplant units.

In its current form, Strimvelis can only be administered at a single treatment centre in Milan meaning that there is no impact on UK clinical infrastructure. Prior

to treatment, patients are required to donate, and have stored a ‘back up’ bone marrow transplant that could be used in the event of a failed manufacturing run or other complications; this is not routinely done for allogenic transplant or ERT but extraction and storage of bone marrow cells is routine practice and requires no new capabilities. This procedure will currently be conducted in Milan approximately 3 weeks prior to Strimvelis administration. In the future, a cryopreserved formulation may become available, enabling treatment closer to the patient’s home such as in specialist UK hospitals but no specialist infrastructure would be required to support administration. The tests investigations, facilities, and technologies required to administer Strimvelis are very similar to those normally used in bone marrow transplant units; however, some specialist laboratory assessments do exist for gene therapy (for example, vector copy number assessment in peripheral blood). This will be available from specific laboratory providers and a list can be obtained from the marketing authorisation holder by the referring physicians should they request this test be performed. The cost of sample shipment will be supported by the treating centres.

8.9 Describe any tests, investigations, interventions, facilities or technologies that would no longer be needed with using this technology.

Currently, Strimvelis can only be administered in Italy; however, UK hospitals would still be expected to complete the necessary diagnosis and deliver emergency care prior to referral. After referral, treatment is administered in Milan, and children recover in Milan prior to discharge and coming home. This alleviates the need for UK-based hospitals to conduct a protracted search for unrelated bone marrow donors, collect and administer bone marrow transplantation, and administer short-term care and hospitalisation for the patient during recovery. There is no risk of GvHD with Strimvelis, so it is expected that the UK care system will not be required to manage acute or chronic graft vs host disease in patients with ADA-SCID treated with Strimvelis. UK patients with ADA-SCID are usually treated with ERT while a bone marrow transplant donor is found (approximately 19 weeks on average [Gaspar, 2013]). As Strimvelis is available independently of the need for a donor, ERT use is likely to be reduced (to approximately 9 weeks for Strimvelis, 10 weeks shorter than with HSCT). Successful treatment with Strimvelis means that ERT is no longer required.

Section C – Impact of the new technology

9 Published and unpublished clinical evidence

Summary

- Survival rate after Strimvelis in the Integrated Population was 100% and intervention-free survival for patients with available data was 82%.
- The frequency of severe infections was significantly reduced after treatment with Strimvelis.
- Overall the safety findings of Strimvelis are in line with those expected in an ADA-SCID population which has undergone busulfan conditioning and is undergoing immune reconstitution.
- Some patients develop acute or chronic GvHD after treatment with HSCT from a MUD or haploidentical donor but not after treatment with Strimvelis. GvHD can result in significant morbidity and mortality.

9.1 Identification of studies

Published studies

9.1.1 Describe the strategies used to retrieve relevant clinical data from the published literature. Exact details of the search strategy used should be provided in the appendix.

GSK conducted a systematic review of the published English language literature for the past 16 years (01 Jan 2000 to 20 May 2016) to summarise outcomes related to the treatment of ADA-SCID with HSCT from a MUD or haploidentical donor, or gene therapy. The start year of 2000 for this search was chosen because that was the year of the first investigations with Strimvelis. Embase, hosted by Elsevier, was chosen as the search engine because it is the most comprehensive search engine available. PubMed was not searched separately because Embase includes the PubMed database. The search strategy used is presented in the Appendix 1.

Unpublished studies

9.1.2 Describe the strategies used to retrieve relevant clinical data from unpublished sources.

Publication database searches were supplemented with unpublished data of completed and ongoing GSK studies of Strimvelis.

In addition to EMBASE searches for published literature relevant to the decision problem, ClinicalTrials.gov, the Cochrane Central Register of Controlled Trials (CENTRAL), the UK Clinical Trials Gateway, the EU Clinical Trials Register, and the World Health Organisation International Clinical Trials Registry Platform were searched from inception up to 20 May 2016. Search terms used were: adenosine deaminase deficiency and ADA-SCID. Details of the search strategy used are presented in the Appendix 1.

9.2 Study selection

Published studies

9.2.1 Complete table C1 to describe the inclusion and exclusion criteria used to select studies from the published literature. Suggested headings are listed in the table below. Other headings should be used if necessary.

Table C 1 Selection criteria used for published studies

Inclusion criteria	
Population	Patients with ADA-SCID
Interventions	HSCT from an HLA-matched unrelated donor or HLA haploidentical donor, gene therapy
Outcomes	Overall survival, intervention-free survival, rate of severe infections, in-patient hospital stay, lymphocyte counts, AEs, quality of life, and neurological/neurodevelopment events (including deafness)
Study design	No restriction
Language restrictions	English
Search dates	01Jan2000 to 20May2016
Exclusion criteria	
Population	Other than those described above
Interventions	Other than those described above
Outcomes	Does not report outcomes identified above
Study design	No restriction
Language restrictions	English
Search dates	01Jan2000 to 20May2016

Abbreviations: ADA-SCID=adenosine deaminase-severe combined immunodeficiency; AEs=adverse events; HLA=human leukocyte antigen; HSCT=hematopoietic stem cell transplant

9.2.2 Report the numbers of published studies included and excluded at each stage in an appropriate format.

As ADA-SCID is an extremely rare disease, we included all sources of information and thus included case-reports and case-series in our literature search.

Screening Stage One:

In addition to the 554 results identified in our search, an additional 7 articles were identified through review of references used in support of the marketing authorisation application for a total of 561. All 561 abstracts were reviewed for reporting of outcomes in patients with ADA-SCID treated with HSCT from a MUD or haploidentical donor (as defined in the publication) or gene therapy. Citations were designated as ‘Exclude’ or ‘Include’. This resulted in 79 potentially eligible studies.

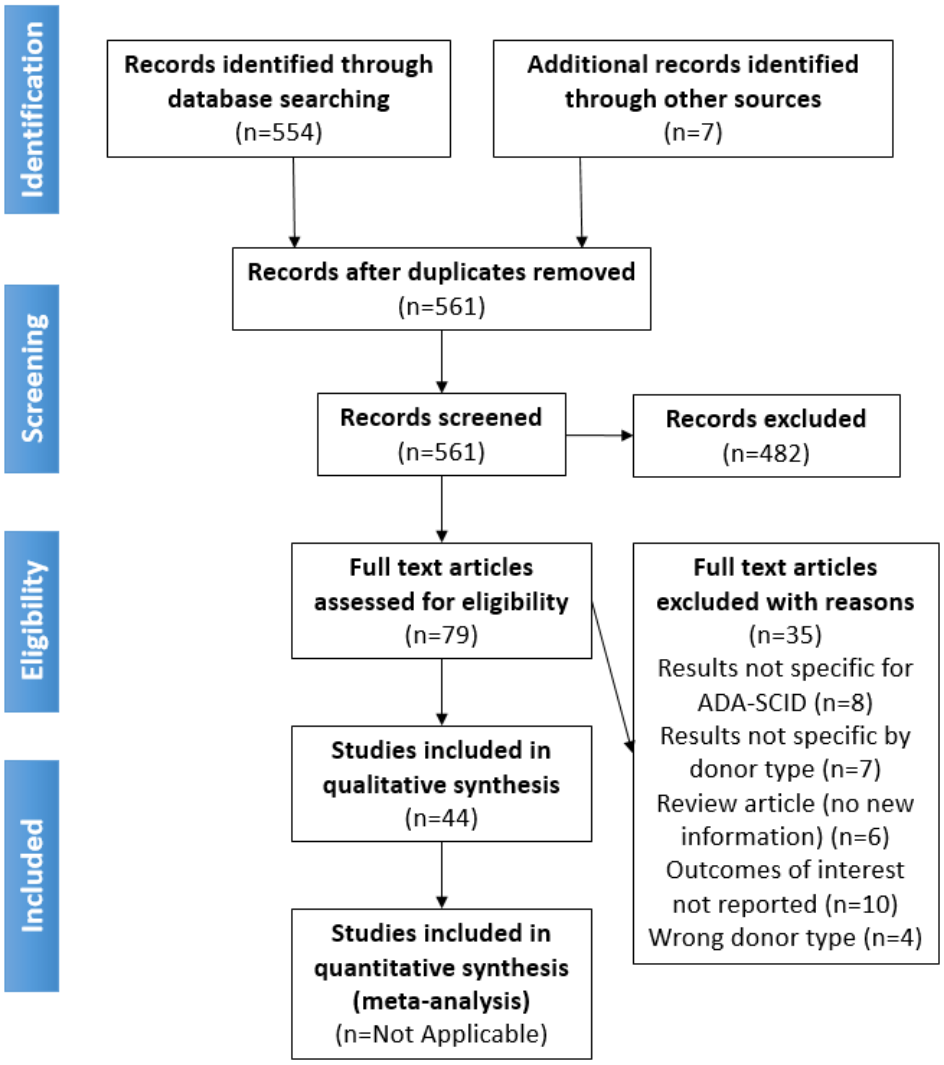
Screening Stage Two:

Seventy-nine full text articles identified as ‘Include’ in Screening Stage One were reviewed. The articles were screened against the inclusion and exclusion criteria listed above. Articles that provided outcomes for HSCT but that did not provide results by donor type or results specifically for MUD or haploidentical donors were excluded as were articles that provided outcomes for patients with SCID but not patients with ADA-SCID specifically. Forty-four articles were included as relevant to the primary objectives, while 35 were excluded.

The result of implementing the search and screening strategies is displayed in Figure 1.

No comparative studies of Strimvelis versus other treatment options were identified, so all information summarised from chosen publications is for indirect comparison only. As clinical data on Strimvelis is critical for evaluation of the decision problem, Sections 9.3 to 9.7 include information from the Strimvelis clinical programme. Information on indirect comparisons of Strimvelis versus relevant competitors is provided in Section 9.8.

Figure 1 PRISMA Diagram Published Studies



Unpublished studies

9.2.3 Complete table C2 to describe the inclusion and exclusion criteria used to select studies from the unpublished literature. Suggested headings are listed in the table below. Other headings should be used if necessary.

Table C 2 Selection criteria used for unpublished studies

Inclusion criteria	
Population	Patients with ADA-SCID
Interventions	HSCT from an HLA-matched unrelated donor or HLA haploidentical donor, gene therapy
Outcomes	Overall survival, intervention-free survival, rate of severe infections, in-patient hospital stay, lymphocyte counts, AEs, quality of life, and neurological/neurodevelopment events (including deafness)
Study design	No restriction
Language restrictions	English
Search dates	01Jan2000 to 20May2016
Exclusion criteria	
Population	Other than those described above
Interventions	Other than those described above
Outcomes	Does not report outcomes identified above
Study design	No restriction
Language restrictions	Not written in English
Search dates	01Jan2000 to 20May2016

Abbreviations: ADA-SCID=adenosine deaminase-severe combined immunodeficiency; AEs=adverse events; HLA=human leukocyte antigen; HSCT=hematopoietic stem cell transplant

9.2.4 Report the numbers of unpublished studies included and excluded at each stage in an appropriate format.

Please see Section 17.1.4 for the number of unpublished studies identified in each database. All identified unpublished studies were excluded because outcomes data were not provided.

Since the NPP is an investigator-sponsored study and has not been completed, and therefore a full dataset has not been generated, the NPP 200893 has been excluded. In the interest of full disclosure, the limited available data from the NPP 200893 are presented in Appendix 6.

Some level of information has been published for 5 clinical studies in the Strimvelis clinical programme, but not all data have been published. Where needed, information from the publications has been supplemented with unpublished information from the clinical study reports. Details of the sources used for each study are presented in Section 9.4.2.

9.3 Complete list of relevant studies

9.3.1 Provide details of all published and unpublished studies identified using the selection criteria described in tables C1 and C2.

There are no studies that compare Strimvelis directly against the comparators defined in the decision problem: HSCT from an HLA-MUD and HSCT from an HLA haploidentical donor. In the submitted marketing authorisation application as well as in the publications shown in Table C 3, indirect comparisons against historical data are discussed for Strimvelis versus these comparator treatments.

The use of Strimvelis in patients with ADA-SCID is supported by a primary data package comprising 18 patients: 15 patients treated in clinical studies, including a pivotal study (n=12) and 3 patients treated via early pilot studies, conducted over a treatment and maximum follow-up period of approximately 13 years, and 3 patients who received Strimvelis gene therapy under compassionate use. These studies were as follows: 1 single arm, open-label, historically controlled pivotal trial with a LTFU (AD1115611; n=12), 2 early open-label uncontrolled pilot studies (AD1117054/AD1117056; n=3), and a compassionate use programme (AD1117064; n=3). Though the LTFU was a component of the pivotal study protocol, it was amended to permit enrolment of patients from the pilot studies and the CUP to participate in long-term assessments beyond the initial follow-up period of each study. In total, 18 patients across all studies and the CUP were treated with Strimvelis at the time of the data cut-off for the marketing application (see Table A 3).

Data for the first 10 patients enrolled in these studies with clinical follow-up ranging from 1.8 to 8 years have been published [Aiuti, 2002a; Aiuti, 2009b; Selleri, 2011], and a manuscript that expands on those data with long-term (2.3 to 13.4 years, median 6.9 years) safety and efficacy results in those and 8 additional patients has recently been published [Cicalese, 2016]. The results presented by Cicalese et al. include the most recent data cut available.

Table C 3 List of relevant published studies

Primary study reference	Study name (acronym)	Population	Intervention	Comparator
Aiuti A, Slavin S, Aker M, et al. Correction of ADA-SCID by stem cell gene therapy combined with nonmyeloablative conditioning. Science. 2002a Jun 28;296(5577):2410-3.	AD1117054 (Pilot 1); AD1117056 (Pilot 2)	ADA-SCID paediatric patients who lacked HLA-matched sibling donor	Strimvelis gene therapy preceded by conditioning with busulphan (2 mg/kg/day on 2 consecutive days) was administered IV. (3 doses/day) in Pt1, and orally (4 doses/day) in Pt2 on days –3 and -2)	none
Aiuti A, Cattaneo F, Galimberti S, Benninghoff U, et al. Gene therapy for immunodeficiency due to adenosine deaminase deficiency. N Engl J Med. 2009 Jan 29;360(5):447-58.	AD1115611 (Pivotal); AD1117054 (Pilot 1); AD1117056 (Pilot 2);	ADA-SCID paediatric patients who lacked HLA-matched sibling donor	Strimvelis gene therapy preceded by conditioning with busulfan (2 mg/kg/day)	none
Cicalese MP, Ferrua F, Castagnaro L, et al. Update on the safety and efficacy of retroviral gene therapy for immunodeficiency due to adenosine deaminase deficiency. Blood. 2016 128:45-54.	AD1115611 (Pivotal); AD1117054 (Pilot 1); AD1117056 (Pilot 2); AD1117064 (CUP); AD1115611 LTFU	ADA-SCID paediatric patients who lacked HLA-matched sibling donor	Strimvelis gene therapy preceded by conditioning with busulfan (2 mg/kg/day)	none

Abbreviations: ADA-SCID=adenosine deaminase-severe combined immunodeficiency; AEs=adverse events; HLA=human leukocyte antigen; IV=intravenous

Table C 4 List of relevant unpublished studies

An article on the safety of Strimvelis is in progress. This article will provide information on the safety data from the studies included in the marketing authorisation application for Strimvelis. The safety data from the CSRs and marketing authorisation application are included in this NICE evidence submission.

9.3.2 State the rationale behind excluding any of the published studies listed in tables C3 and C4.

None of the above listed studies were excluded from discussion in this dossier.

No studies were identified that directly compare Strimvelis with the comparator therapies defined in the decision problem. All comparisons summarised in this document or in the published literature shown in Table C 3 are indirect. As information on the Strimvelis clinical programme is critical to the decision problem, these studies are presented in Sections 9.4 to 9.7. All identified published studies of competitors defined in the decision problem are presented in Section 9.8 for indirect comparison.

9.4 Summary of methodology of relevant studies

9.4.1 Describe the study design and methodology for each of the published and unpublished studies using tables C5 and C6 as appropriate. A separate table should be completed for each study.

All clinical studies in the Strimvelis programme listed in Table A 3 and in Table C 3 were non-randomised, single-arm, single-centre, open-label studies.

The pivotal trial AD1115611 was classified as a Phase 1/2, prospective, historical control study. After Strimvelis was in-licensed in 2010, GSK implemented a protocol amendment (AD1115611 Protocol Amendment 5) to the pivotal study AD1115611 that formally extended longer-term follow-up to >3 years, and also enrolled patients from Pilot Study 2 (AD1117056) and the CUP (AD1117064) after 3 years of post-treatment follow-up in their respective study/programs. The single patient treated in Pilot Study 1 (AD1117054) joined AD1115611 LTFU [redacted] years post-treatment. Follow-up data captured from Year 4 onwards are considered AD1115611 LTFU and presented as an extension of the pivotal study evidence of efficacy.

Cicalese, 2016 presents the patients enrolled from the 2 pilot studies, one pivotal study with a LTFU component, and the CUP. LTFU permitted enrolment of patients from the pilot studies and CUP to participate in long-term assessments beyond the initial follow-up period.

No randomised controlled studies were conducted so the following tables describe single-arm studies that may include comparison versus a historical

control (AD1115611). Information from the publications describing these studies has been augmented with unpublished information from the respective CSRs.

Table C 5 Summary of methodology for AD1115611 (pivotal; single arm study versus historical control; published)

Study name	ADA gene transfer into haematopoietic stem/progenitor cells for the treatment of ADA-SCID (AD1115611 Pivotal)
Objectives	1. Evaluation of the safety and the clinical efficacy of gene therapy, in the absence of enzyme replacement therapy. 2. Evaluation of biological activity (engraftment, ADA expression) of ADA-transduced CD34+ cells and their haematopoietic progeny. 3. Evaluation of immunological reconstitution and purine metabolism after gene therapy.
Location	Hadassah University Hospital (Hadassah) San Raffaele Scientific Institute (SR-I or SR-II).
Design	Open-label, prospective, sequential, controlled study (comparison with historical control data for patients receiving HSCT from a MUD)
Duration of study	3 years
Sample size	12 Patients
Inclusion criteria	• Aged <18 years suffering from SCID with ADA deficiency, as assessed by ADA enzymatic activity and/or genetic analysis, and for whom an HLA-identical healthy sibling was not available as suitable bone marrow donor • Exhibited lack of efficacy (defined by immunological measurements) with at least 6 months of treatment with PEG-ADA prior to enrolment; OR had PEG-ADA discontinued due to intolerance, allergic reaction, or autoimmunity, OR enzyme replacement therapy was not a lifelong therapeutic option
Exclusion criteria	Infected with human immunodeficiency virus (HIV) and those with a current malignancy or a history of malignancy, or who received a previous gene therapy treatment in the 12 months preceding the enrolment
Method of randomisation	NA
Method of blinding	NA
Intervention(s) (n = 12) and comparator(s) (n = 15)	Infusion of autologous CD34+ cells transduced ex vivo with retroviral vector encoding ADA after non-myeloablative conditioning with busulfan compared with historical control of HSCT from a MUD [Hassan, 2012]

Baseline differences	Two patients had previously received an unsuccessful BMT from a haploidentical donor; all had previously received PEG-ADA.
Duration of follow-up, lost to follow-up information	AD1115611 was a 3-year study with a separate LTFU component. All patients completed Year 1 assessments, 1 patient was withdrawn at 2.3 years, and all 11 remaining patients completed Year 3 assessments. The primary reason for withdrawal was recorded as investigator discretion: the patient was a candidate for allogeneic transplant and was moved to another clinical centre. This patient received a sibling-matched BMT from a relative that had not been available at the time of gene therapy treatment.
Statistical tests	All patients treated with Strimvelis and their data as observed during the study were used for statistical analyses. Missing data were treated as missing at random, and no imputations for missing data or withdrawals were performed (with the exceptions noted below). Given the small sample size in the study, any statistical imputations for missing data were not considered appropriate. The following exceptions were made: the baseline visit window (end of screening, Day -5) was extended by 1 day to Day -4 for 2 patients only to capture their missing baseline data (Patients [redacted]); and missing CD3+ values were imputed as the average of CD4+ and CD8+ values obtained from the same sample. If there was more than 1 baseline value, the last value prior to gene therapy treatment was used as a baseline. The Intent-to-treat (ITT) population included all patients who received gene therapy and had at least 1 post-therapy evaluation during the 3-year follow-up. Data collected after the 3-year visit were excluded from the analysis. The ITT population was the primary efficacy analysis population. The primary efficacy endpoint of survival was determined from the date of therapy until death (event of interest). Since there were no deaths in the study (100% survival), the Log-Rank test could not be applied for comparison to the 50% reference survival rate. However, survival at 3 years was compared to the postulated alternate hypothesis of 85%. The Kaplan-Meier product limit method was used to estimate survival for both ITT (all patients who received Strimvelis and had at least 1 post-therapy evaluation) and Per Protocol (patients in the ITT population who did

	not violate the protocol) populations, accounting for censored observations. For secondary efficacy endpoints, all continuous efficacy variables were examined, using error diagnostics from the analysis of residuals, to assess departure from assumptions of normality underlying the statistical model. If the assumptions were violated, log-transformation was applied to improve compliance with normality assumption, and analyses were carried out for both untransformed and log-transformed data. A small positive number was added to zero to enable log-transformation if the original observed value was zero. For such variables, the interpretation and inferences were drawn primarily from the log-transformed analysis results. Unless otherwise stated, all statistical analyses were 2-sided and performed at the 5% level of significance. Summary statistics including 95% confidence intervals (CIs) and appropriate plots were presented for all efficacy endpoints. The rate of severe infections was defined as the number of severe infections over person-years of observation (free from severe infections) before and after treatment administration. The first 3 months of observation after gene therapy were not considered in the analysis, because patients were already hospitalised during this period. Time free from severe infections was derived as total follow-up minus 3 months minus time under each infection (resolution date minus onset date). For pre-treatment severe infections, the total follow-up period was defined as the time from the date of birth to the day before the date of the gene therapy treatment. Therefore, time free from severe infections was derived as total follow-up (date of gene therapy minus date of birth minus 1) minus time under each infection. Statistical outputs of pre-treatment SAEs reflect the data reported by the investigator on AE and concomitant diseases CRF pages only
Primary outcomes (including scoring methods and timings of assessments)	Survival at 3 years
Secondary outcomes (including scoring methods and timings of assessments)	All efficacy endpoints were evaluated at 1, 2, and 3 years. A total of 14 secondary endpoints were included in the protocol in hierarchical order (see list below), among which 3 were considered as key: change in severe infection rates, change in T cell counts, and

modification of the systemic metabolic defects measured by dAXP levels in RBCs.

1.1. Change in the rate of severe infections (defined as infections requiring hospitalisation or prolonging hospitalisation)

1.2. Change in T cell counts

1.3. Modification of the systemic metabolic defect, assessed by levels of purine metabolites in RBCs; defined as percent of patients who reached adequate systemic metabolic detoxification, according to observations in patients treated with standard HLA-identical sibling donor SCT (where dAXP levels of <100 mmol/mL at Year 1 or longer are considered indicative of correction of the systemic metabolic defect in ADA-SCID) [Carlucci, 2003; Hirschhorn, 1981; Rogers, 2001; Ochs, 1992; Booth, 2007]

2.1. Change in the proliferative response to polyclonal stimuli

2.2. Change in thymic activity (T cell receptor excision circles [TREC])

2.3. Presence of genetically modified cells in the bone marrow compartment and presence of ≥10% genetically modified cells in peripheral blood lymphocytes

2.4. Lymphocyte ADA enzyme activity

2.5. Change in lymphocyte counts

3.1. Recovery of physical growth

3.2. Reintroduction of PEG-ADA in patients previously treated with PEG-ADA

3.3. Antibody response to vaccination.

Safety endpoints were as follows:

- Adverse events (expected or unexpected)
- Serious adverse events (expected or unexpected)

Safety assessments included monitoring and recording of AEs and serious adverse events (SAEs), laboratory

	parameters including clinical chemistry, haematology, and urinalysis,
Source(s)	Aiuti, 2009b; Selleri, 2011; Cicalese, 2014; AD1115611 CSR, 2015; Cicalese, 2016

Table C 6 Summary of methodology for AD1115611 LTFU 4-7 years (pivotal; single arm study versus historical control; submitted for publication)

Study name	Long-term follow-up of ADA gene transfer into haematopoietic stem/progenitor cells for the treatment of ADA-SCID (AD1115611 LTFU)
Objectives	To extend follow-up of patients who received gene therapy with transduced autologous CD34+ cells for the: 1. Evaluation of the safety and the clinical efficacy of gene therapy, in the absence of enzyme replacement therapy. 2. Evaluation of biological activity (engraftment, ADA expression) of ADA-transduced CD34+ cells and their haematopoietic progeny. 3. Evaluation of immunological reconstitution and purine metabolism after gene therapy. 4. Evaluation of change in quality of life over time in ADA-SCID patients following treatment with Strimvelis
Location	Hadassah University Hospital (Hadassah) San Raffaele Scientific Institute (SR-I or SR-II).
Design	Open-label, single arm Patients were enrolled via 2 pilot studies (AD1117054 [Aiuti, 2002a] and AD1117056 [Aiuti, 2002a], one pivotal study (AD1115611 [Aiuti, 2009b]) with a long-term follow-up (LTFU) component, and a compassionate use programme (CUP) (AD1117064, [unpublished, AD1117064 CSR]
Duration of study	Expanded on previous data from the feeder studies; as of the data cut-off for the marketing authorisation application and Cicalese 2016 publication, one patient had Year 13 follow-up data available and 5 patients had completed the Year 8 visit. The median duration of follow-up was 4.0 years from the Year 3 visit that was the baseline for the LTFU study.
Sample size	14 Patients
Inclusion criteria	Open to all patients who had received Strimvelis in any previous feeder study (Pilot Studies 1 [AD1117054] and 2 [AD1117056] and pivotal trial [AD1115611]) or in the

	CUP [AD1117064] and consented to take part in the LTFU Patients with ADA-SCID who lacked an HLA-identical sibling donor and (1) had received ≥6 months of PEG-ADA treatment with demonstrated inefficacy or intolerance, or (2) for whom PEG-ADA was not a long-term treatment option
Exclusion criteria	Patients infected with human immunodeficiency virus and those with a current malignancy or a history of malignancy, or who received a previous gene therapy treatment in the 12 months preceding the enrolment were excluded from the study.
Method of randomisation	NA
Method of blinding	NA
Intervention(s) (n = 14) and comparator(s) (n = 15)	Infusion of autologous CD34+ cells transduced ex vivo with retroviral vector encoding ADA after non-myeloablative conditioning with busulfan
Baseline differences	Two patients had previously received an unsuccessful BMT from a haploidentical donor; all but 3 had previously received PEG-ADA.
Duration of follow-up, lost to follow-up information	Data from 14 patients were included: 1 patient from Pilot Study 1 (AD1117054), 2 patients from Pilot Study 2 (AD1117056), and 11 patients from the pivotal study (AD1115611). [redacted] was withdrawn from the pivotal study and thus did not take part in the LTFU. Seventeen patients consented to the LTFU, and data from 14 patients are included in this report. Three patients from the compassionate use programme (AD1117064) are not included for the following reasons. Two patients consented to the LTFU but no data are published yet as Year 4 visit data were not available in time for the May 2014 cut-off; and 1 patient, who had not optimally responded to gene therapy treatment, consented to participate but withdrew before the Year 4 visit when a sibling matched BMT became available.
Statistical tests	For efficacy endpoints, all available data through the 8-year time points were used for statistical analysis. Within-patient changes were used for efficacy comparisons. Efficacy data collected after receipt of ≥3 continuous months of PEG-ADA or allogeneic SCT were excluded. Dichotomous and categorical endpoints, percentages and 95% confidence intervals were calculated. Continuous endpoints, the changes from pre-treatment baseline were analysed by mixed model repeated

	measures (MMRM) analyses fitting Visit and Baseline as fixed effects and Patient as the random effect. Where normality assumptions were violated, the data were log transformed. No adjustments were made for multiplicity; significance calculations are of limited value, and P values are not shown. No deaths occurred during the studies; therefore, no formal survival analysis was performed. However, Kaplan-Meier survival curves were plotted for intervention-free survival. Severe infections were defined as those leading to hospitalisation or prolonging hospitalisation and were reported as the number of severe infections per person-year of observation. Events during the 0-3 month post-treatment monitoring period were not included in adverse event (AE) analysis, as patients were generally confined to hospital (per protocol) with an expected risk of infections due to incomplete immune reconstitution and the neutropenia following busulfan conditioning. Height and weight for all patients were compared with age-appropriate growth charts. Not all patients had data available for each time point due to exact timing of follow-up visits.
Primary outcomes (including scoring methods and timings of assessments)	Survival
Secondary outcomes (including scoring methods and timings of assessments)	Intervention-free survival (defined as survival without receiving a post-gene therapy HSCT or continuous PEG-ADA treatment for ≥3 months) Infection rates. Assess engraftment and transgene function (vector copy number (VCN), lymphocyte ADA activity, and red blood cell (RBC) dAXP levels). Immune reconstitution (lymphocyte subset counts, T cell receptor excision circle (TREC) analysis, T cell proliferative capacity) Physical growth. Post-hoc analyses included transduced cell engraftment in CD15+ and CD34+ cells, antibody response to vaccination, and duration of IVIG administration. Safety endpoints were as follows: • Adverse events (expected or unexpected) • Serious adverse events (expected or unexpected) The long-term safety monitoring plan included replication competent retrovirus testing (archived

	samples), safety tests for genotoxicity, patient status questionnaire, vital signs, ECG, physical examination, specialist examinations, instrumental tests, and clinical laboratory assessments.
Source(s)	Cicalese, 2014; AD1115611 LTFU Interim CSR, 2015; Cicalese, 2016

Table C 7 Summary of methodology for Pilot Study 2 AD1117056

Study name	A summary of the safety and efficacy for the first 3 years post-gene therapy for 2 patients treated with Strimvelis (AD1117056 Pilot 2)
Objectives	1. To evaluate safety and efficacy of the administration to adenosine deaminase (ADA)-deficient patients of autologous lymphocytes transduced with a normal hADA gene. 2. To evaluate safety and efficacy of the administration to ADA-deficient patients of autologous haematopoietic stem cells transduced with a normal hADA gene. 3. To identify the relative role of peripheral blood lymphocytes, and haematopoietic stem cells and progenitor cells in the long-term reconstitution of immune functions after retroviral vector-mediated ADA gene transfer. 4. To evaluate the in vivo survival of autologous T-cells and the duration of expression of the inserted genes. 5. To define the potential selective advantage of ADA-positive cells over untransduced ADA-negative cells, and survival and expansion of peripheral blood lymphocytes. 6. To determine the extent, the kinetics and the duration of that engraftment in different haematological cell lineages in the course of time. 7. To determine whether ADA gene transfer into human long-term reconstituting stem cells could be achieved.
Location	San Raffaele Telethon Institute for Gene Therapy (HSR-TIGET), Milan, Italy
Design	Open-label, single arm
Duration of study	Through Year 3 of follow-up
Sample size	2 Patients
Inclusion criteria	Patients with ADA-SCID who lacked an HLA-identical sibling donor were included in this study. It was planned to recruit patients who had been treated with PEG-ADA for at least 6 months (unless they became allergic to this drug) before treatment. Patients were to have shown evidence of failure of enzyme replacement therapy, including persistence of recurrent infections.

	However, in a deviation to the entry criteria, neither of the 2 patients received PEG-ADA before gene therapy because it was not available in their country and the 2 patients had already failed the standard BMT therapy.
Exclusion criteria	Patients with a genetically HLA-identical bone marrow donor, patients infected with HTLV-1, HIV-1 (or HIV-2), and patients with malignancy
Method of randomisation	NA
Method of blinding	NA
Intervention(s) (n =2) and comparator(s) (n =0)	Infusion of autologous CD34+ cells transduced ex vivo with retroviral vector encoding ADA. Busulfan preconditioning was not included in the protocol for this study; however, a protocol deviation occurred and patients did receive non-myeloablative conditioning with busulfan. [redacted] received busulfan pre-conditioning at approximately 2 mg/kg/day before the first dose of gene therapy, but did not receive busulfan pre-conditioning before a second dose of gene therapy. [redacted] received IV busulfan pre-conditioning before gene therapy at approximately 2 mg/kg/day.
Baseline differences	Both patients had previously received an unsuccessful stem cell transplant from a haploidentical donor and neither had received PEG-ADA because it was not available in their country.
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	Both patients completed Year 3 follow-up assessments and then were enrolled into the AD1115611 LTFU study.
Statistical tests	No statistical analyses were pre-defined for the first 3 years of the study but were developed retrospectively.

Outcomes (including scoring methods and timings of assessments)	Outcomes were not designated as primary or secondary for this study. Outcomes included: Survival Change in rate of severe infections (defined as infections requiring hospitalisation or prolonging hospitalisation) Change in T lymphocyte counts (cells/μL) Modification of the 'systemic' metabolic defect, analysed by levels of purine metabolites in RBCs Change in the proliferative response to polyclonal stimuli Presence of genetically modified cells in the bone marrow compartment and presence of ≥10% genetically modified cells in peripheral blood lymphocytes Lymphocyte ADA enzyme activity Change in total lymphocyte counts (cells/μL) Recovery of physical growth Need for reintroduction of PEG-ADA (in patients previously treated with PEG-ADA) Antibody response to vaccination
Publication Source(s)	Bordignon, 1993; Aiuti, 2002a; Aiuti, 2009b; Cicalese, 2014; Abbreviated CSR AD1117056, 2015; Cicalese, 2016

Table C 8 Summary of methodology for Pilot Study 1 AD1117054

Study name	Treatment, clinical course and outcomes of the first patient treated with Strimvelis (AD1117054 Pilot 1)
Objectives	Evaluate the clinical efficacy and long-term outcomes in a patient with ADA-SCID treated with non-myeloablative conditioning followed by infusion of autologous bone marrow derived CD34+ cells transduced with a viral vector carrying the ADA gene
Location	[redacted]
Design	Open label, single patient
Duration of study	[redacted] years before the patient entered the LTFU
Sample size	1 Patient
Inclusion criteria	Children with ADA-SCID who lacked a healthy HLA-identical sibling and who had shown treatment failure with 6+ months PEG-ADA therapy or who had PEG-ADA intolerance, allergy or autoimmunity
Exclusion criteria	Not defined
Method of randomisation	NA
Method of blinding	NA

Intervention(s) (n =1) and comparator(s) (n =0)	Infusion of autologous CD34+ cells transduced ex vivo with retroviral vector encoding ADA after non-myeloablative conditioning with busulfan
Baseline differences	The patient did not receive BMT before gene therapy. In a protocol violation, the patient had not received PEG-ADA therapy as it was not available in [redacted] country.
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	This patient was followed for [redacted] years before [redacted] was enrolled in the AD1115611 LTFU study.
Statistical tests	NA
Primary outcomes (including scoring methods and timings of assessments)	Not available
Secondary outcomes (including scoring methods and timings of assessments)	Not available
Source(s)	Aiuti, 2002a; Aiuti, 2009b; Cicalese, 2014; Synoptic CSR AD1117054, 2015; Cicalese, 2016

Table C 9 Summary of methodology for Compassionate Use Programme Study AD1117064

Study name	Treatment and outcomes for ADA-SCID patients that received Strimvelis under compassionate use (AD1117064 CUP)
Objectives	To provide a mechanism to supply Strimvelis on a compassionate use basis for the treatment of patients with ADA-SCID
Location	San Raffaele Telethon Institute for Gene Therapy (HSR-TIGET), Milan, Italy
Design	Strimvelis was administered under compassionate use (open label). Patients were treated and followed up using the same assessments and procedures as the Pivotal AD1115611 study.
Duration of study	3 years and then patients could enrol in the AD1115611 LTFU study
Sample size	3
Inclusion criteria	• Aged <18 years suffering from SCID with ADA deficiency, as assessed by ADA enzymatic activity and/or genetic analysis, and for whom an HLA-identical healthy sibling was not available as suitable bone marrow donor

	• Exhibited lack of efficacy (defined by immunological measurements) with at least 6 months of treatment with PEG-ADA prior to enrolment; OR had PEG-ADA discontinued due to intolerance, allergic reaction, or autoimmunity, OR enzyme replacement therapy was not a lifelong therapeutic option
Exclusion criteria	Infected with HIV and those with a current malignancy or a history of malignancy, or who received a previous gene therapy treatment in the 12 months preceding the enrolment
Method of randomisation	NA
Method of blinding	NA
Intervention(s) (n =3) and comparator(s) (n =0)	Infusion of autologous CD34+ cells transduced ex vivo with retroviral vector encoding ADA after non-myeloablative conditioning with busulfan
Baseline differences	
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	Follow-up was consistent with follow-up in the Pivotal AD1115611 study. Patients were followed for 3 years and then allowed to enrol in the AD1115611 LTFU study.
Statistical tests	NA
Primary outcomes (including scoring methods and timings of assessments)	Safety of Strimvelis over 3 years
Secondary outcomes (including scoring methods and timings of assessments)	No formal endpoints were pre-specified for analysis; however, endpoints were defined *post hoc* to be in line with those in the Pivotal AD1115611 study. 1. Survival at 3 years post-gene therapy. 2. Change in the rate of severe infections (defined as infections requiring hospitalisation or prolonging hospitalisation). 3. Change in T lymphocyte counts (cells/μL). 4. Modification of the 'systemic' metabolic defect, analysed by levels of purine metabolites in red blood cells (RBCs). 5. Change in the proliferative response to polyclonal stimuli. 6. Change in thymic activity (T-cell receptor excision circles; TREC). 7. Presence of genetically modified cells in the bone marrow compartment and presence of

	≥10% genetically modified cells in peripheral blood lymphocytes. 8. Lymphocyte ADA enzyme activity. 9. Change in lymphocyte counts (cells/μL). 10. Recovery of physical growth. 11. Need for reintroduction of PEG-ADA (in patients previously treated with PEG-ADA). 12. Antibody response to vaccination.
Source(s)	Cicalese, 2014; AD1117064 Interim CSR 2015; Cicalese, 2016

9.4.2 Provide details on data from any single study that have been drawn from more than one source (for example a poster and unpublished report) and/or when trials are linked this should be made clear (for example, an open-label extension to randomised controlled trial).

The data presented for each study from the Strimvelis clinical programme were pulled from multiple sources as presented in the table below.

Table C 10 Sources by study

Study ID	Sources
AD1117054 Pilot 1	Aiuti, 2002a; Aiuti, 2009b; Cicalese, 2014; Synoptic CSR AD1117054, 2015; Cicalese, 2016
AD1117056 Pilot 2	Bordignon, 1993; Aiuti, 2002a; Aiuti, 2009b; Cicalese, 2014; Abbreviated CSR AD1117056, 2015; Cicalese, 2016
AD1115611 Pivotal	Aiuti, 2009b; Selleri, 2011; Cicalese, 2014; AD1115611 CSR, 2015; Cicalese, 2016
AD1117064 CUP	Cicalese, 2014; AD1117064 Interim CSR; Cicalese, 2016
AD1115611 LTFU	Cicalese, 2014; AD1115611 LTFU Interim CSR, 2015; Cicalese, 2016

9.4.3 Highlight any differences between patient populations and methodology in all included studies.

Patients enrolled in the Strimvelis clinical programme were generally similar across studies except that [redacted] had no prior exposure to PEG-ADA while all subsequent patients had received some level of PEG-ADA treatment. [redacted] from the AD1115611 Pivotal study had failed prior SCT from a haploidentical donor.

9.4.4 Provide details of any subgroup analyses that were undertaken in the studies included in Section 9.4.1. Specify the rationale and state whether these analyses were pre-planned or post-hoc.

No subgroup analyses were performed for any of the studies included in Section 9.4.1.

9.4.5 If applicable, provide details of the numbers of patients who were eligible to enter the study(s), randomised, and allocated to each treatment in an appropriate format.

Not applicable.

9.4.6 If applicable provide details of and the rationale for, patients that were lost to follow-up or withdrew from the studies.

One patient ([redacted]) withdrew from the Pivotal AD1115611 Study 2.3 years after receiving Strimvelis due to investigator discretion. After an unsuccessful response to gene therapy, the patient withdrew to receive an HLA-matched SCT from a sibling donor that had not been available prior to Strimvelis therapy. One patient ([redacted]) from the AD1117064 CUP enrolled in the AD1115611 LTFU study but withdrew from the LTFU before the Year 4 visit due to patient decision. After an unsuccessful response to gene therapy, the patient withdrew to receive HSCT from an MSD that had not been available prior to Strimvelis therapy. Both these patients are considered in the analyses as an unsuccessful response to Strimvelis. Details on these 2 patients are included in Table C 21.

9.5 Critical appraisal of relevant studies

9.5.1 Complete a separate quality assessment table for each study.

As described previously, all clinical studies were non-randomised, single-arm, single-centre, open-label studies.

The discovery and development of Strimvelis was initially conducted in an academic setting and largely sponsored by HSR-TIGET, the research arm of an Italian Charity. The development programme was started in 1990. Given the very long history of the development programme, some elements are not consistent

with current standards of International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice (GCP). In particular, substantial supporting study documents for the 2 pilot clinical studies (AD1117056 and AD1117054) are not available (additional details are available in the AD1117054 Pilot 1 synoptic CSR and the AD1117056 Pilot 2 abbreviated CSR). Furthermore, 3 of the patients reported in the marketing authorisation application received treatment under a compassionate use programme (AD1117064) and were not initially part of a formal prospectively defined safety and efficacy study. Patient-level data on items such as resource use and costs are not readily available.

The pivotal study protocol, amendments, informed consent, and other information that required pre-approval were reviewed and approved by a national, regional, or investigational centre ethics committee or institutional review board, in accordance with GCP and applicable country-specific requirements. More information about studies AD1117056, AD1117054, AD1117064, and the LTFU under study AD1115611 are provided below.

Pivotal Study (AD1115611)

The pivotal study AD1115611 was sponsored by HSR-TIGET and GSK. The original protocol and the first 4 amendments were the responsibility of HSR-TIGET. The last 4 amendments were the responsibility of GSK. The study was conducted in accordance with the International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use GCP standards (2007 edition), all applicable patient privacy requirements, and the ethical principles outlined in the Declaration of Helsinki 2000. The study protocol, amendments, informed consent, and other information that required pre-approval were reviewed and approved by a national, regional, or investigational centre ethics committee or institutional review board and approvals are maintained in the Sponsor's study file. Following the transfer of sponsorship to GSK, in compliance with GSK policies, investigators were trained to conduct the study in accordance with GCP and the study protocol as defined in ICH E3, Section 9.6. The study was monitored in accordance with ICH E6, Section 5.18.

AD1115611 Long-Term Follow-Up

After the Strimvelis product was in-licensed in 2010, GSK implemented a protocol amendment (AD1115611 Protocol Amendment 5) to AD1115611 (pivotal study) that formally extended longer-term follow-up to >3 years, and also enrolled patients from Pilot Study 2 (AD1117056) and the CUP (AD1117064) after 3 years of post-treatment follow-up in their respective study/programme. The single patient who was treated in Pilot Study 1 (AD1117054) joined AD1115611 LTFU [redacted] years post-gene therapy.

This study was sponsored by HSR-TIGET and GSK. The original protocol and the first 4 amendments were the responsibility of HSR-TIGET. The last 4 amendments were the responsibility of GSK. The AD1115611 study protocol,

amendments, informed consent, and other information that required pre-approval were reviewed and approved by a national, regional, or investigational centre ethics committee or institutional review board in accordance with ICH GCP and applicable country-specific requirements, including US 21 Code of Federal Regulations 312.3(b) for constitution of independent ethics committees. This study was conducted in accordance with ICH GCP (2007 edition) and all applicable patient privacy requirements, and the ethical principles that are outlined in the Declaration of Helsinki 2000. Following the transfer of sponsorship to GSK, in compliance with GSK policies, investigators were trained to conduct the study in accordance with GCPs and the study protocol as defined in ICH E3, Section 9.6. The study was monitored in accordance with ICH E6, Section 5.18.

Pilot Study 2 (AD1117056)

Pilot Study 2 (AD1117056) represents 2 patients with ADA-SCID treated with GSK6796273 under a pilot study protocol [Bordignon, 1993] that described multiple investigational treatments. The study was conducted at Fondazione Centro San Romanello del Monte Tabor, predecessor of the Fondazione Centro San Raffaele del Monte Tabor (Milan, Italy). This study was not conducted under a GSK-approved protocol. GSK cannot demonstrate that the study protocol, informed consent, and conduct of the study conformed to ICH GCP standards. GSK can confirm that the study protocol, informed consent, and other information that required pre-approval were reviewed and approved by Ethical Committee of the Fondazione Centro San Romanello del Monte Tabor and by the Comitato Nazionale di Bioetica (National Italian Committee for Bioethics).

Upon in-licensing of the product by GSK in 2010, both patients signed a GSK informed consent which granted GSK access to the prior data from their participation in the trial. GSK accessed these historical study data and medical records and transferred their data onto a retrospectively designed CRF. The process undertaken by GSK for the acquisition and reporting of these historical data was compliant with ICH GCP and all applicable patient privacy requirements. Further, this process was monitored in accordance with ICH E6, Section 5.18.

Pilot Study 1 (AD1117054)

Pilot Study 1 (AD1117054) covers the treatment and first [redacted] years of follow-up for [redacted] patient receiving Strimvelis. In 2013, [redacted]'s parent/guardian signed a GSK consent to participate in the LTFU of study AD1115611. This consent also granted GSK retrospective access to this patient's data from for the first [redacted] years after gene therapy.

Limited source documents are available with which to validate the published data for this patient [Aiuti, 2002a; Aiuti, 2009b]. Available source data for this patient covering the pre-treatment, treatment, and first [redacted] years of follow up primarily consist of sparse clinical laboratory results and bio-analytical outputs that have been captured onto an Excel spreadsheet (no CRF exists). In addition, physician letters from hospital admissions and emergency room visits have been made

available for review. No study conduct documentation including drug product batch record, study protocol, ethics approval documentation, or other source documentation to support the design and conduct of this trial are available to GSK to demonstrate GCP compliance of this study. Therefore, GSK cannot demonstrate that the study protocol, informed consent, and conduct of the study conformed to the ICH GCP standards. The publications indicate that the protocol was approved by the Institutional Review Board at [redacted] and the [redacted] Ministry of Health [Aiuti, 2002a Suppl; Aiuti, 2009b]; however, no source documentation is available to GSK to support these statements. The existing data have been summarized in a narrative format in a synoptic study report and supporting data are only available in the formats outlined above. No CRF or formal statistical output is available for AD1117054.

CUP (AD1117064)

Patients in the CUP (AD1117064) received gene therapy in accordance with the Italian Ministerial Decree of 08 May 2003 (D.M. 8/5/2003). Each treatment was approved by the Ospedale San Raffaele Ethics Committee and notified to the Istituto Superiore di Sanita (ISS) and The Italian Medicines Agency. Additionally, in accordance with Italian law, patient data were updated in the ISS Italian Monitoring Database for Gene and Cell Therapy, Banca Dati per il Monitoraggio della Terapia Genica e Cellulare Somatica.

Although the CUP was not a formal prospectively defined safety and efficacy study, GSK has retrospectively sought and received ethics approval and patient/carer consent to use these data for registration purposes. All patients who received Strimvelis as part of the CUP were treated at the same clinical site that conducted study AD1115611, and the same eligibility criteria, treatment procedures, and assessments were followed as for patients in the pivotal study AD1115611. GSK has entered the patients' data onto CRFs, constructed a clinical database, and verified that the information captured on these CRFs corresponds to the information in the source documents for these patients.

Table C 11 Critical appraisal of AD1115611 Pivotal 0-3 Year Study

Study question	Response yes/no/not clear/N/A)	How is the question addressed in the study?
Was the cohort recruited in an acceptable way?	Yes	Recruitment was suitable and based on the study protocol.
Was the exposure accurately measured to minimise bias?	Yes	Exposure was measured and documented as per the study protocol.
Was the outcome accurately measured to minimise bias?	Yes	Outcomes for the years 0-3 were reported for some patients in Aiuti, 2009b and complete results are now summarised in Cicalese, 2016.

		These results were collected using GCP and have been carefully assessed.
Have the authors identified all important confounding factors?	Yes	Results have focused on descriptive analysis of efficacy and safety for these patients.
Have the authors taken account of the confounding factors in the design and/or analysis?	Yes	Relevant factors have been discussed, but due to small sample size, formal analyses were not performed.
Was the follow-up of patients complete?	N/A	Eleven of the 12 patients completed the 3-year study as planned and are still participating in long-term follow-up. [redacted] required PEG-ADA reintroduction and corticosteroid therapy approximately 5 months after gene therapy due to SAEs of neutropenia and autoimmune thrombocytopenia. This patient was withdrawn from the study approximately 2.3 years after gene therapy and is not a participant in long-term follow-up. The primary reason for withdrawal was recorded as investigator discretion: the patient was a candidate for allogeneic transplant and was moved to another clinical centre. This patient received a sibling-matched BMT from a relative that had not been available at the time of gene therapy treatment.
How precise (for example, in terms of confidence interval and p values) are the results?	N/A	Results are descriptive as there is no comparative arm
Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence 12 questions to help you make sense of a cohort study		

Table C 12 Critical appraisal of AD1115611 LTFU

Study question	Response yes/no/not clear/N/A)	How is the question addressed in the study?
Was the cohort recruited in an acceptable way?	N/A	This study was a LTFU extension based on an amendment of the AD1115611 and included patients previously recruited and treated in the other clinical studies described in the tables above.

Was the exposure accurately measured to minimise bias?	N/A	This is a LTFU study of patients previously treated.
Was the outcome accurately measured to minimise bias?	Yes	Outcomes based on interim data are now summarised in Cicalese, 2016. These results were collected using GCP and have been carefully assessed.
Have the authors identified all important confounding factors?	Yes	Results have focused on descriptive analysis of efficacy and safety for these patients
Have the authors taken account of the confounding factors in the design and/or analysis?	Yes	Relevant factors have been discussed, but due to small sample size, formal analyses were not performed.
Was the follow-up of patients complete?	N/A	This LTFU study is ongoing. Seventeen patients consented to the LTFU, and LTFU data from 14 patients were included in the interim CSR as well as in Cicalese, 2016. Three patients from the compassionate use programme (AD1117064) were not included for the following reasons. Two patients consented to the LTFU but no data were reported since the Year 4 visit data were not available in time for the May 2014 cut-off for the marketing authorisation application ; and 1 patient ([redacted]), who had not optimally responded to gene therapy treatment, consented to participate but withdrew before the Year 4 visit when a sibling matched BMT became available. [redacted] from Pilot Study 1 (AD1117056) entered the LTFU only at Year [redacted]. At this time the Year 8 assessments were done so that both efficacy and safety parameters could be captured for this patient (as the Year [redacted] visit would have included predominantly safety evaluations).
How precise (for example, in terms of confidence interval and p values) are the results?	N/A	Results are descriptive as there is no comparative arm
Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence 12 questions to help you make sense of a cohort study		

Table C 13 Critical appraisal of AD1117056 Pilot 2

Study question	Response yes/no/not clear/N/A)	How is the question addressed in the study?
Was the cohort recruited in an acceptable way?	Yes	This study was a pilot study of 2 patients. GSK cannot confirm if a formal protocol was utilized but methodology is described in Bordignon, 1993.
Was the exposure accurately measured to minimise bias?	not clear	To date, the lowest dose of CD34+ cells/kg delivered with Strimvelis gene therapy was in [redacted] from study AD1117056. This patient received Strimvelis gene therapy on 2 occasions, 2 years and 7 months apart. At the first gene therapy, this patient received a low dose of CD34+cells (0.9×10^6/kg) due to the limited content of CD34+ cells at the time of bone marrow explant. The patient remained lymphopenic and PEG-ADA was administered for 7 weeks, starting 2 years and 5 months after [redacted] first gene therapy due to the lymphopenia. A second gene therapy procedure (2.1×10^6/kg of CD34+ cells) without busulfan conditioning was then performed, 3.5 weeks after PEG-ADA had been discontinued
Was the outcome accurately measured to minimise bias?	Yes	Patients [redacted] who were treated in Pilot Study 2 (AD1117056) had their clinical data retrospectively entered into CRFs with subsequent validation by GSK, and efficacy endpoints were defined post hoc for analysis. GSK cannot verify study conduct was in accordance with GCP, but can confirm data accuracy and GCP compliance since the study responsibility was assumed by GSK and the CRFs were created in which the data were retrospectively captured.
Have the authors identified all important confounding factors?	Yes	Results have focused on descriptive analysis of efficacy and safety
Have the authors taken account of the confounding factors in the design and/or analysis?	Yes	Relevant factors have been discussed, but due to small sample size, formal analyses were not performed.

Was the follow-up of patients complete?	N/A	Both patients are still participating in the LTFU component of AD1115611 and interim long-term data are provided in the AD11156111 LTFU interim CSR as well as in Cicalese, 2016
How precise (for example, in terms of confidence interval and p values) are the results?	N/A	Results are descriptive as there is no comparative arm
Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence 12 questions to help you make sense of a cohort study		

Table C 14 Critical appraisal of AD1117054 Pilot 1

Study question	Response yes/no/not clear/N/A)	How is the question addressed in the study?
Was the cohort recruited in an acceptable way?	Yes	This study was a pilot study of 1 patient and methodology, as well as protocol approval, is described in: [Aiuti, 2002a Suppl; Aiuti, 2009b]
Was the exposure accurately measured to minimise bias?	N/A	This was a single patient study
Was the outcome accurately measured to minimise bias?	Not clear	See text above in this section. No CRF or formal statistical output is available.
Have the authors identified all important confounding factors?	Yes	Results have focused on descriptive analysis of efficacy and safety for this single patient
Have the authors taken account of the confounding factors in the design and/or analysis?	Yes	Relevant factors have been discussed, but due to a sample size of 1, formal analyses were not performed
Was the follow-up of patients complete?	N/A	This patient is still participating in the LTFU component of AD1115611 and interim long-term data are provided in the AD11156111 LTFU interim CSR as well as in Cicalese, 2016

How precise (for example, in terms of confidence interval and p values) are the results?	N/A	Results are descriptive as there is no comparative arm
Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence 12 questions to help you make sense of a cohort study		

Table C 15 Critical appraisal of AD1117064 CUP

Study question	Response yes/no/not clear/N/A)	How is the question addressed in the study?
Was the cohort recruited in an acceptable way?	Yes	At the time of the marketing authorisation application submission data cut, 3 patients who were treated via compassionate use had data available. The same eligibility criteria as used for the pivotal AD1115611 study applied to these patients.
Was the exposure accurately measured to minimise bias?	Yes	All 3 patients treated as of the marketing authorisation application data cut-off received a single infusion.
Was the outcome accurately measured to minimise bias?	Yes	GSK has entered the patients' data onto CRFs, constructed a clinical database, and verified that the information captured on these CRFs corresponds to the information in the source documents
Have the authors identified all important confounding factors?	Yes	Results have focused on descriptive analysis of efficacy and safety for these patients
Have the authors taken account of the confounding factors in the design and/or analysis?	Yes	Relevant factors have been discussed, but due to small sample size, formal analyses were not performed
Was the follow-up of patients complete?	N/A	Two of the 3 patients are still participating in the LTFU component of AD1115611 but Year 4 data were not available by the data cut used for the AD11156111 LTFU interim CSR or the Cicalese, 2016 publication. [redacted] patient, [redacted] had low engraftment and lack of immune reconstitution, which led to reintroduction of PEG-ADA at 0.34 years post-gene therapy, initially intermittently and then continuously through the end of Year 3. The patient withdrew from LTFU prior to the Year 4

		assessment when an HLA-matched sibling donor was born, enabling a BMT. These events resulted in the decision to withdraw by the consented carers and treating physician.
How precise (for example, in terms of confidence interval and p values) are the results?	N/A	Results are descriptive as there is no comparative arm
Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence 12 questions to help you make sense of a cohort study		

9.6 Results of the relevant studies

9.6.1 Complete a results table for each study with all relevant outcome measures pertinent to the decision problem. A suggested format is given in table C9.

Table C 16 Summary of results for Pivotal Study AD1115611

Study name	ADA gene transfer into haematopoietic stem/progenitor cells for the treatment of ADA-SCID
Size of study groups	12 in the study compared with a historical control of 15 patients [Hassan, 2012]
Outcomes Primary	Survival at 3 years post-gene therapy 100% survival 3-years after Strimvelis therapy intent to treat and per protocol. Since there were no deaths, the 1-sample Log-Rank test could not be applied for comparison with the historical control.
Outcomes Secondary	Change in rate of severe infections 14 severe infections were reported in 7 patients, with the rate of infection estimated as 0.429 events per person-year of observation in the ITT Population after Strimvelis therapy, compared with 1.100 events per person-year of observation before Strimvelis therapy (p=0.005). 8 severe infections were reported between 3 months and 1 year after gene therapy, decreasing to 6 severe infections between 1 and 2 years, and none between 2 and 3 years after gene therapy. One-year change in T lymphocyte counts Plots of geometric mean CD3+ T lymphocyte counts in the ITT Population showed a clear trend to increase over time from baseline to 3 years following gene therapy (the baseline mean was influenced by a particularly high cell count for [redacted]) One-year modification of the 'systemic' metabolic defect, analysed by levels of purine metabolites in RBCs Metabolic detoxification was observed in nearly all patients in both bone marrow and peripheral blood, with 100% of patients in the ITT Population showing metabolic detoxification at Year 2 and Year 3 in both sample matrices. When detoxification data were compared against the reference value of 10%, a p-value of <0.001 was observed at all time points for both bone marrow and blood samples. One-year change in the proliferative response to polyclonal stimuli Ex vivo lymphocyte proliferation in response to a CD3 antibody stimulus increased numerically from baseline following gene therapy at the 1-, 2- and 3-year time points. Positive T cell proliferation (values >20,000 cpm) was demonstrated in response to

	stimulation with anti CD3 antibodies from Year 1 post treatment onwards. From Year 1 post gene therapy onwards, ex vivo lymphocyte proliferation in response to stimulation with PHA was increased numerically from baseline, with a positive T cell proliferation response (>100,000 cpm) demonstrated at Year 3. One-year change in thymic activity (T-cell receptor excision circles; TREC) A plot of geometric mean TREC values in the ITT Population showed increases in thymic activity over time. By Year 1 after gene therapy geometric mean and median TREC levels (159.9 and 110.5 copies/100 ng DNA, respectively) were increased relative to pre-treatment values (67.3 and 23.0 copies/100 ng DNA, respectively), and these levels remained increased with subsequent visits through Year 3. From Year 1 onwards the majority of patients consistently had TREC values at, or exceeding, 100 copies/ng DNA. Presence of genetically modified cells in the bone marrow compartment and presence of ≥10% genetically modified cells in peripheral blood lymphocytes The geometric mean percentage of genetically modified cells in peripheral blood at Year 3 was 58.4% (95% CI 46.66, 73.10) for CD3+, 0.68% (0.32, 1.42) for CD15+, 25.57% (15.88, 41.17) for CD19+, 55.95% (46.95, 66.67) for CD4+, 39.08% (14.55, 105.01) for CD56+, and 60.07 (45.04, 80.12) for CD8+ cells. Lymphocyte ADA enzyme activity The presence of lymphocyte ADA activity (≥210 nmol/h/mg) in the ITT Population was demonstrated in 4 of 10 patients (40%) at Year 1, 5 of 10 patients (50%) at Year 2 and 8 of 11 patients (73%) at Year 3. One-year change in lymphocyte counts (cells/μL) Plots of geometric mean lymphocyte counts in peripheral blood over time in the ITT Population showed a numerical increase over time between Year 1 and Year 3. In most patients, lymphocyte counts decreased between baseline and the day of gene therapy, increasing thereafter out to 3 years post-treatment. Recovery of physical growth While generally remaining below the 50th percentile, boys and girls showed increases in weight and height over the period for which data were collected. The height of [redacted], who was subsequently withdrawn from the study, remained below the third percentile at all time points. Need for reintroduction of PEG-ADA (in patients previously treated with PEG-ADA) [redacted] required reintroduction of PEG-ADA for the management of autoimmune phenomena. Antibody response to vaccination 7 patients had records of vaccinations in the 0-3 years period post-gene therapy. Of these, patients had antibodies to a range of infectious antigens at 1 or more time points after discontinuing IVIG. Detectable antibodies to pertussis, diphtheria, tetanus toxoid, and Haemophilus B were seen in [redacted], respectively, and corresponded with vaccination records. [redacted] also had evidence of antibody production to hepatitis B surface antigen post vaccination. [redacted] also had discontinued IVIG and received immunizations in Year 3, but did not have post-vaccination antibody response data available during 0-3 year follow-up. Additionally, [redacted] had detectable antibodies to hepatitis B surface antigen and tetanus toxoid without a corresponding vaccination record and was receiving IVIG at the time of antibody assessment, which may have confounded the results. One remaining patient ([redacted]) received a tick-born encephalitis vaccination 21.5 months after gene therapy but did not have antibody responses available.
Comments	[redacted] withdrew from the study at 2.3 years for BMT when an HLA-identical sibling/family member became available.

Table C 17 Summary of the interim results for AD1115611 LTFU

Study name	Long-term follow-up of ADA gene transfer into haematopoietic stem/progenitor cells for the treatment of ADA-SCID

Size of study groups	14 in the study compared with a historical control of 15 patients
Outcomes Primary	Survival 100% survival as of the data cut (May 2014). As there were no deaths, no statistical analysis of fatal events could be carried out.
Outcomes Secondary	Change in the rate of severe infections (defined as infections requiring hospitalisation or prolonging hospitalisation) Four severe infections were reported in 4 patients in the LTFU (excluding Patient 1), with the rate of infection estimated as 0.066 events per person-year of observation. There were no severe infections during Year 3. As Year 3 post-treatment was used as baseline for this LTFU report, no statistical analysis of change in the rate of severe infections from baseline was performed and a p-value could not be obtained for comparison of the follow-up infections rates with baseline. Two severe infections were reported between 4 and 5 years after gene therapy (pneumonia in [redacted] and pyoderma in [redacted]), decreasing to 1 severe infection between 6 and 7 years (Varicella in [redacted]), and 1 between 10 and 11 years after gene therapy (pneumonia in [redacted]). In addition, [redacted] had a severe urinary tract infection at Year 13. [redacted] is excluded from the analyses because data regarding severe infections before Year [redacted] were not complete in the clinical database for this patient. Change in T lymphocyte counts (cells/μL) CD3+ T lymphocyte counts were generally stable over the course of the LTFU. Overall, lymphocyte subset counts remained relatively stable over the duration of the LTFU, and statistical analysis showed no evidence of a consistent change over time compared with LTFU baseline. Modification of the 'systemic' metabolic defect, analysed by levels of purine metabolites in RBCs Geometric mean RBC dAXP levels were consistently low throughout the follow-up and remained below the pre-specified target of 100 nmol/mL in the majority of patients at all time points. Change in the proliferative response to polyclonal stimuli Robust T cell proliferation responses (exceeding 20,000 cpm) to stimulation with anti-CD3 antibody were observed at the LTFU baseline and Year 8. Similarly, positive proliferative responses (geometric mean and median values exceeding 100,000 cpm) to stimulation with PHA were observed at the LTFU baseline and Year 8. Small patient numbers may have contributed to the large variability observed at Year 8. Change in thymic activity (TREC) Geometric mean TREC levels were greater at Year 3 (LTFU baseline) than at Years 5 and 8 after gene therapy, i.e. a decrease was observed during LTFU, although levels remained above the pre-treatment levels at all LTFU time points. Small patient numbers may have contributed to the large variability observed at Year 8. Presence of genetically modified cells in the bone marrow compartment and presence of ≥10% genetically modified cells in peripheral blood lymphocytes A trend toward an increase in bone marrow CD56+ natural killer cell VCN was observed in the LTFU over time, although data were variable at Year 5. There was a similar trend in bone marrow CD34+, CD19+ and CD15+ cells, but not for CD3+ cells. These apparent trends should be considered relative to the small number of patients with data available at the later time point (Year 8). Overall, therefore, engraftment was durable over the period of follow-up. Lymphocyte ADA enzyme activity Lymphocyte ADA activity remained relatively stable over time in the LTFU with no apparent upward or downward trend. Change in lymphocyte counts (cells/μL) Statistical analysis of log-transformed data for CD3+ T lymphocyte counts showed cell counts were generally stable over 4 to 8 years, and there was no evidence of a consistent change in CD3+ cell counts over the duration of follow-up Recovery of physical growth

	Boys and girls showed increases in height and weight over the period for which data were collected, within age-appropriate ranges; although they remained generally below the 50th percentile, most patients continued to track along their original percentiles for growth. The weight of [redacted], however, was below the third percentile for most of the LTFU period. Need for reintroduction of PEG-ADA (in patients previously treated with PEG-ADA) [redacted] received treatment with PEG-ADA throughout most of the LTFU, starting on 01 September 2005 (4.4 years after gene therapy). No reason for PEG-ADA administration was recorded, but this patient, who was treated in Pilot Study 2, was considered to have an unsuccessful response to gene therapy]. PEG-ADA treatment was ongoing at the time of data cut-off. No other patient received PEG-ADA during the LTFU period. Antibody response to vaccination During the LTFU, antibodies to a range of infectious antigens were reported for 11 patients. Antibodies were generally detectable at multiple time points during the LTFU and in a number of patients, continuing from the 0–3 year follow-up, indicating long-lived antibody production.

Table C 18 Summary of results for AD1117056 Pilot 2

Study name	A summary of the safety and efficacy for the first 3 years post-gene therapy for 2 patients treated with Strimvelis
Size of study groups	2 patients
Outcomes	Survival 100% survival Change in rate of severe infections (defined as infections requiring hospitalisation or prolonging hospitalisation) No severe infections were reported between 3 months and 3 years after gene therapy: the estimate of the rate of infection is 0 events per person-year of observation after gene therapy, compared with 2.584 events per person-year of observation before gene therapy. Change in T lymphocyte counts (cells/μL) [redacted] Modification of the 'systemic' metabolic defect, analysed by levels of purine metabolites in RBCs [redacted] Change in the proliferative response to polyclonal stimuli Ex vivo lymphocyte proliferation in response to a CD3 antibody or PHA stimulus showed increases from baseline at Years 1, 2 and 3 in [redacted]. Presence of genetically modified cells in the bone marrow compartment and presence of ≥10% genetically modified cells in peripheral blood lymphocytes [redacted] Lymphocyte ADA enzyme activity [redacted] Change in total lymphocyte counts (cells/μL) [redacted] Recovery of physical growth [redacted] Need for reintroduction of PEG-ADA (in patients previously treated with PEG-ADA) [redacted] Antibody response to vaccination [redacted]
Comments	[redacted]

Table C 19 Summary of results for AD1117054 Pilot 1

Study name	Treatment, clinical course and outcomes of the first patient treated with Strimvelis
Size of study groups	1 patient
Outcomes	The patient was alive at [redacted] post gene therapy ([redacted]), at which time [redacted] entered the LTFU of Study AD1115611. [redacted]

Table C 20 Summary of results for AD1117064 CUP

Study name	Treatment and outcomes for ADA-SCID patients that received Strimvelis under compassionate use
Size of study groups	3 patients
Outcomes	Survival at 3 years post-gene therapy Survival was 100%. Change in the rate of severe infections (defined as infections requiring hospitalisation or prolonging hospitalisation) Change in the rate of severe infections (defined as those that led to or prolonged hospitalisation) showed a reduction post-treatment, although the absolute number of infections was low. Severe infections were not considered from the time of gene therapy to 3 months post gene therapy because patients were already hospitalized during that time per protocol [redacted]. Change in lymphocyte counts (cells/μL) [redacted] Cell counts generally showed a post-baseline decrease associated with busulfan conditioning and PEG-ADA discontinuation. [redacted] Modification of the 'systemic' metabolic defect, analysed by levels of purine metabolites in RBCs [redacted] Change in the proliferative response to polyclonal stimuli [redacted] While data were variable, patients showed a transient reduction in ex vivo proliferative response, consistent with cytoreduction following busulfan. Increases in proliferation in response to anti-CD3 and phytohaemagglutinin were observed in all [redacted] Change in thymic activity (TREC) No clear pattern in thymic activity (TREC) was observed. Presence of genetically modified cells in the bone marrow compartment and presence of ≥10% genetically modified cells in peripheral blood lymphocytes [redacted] Lymphocyte ADA enzyme activity [redacted] Recovery of physical growth [redacted] Need for reintroduction of PEG-ADA (in patients previously treated with PEG-ADA) [redacted] Antibody response to vaccination [redacted]

9.6.2 Justify the inclusion of outcomes in table C9 from any analyses other than intention-to-treat.

Not applicable.

9.7 Adverse events

9.7.1 Using the previous instructions in sections 9.1 to 9.6, provide details of the identification of studies on adverse events, study selection, study methodologies, critical appraisal and results.

No specific literature review was undertaken to identify studies on adverse events over and above the review described in Section 9.1 Adverse event information is provided for each study from the Strimvelis clinical programme in Appendix 7. The methodology and critical appraisal of these studies is included in Sections 9.4 and 9.5. Adverse events for the Integrated Population are provided in Section 9.8. Additionally, safety information on other gene therapies for ADA-SCID from studies identified in the literature search described in Section 9.1 is presented in Appendix 7.

9.7.2 Provide details of all important adverse events reported for each study.

Adverse events for each study in the Strimvelis clinical programme are provided in Appendix 7. Adverse events in the Integrated Population are discussed in Sections 9.7.3 and 9.8.

9.7.3 Provide a brief overview of the safety of the technology in relation to the scope.

Patient Exposure and Follow-Up

Safety data are available for 18 patients with ADA-SCID who received Strimvelis in the clinical programme. Gene therapy with Strimvelis has led to the long-term survival of 100% of the patients in the programme with median follow-up of 6.9 years and a maximum follow-up of 13 years.

Adverse Events

All 18 patients reported AEs. AEs were predominantly Grade 1 and Grade 2. The Medical Dictionary for Regulatory Activities (MedDRA) System Organ Classes (SOCs) with the most frequently reported AEs were infections and infestations, investigations, blood and lymphatic system disorders, and skin and subcutaneous tissue disorders. In each of these SOCs, the incidence rate of events per 100 patient years was greatest during phases before or during hospitalisation (pre-treatment, treatment, and 3-month hospitalisation phases) compared with the follow-up phases (3 months and later). One patient had 2 AEs

that were considered by the investigator to be possibly related to study treatment (hepatic steatosis and white blood cell analysis abnormal).

Serious Adverse Events

Fifteen patients experienced SAEs. Infections were the most frequent SAEs (device-related infections, gastroenteritis, and pneumonia). None of the SAEs were considered by the investigator to be related to study treatment.

Infections

All 18 patients reported infection AEs. The 3 most frequently reported infection AEs were normal, expected childhood infections: upper respiratory tract infection, gastroenteritis, and rhinitis [Hay, 2005]. Serious opportunistic infections, which are often observed in patients with immunodeficiencies, were not common; 1 patient each reported events of *Aspergillus* infection, gastroenteritis cryptosporidial, and pulmonary mycosis. The majority of severe infections (12 of 15) were reported during the 3-month to 3-year treatment phase, which is not unexpected as immune reconstitution occurs over time.

Busulfan-Related Adverse Events

AEs of cytopenias, elevations in transaminases and hypertension were observed post-treatment, which generally resolved over time and were likely related to busulfan conditioning.

CNS Abnormalities

Seventeen of 18 patients had a neurologic, CNS, or hearing impairment AE reported at any time during the studies (including pre-treatment). Fourteen patients had neurologic, CNS, or hearing conditions ongoing at Screening or events during the pre-treatment phase of the studies. Ten of these 14 patients also had events on or after Strimvelis gene therapy. The neurological events, including the cognitive and audiological events, observed to date in some of the patients treated with Strimvelis were similar to those observed in patients treated with BMT or PEG-ADA [Rogers, 2001; Booth, 2007].

Leukaemia

No events indicative of leukaemic transformation have been reported with Strimvelis. None of the 40 patients with ADA-SCID who have received gene therapy with either Strimvelis (n=18) or other comparable gamma retroviral vectors (n=22) with an extended follow-up period have developed leukaemia [Mukherjee, 2013].

Autoimmunity

Overall, 12 patients reported a total of 27 AEs considered potentially related to autoimmunity. Antinuclear antibody positive was the most frequently reported

event. Four patients had 6 SAEs of autoimmunity (anti-neutrophil antibody-induced neutropenia, autoimmune thrombocytopenia [2 events], autoimmune aplastic anaemia, autoimmune hepatitis, and Guillain-Barré syndrome) and 2 of these patients required reintroduction of PEG-ADA in order to attempt to restore immune function and reduce the observed autoimmunity.

Conclusion

Overall, the safety findings of Strimvelis are in line with those expected in an ADA-SCID population that has undergone busulfan conditioning and is undergoing immune reconstitution. The very common adverse drug reactions were those considered related to busulfan (anaemia, neutropenia, hepatic enzyme increased, and hypertension) and those associated with immune reconstitution (asthma, autoimmune hepatitis, dermatitis atopic, eczema, hypothyroidism, pyrexia, and rhinitis allergic). Complications specific to allogeneic BMT/HSCT (e.g., GvHD) were not observed as Strimvelis is an autologous gene therapy.

9.8 Evidence synthesis and meta-analysis

9.8.1 Describe the technique used for evidence synthesis and/or meta-analysis. Include a rationale for the studies selected, details of the methodology used and the results of the analysis.

Integrated analyses were performed for the marketing authorisation application for Strimvelis. Outcomes from the 5 studies in the Strimvelis clinical programme (AD1117054 Pilot 1, AD1117056 Pilot 2, AD1115611 Pivotal, AD1117064 CUP, and AD1115611 LTFU) have been integrated by a simple merging of all relevant studies in support of the marketing authorisation application for Strimvelis. Additional details on the integrated analyses are available in the Summary of Clinical Efficacy Section 1.5 and the Summary of Clinical Safety Section 1.1.7.

In total, 18 patients who were treated with Strimvelis as of the clinical data cut-off for the marketing authorisation application (08 May 2014) were included in the integrated analyses. Efficacy data collected after receipt of a rescue intervention (≥3 continuous months of PEG-ADA or allogeneic HSCT occurring post-gene therapy) were excluded from the analyses and data displays. This is an important difference from the data presented for the individual studies. In this integrated analysis, the decision was made to allow differentiation of any treatment effect from the effects of rescue treatment (PEG-ADA or HSCT). Data for Patient 1, the single patient enrolled in AD1117054 Pilot Study 1, from Years 0 to 12 were not included in the integrated analyses, with the exception of the date of gene therapy which was used to determine duration of follow-up, because compliance with ICH GCP standards could not be confirmed. Safety data collected for Patient 1 as part of Study AD1115611 LTFU (Year [redacted] onward) were included in the integrated safety data. Details of data handling for this patient are summarised in Summary of Clinical Safety Section 1.1.7.1.

Demographic and baseline characteristics and details of Strimvelis therapy are provided in Table C 21. The median age of subjects at the time of Strimvelis administration was 1.37 years (range 0.5 to 6.1 years). The Integrated Population included patients from a variety of races and of both sexes. Four patients had previously received an unsuccessful HSCT from a haploidentical donor, and 15 patients had previously received PEG-ADA.

Integration of comparator data is not considered feasible for reasons described in Section 9.8.2.

Table C 21 Summary of Subjects Treated in the Strimvelis Clinical Programme

Subject	GSK study	Sex	Race	Country of origin at diagnosis	Prior HSCT or PEG-ADA, duration	Age at gene therapy, yrs	GSK2696273 treatment date	GSK2696273 dose, CD34+ cells x10^6/kg	VCN of product	Follow-up duration, yrs[h]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	8.5	2.28	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.9	NR	[redacted]
			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	2.1[b]	2.15	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	6.7	0.85	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	3.8	NR	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	9.6	1.89	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	9.46	1.05	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	9.0	0.83	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	10.6	0.12	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	13.6	0.57	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	10.7	0.35	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	6.35	0.17	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	11.5	0.14	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	18.15	0.06	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	5.97	0.54	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	5.94	0.38	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	6.91	0.17	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	12.95	0.24	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	9.9	0.11	[redacted]

Abbreviations: AA = African-American/African heritage; F = female; HSCT=hematopoietic stem cell transplantation; iv = intravenous; M = male; NR = not reported; PEG-ADA = polyethylene glycol adenine deaminase; haplo-SCT = haploidentical stem cell transplant; VCN=vectory copy number.

a. [redacted] data from Years 0 to [redacted] limited to the date of gene therapy (for duration of follow-up and survival analysis) and data collected in Study AD1115611 LTFU ([redacted] onwards).
b. [redacted] received a second dose of Strimvelis that did not include busulfan pre-conditioning.
c. The Year 8 visit for [redacted] was delayed from 2013 to 2014; therefore, full data were not available at the time of the integrated analysis.
d. [redacted]
e. [redacted] his race incorrectly identified in the 0-3 year phase of AD1115611, which was later corrected as Asian in the LTFU data set.
f. [redacted] had [redacted] race incorrectly identified in the 0-3 year phase of AD1115611, which was later corrected as White/Arabic in the LTFU data set.
g. [redacted]
h. Duration of follow-up calculated from date of last assessment relative to the date of gene therapy.

9.8.2 If evidence synthesis is not considered appropriate, give a rationale and provide a qualitative review. The review should summarise the overall results of the individual studies with reference to their critical appraisal.

Apart from the integrated analyses for the Strimvelis clinical programme described above in Section 9.8.1, evidence synthesis using comparator data is not considered appropriate or methodologically possible due to the heterogeneity of the studies and their design: in particular, differences in the populations studied, the inclusion and exclusion criteria, study duration, and endpoints. Even after considering newer population-adjusted methodologies [Phillippo, 2016], a formal indirect comparison was not considered possible due to the lack of a common comparator arm, the extremely low patient numbers, and the lack of data. Specifically, the lack of information on relevant population characteristics of the studies providing information on efficacy after HSCT prevents proper accounting for all effect modifiers and prognostic factors. In addition, given the potential heterogeneity of the patients included in the literature on HSCT, it would not be correct to assume this population to be closer to the population in England than the Strimvelis Integrated Population itself.

The overall results of all studies identified in the literature search described in Section 9.1 that provided comparator information relevant to the outcomes defined in the decision scope are described qualitatively below for the purpose of indirect comparison.

For each outcome defined in the decision scope, information from the Strimvelis integrated analyses is presented followed by a qualitative description of the available literature on competitor therapies. A table showing the detail of each report will be provided for outcomes with a large number of relevant studies. Tables are divided by donor type (MUD or haploidentical) and then arranged chronologically by publication date of the reference. As many references provide information on the same cohort of patients over time, cohorts have been grouped together whenever this could be determined with older publications indented from the most recent publication. Additional overlap of the cohorts is likely, particularly for the larger registries and surveys.

Overall Survival

A 100% survival rate has been observed for all patients (N=18) who received Strimvelis treatment in the Integrated Population, with a median follow-up time of 6.9 years. The 100% survival observed compares favourably to the 67% overall survival rate following MUD HSCT reported in the historical control prespecified in the pivotal AD1115611 study and also to the 71% overall survival following haploidentical HSCT in the 2000s reported in that same reference; median follow-up for HSCT regardless of donor source was 6.5 years [Hassan, 2012]. Intervention-free survival is discussed in the next section.

Most literature reports included small numbers of patients with ADA-SCID who received HSCT from a MUD or haploidentical donor (Table 26). In cohorts of at least 5 patients, the overall survival rate following HSCT from a MUD ranged from 60% to 71% [Booth, 2007; Gaspar, 2009; Hassan, 2012; Dvorak, 2014] and following HSCT from a haploidentical donor ranged from 23% to 68% [Booth, 2007; Honig, 2007; Gaspar, 2009; Buckley, 2011; Hassan, 2012]. As survival following HSCT has improved over time, the 71% overall survival following HSCT from a haploidentical donor reported by the most recent reference for the most recent time period (2000-2009) has been used for comparison in this document; information on survival after HSCT from a MUD by time period is not available [Hassan, 2012].

Table C 22 Overall survival following HSCT from a MUD or haploidentical donor

Cohort	Donor Type	N	FU Duration[a]	% Alive at Writing	1 yr Survival	3 yr Survival	5 yr Survival	Cause of Death	Comments	Reference
Brescia, Italy *1997-2013*	MUD	4	6.5 yrs[c] (1.5-11.4)	100% (n=4)	4/4	3/3	3/3	NA	3 received conditioning and 1 did not. All BMT	Baffelli, 2015
Brescia, Italy *2002-2010*	MUD	2	20-67 mos	100% (n=2)	2/2	1/1	1/1	NA	Both received conditioning	Serana, 2010
Brescia, Italy *no date*	MUD	1	-	100% (n=1)	-	-	-	NA		Booth, 2007
PIDTC/ IEWP-EBMT Survey *1993-2012*	MUD	7	2.5 (1.1-12.3) yrs for survivors (n=5)	71% (n=5)	-	-	-	Ongoing parainfluenza (n=1), ongoing neuro (n=1)	No conditioning, 1 BMT and 6 cord blood	Dvorak, 2014
ESID Survey *1981-2009*	MUD	15	6.5 yrs for all donors	67%	-	-	-	-	3 were no conditioning	Hassan, 2012
SCETIDE *1968-2009/* **Italy/Canada** *1990-2009*	MUD	11	-	-	67%	-	-	-		Gaspar, 2009

Cohort	Donor Type	N	FU Duration[a]	% Alive at Writing	1 yr Survival	3 yr Survival	5 yr Survival	Cause of Death	Comments	Reference
Italy/ Canada *1990-2004*	MUD	2	3-11 mos	50% (n=1)	NA	NA	NA	Pulmonary alveolar proteinosis (n=1)		Grunebaum, 2006
Texas *1998-2007*	MUD	1	30 mos	100%	1/1	NA	NA	NA	HSCT with conditioning at 53 mos. Alive and in elementary school at 7 years of age	Patel, 2009
London *no dates*	MUD	5	-	60% (n=3)	-	-	-	-		Booth, 2007
London *no dates*	MUD	1	2.3yrs	100% (n=1)	1/1	NA	NA	NA	With conditioning	Albuquerque, 2004
London *no dates*	MUD	2	0.3-2.8yrs	100% (n=2)	1/1	NA	NA	NA	With conditioning	Rogers, 2001
London *no dates*	MUD	1	1 yr	100% (n=1)	1/1	1/1	1/1	NA	With partial conditioning	Amrolia, 2000
Germany *1982-2006*	MUD	2	mean 14.6 yrs (4.6-22.2) among survivors in a larger group	50% (n=1)	1/2	1/2	-	CMV, adenovirus (n=1)		Honig, 2007

Cohort	Donor Type	N	FU Duration[a]	% Alive at Writing	1 yr Survival	3 yr Survival	5 yr Survival	Cause of Death	Comments	Reference
Case report *9 mo old boy, Toronto, 1991-2007*	MUD	1	2.5 mos	0%	NA	NA	NA	Respiratory insufficiency and multiorgan failure		Nofech-Mozes, 2007
Newcastle *2000-2004*	MUD	3	-	67% (n=2)	-	-	-	-	Umbilical cord blood transplants only, conditioning in 1	Bhattacharya, 2005
Newcastle *1987-1998*	MUD	1	3.5yrs	100% (n=1)	1/1	1/1	NA	NA	BMT with conditioning	Gennery, 2001
ESID Survey *1981-2009*	Haplo[d]	30	6.5 yrs for all donors	43%	-	-	-	-	Survival by decade: 40% (n=20) before 1991, 0% (n=3) 1991-2000, and 71.4% (n=7) 2000-2009 6 patients did not have conditioning	Hassan, 2012
Duke *1982-2010*	Haplo	19	1.5-25.8 yrs	68% (n=13)	-	-	-	-	None	Buckley, 2011
Duke *1984-2006*	Haplo	19	-	74% (n=14)	-	-	-	Viral infections (n=4); pulmonary hypertension (n=1)		Booth, 2007

Cohort	Donor Type	N	FU Duration[a]	% Alive at Writing	1 yr Survival	3 yr Survival	5 yr Survival	Cause of Death	Comments	Reference
Duke *1981-2000*	Haplo	13	1.1-17.5 yr	77% (10/13)	-	-	-	-		Buckley, 2000
SCETIDE *1968-2009/* **Italy/Canada** *1990-2009*	MMFD (mainly haploidentical)	30	-	-	43%	-	-		Majority of deaths occurred in first few mos after HSCT	Gaspar, 2009
London *no dates*	Haplo	13	-	23% (n=3)	-	-	-	-		Booth, 2007
London *no dates*	Haplo	3	13.3–19.5yrs	100% (n=3)	3/3	3/3	3/3	NA		Albuquerque, 2004
London *no dates*	Haplo	2	12.9-17.5yrs	100% (n=2)	2/2	2/2	2/2	NA	1 with conditioning	Rogers, 2001
Germany *1982-2006*	Haplo	6	mean 14.6 yrs (4.6-22.2) among survivors in a larger group	67% (n=4)	4/6	4/6	-	Aspergillosis (n=2)	2 PBSC, 4 BMT	Honig, 2007
Paris *no dates*	Haplo	4	-	0%	-	-	-	-		Booth, 2007
Netherlands *1968-1997*	Haplo	1	15.1 yrs	100% (n=1)	1/1	1/1	1/1	NA	With conditioning	Borghans, 2006

Cohort	Donor Type	N	FU Duration[a]	% Alive at Writing	1 yr Survival	3 yr Survival	5 yr Survival	Cause of Death	Comments	Reference
Case Report *8 year old girl, Los Angeles, no date*	Haplo	1	40 days	0%	0/1	0/1	0/1	EBV-associated leiomyomatosis and polymorphic lymphoproliferative disorder, adenovirus, cryptosporidium		Monforte-Muñoz, 2003
Newcastle *1987-1998*	Haplo	1	10.5 yrs	100% (n=1)	1/1	1/1	1/1	NA		Gennery, 2001

Abbreviations: -=not reported; BMT=bone marrow transplant; CMV=cytomegalovirus; EBV=Epstein-Barr virus; ESID=European Society of Immunodeficiency Diseases; FU=follow-up; Haplo=haploidentical; HSCT=haematopoietic stem cell transplantation; IEWP-EBMT=Inborn Errors Working Party of the European Blood and Marrow Transplant Society; MMFD=mismatched family donor; mos=months; MUD=matched unrelated donor; NA=not applicable; PBSC=peripheral blood stem cells; PIDTC=Primary Immune Deficiency Treatment Consortium; SCETIDE=stem cell transplantation for immunodeficiencies; tx=treatment; wks=weeks; yr=year

a. Reported as median and/or range unless otherwise noted.
b. Presented as number alive over number followed for at least 1, 3, and 5 years, respectively, including previous deaths, or % survival if presented in paper as such.
c. Median calculated from data
d. Haploidentical donors were antigen mismatched at >2 loci.

Intervention-Free Survival

Intervention-free survival was defined in the Strimvelis clinical programme as survival without post-gene therapy PEG-ADA use for a continuous period of ≥3 months, SCT, or death. No deaths have occurred in the Strimvelis clinical programme. Intervention-free survival represents a sensitivity analysis of the overall survival rate.

Three patients ([redacted] from the AD1115611 Pivotal study, [redacted] from the AD1117056 Pilot 2 study, and [redacted] from the AD1117064 CUP) required long-term PEG-ADA post-gene therapy. Two patients ([redacted] from the AD1115611 Pivotal study and [redacted] from the AD1117064 CUP) each received a post-gene therapy HLA-matched sibling donor HSCT, both of whom had started continuous PEG-ADA prior to withdrawing from their respective study to receive a SCT.

- [redacted]
- [redacted]
- [redacted]

Therefore, 14 of 17 patients (82%) with available data were considered to have met the criteria for intervention-free survival by the time of data cut-off. One patient treated in a pilot study did not have PEG-ADA re-introduction data, and thus was excluded from the intervention-free survival in the Integrated Population. The 82% intervention-free survival rate in the Integrated Population compares favourably to the 67% overall survival rate following MUD HSCT and the 71% overall survival rate following haploidentical HSCT reported by Hassan et al [Hassan, 2012].

Intervention-free survival, defined as survival without receipt of a post-gene therapy SCT or ≥3 months continuous PEG-ADA, was only reported in the Strimvelis clinical programme. Comprehensive reference data on intervention-free survival following HSCT are not available; however, when reported in the literature, information on subsequent treatments after HSCT is provided here. The 82% intervention-free survival rate observed in the Strimvelis integrated population compares favourably to the calculated intervention-free survival for all reports from HSCT from a MUD or haploidentical donor. Interpretation of the information is limited as a standard definition of intervention-free survival is not being used and information, such as follow-up PEG-ADA use, may be missing from the literature references.

None of the 7 patients in the PIDTC/IEWP-EBMT survey with ADA-SCID treated with HSCT without conditioning from a MUD received a second HSCT. PEG-ADA use was not reported. The survival in this cohort was 71% [Dvorak, 2014].

The 67% overall survival for MUD HSCT (N=15) percentage reported by Hassan et al includes one patient (7%) who required a second transplant. The 71% (5/7) overall survival for haploidentical HSCT percentage reported by Hassan et al for

procedures performed in the 2000s includes 1 patient who proceeded to receive gene therapy and 1 patient who received long-term PEG-ADA, required a second HSCT from a new matched sibling donor, and subsequently died. Therefore, intervention-free survival, defined as survival without GT or further HSCT, was 42.9% for haploidentical SCT performed in the 2000s in this cohort. In addition, Hassan et al reported 52% overall survival among 52 children who received transplants from donor sources other than matched siblings or family members. Nine of these patients went on to receive at least one additional transplant, indicating that less than half of patients receiving non-sibling/family matched HSCT survived the transplant procedure without the need for additional intervention. Note that Hassan et al did not report on patients (if any) who required reintroduction of PEG-ADA in addition to repeat transplantation [Hassan, 2012].

New techniques have been explored, but outcomes reported in the literature since 2000 for patients with ADA-SCID have not been superior to normal transplant techniques. Of 19 patients treated with HSCT without conditioning from T-cell depleted haploidentical parental marrow between 1984 and 2006 at Duke, 14 (74%) survived and 5 of those went on to receive continuous PEG-ADA while awaiting gene therapy; however, the exact length of PEG-ADA treatment was not reported. Two additional patients subsequently received GT. This would equate to an intervention-free survival rate of 36.8% (7 of 19) if intervention-free survival was defined as survival without receipt of post-therapy PEG-ADA or GT. Follow-up duration was not reported [Booth, 2007]. Results were also reported for the same centre at earlier timeframes [Buckley, 2000; Booth, 2007]. No other sources reported information on PEG-ADA use or subsequent treatment after HSCT from a MUD or haploidentical donor for patients with ADA-SCID.

Immune Function

Rate of Severe Infections

The rate of severe infections (defined as those that led to hospitalisation or prolonged hospitalisation) for the Strimvelis Integrated Population before gene therapy was compared with the rate after gene therapy (not including the 3-month period after gene therapy during which patients were already hospitalised). The rates of severe infections were reduced post-gene therapy (0.26 for 4 months to 3 years and 0.17 through 8 years of follow-up) when compared with the pre-gene therapy period (1.17). The pre- gene therapy infections may have been under-reported as they were collected as part of the patient history and screening (including carer-recalled infections from birth up to the time of gene therapy) rather than prospectively reported.

A total of 15 severe infections were reported after Strimvelis treatment and most of these infections (12/15 events) occurred during the 3-year follow-up, which is not unexpected as immune reconstitution occurs over time and because patients' CVCs (which can become infected) remained in place long-term during the 0-3 years follow-up period. All severe infections in the Strimvelis programme were reported as resolved.

The most frequently reported severe infections were device-related infections (n=5) and gastroenteritis (n=3); the device-related infections were expected due to long-term placement of CVCs, and gastroenteritis is a common childhood illness. Of note, 2 patients reported Varicella infection ([redacted]) and one patient had Staphylococcal sepsis ([redacted]).

Table C 23 Summary of severe infections pre- and post-gene therapy (Integrated Populations)

	Integrated Population[a] (N=18)	
	Pre-GT	**Post-GT[b]**
N[a]	17	17
Number of patients with events, n (%)	14 (82)	10 (59)
Number of events		
Total	40	15
4 months to 3 years follow-up[b]		12
4 to 8 years follow-up		3
Person-years of observation (free from infection)		
Total	34.30	89.23
4 months to 3 years follow-up[b]		45.81
4 to 8 years follow-up		43.42
Rate of infection[c]		
Total	1.17	0.17
4 months to 3 years follow-up[b]		0.26
4 to 8 years follow-up		0.07
Number of occurrences per patient, n (%)		
n	14	10
1	4 (29)	7 (70)
2	4 (29)	1 (10)
≥3	6 (43)	2 (20)

Abbreviations: GT = gene therapy.

Note: Only data collected prior to PEG-ADA intervention (≥3 months of treatment with PEG-ADA) are included.

a. [redacted] (Pilot 1 Study) is excluded from this analysis as this patient's data regarding severe infections prior to Year 13 are not included in the clinical database.

b. Excludes 3-month hospitalisation period post-gene therapy.

c. Rate of infection estimated as number of infections over person-years of observation (free from infection)

Severe infections, defined as infections that led to or prolonged hospitalisation, were not clearly reported by that definition in the available literature for HSCT. However, infections that were reported in the literature for HSCT are discussed below under adverse events and provided in Table C 28. Several infections, including infections resulting in deaths, were reported but details were limited in many cases and not enough information was provided to determine a severe infection rate after HSCT.

Lymphocyte Counts

In the Strimvelis clinical programme, lymphocytes in general and CD3+ T cell counts in particular were increased compared to baseline. This clinically relevant increase was demonstrated from Year 1 post-treatment and maintained throughout the duration of follow-up (Table C 24). In contrast, changes from baseline were variable for CD19+ B cells and CD16+ CD56+ NK cells, with counts for both cell types decreasing from baseline to Year 1 and then increasing above the Year 1 counts from Year 2 onwards. As per the marketing authorisation application , cell counts were log transformed for analysis because the data violated assumptions of normality. In the pivotal AD1117054 study, CD3+ cells increased from a median (range) of 88.0 x 10^6/L (19-2718 x 10^6/L) at baseline to 828 x 10^6/L (309-2458 x 10^6/L) at 3 years after gene therapy.

Table C 24 Summary statistics for log-transformed lymphocyte subsets

Cell marker Visit	Integrated Population (N=18)		
	n	Geo mean (95% CI), x10^6/L	Median (min-max), x10^6/L
CD3+			
Baseline	15	146.4 (53.1, 403.3)	88.0 (19-5708)
Month 6	16	207.5 (133.9, 321.7)	219.5 (41-580)
Year 1	15	473.8 (336.6, 666.9)	502.0 (139-1929)
Year 2	15	664.0 (478.2, 921.9)	591.0 (222-2034)
Year 3	14	774.2 (485.0, 1235.7)	859.5 (124-2768)
Year 4	10	673.1 (467.6, 969.0)	604.5 (317-1480)
Year 5	10	802.3 (525.0, 1226.1)	816.0 (266-1844)
Year 6	6	1478.3 (825.0, 2649.1)	1325.5 (658-2911)
Year 7	6	907.3 (393.5, 2092.0)	1097.0 (203-1738)
Year 8	3	1214.5 (728.7-2024.1)	1356.0 (958-1379)
CD19+			
Baseline	15	114.8 (40.4, 326.3)	213.0 (1-488)
Month 6	16	18.6 (10.2, 34.1)	22.5 (0-95)
Year 1	15	50.7 (31.0, 83.1)	55.0 (10-221)
Year 2	15	69.0 (37.6, 126.6)	86.0 (5-252)
Year 3	14	72.7 (30.5, 173.4)	86.0 (1-380)
Year 4	10	65.8 (22.9, 188.9)	67.5 (2-542)
Year 5	10	54.9 (16.9, 177.6)	56.5 (0-318)
Year 6	6	112.4 (53.3, 237.3)	85.0 (51-335)
Year 7	6	72.1 (13.9, 372.8)	141.5 (3-161)
Year 8	3	176.6 (52.9, 589.1)	136.0 (131-309)
CD16+CD56+			
Baseline	15	60.6 (34.4, 107.0)	58.0 (10-341)
Month 6	16	16.6 (6.7, 41.2)	18.5 (0-173)
Year 1	15	27.0 (14.5, 50.2)	24.0 (2-237)
Year 2	15	51.0 (29.3, 88.8)	51.0 (5-210)
Year 3	14	52.9 (22.9, 122.5)	70.5 (3-540)
Year 4	10	41.1 (13.0, 129.7)	35.5 (1-261)
Year 5	10	40.4 (11.0, 147.8)	72.5 (2-368)
Year 6	6	138.7 (28.6-672.3)	178.5 (20-1349)
Year 7	6	126.0 (44.1, 360.5)	105.5 (41-680)
Year 8	3	109.9 (33.8, 356.7)	108.0 (69-178)

Abbreviations: CI = confidence interval; Geo mean = geometric mean; max = maximum; min = minimum; NK=natural killer.

Note: An imputation was applied to any value where the observed value=0 in order to log-transform the data.

CD16+ CD56+ NK cell data were not reported separately for Pivotal population.

Cell counts from the available literature in patients with ADA-SCID after HSCT from a MUD or haploidentical donor are presented in Table C 25. Interpretation of the literature search results is limited by differences in the method (cell counts versus number normal) and timing of reporting as well as whether data are reported for all patients or only survivors. In general, many but not all patients with ADA-SCID were able to achieve normal cell counts after HSCT from a MUD or haploidentical donor. As a comparison, at the time of last follow-up in the Hassan et al report [Hassan, 2012] (median of 6.5 years regardless of SCT donor source), the total lymphocytes; CD3+, CD4+, and CD8+ T cell counts; and CD19+ B cell counts for all donors were similar to those observed in the Strimvelis programme after a median follow-up of 6.9 years.

Table C 25 Immune function after HSCT from a MUD or haploidentical donor

Cohort	Donor Type	N	FU Duration[a]	CD3+ (cells/ mm^3)[b] # normal	CD4+ (cells/ mm^3)[b] # normal	CD8+ (cells/ mm^3)[b] # normal	CD19 (cells/ mm^3)[b] # normal	NK cells (cells/ mm^3)[b] # normal	TREC (copies/ 100 ng)[b] # normal	# not on IVIG	Vaccination Response	Reference
Brescia, Italy *1997-2013*	MUD	4	6.5 yr[c] (1.5-11.4)	- (2/4)	-	-	- (3/4)	-	(1/4)	3/4	3 yes, 1 NA	Baffelli, 2015
Brescia, Italy *2002-2010*	MUD	2	20-67 mos	- (0/2)	-	-	- (2/2)	-	0/2	1/2	1/1	Serana, 2010
PIDTC/ IEWP-EBMT Survey *1993-2012*	MUD	5	2.5 (1.1-12.3) yrs	1328 (assessed for survivors only, n=5/7)	506 (assessed for survivors only, n=5/7)	613 (assessed for survivors only, n=5/7)	47 (assessed for survivors only, n=5/7)	98 (assessed for survivors only, n=5/7)	-	2/5 (assessed for survivors only, n=5/7)	-	Dvorak, 2014
ESID Survey *1981-2009*	MUD	7	6.5 yrs for all donors	71% >1000 at 2 yrs	86% >300 at 2 yrs	-	mean ~100	-	-	5/7	-	Hassan, 2012
Texas *1998-2007*	MUD	1	30 mos.	1,851 (1/1)	-	-	-	-	-	1/1	1/1	Patel, 2009
Germany *1982-2006*	MUD	1	3.2 yrs	1,580 (assessed for survivor only, n=1/2)	850 (assessed for survivor only, n=1/2)	500 (assessed for survivor only, n=1/2)	470 (assessed for survivor only, n=1/2)	-	-	1/1 (assessed for survivor only, n=1/2)	1/1 Tet/Dip assessed for survivor only, n=1/2)	Honig, 2007

Cohort	Donor Type	N	FU Duration[a]	CD3+ (cells/ mm^3)[b] # normal	CD4+ (cells/ mm^3)[b] # normal	CD8+ (cells/ mm^3)[b] # normal	CD19 (cells/ mm^3)[b] # normal	NK cells (cells/ mm^3)[b] # normal	TREC (copies/ 100 ng)[b] # normal	# not on IVIG	Vaccination Response	Reference
Canada/ Italy *1990-2004*	MUD	1	11 mo	-	-	-	-	-	-	-	Pos Tet/Pol/ Hep B (assessed for survivors only, n=1 of 2)	Grunebaum, 2006
Newcastle *2000-2004*	MUD	1	-	-	-	-	-	-	-	1/1 (assessed for survivor only, n=1 of 3)	1/1 Tet/Hb (assessed for survivor only, n=1 of 3)	Bhattacharya, 2005
Newcastle *1987-1998*	MUD	1	3.5 yrs	Overall T count low	Overall T count low	Overall T count low	-	-	-	1/1	-	Gennery, 2001
London *no dates*	MUD	1	1 yr.	~700 – 800	~350 – 400	~300 – 400	~200	-	-	-	-	Amrolia, 2000
ESID Survey *1981-2009*	Haplo	9	6.5 yrs for all donors	63% at 2 yrs	100% at 2 yrs	-	mean ~400	-	-	7/7	-	Hassan, 2012
Germany *1982-2006*	Haplo	4	20.9 yrs[c] (4.4-21.5 yrs)	1895[d] (3/3)	1035[d] (3/3)	660[d] (3/3)	260[d] (3/3)	-	-	4/4	4/4 Tet/Dip	Honig, 2007
Newcastle *1987-1998*	Haplo	1	10.5 yrs	Overall T count low	Overall T count low	Overall T count low	Overall low B-cell	-	-	1/1		Gennery, 2001

Abbreviations: -=not reported; DIP=diphtheria; ESID=European Society of Immunodeficiency Diseases; FU=follow-up; Haplo=haploidentical; Hb= Haemophilus influenzae type b; Hep B=hepatitis B; HSCT=haematopoietic stem cell transplantation; IEWP-EBMT=Inborn Errors Working Party of the European Blood and Marrow Transplant Society; mos=months; MUD=matched unrelated donor; NA=not applicable; PIDTC=Primary Immune Deficiency Treatment Consortium; pol=polio; TET=tetanus; yr=year

a. Reported as median and/or range unless otherwise noted.
b. Most recent values reported unless otherwise specified. Mean or median as reported in the literature.
c. Median calculated from data
d. Median calculated from 4 children with reported values. Age-appropriate normal range was only reported for 3 children; therefore, number normal is based on 3 children.

Thymopoiesis

T cell receptor excision circles (TREC) are DNA fragments formed in T cells during the T cell receptor generation which occurs during the development of T cells in the thymus. They are non-replicative; thus, when immune cells divide in response to antigen the TREC do not. For this reason, their presence in peripheral blood T cells is a useful marker of thymic activity (i.e., production of newly formed naïve CD45RA+ T cells). The contribution of the thymus to immune development in adults has historically been unclear; however, an age-related decrease in thymus size and activity is expected as children approach adolescence and the thymus atrophies [den Braber, 2012].

In the pivotal AD1115611 population, the between-patient variability in thymic activity (as measured using TREC) observed at baseline was likely due to the fact that all patients were receiving PEG-ADA prior to gene therapy, which has been reported to have a variable effect on thymopoiesis [Booth, 2007; Malacarne, 2005; Gaspar, 2006]. TREC in peripheral blood lymphocytes were increased above baseline from Years 1 to 3 post-treatment, and gradually declined (though remained greater than baseline) at Years 5 and 8. The majority of patients had TREC values at or exceeding 100 copies/ng DNA, up to approximately 1000 copies/ng DNA. These post-gene therapy values are broadly in line with those reported for healthy age-matched children, and are in contrast with TREC levels in children with SCID which are generally very low or below the limit of detection [Morinishi, 2009; Somech, 2011]. Furthermore, by Year 1, naïve T cell (CD4+ CD45RA+) counts were increased relative to pre-treatment counts and were consistent over the duration of follow-up, providing further evidence of robust T cell function after gene therapy. A similar trend was observed in the Integrated Population.

The increase in TREC observed beginning at Year 1 after gene therapy corresponds with increased T cell counts from Year 1 onwards, in particular the emergence of increased numbers of peripheral CD4+ CD45RA+ naïve T cells that are the product of thymic selection and successful recombination of T cell receptor chains in thymocyte precursors from the bone marrow. It also is in line with the decline in severe infection rates from Year 1 onwards after gene therapy. Additionally, some of the apparent decrease in TREC at later time points may not be unexpected in the context of the normal physiology of the thymus associated with aging. Together, these endpoints are supportive of a strong T cell-mediated immune system following gene therapy.

Two references reported information from the same centre on TREC levels in patients with ADA-SCID following HSCT from a MUD [Serana, 2010; Baffelli, 2015]. In the most recent reference, TREC levels were normal in 1 of 4 patients. No references reported information on TREC levels in patients with ADA-SCID following HSCT from a haploidentical donor (Table C 25).

Use of Intravenous Immunoglobulin (IVIG)

In the Strimvelis Pivotal Population (AD1115611), all 12 patients were receiving IVIG replacement at the time of screening, and all received post-gene therapy maintenance IVIG. Seven patients ([redacted]) were able to discontinue IVIG replacement during the 0-3 years follow-up. Nine of 12 patients (75%) had discontinued IVIG replacement therapy at the time the data cut-off date (08 May 2014). Two patients ([redacted]) continued to receive maintenance IVIG and one additional patient ([redacted]) who had an unsuccessful response to gene therapy received IVIG replacement until withdrawal from the study to [redacted]. Thus, replacement IVIG use declined as follow-up progressed in Years 4 to 8 after gene therapy, providing evidence for functional B cell and immunoglobulin production in the periphery.

Supportive studies for Strimvelis were similar with regard to IVIG use pre- and post-gene therapy. Both patients in Pilot Study 2 (AD1117056) received IVIG replacement therapy at the time of screening, which was stopped for [redacted] within 18 months of gene therapy. However, [redacted], who had an unsuccessful response to gene therapy, has continued to receive IVIG throughout the duration of follow-up. In the CUP (AD1117064), [redacted] had reported IVIG therapy ongoing at screening, which continued during post-gene therapy 0-3 years follow-up, and was ongoing as of the clinical data cut-off (08 May 2014). Replacement IVIG use for [redacted] was reported to begin 3 days post-gene therapy and was discontinued by approximately 18 months post-gene therapy.

Discontinuation of IVIG reported in the literature for patients with ADA-SCID after HSCT from a MUD or haploidentical donor is presented in Table C 25. Hassan et al evaluated IVIG discontinuation and reported that among survivors of MUD transplant with available data (N=7), all but 2 had discontinued IVIG after HSCT following normalization of serum immunoglobulin production. IVIG discontinuation was also reported for 7 of 7 survivors after HSCT from a haploidentical donor [Hassan, 2012]. Note that the timing of post-transplant IVIG discontinuation in this historical reference was not given, and the median time of follow-up post-HSCT was 6.5 years (cited for all HSCT recipients regardless of donor source). These data were also reported only for the surviving HSCT recipients, whereas in the Strimvelis programme all gene therapy recipients (100%) are survivors. In the most recently reported survey, 2 of 5 survivors (excludes 2 patients who died) were able to discontinue use of IVIG after HSCT from a MUD [Dvorak, 2014].

Vaccination Response

In the Strimvelis AD1115611 Pivotal Population, a majority of patients had antibodies to a range of infectious antigens at one or more time points after IVIG had been stopped, reflective of B cell antibody forming capacity after gene therapy. Among the 9 patients who discontinued IVIG therapy post-gene therapy, detectable antibodies to pertussis, tetanus toxoid, and hepatitis B surface antigen

were seen in 9, 9, and 7 patients, respectively, and corresponded with vaccination records for these patients with the exception of [redacted], for whom vaccination records were not available. [redacted] also had detectable antibodies to diphtheria and Haemophilus B. [redacted] had a record of receiving live attenuated measles mumps rubella (MMR) vaccination and had detectable antibodies post-vaccination. Antibodies were generally detectable at multiple time points during follow- up, and in a number of patients were continuing from the 0-3 years follow-up, suggesting long-lived antibody production.

Detectable antibodies to infectious antigens were also reported for patients in the supportive studies. In Pilot Study 2 (AD1117056), [redacted] demonstrated durable antibody forming capacity to diphtheria, tetanus toxoid, and hepatitis B vaccinations after IVIG was stopped, and was also able to mount a robust response to Haemophilus B vaccination. This patient also had a record of detectable rubella and rubeola antibodies after vaccination for MMR that remained stable 3 years after immunization without further booster. Antibody forming capacity following vaccination was also observed in the one CUP patient ([redacted]) with vaccination and antibody response data available after IVIG discontinuation. This patient had antibodies detected to diphtheria, pertussis, Haemophilus B, and tetanus toxoid at 10 months post-vaccination that remained stable 1 year later with no further booster.

Detailed information on vaccine response after HSCT from a MUD is not available, but successful vaccine response has been reported in a few patients [Bhattacharya, 2005; Grunebaum, 2006; Honig, 2007; Patel, 2009; Baffelli, 2015] (Table C 25). Vaccine response after HSCT from a haploidentical donor has not been reported in the literature.

Non-Immunological Aspects of ADA-SCID (Including Neurological and Developmental Effects)

A manual MedDRA query for neurologic, CNS, and hearing AEs showed 17 of the 18 patients in the Strimvelis programme had events during treatment or post-treatment ([redacted] had no events), and many patients reported events pre-treatment. The most frequently reported event was cognitive disorders (5 patients). The other events reported in more than 1 patients were deafness (2 patients), bilateral deafness (2 distinct patients to those reporting ‘deafness’), and psychomotor hyperactivity (3 patients). A standardized MedDRA query for hearing impairment identified 9 patients with 12 AEs during treatment or post-treatment, with the median time to onset being 2.90 years (range 0.16 to 12.47). Fourteen of the 17 patients with neurologic, CNS, or hearing events on or after gene therapy had either relevant conditions ongoing at Screening or events during the pre-treatment phase. Nine of these 10 patients were on PEG-ADA prior to gene therapy. It is noteworthy that parental consanguinity was reported in 9 of 18 patients.

Similarly, presence of sensori-neural deafness and neurological and behavioural abnormalities has been consistently reported among patients treated with BMT [Booth, 2007]. The neurological events present at baseline and observed in

LTFU in the Strimvelis programme are similar to those observed in patients treated with BMT [Rogers, 2001] in which BMT does not appear to prevent the appearance of these events. Like BMT, Strimvelis was not expected to impact neurological events as evidenced by the finding of these events at baseline and throughout the LTFU. These events may be directly related to the underlying disease of ADA-SCID, comorbidities (e.g., Arnold Chiari malformation), to infections that patients may have experienced (e.g., meningitis, otitis media) or to other medications received (e.g., antibiotics such as gentamycin).

Development of a functional immune system and a decrease in severe infection rates are both critical to ongoing physical growth. The majority of treated children in the Strimvelis clinical programme either maintained or improved their age-appropriate height and weight relative to standard curves, but several had height or weight measures that transiently fell below their individual growth curves at a few time points. Shifts in growth from above the fifth percentile to below this threshold were uncommon.

Information on quality of life (QoL) measures, including school attendance, is presented in Section 10.1.3.

Further effects of HSCT from a MUD or haploidentical donor on the non-immunological aspects of ADA-SCID have not been systematically described. Reports of neurological events and developmental/growth delays in the literature are provided in Table C 26.

Table C 26 Non-immunological aspects of ADA-SCID (including neurological and developmental effects) after HSCT from a MUD or haploidentical donor

				Number of subjects (% of subjects)										
Cohort	**Donor Type**	**N**	**FU Duration[a]**	**Neurologic**	**Hyperactivity**	**Motor function**	**Hearing**	**Seizure**	**Cognitive function/ learning**	**Behavioural/ emotional**	**Developmental / Growth**	**Specific Conditions (If Reported)**	**Comments**	**Reference**
Germany *1982-2006*	MUD	1	3.2 yrs.	0	0	0	0	0	0	-	-		Only assessed in long term survivors (n=1 of original 2)	Honig, 2007
Italy/ Canada *1990-2004*	MUD	1	11 mos	0	-	-	-	-	-	-	-			Grunebaum, 2006
London *(no dates)*	MUD	1	2.3 yrs	-	-	-	0	-	-	-	-			Albuquerque, 2004

				Number of subjects (% of subjects)										
Cohort	**Donor Type**	**N**	**FU Duration[a]**	**Neurologic**	**Hyperactivity**	**Motor function**	**Hearing**	**Seizure**	**Cognitive function/ learning**	**Behavioural/ emotional**	**Developmental / Growth**	**Specific Conditions (If Reported)**	**Comments**	**Reference**
Germany *1982-2006*	Haplo	4	20.9 yrs[b] (4.4-21.5 yrs)	2 (50)	1 (25)	2 (50)	2 (50)	0	2 (50)	-	-	Reduced expressive speech (n=1), attention deficit (n=2), hyperactivity (n=1), learning disability (n=2, generalized muscular hypertonia (n=1), fine motor and coordination deficit (n=1)		Honig, 2007
Netherlands *1968-1997*	Haplo	1	15.1 yrs	1 (100)	-	-	-	-	1 (100)	-	-	Spastic diplegia, retardation, and learning problems		Borghans, 2006

				Number of subjects (% of subjects)										
Cohort	**Donor Type**	**N**	**FU Duration[a]**	**Neurologic**	**Hyperactivity**	**Motor function**	**Hearing**	**Seizure**	**Cognitive function/ learning**	**Behavioural/ emotional**	**Developmental / Growth**	**Specific Conditions (If Reported)**	**Comments**	**Reference**
London *(no dates)*	Haplo	3	13.3-19.5 yrs	-	-	-	3 (100)	-	-	-	-	Requires hearing aids (n=1); moderate to severe deafness (n=1); moderate high frequency deafness (n=1)		Albuquerque, 2004

Abbreviations: -=not reported; FU=follow-up; Haplo=haploidentical; HSCT= hematopoietic stem cell transplant; mos=months; MUD=matched unrelated donor; yr=year

a. Reported as median and/or range unless otherwise noted.
b. Median calculated from data.

Need and Duration of In-Patient Treatment
In the Strimvelis clinical programme, patients were hospitalised for a median of 45 days (range: 34 to 110 days) after receipt of gene therapy, and we expect that patients who receive Strimvelis in the future will be hospitalised for a similar period (average 50 days).

The UK Stem Cell Strategy Oversight Committee guidelines on Unrelated Donor Stem Cell Transplantation in the UK states that recovery from HSCT typically takes 4-8 weeks as an inpatient [NHS, 2014].

Adverse Effects of Treatment
As would be expected given the nature of the disease under study, all patients in the Strimvelis clinical programme experienced an AE on or after gene therapy (Table C 27). The MedDRA SOCs with the most frequently reported AEs were infections and infestations, investigations, blood and lymphatic system disorders, and skin and subcutaneous tissue disorders. For each of these SOCs, the AE density (exposure adjusted incidence of events per 100 patient years) for the SOC was greatest during a phase before (pre-treatment phase) or during hospitalisation (treatment and 3-month hospitalisation phases) compared with the AE densities recorded for follow-up phases beginning 3 months post Strimvelis gene therapy and later. The timing suggests that the infection AEs observed are related to the low-dose chemotherapy conditioning provided before Strimvelis and immune reconstitution within the first 3 months after administration of Strimvelis.

Due to the autologous nature of Strimvelis, no GvHD AEs were observed.

Table C 27 Summary of adverse events reported in 3 or more patients, by System Organ Class and Preferred Term (Integrated Population)

System Organ Class Preferred Term, (data presented as n [%])	Pre-Treatment (N=17)	Treatment (N=17)	3-Month Hospitali-sation (N=17)	3 Months to 3 Years Follow-up (N=17)	4-7 Years Follow-up (N=13)	≥8 Years Follow-up (N=6)	Total (N=18)
Infections and infestations	12 (71)	2 (12)	14 (82)	17 (100)	12 (92)	5 (83)	18 (100)
Upper respiratory tract infection	1 (6)	0	3 (18)	8 (47)	5 (38)	1 (17)	12 (67)
Gastroenteritis	2 (12)	0	2 (12)	8 (47)	2 (15)	0	10 (56)
Rhinitis	2 (12)	0	0	8 (47)	3 (23)	0	9 (50)
Bronchitis	0	0	1 (6)	5 (29)	3 (23)	0	6 (33)
Device-related infection	0	0	3 (18)	4 (24)	0	0	6 (33)

System Organ Class Preferred Term, (data presented as n [%])	Pre-Treatment (N=17)	Treatment (N=17)	3-Month Hospitali-sation (N=17)	3 Months to 3 Years Follow-up (N=17)	4-7 Years Follow-up (N=13)	≥8 Years Follow-up (N=6)	Total (N=18)
Ear infection	1 (6)	0	1 (6)	3 (18)	2 (15)	0	6 (33)
Oral candidiasis	3 (18)	0	4 (24)	2 (12)	1 (8)	0	6 (33)
Nasopharyngitis	1 (6)	0	2 (12)	4 (24)	0	0	5 (28)
Pneumonia	0	0	1 (6)	1 (6)	2 (15)	1 (17)	5 (28)
Sinusitis	2 (12)	0	0	2 (12)	5 (38)	0	5 (28)
Urinary tract infection	0	0	2 (12)	3 (18)	1 (8)	2 (33)	5 (28)
Candida infection	2 (12)	0	1 (6)	1 (6)	0	0	4 (22)
Otitis media	0	0	1 (6)	2 (12)	0	1 (17)	4 (22)
Pharyngitis	0	0	0	1 (6)	2 (15)	0	4 (22)
Varicella	0	0	0	3 (18)	1 (8)	0	4 (22)
Escherichia urinary tract infection	0	0	1 (6)	3 (18)	1 (8)	0	3 (17)
Fungal skin infection	0	0	2 (12)	0	0	1 (17)	3 (17)
Haemophilus infection	0	0	0	3 (18)	0	0	3 (17)
Influenza	0	0	0	1 (6)	2 (15)	0	3 (17)
Respiratory tract infection	1 (6)	0	1 (6)	2 (12)	0	0	3 (17)
Staphylococcal sepsis	1 (6)	0	1 (6)	1 (6)	0	0	3 (17)
Upper respiratory tract infection bacterial	0	0	2 (12)	1 (6)	0	0	3 (17)
Urinary tract infection pseudomonal	1 (6)	1 (6)	3 (18)	0	0	0	3 (17)
Investigations	12 (71)	2 (12)	10 (59)	13 (76)	10 (77)	3 (50)	17 (94)
Antinuclear antibody positive	1 (6)	0	0	0	4 (31)	0	5 (28)
Blood immunoglobulin E increased	0	0	0	3 (18)	3 (23)	0	5 (28)

System Organ Class Preferred Term, (data presented as n [%])	Pre-Treatment (N=17)	Treatment (N=17)	3-Month Hospitali-sation (N=17)	3 Months to 3 Years Follow-up (N=17)	4-7 Years Follow-up (N=13)	≥8 Years Follow-up (N=6)	Total (N=18)
Hepatic enzyme increased	0	0	4 (24)	2 (12)	0	0	5 (28)
Computerized tomography thorax abnormal	3 (18)	0	0	1 (6)	0	0	4 (22)
Tympanometry abnormal	1 (6)	0	0	2 (12)	1 (8)	0	4 (22)
Blood alkaline phosphatase increased	1 (6)	1 (6)	1 (6)	1 (6)	0	0	3 (17)
Electrophoresis protein abnormal	0	0	1 (6)	2 (12)	0	0	3 (17)
Nuclear magnetic resonance image brain abnormal	3 (18)	0	0	0	0	0	3 (17)
Pulmonary function test abnormal	0	0	0	1 (6)	2 (15)	1 (17)	3 (17)
Weight decreased	0	0	0	2 (12)	1 (8)	0	3 (17)
Skin and subcutaneous tissue disorders	4 (24)	0	7 (41)	10 (59)	5 (38)	2 (33)	16 (89)
Dermatitis atopic	1 (6)	0	0	2 (12)	2 (15)	0	5 (28)
Skin lesion	1 (6)	0	1 (6)	2 (12)	0	0	4 (22)
Dermatitis	0	0	2 (12)	0	1 (8)	0	3 (17)
Rash	0	0	1 (6)	2 (12)	0	0	3 (17)
Blood and lymphatic system disorders	4 (24)	0	11 (65)	8 (47)	2 (15)	0	16 (89)
Anaemia	1 (6)	0	3 (18)	3 (18)	0	0	7 (39)
Neutropenia	0	0	5 (29)	2 (12)	0	0	6 (33)
Eosinophilia	1 (6)	0	1 (6)	2 (12)	0	0	4 (22)
Respiratory, thoracic and mediastinal disorders	7 (41)	0	2 (12)	12 (71)	6 (46)	3 (50)	14 (78)

System Organ Class Preferred Term, (data presented as n [%])	Pre-Treatment (N=17)	Treatment (N=17)	3-Month Hospitali-sation (N=17)	3 Months to 3 Years Follow-up (N=17)	4-7 Years Follow-up (N=13)	≥8 Years Follow-up (N=6)	Total (N=18)
Cough	1 (6)	0	0	5 (29)	3 (23)	1 (17)	8 (44)
Interstitial lung disease	2 (12)	0	1 (6)	0	0	0	3 (17)
Pneumonitis	2 (12)	0	1 (6)	0	0	0	3 (17)
Productive cough	1 (6)	0	0	1 (6)	1 (8)	0	3 (17)
Gastrointestinal disorders	4 (24)	2 (12)	7 (41)	7 (41)	6 (46)	1 (17)	13 (72)
Diarrhoea	3 (18)	1 (6)	4 (24)	6 (35)	3 (23)	0	10 (56)
Vomiting	2 (12)	1 (6)	1 (6)	1 (6)	1 (8)	0	6 (33)
Enteritis	0	0	1 (6)	1 (6)	1 (8)	1 (17)	3 (17)
General disorders and administration site conditions	6 (35)	3 (18)	1 (6)	9 (53)	5 (38)	0	12 (67)
Pyrexia	4 (24)	1 (6)	1 (6)	6 (35)	4 (31)	0	8 (44)
Nervous system disorders	3 (18)	0	0	7 (41)	3 (23)	1 (17)	12 (67)
Cognitive disorder	0	0	0	3 (18)	2 (15)	0	5 (28)
Psychomotor hyperactivity	1 (6)	0	0	2 (12)	0	0	3 (17)
Congenital, familial and genetic disorders	8 (47)	0	0	6 (35)	2 (15)	0	11 (61)
Cryptorchism	3 (18)	0	0	3 (18)	2 (15)	0	6 (33)
Phimosis	2 (12)	0	0	5 (29)	0	0	6 (33)
Hepatobiliary disorders	2 (12)	0	4 (24)	3 (18)	2 (15)	2 (33)	10 (56)
Hepatic steatosis	0	0	1 (6)	0	1 (8)	2 (33)	4 (22)
Hepatomegaly	2 (12)	0	0	1 (6)	0	0	3 (17)
Musculoskeletal and connective tissue disorders	4 (24)	0	0	2 (12)	2 (15)	0	7 (39)

System Organ Class Preferred Term, (data presented as n [%])	Pre-Treatment (N=17)	Treatment (N=17)	3-Month Hospitali-sation (N=17)	3 Months to 3 Years Follow-up (N=17)	4-7 Years Follow-up (N=13)	≥8 Years Follow-up (N=6)	Total (N=18)
Foot deformity	1 (6)	0	0	0	2 (15)	0	3 (17)
Muscle atrophy	1 (6)	0	0	0	2 (15)	0	3 (17)
Endocrine disorders	3 (18)	0	0	2 (12)	1 (8)	1 (17)	6 (33)
Hypothyroidism	2 (12)	0	0	2 (12)	0	0	4 (22)
Vascular disorders	2 (12)	0	3 (18)	1 (6)	1 (8)	0	6 (33)
Hypertension	1 (6)	0	3 (18)	0	1 (8)	0	5 (28)
Neoplasms[a]	1 (6)	0	1 (6)	1 (6)	1 (8)	3 (50)	5 (28)
Skin papilloma	0	0	0	0	1 (8)	3 (50)	3 (17)

Notes: Patients are included in the denominator if follow-up is ongoing for the period considered. Patient 1 started follow-up at Year 13 but has AEs reported at Year 8 and Year 12, which are included. Patient 4 had an AE of Pharyngitis which occurred in the LTFU but the dates were not known so it appears in the Total column only.

a. The neoplasms SOC includes benign, malignant and unspecified, including cysts and polyps.

Adverse events from other gene therapy trials for ADA-SCID also support the safety of Strimvelis. Since 2000, 40 patients with ADA-SCID have been treated with gamma retroviral vectors and 20 have been treated with lentiviral vectors. All 60 patients are alive with no reports of leukaemia [Farinelli, 2014; Gaspar, 2015; Cicalese, 2016]. Adverse events from other gene therapy trials for ADA-SCID have not been systematically described, but reported AEs in the published literature are provided in Appendix 7.

Adverse events after HSCT from a MUD or haploidentical donor for patients with ADA-SCID have not been systematically described. Reported AEs in the literature are provided in Table C 28, but it is important to note that AEs were typically only mentioned if they were of special interest.

Several cases of GvHD have been described following both HSCT from MUDs and haploidentical donors [Gennery, 2001; Bhattacharya, 2005; Borghans, 2006; Grunebaum, 2006; Booth, 2007; Honig, 2007; Dvorak, 2014; Baffelli, 2015]. In the UK, the classic categorisation is that acute GvHD occurs within the first 100 days after HSCT while chronic GvHD occurs at least 100 days after HSCT [Cancer Research UK, 2014]. However, the definitions used to categorise GvHD are not widely agreed upon. The classification may not be that simple, there may be some overlap of symptoms, and time since HSCT is not the only factor important to determining the characterisation [Filipovich, 2005; Dhir, 2014].

Unfortunately, none of the literature reports of GvHD in patients with ADA-SCID identified in the literature search provided the definition used in reporting terms such as acute, chronic, severe, or specific grades. Acute GvHD may cause rash, nausea, vomiting, anorexia, profuse diarrhoea, ileus, and cholestatic hepatitis. Chronic GvHD could be limited to a single organ or could be more widespread. Chronic GvHD can lead to debilitating consequences, such as loss of sight, joint contractures, end-stage lung disease, or death [Filipovich, 2005]. This is an important differentiating factor between Strimvelis and HSCT from a MUD or haploidentical donor. GvHD is not observed after Strimvelis.

Table C 28 Adverse events reported for patients with ADA-SCID after HSCT from a MUD or haploidentical donor

Cohort	Donor Type	N	FU Duration[a]	Deaths	Treatment-related AEs	Infections Post-Treatment	Malignancies Post-Treatment	Other Events Post-Treatment	Comments	Reference
Brescia, Italy *1997-2013*	MUD	4	6.5 yr[b] (1.5-11.4)	0	Acute GvHD, grade II (n=1)	-	-	Haemolytic anaemia	3 received conditioning, 1 did not.	Baffelli, 2015
Brescia, Italy *2002-2010*	MUD	2	20-67 mos	0	Acute GvHD grade II (n=1)				Both received conditioning	Serana, 2010
PIDTC/ IEWP-EBMT Survey *1993-2012*	MUD	7	2.5 (1.1-12.3) yrs for survivors (n=5)	2	Acute GvHD (n=4, Grade I n=1, Grade II n=1, Grade III n=2) Chronic GvHD (n=1)	CMV (n=1), pneumonitis (n=3)	-	nephrotic syndrome (n=1)	No conditioning	Dvorak, 2014
Texas *(1998-2007)*	MUD	1	30 mos	0	-	-	-	Asthma, eczema		Patel, 2009

Cohort	Donor Type	N	FU Duration[a]	Deaths	Treatment-related AEs	Infections Post-Treatment	Malignancies Post-Treatment	Other Events Post-Treatment	Comments	Reference
SCETIDE (London, Ulm, Brescia, Paris) *(no dates)*	MUD	8	-	3	-	Gram negative sepsis (n=1 death) CMV and adenoviremia (n=1 death) Unexplained sepsis (n=1 death)	-	-		Booth, 2007
Germany *1982-2006*	MUD	2	Mean: 14.6 yrs for a larger group, n=5	1	No GvHD	CMV, adenovirus (n=1 death)	-	-		Honig, 2007
Italy/Canada *1990-2004*	MUD	2	Mean: 7 mos	1	Acute GvHD, grade III (n=1)	-	-	Pulmonary alveolar proteinosis (n=1 death)		Grunebaum, 2006

Cohort	Donor Type	N	FU Duration[a]	Deaths	Treatment-related AEs	Infections Post-Treatment	Malignancies Post-Treatment	Other Events Post-Treatment	Comments	Reference
Newcastle *2000-2004*	MUD	3	-	2	GvHD, skin, gut (III), MFE	PFIII (n=1)	-	Respiratory failure in pt with PFIII	Umbilical cord blood transplants only, conditioning in 1, one death from multiorgan failure related to pre-existing viral infection and GvHD and the other from multi-organ failure related to pre-existing inflammatory complications	Bhattacharya, 2005
Newcastle *1987-1998*	MUD	1	3.5 yrs	0	Mild skin acute GvHD	-	-	-		Gennery, 2001
SCETIDE (London, Ulm, Brescia, Paris) *(no dates)*	Haplo	23	-	16	GvHD (n deaths not reported)	Viral pneumonitis, aspergillosis (n deaths not reported)	-	-		Booth, 2007

Cohort	Donor Type	N	FU Duration[a]	Deaths	Treatment-related AEs	Infections Post-Treatment	Malignancies Post-Treatment	Other Events Post-Treatment	Comments	Reference
Germany *1982-2006*	Haplo	6	Mean 14.6 yrs among survivors in a larger group	2	GvHD, grade II (n=1) GvHD grade III (n=1)	Aspergillosis (n=2 deaths)	-	-		Honig, 2007
Netherlands *1968-1997*	Haplo	1	15.1 yrs	0	Acute GvHD, grade I	-	-	-		Borghans, 2006
Case Report *8 year old girl, Los Angeles, no date*	Haplo	1	40 days	1		adenovirus, cryptosporidium	EBV-associated leiomyomatosis and polymorphic lymphoproliferative disorder			Monforte-Muñoz, 2003
Newcastle *1987-1998*	Haplo	1	10.5 yrs	0	auto-immune haemolytic anaemia	-	-	-	With conditioning	Gennery, 2001

Abbreviations: -=not reported; AEs=adverse events; CMV=cytomegalovirus; EBV=Epstein-Barr virus; FU=follow-up; GvHD=graft-versus-host disease; Haplo=haploidentical; mos=months; MUD=matched unrelated donor; PFIII=parainfluenza 3; yr=year

a. Reported as median and/or range unless otherwise noted.
b. Median calculated from data

9.9 Interpretation of clinical evidence

9.9.1 Provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and any risks relating to adverse events from the technology. Please also include the Number Needed to Treat (NNT) and Number Needed to Harm (NNH) and how these results were calculated.

Patients with ADA-SCID who lack an MRD account for the majority of patients with ADA-SCID. There is a high unmet need for these patients for new treatment options that provide long-term corrective therapy with an improved probability of survival and without additional complications associated with GvHD. Strimvelis is a step-change in the management of patients with ADA-SCID without an MRD, as recognised by the ESID/EBMT guidelines [ESID/EBMT Guidelines, 2017].

A 100% survival rate at 3 years after Strimvelis one-time therapy (primary endpoint of AD1115611 pivotal study), and in their long-term follow-up has been observed for all 12 patients within the pivotal AD1115611 population (and also for the 18 patients in the integrated analysis), with a median follow-up duration of 6.9 years (up to a maximum of 11.5 years for the AD1115611 Pivotal Population and 13 years for all patients). Intervention-free survival for patients with available data was 82%.

Severe infections, one of the key secondary endpoints for the pivotal study and a common cause of increased morbidity and mortality in this population, were significantly reduced after gene therapy relative to baseline rates and the benefits of Strimvelis on infections were shown to be durable throughout the follow-up period. Evidence of immune reconstitution was observed from 6 months post-gene therapy, with significant increases in numbers of T cell subsets and specifically peripheral CD3+ T cells, another key secondary endpoint for the pivotal AD1115611 study. The numerical increases in T cell subsets were supported by evidence of thymopoiesis and peripheral T cell function (i.e., robust T cell proliferative capacity suggests that the increased cell numbers observed in the periphery represent functional T cells capable of clonal expansion) from Year 1 onwards. B cell function was evidenced by observed immunoglobulin production, antibody forming capacity after vaccination, and decreased dependence on IVIG use over time. In the Strimvelis AD1115611 Pivotal Population, a majority of patients had antibodies to a range of infectious antigens at one or more time points after IVIG had been stopped; antibodies were also observed in patients in the supportive studies.

Like HSCT, Strimvelis has not yet shown an impact the CNS component of ADA-SCID. CNS abnormalities are frequent manifestations of ADA-SCID in long-term survivors of BMT [Rogers, 2001; Booth, 2007]. The neurological events observed both pre- and post-treatment in some of the ADA-SCID patients treated with Strimvelis, including cognitive and audiological events,

were similar to those observed in patients treated with BMT or PEG-ADA [Rogers, 2001; Booth, 2007]. These events may be directly related to the underlying ADA-SCID disease, to infections that patients may have experienced (e.g., meningitis), comorbidities (e.g., Arnold Chiari malformation), or to other medications received (e.g., antibiotics such as gentamycin).

The majority of treated children in the Strimvelis clinical programme either maintained or improved their age-appropriate height and weight relative to standard curves. The majority of patients across all studies who had available LTFU data (which includes patients from pivotal and supportive studies) reported on-time vaccinations, attendance at school or pre-school as appropriate for the patient's age (12 out of 14 patients [86%]), and eating well with a varied and adequate diet.

In the Strimvelis clinical programme, patients were hospitalised for a median of 45 days (range: 34 to 110 days), and we expect that patients who receive Strimvelis in the future will be hospitalised for a similar period (average 50 days).

Overall the safety findings of Strimvelis are in line with those expected in an ADA-SCID population which has undergone busulfan conditioning and is undergoing immune reconstitution. As Strimvelis is an autologous treatment, GvHD was not observed. No events indicative of leukaemic transformation or myelodysplasia were reported and no issues around immunogenicity were evident.

Based on the positive benefit-to-risk profile, the limitations associated with current therapeutic treatment options, and the significant mortality experienced by patients with ADA-SCID, there is an urgent medical need for additional therapeutic options. As reflected in the EBMT/ESID guidelines [EBMT/ESID Guidelines, 2017], Strimvelis therapy with long-term post-treatment follow-up will provide a significant improvement in the treatment of patients with ADA-SCID without a MRD based on the evidence presented. Strimvelis offers increased survival when compared indirectly with HSCT from a MUD or haploidentical donor without the risk of GvHD.

9.9.2 Provide a summary of the strengths and limitations of the clinical-evidence base of the technology.

The use of an objective primary endpoint (survival) rather than a subjective endpoint or surrogate endpoint, the length of follow-up, and the inclusion of a diverse patient population with various previous treatments are strengths of the Strimvelis clinical programme. Supportive endpoints corroborate the long-term effect of Strimvelis. Limitations include the lack of a study control group and the small number of study participants due to the rarity of the condition.

9.9.3 Provide a brief statement on the relevance of the evidence base to the scope. This should focus on the claimed patient- and specialised service-benefits described in the scope.

Data from the Strimvelis clinical programme and relevant literature published on alternative treatments (HSCT from matched unrelated donors and haploidentical donors) are relevant to the decision problem defined in the scope. The Strimvelis clinical programme included a diverse patient population with various previous treatment histories and evaluated endpoints detailed in the final scope. Comparison with all available literature on the alternative treatment of HSCT from a matched unrelated donor or haploidentical donor is complete. Although formal indirect comparison between Strimvelis and the comparator treatment is not possible due to methodological reasons, examination of the endpoints in the Strimvelis clinical programme and all available literature on the alternative treatment allows for a reasonable comparative evaluation of the benefits for each treatment option.

9.9.4 Identify any factors that may influence the external validity of study results to patients in routine clinical practice.

GSK is not aware of any such factors. Patients treated with Strimvelis will be treated at the same facility in Milan, Italy in a similar manner as the clinical programme.

In the Integrated Population for Strimvelis, no notable differences in AEs were observed by gender or age at the time of Strimvelis administration. AEs were not evaluated by race due to the small number of non-White patients enrolled; however, patients of Caucasian, Arabic, African-American, and Asian origin were included in the Integrated Population.

Exploratory analyses of baseline predictors of efficacy (age at GT, CD34+ cells/kg dose, cells/kg 3 vector copy number dose, baseline values for peripheral CD3+ T cell counts, TREC counts, peripheral RBC levels of dAXP, and body mass index) found that benefit from Strimvelis treatment can be achieved across a range of doses and diverse subject characteristics [Cicalese, 2016].

Nevertheless, Strimvelis should be used with caution in patients older than 6 years and 1 month and younger than 6 months as there are no data from clinical trials in these age ranges. Older patients are typically less able to donate high numbers of CD34+ cells which may mean that older patients cannot be treated. Successful generation of T cells after Strimvelis is also likely to be affected by residual thymic function, which can become impaired in older children. Use of Strimvelis in patients older than those previously studied should be carefully considered and reserved only for occasions where all other reasonable treatment options have been exhausted.

Analyses performed to compare patients with prior PEG-ADA exposure to those without were limited by low patient numbers, particularly in the group

without prior PEG-ADA exposure. However, the available data did not suggest that prior exposure to PEG-ADA affected outcomes for Strimvelis.

All in all, the Strimvelis Integrated Population is reflective of the patient population expected to receive Strimvelis in England. The approved indication for Strimvelis is similar to the patients included in the Integrated Population. It is likely that results for newly diagnosed patients in England would be better than results in the studies because the Integrated Population included some patients who had failed previous HSCT or ERT and thus were considered harder patients to treat.

9.9.5 Based on external validity factors identified in 9.9.4 describe any criteria that would be used in clinical practice to select patients for whom the technology would be suitable.

Not applicable.

10 Measurement and valuation of health effects

Patient experience

10.1.1 Please outline the aspects of the condition that most affect patients' quality of life.

Information on patient quality of life is provided in Section 7.1.

10.1.2 Please describe how a patient's health-related quality of life (HRQL) is likely to change over the course of the condition.

Information on patient's HRQL is provided in Section 7.1.

HRQL data derived from clinical trials

10.1.3 If HRQL data were collected in the clinical trials identified in section 9 (Impact of the new technology), please comment on whether the HRQL data are consistent with the reference case. The following are suggested elements for consideration, but the list is not exhaustive.

- Method of elicitation.
- Method of valuation.
- Point when measurements were made.
- Consistency with reference case.
- Appropriateness for cost-effectiveness analysis.
- Results with confidence intervals.

Health outcome measures in the LTFU study AD1115611 included Lansky Performance status index (all LTFU patients) and the Paediatric Quality of Life Inventory (PedsQL) (not collected for subjects younger than 5 years of age). Lansky performance status index was queried in 14 patients; all patients were reported as 'fully active, normal' during LTFU, with 1 exception, who had minor restrictions in strenuous physical activity recorded at Year 7 [Cicalese, 2016]. [redacted] completed the PedsQL questionnaire for [redacted] age, at the Year [redacted] visit. The totality of [redacted] score, including the score by question and dimension, was as expected in an average healthy adolescent of [redacted] age, based on a paediatric assessment.

Additionally, non-standardised and informal paediatric quality-of-life assessments were made in the LTFU study AD1115611 by means of patient status updates at annual follow-up visits. These assessments included attendance at school, participation in sports, eating habits, and receipt of childhood vaccinations. These LTFU assessments were not pre-specified as efficacy endpoints, and baseline assessments were not collected; however, they provide some indication of the clinical benefit of Strimvelis at LTFU time points with regard to overall well-being and daily function. The majority of patients across all studies who had available LTFU data (which includes patients from pivotal and supportive studies) reported on-time vaccinations, attendance at school or pre-school as appropriate for the patient's age (12 out of 14 patients [86%]), and eating well with a varied and adequate diet. Most patients did not report participating in sports during the LTFU, primarily due to their parents' choice.

Mapping

10.1.4 If mapping was used to transform any of the utilities or quality-of-life data in clinical trials, please provide the following information.

- Which tool was mapped from and onto what other tool? For example, SF-36 to EQ-5D.
- Details of the methodology used.
- Details of validation of the mapping technique.

Not applicable.

HRQL studies

10.1.5 Please provide a systematic search of HRQL data. Consider published and unpublished studies, including any original research commissioned for this technology. Provide the rationale for terms used in the search strategy and any inclusion and exclusion criteria

used. The search strategy used should be provided in appendix 17.1.

Embase, hosted by Elsevier, was chosen as the search engine for all systematic reviews conducted for this submission because it is the most comprehensive search engine available. PubMed was not searched separately because Embase includes the PubMed database.

A systematic search for HRQL was performed in conjunction with a systematic search for economic studies in ADA-SCID (Section 11.1.1). The search terms included keywords for the disease terms ('adenosine deaminase deficiency', 'ADA deficiency', and 'ADA SCID') and search terms for economic modelling ('cost effectiveness', 'cost utility', 'economic evaluation', 'economic model', 'Markov model', and 'discrete event simulation'). No time or language restrictions were applied. Details are provided in Section 17.3 Appendix 3. The search yielded 6 results, but none of them contained relevant HRQL data.

A study of the cost-effectiveness of newborn screening for ADA-SCID [Ding, 2016] was excluded from the economic literature search because it did not provide HRQL data for ADA-SCID or an economic evaluation of treatments for ADA-SCID. However, this article was useful in identifying an approach that could be taken to provide utility values for patients with ADA-SCID in the absence of specific data in this disease state. The Ding model referenced an article [McGhee, 2005] that used a utility value for survivors of ADA-SCID treatment based on health preference scores estimated by investigators after successful BMT for chronic myelogenous leukaemia. The same article [Ding, 2016] also used a utility value for patients receiving IVIG based on values for patients with chronic lymphocytic leukaemia [Weeks, 1991]. These utility values were not specific to patients with ADA-SCID, but they were identified as possibly useful for inclusion in a sensitivity analysis.

All references identified in the literature search for clinical data (Section 9.1) were also searched for HRQL data. References that did not provide results by HSCT donor type were not excluded from the HRQL results because HRQL information was so scarce, but references that did not provide results specific to ADA-SCID were excluded. Three relevant studies, besides the Strimvelis programme, were identified by this method.

Because no information was found on utilities for patients with ADA-SCID, additional literature searches were conducted to identify utility values for relevant health states and events.

NICE commissioned a report to assess whether the existing methods are adequate to assess regenerative therapies, which was subsequently published [Hettle, 2017]. Some elements of the economic model developed for that purpose are similar to the Strimvelis model. When applicable, assumptions in the assessment of Strimvelis presented herewith mirror those in the Hettle analysis. The Hettle analysis was also used to identify potentially relevant utility values that could be applicable in the assessment of gene therapy for patients with ADA-SCID. References identified in this way are

included in the PRISMA diagrams as ‘additional records identified through other sources’.

A systematic search for health-related utility values after HSCT was performed (Figure 2). The search terms included keywords for quality of life (‘quality of life’ and ‘health utilities’) and keywords for HSCT (‘stem cell transplantation’, ‘HSCT’, ‘bone marrow transplantation’ and ‘umbilical cord blood cell transplantation’). The search was limited to the last 10 years (from 2007 onwards). Details are provided in Section 17.5 Appendix 5. After removing duplicates, the search yielded 5,031 articles. Articles were searched using reference software for utility data in any field, further screened using reference software based on the title and abstract, and then included or excluded based on the full text article. No relevant articles on ADA-SCID were identified. Two articles with potentially applicable utility information were identified: 1 in chronic lymphocytic leukaemia [Kharfan-Dabaja, 2012] and 1 in chronic myelogenous leukaemia [Rochau, 2015]. The analysis by Kharfan-Dabaja et al. used utility data from Sung et al. [Sung, 2003; Kharfan-Dabaja, 2012], which had previously been identified as an applicable source of utility data after HSCT during review of Hettle 2017. The analysis by Rochau et al did not directly report utilities values, but did use a weighted method for assigning utility values [Rochau, 2015]. This method was considered applicable to the model for ADA-SCID. Additionally, an article [Swinburn, 2015] with potentially relevant utilities for patients experiencing GvHD was identified by reviewing the references of the full text articles examined.

A systematic search for health-related utility values in GvHD was performed (Figure 3). The search terms included keywords for quality of life (‘quality of life’, ‘healthy utility’, ‘HRQL’, and ‘QALY’) and keywords for GvHD (‘graft versus host’). The search was limited to the last 10 years (2007 onwards) and yielded 1,203 articles. Details are provided in Section 17.5 Appendix 5. Duplicates were removed from the 1,203 articles, titles and abstracts were screened using reference software, and then articles were included or excluded based on the full text article. One article that directly reported preference-based utilities in GvHD was identified [Swinburn, 2015].

Figure 2 PRISMA diagram of search for utilities after HSCT

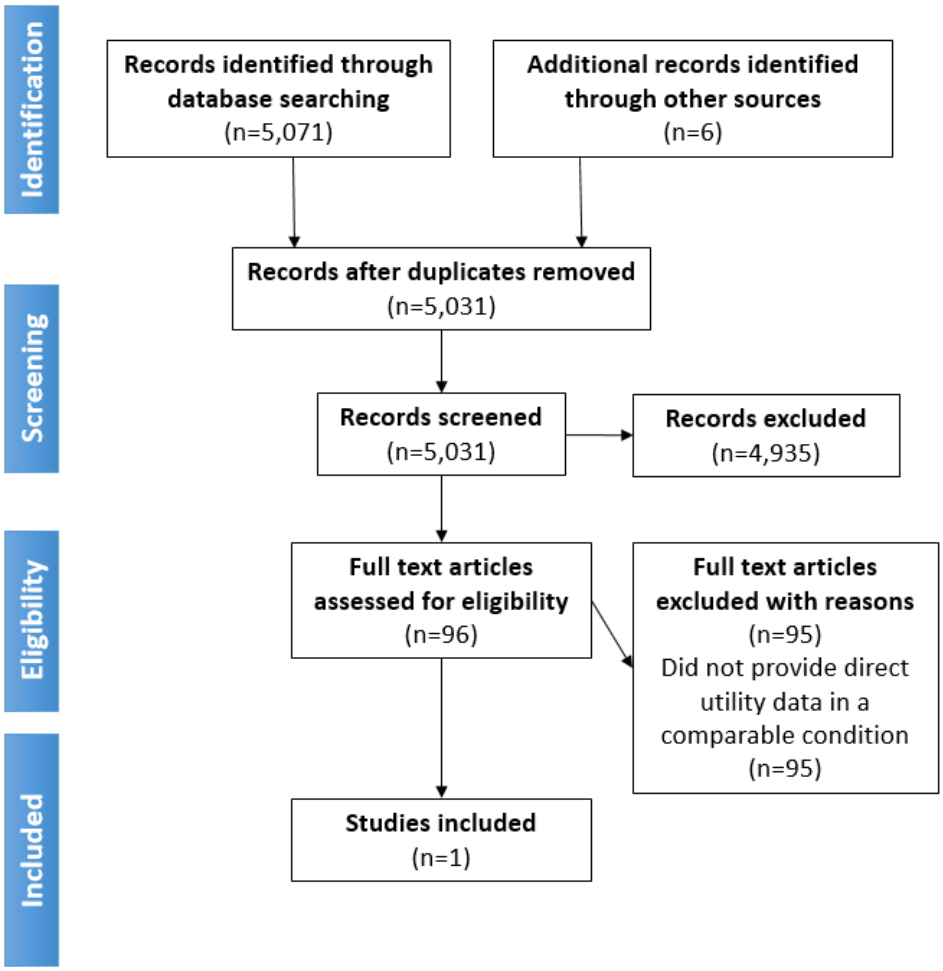
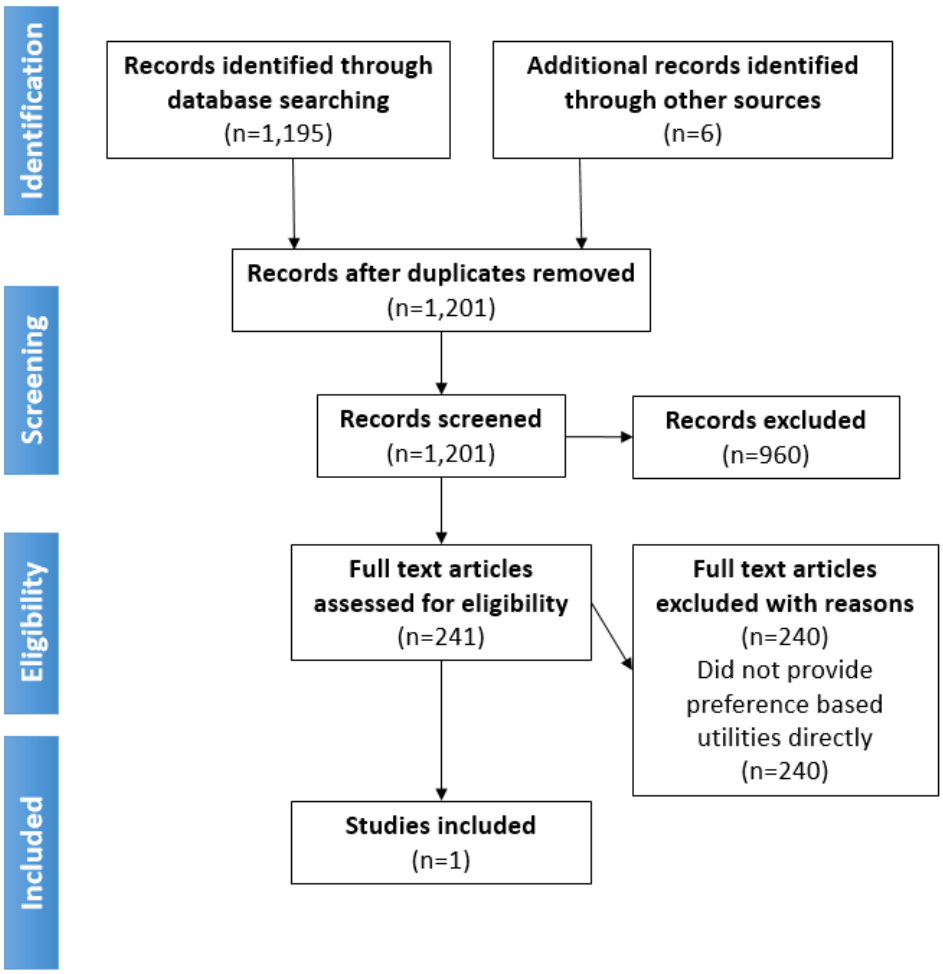


Figure 3 PRISMA diagram of search for utilities in GvHD



10.1.6 Provide details of the studies in which HRQL is measured. Include the following, but note that the list is not exhaustive.

- Population in which health effects were measured.
- Information on recruitment.
- Interventions and comparators.
- Sample size.
- Response rates.
- Description of health states.
- Adverse events.
- Appropriateness of health states given condition and treatment pathway.
- Method of elicitation.

- Method of valuation.
- Mapping.
- Uncertainty around values.
- Consistency with reference case.
- Results with confidence intervals.

Besides the Strimvelis clinical programme, 3 reports provided information relevant to HRQL.

A study of quality of life in patients with SCID treated with HSCT (donor source not specified) in Newcastle included 12 patients with ADA-SCID. Fifty-nine of 88 patients or their parents (67%) completed the Pediatric Quality of Life Inventory, including 12 patients with ADA-SCID. Parent-reported scores for patients with ADA-SCID were significantly ($p<0.05$) lower than the UK normal across all aspects except the emotional components [Hamid, 2016].

A study of cognitive and behaviour abnormalities in children with SCID treated with HSCT at the Great Ormond Street Hospital, London, between 1979 and 2003 included 13 patients with ADA-SCID. Donor source was not specified for the children with ADA-SCID. Ninety percent of qualifying patients with SCID (105/117) completed the assessment. Patients with ADA-SCID had a mean IQ of approximately 65, which was significantly lower ($p<0.01$) than the mean IQ of patients with other forms of SCID (approximately 90) and the mean IQ of the normal population (100). Patients with ADA-SCID also had significantly ($p<0.01$) higher scores, indicating more difficulties, on a parent-rated Strengths and Difficulties Questionnaire that included items like emotional difficulties, hyperactivity, and peer relationships [Titman, 2008].

In patients (n=20) with ADA-SCID treated with lentiviral gene therapy in London and Los Angeles, it was noted that the earliest treated patients were free of social restriction. The specifics of how social restriction was assessed and the number of patients considered earliest treated was not made publicly available [Gaspar, 2015].

10.1.7 Please highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.

The available literature on HRQL in patients with ADA-SCID is consistent with the information obtained in the LTFU for Strimvelis. Patients in the LTFU for Strimvelis (12 out of 14 patients [86%]) were able to enter and maintain regular attendance at school or pre-school as appropriate for the patient's age. This is consistent with the findings by Gaspar that patients treated early with gene therapy were free of social restrictions [Gaspar, 2015]. These findings are critically important because isolation was identified as one of the key concerns affecting HRQL in a telephone survey of carers of patients with ADA-SCID who were treated with HSCT or PEG-ADA [Data on file].

Strimvelis was not expected to impact neurological events associated with ADA-SCID. Indeed, the neurological events observed both pre- and post-treatment in some of the patients with ADA-SCID treated with Strimvelis, including cognitive and audiological events, were similar to those observed in patients treated with BMT or PEG-ADA [Rogers, 2001; Booth, 2007]. These observations in the Strimvelis clinical programme were consistent with observations by Titman of cognitive-behavioural deficits in patients with ADA-SCID [Titman, 2008].

Adverse events

10.1.8 Please describe how adverse events have an impact on HRQL.

In the Strimvelis clinical programme, most adverse drug reactions were considered to be related to busulfan conditioning or immune reconstitution. Low-dose busulfan is used as pre-treatment for Strimvelis. This low-dose regimen would be expected to produce fewer AEs than the full-dose chemotherapy regimens used in some HSCT protocols [Hassan, 2012] and, therefore, a smaller negative impact on HRQL. Infection AEs were reported for all patients in the Strimvelis clinical programme, but the most common infection AEs were normal, expected childhood infections. In the Pivotal AD1115611 study, severe infections were reduced after Strimvelis therapy compared with before Strimvelis therapy and declined over time during the LTFU AD1115611 study. A decrease in severe infection rates would be expected to improve HRQL.

The neurological events, including cognitive and audiological events, observed both pre- and post-treatment in some of the patients treated with Strimvelis were similar to those observed in patients treated with BMT or PEG-ADA [Rogers, 2001; Booth, 2007].

For HSCT, in addition to what would be seen for Strimvelis, GvHD is the main AE that would be expected to affect HRQL. Acute GvHD may cause rash, nausea, vomiting, anorexia, profuse diarrhoea, ileus, and cholestatic hepatitis. Chronic GvHD could be limited to a single organ or could be more widespread. Chronic GvHD can lead to debilitating consequences, such as loss of sight, joint contractures, end-stage lung disease, or death [Filipovich, 2005].The effects of GvHD on HRQL may depend upon the type and severity of GvHD.

Utility data on the effects of GvHD in ADA-SCID are not available, but the utility value for UK patients in complete remission of relapsed/refractory Hodgkin lymphoma or systemic anaplastic large cell lymphoma experiencing acute GvHD is 0.39 and for those experiencing chronic GvHD is 0.52 [Swinburn, 2015]. Not all patients experience the same symptoms with GvHD.

In addition to effects on HRQL for the patient, the death of a child can have a profound impact on the patient's family. No utility data on bereaved family members are available for patients with ADA-SCID, but an approach to handling this effect was identified in an economic evaluation of meningitis vaccination in England [Christensen, 2014].

Quality-of-life data used in cost-effectiveness analysis

10.1.9 Please summarise the values you have chosen for your cost-effectiveness analysis in the following table. Justify the choice of utility values, giving consideration to the reference case.

Utility values were applied in the cost-effectiveness analysis for the following health states and AEs:

- The first 6 months after treatment with Strimvelis, HSCT from a MUD or haploidentical donor, or rescue transplant
- Health states for all surviving patients via age-related EQ-5D scores with weighting based on the probability of incurring a decrement to health state from serious acute or chronic GvHD

Table C 29 Summary of quality-of-life values for cost-effectiveness analysis

	Value	Reference in submission	Justification
Health utility in the period before HSCT or Strimvelis	0.98		Assumed equal to the general population utility at age 1. We do not consider the potential disutility patients incur whilst waiting for Strimvelis or HSCT (e.g. due to being in isolation and receiving PEG-ADA). Given that patients receiving Strimvelis are likely to wait less than patients receiving HSCT, this is a conservative assumption.
Utility decrement during the first 6 months after Strimvelis, HSCT from a MUD or haploidentical donor, or rescue transplant	0.57	Sung, 2003	In the absence of information on utilities after treatment for ADA-SCID, utility values after BMT in leukaemia were considered the best available information
Utility values for surviving patients with ADA-SCID	Age-specific utility	Jones-Hughes, 2016 Ara, 2010	No specific values on utilities of patients with ADA-SCID were identified. Age-specific normal values were used, and the possibility of lowering utilities was explored in the sensitivity analysis

	Value	Reference in submission	Justification
One-off QALY loss due to a utility decrement from acute GvHD	0.41	Swinburn, 2015	The utility value for patients with acute GvHD and complete remission from relapsed/refractory Hodgkin lymphoma or systemic anaplastic large cell lymphoma was used to calculate a utility decrement and then adjusted based on the expected average duration of an episode of acute GvHD (8 months) based on expert clinical advice.
One-off QALY loss due to a utility decrement from chronic GvHD	1.44	Swinburn, 2015	Utility value for patients with chronic GvHD and complete remission from relapsed/refractory Hodgkin lymphoma or systemic anaplastic large cell lymphoma was used to calculate a utility decrement and then adjusted based on the expected duration of an episode of chronic GvHD (3 years) based on expert clinical advice.

Abbreviations: ADA-SCID=adenosine deaminase-severe combined immunodeficiency; BMT=bone marrow transplant; GvHD=graft versus host disease; HSCT=haematopoietic stem cell transplantation; MUD=matched unrelated donor; QALY=quality-adjusted life years.

Specific information on the utility values chosen is provided below.

Consideration was given to weighting the utility score for patients who require IVIG, but no weighting was used in the baseline analysis because there was no reliable evidence on the impact of IVIG administration on patients with ADA-SCID. One article [Weeks, 1991] with utility information on IVIG use in patients with chronic lymphocytic leukaemia was identified in the search for utilities on IVIG. However, this study is dated and probably is not reflective of current care. Disutility in this study was elicited through a non-referenced method from a small sample of physicians treating patients in the context of a different disease. The consideration of disutility due to IVIG is fully explored in sensitivity analyses.

Utility value for the first 6 months after treatment with Strimvelis, HSCT from a MUD or haploidentical donor, or rescue transplant

No utility values after treatment for ADA-SCID were identified in a systematic literature search. A utility decrement of 0.57 was applied to the first 6 months after the initial intervention (Strimvelis or HSCT from a MUD or haploidentical donor) or rescue transplant. This value was drawn from a study of patients

with acute myeloid leukaemia after BMT [Sung, 2003]. This source was identified during review of the analysis by Hettle [Hettle, 2017].

Utility value of surviving patients in all health states

Age-specific utility values were applied to all surviving health states. Values were drawn from the Jones-Hughes analysis of the Health Survey for England - 2012 [Jones-Hughes, 2016] using the methodology of Ara [Ara, 2010]. The Jones-Hughes formula is:

$$\text{Utility} = 0.967981 + 0.023289*\text{male} - 0.001807*\text{age} - 0.000010*\text{age}^2$$

GSK calculated exact values for the ages of 12, 30, 40, 50, 60, 70, and 80 for both males and females. The average of the male/female scores as a single value in each of the age bands was used. Values used are shown Table C 30.

Table C 30 Age-specific utility scores used in the model [Jones-Hughes, 2016]

Age (years)	Utility value[a]
< 25	0.96
25-34	0.92
35-44	0.89
45-54	0.86
55-64	0.84
65-74	0.80
75+	0.77

a. Rounded, male/female ratio assumed to be 50%/50%

Neither Strimvelis nor HSCT is expected to affect neurologic events in patients with ADA-SCID. Therefore, it is likely that patients with ADA-SCID would have lower utility values than these average UK population values. However, there is a lack of robust quantitative utility evidence on the impact of non-immune complications of ADA-SCID. Additionally, there is evidence that EQ-5D may not sufficiently account for the effect of deafness on HRQL [Brazier, 2011]. The utility value used by McGhee et al was not specific to patients with ADA-SCID and was not based on potential disutility due to non-immune complications of the disease [McGhee, 2005]. Therefore, the average values for the population of England and Wales were used in the base-case, and the effects of possibly lower utility values in patients with ADA-SCID were explored in the sensitivity analysis.

Utility value for GvHD

No utility values for GvHD in ADA-SCID were identified in the literature search. One-off quality-adjusted life year (QALY) losses (0.41 for acute GvHD and 1.44 for chronic GvHD) were applied in the model to account for a utility decrement from acute or chronic GvHD. A utility value of 0.39 was used to calculate a utility decrement for severe acute GvHD, and a utility value of 0.52

was used to calculate a utility decrement for chronic GvHD based on the responses of patients from the UK in a study of health utilities in relation to AEs in relapsed/refractory Hodgkin lymphoma and systemic anaplastic large cell lymphoma [Swinburn, 2015]. Utility decrements were then adjusted based on the expected duration of an acute and chronic GvHD episode based on expert advice.

Formula for one-off utility decrement for acute GvHD:

(1-0.39) x 2/3 year = 0.41

Formula for one-off utility decrement for chronic GvHD:

(1-0.52) x 3 years = 1.44

10.1.10 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[1]:

Clinical advice was sought from Dr. Andrew Gennery, a leading UK HSCT Transplantation expert with clinical experience of managing patients with ADA-SCID in the UK. Dr. Gennery was the only expert approached, and he agreed to participate in this advice seeking activity. No conflict of interest was identified on declaration. Dr. Gennery is a Clinical Reader in Paediatric Immunology and Bone Marrow Transplantation at a UK University Hospital. The advice seeking activity was a direct interview held at the hospital.

The majority of the questions asked focused on the diagnosis and management pathways of patients with ADA-SCID in the UK as described in Section 12.2.5. Additionally, Dr. Gennery was asked about utility values for patients with ADA-SCID. Dr. Gennery agreed there was a high level of uncertainty, so this was explored using sensitivity analyses. This discussion informed the inputs in the analyses and supported the disease pathway presented herewith.

10.1.11 Please define what a patient experiences in the health states in terms of HRQL. Is it constant or does it cover potential variances?

Patients with ADA-SCID experience frequent severe infections, which can require isolation and hospitalisation. The incidence of severe infections should decrease after treatment with either Strimvelis or HSCT and decrease further over time, particularly more than 3 years after treatment [Cicalese, 2016].

Patients with ADA-SCID also experience difficulty eating and gaining weight. After treatment with either Strimvelis or HSCT, patients would be expected to

[1] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

stay on a normal growth curve, although still below the 50th percentile for age and weight [Cicalese,2016].

Neurological abnormalities such as cognitive deficits and hearing impairment are common in patients with ADA-SCID. Treatment would not be expected to affect these neurological abnormalities, which could affect HRQL. The effect would be expected to be constant.

Some patients develop acute or chronic GvHD after treatment with HSCT from a MUD or haploidentical donor. Patients treated with Strimvelis do not develop GvHD. Acute GvHD may cause rash, nausea, vomiting, anorexia, profuse diarrhoea, ileus, and cholestatic hepatitis. Chronic GvHD could be limited to a single organ or could be more widespread. Chronic GvHD can lead to debilitating consequences, such as loss of sight, joint contractures, end-stage lung disease, or death [Filipovich, 2005].

10.1.12 Were any health effects identified in the literature or clinical trials excluded from the analysis? If so, why were they excluded?

Parent decrement due to the loss of their child was not included in the base-case but was explored in sensitivity analyses.

Additional effects on quality of life of carers and patients' families were not included in the analysis because these effects are difficult to quantify. Having a child with ADA-SCID has a dramatic effect on quality of life for carers, who report how debilitating isolation can be and how exhausting providing round-the-clock-care can be. Additionally, carers reported that having a child with ADA-SCID affected the entire family, including marriage and siblings [Data on file]. By excluding these additional caregiver/family burden, the model presents a more conservative estimate of the cost-effectiveness of Strimvelis.

10.1.13 If appropriate, what was the baseline quality of life assumed in the analysis if different from health states? Were quality-of-life events taken from this baseline?

Not applicable.

10.1.14 Please clarify whether HRQL is assumed to be constant over time. If not, provide details of how HRQL changes with time.

HRQL was assumed to vary over time according to age-specific utility values as discussed in Section 10.1.9.

10.1.15 Have the values been amended? If so, please describe how and why they have been altered and the methodology.

The values have not been amended.

Treatment continuation rules

10.1.16 Please note that the following question refers to clinical continuation rules and not patient access schemes. Has a treatment continuation rule been assumed? If the rule is not stated in the (draft) SPC/IFU, this should be presented as a separate scenario by considering it as an additional treatment strategy alongside the base-case interventions and comparators. Consideration should be given to the following.

- The costs and health consequences of factors as a result of implementing the continuation rule (for example, any additional monitoring required).
- The robustness and plausibility of the endpoint on which the rule is based.
- Whether the 'response' criteria defined in the rule can be reasonably achieved.
- The appropriateness and robustness of the time at which response is measured.
- Whether the rule can be incorporated into routine clinical practice.
- Whether the rule is likely to predict those patients for whom the technology constitutes particular value for money.
- Issues with respect to withdrawal of treatment from non-responders and other equity considerations.

Not applicable as Strimvelis is administered as a single, one-time treatment.

Section D – Value for Money and cost to the NHS and personal social services

Section D requires sponsors to present economic evidence for their technology. All statements should be evidence-based and directly relevant to the decision problem.

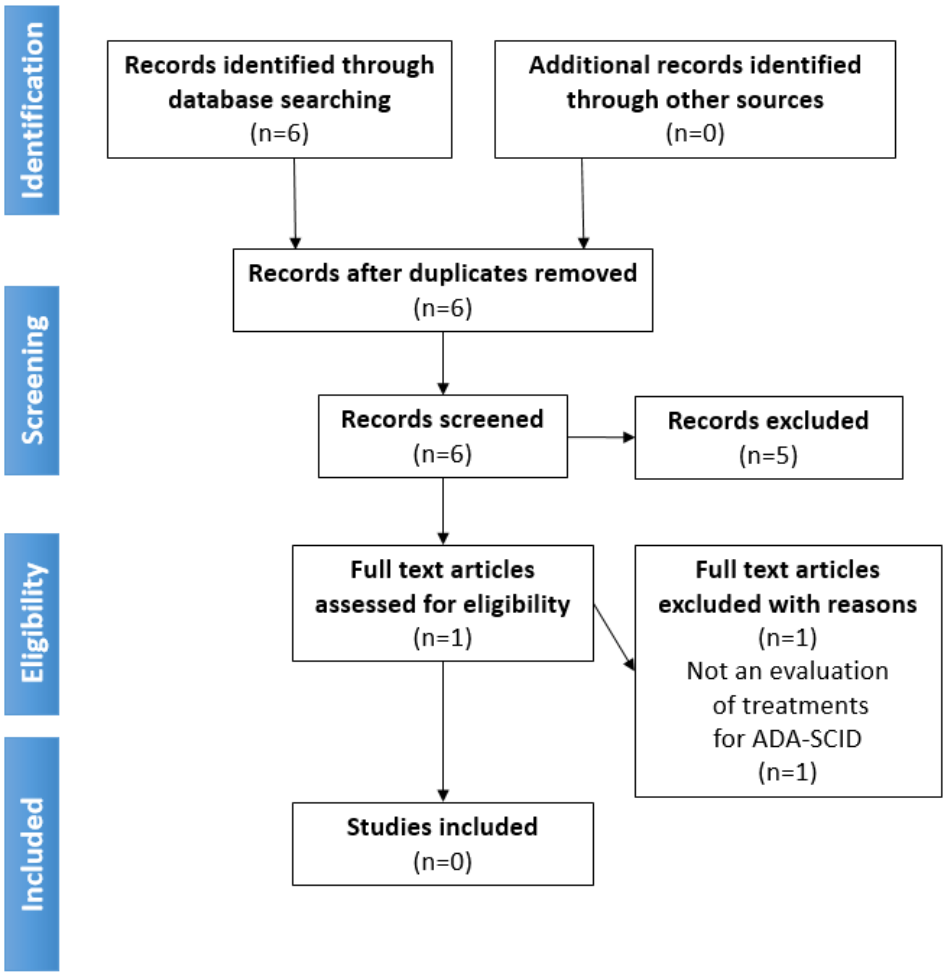
11 Existing economic studies

11.1 Identification of studies

11.1.1 Describe the strategies used to retrieve relevant health economics studies from the published literature and to identify all unpublished data. The search strategy used should be provided as in section 17.3.

A brief discussion of the systematic literature search for economic studies in ADA-SCID is provided in Section 10.1.5. The search yielded 6 results, but none of them contained an economic evaluation relevant to the decision problem. Specifics of the search are provided in the Appendix Section 17.3.

Figure 4 PRISMA diagram for economic studies of treatment for ADA-SCID



11.1.2 Describe the inclusion and exclusion criteria used to select studies from the published and unpublished literature. Suggested headings are listed in Table D1 below. Other headings should be used if necessary.

Table D 1 Selection criteria used for health economic studies

Inclusion criteria	
Population	Patients with ADA-SCID
Interventions	HSCT from a MUD or haploidentical donor OR gene therapy
Outcomes	All
Study design	Any
Language restrictions	None
Search dates	28-Feb-2017
Exclusion criteria	
Population	Other than those described above
Interventions	Other than those described above
Outcomes	No restriction
Study design	No restriction
Language restrictions	No restriction
Search dates	No exclusion

Abbreviations: ADA-SCID=adenosine deaminase-severe combined immunodeficiency; HSCT=haematopoietic stem cell transplantation; MUD=matched unrelated donor.

11.1.3 Report the numbers of published studies included and excluded at each stage in an appropriate format.

The literature search yielded 6 results. All of the results were excluded because they did not provide economic analysis of treatments for ADA-SCID.

11.2 Description of identified studies

11.2.1 Provide a brief review of each study, stating the methods, results and relevance to the scope.

Not applicable.

11.2.2 Provide a complete quality assessment for each health economic study identified. A suggested format is shown in table D3.

Not applicable.

12 Economic analysis

Summary

- Strimvelis generates 13.6 additional QALYS vs HSCT from a MUD.
- Strimvelis generates 11.7 additional QALYS vs HSCT from a haploidentical donor.
- The ICER for Strimvelis versus an HSCT from a MUD is £36,360/QALY gained and the ICER for Strimvelis versus an HSCT from a haploidentical donor is £14,645/QALY gained, which are both considerably below the acceptability threshold for HSCT.
- Strimvelis is highly cost-effective, particularly for an ultra-rare disease with high unmet need.

12.1 Description of the de novo cost-effectiveness analysis

Patients

12.1.1 What patient group(s) is (are) included in the cost-effectiveness analysis?

People with ADA-SCID for whom no suitable HLA-matched related stem cell donor is available are included in the cost-effectiveness analysis.

Technology and comparator

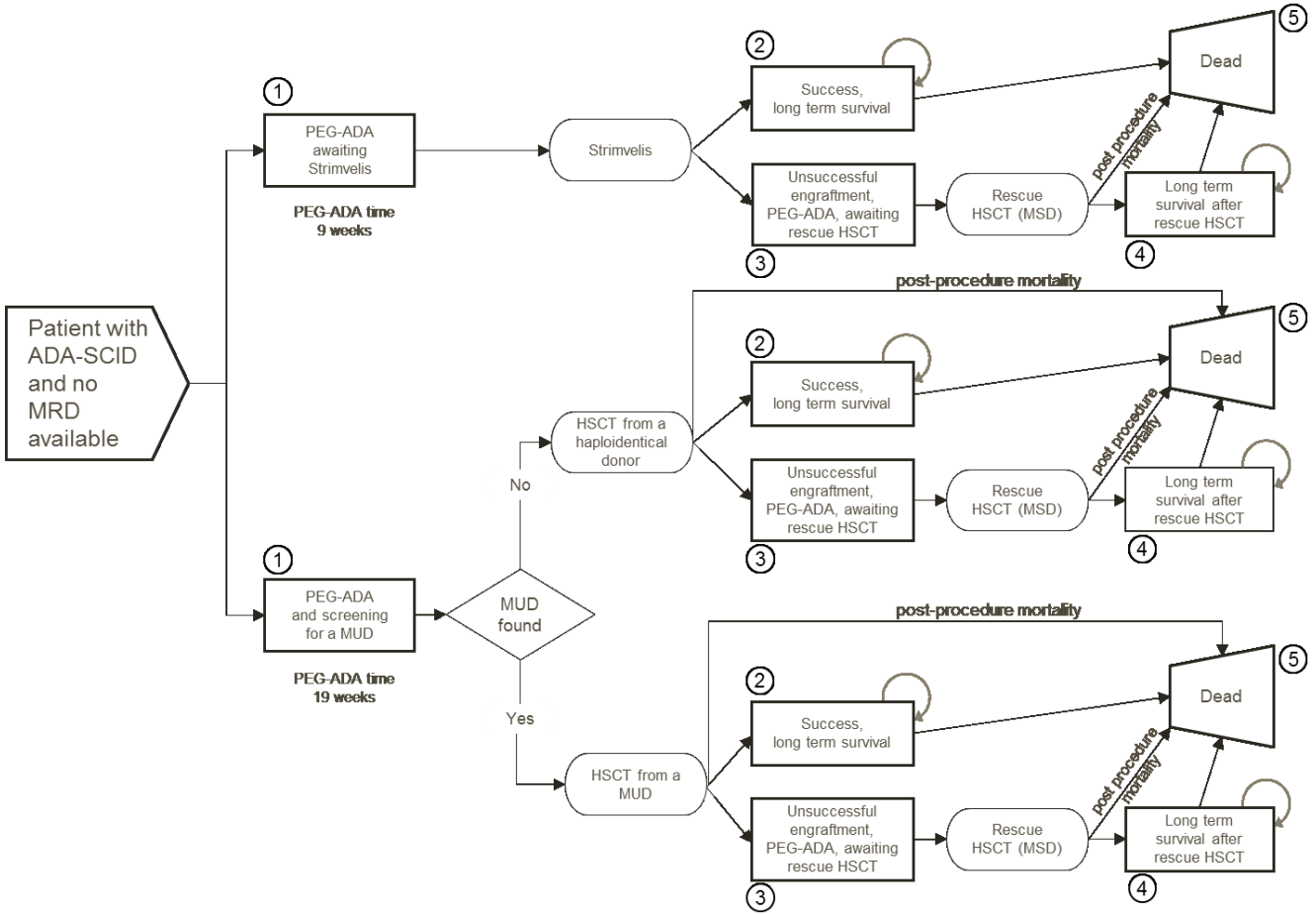
12.1.2 Provide a justification if the comparator used in the cost-effectiveness analysis is different from the scope.

Not applicable.

Model structure

12.1.3 Provide a diagram of the model structure you have chosen.

Figure 5 Diagram representation of model structure



Abbreviations: ADA-SCID=adenosine deaminase-severe combined immunodeficiency; HSCT=haematopoietic stem cell transplantation; MRD=matched related donor; MSD=matched sibling donor; MUD=matched unrelated donor; PEG-ADA=Polyethylene glycol-modified bovine adenosine deaminase

12.1.4 Justify the chosen structure in line with the clinical pathway of care.

The model represented in Figure 5 is an economic model designed for conducting cost-effectiveness and budget impact analyses for ADA-SCID therapies.

The model structure describes the stages in the clinical pathway for patients suffering from ADA-SCID seen in clinical practice. Parameters were drawn from clinical studies, peer-reviewed literature, clinical practice, and expert advice. Plausible assumptions were made, where necessary, and the basis for these assumptions is provided in this report. When data were missing, dated, or uncertain, we explored the consequences of data uncertainties with extensive deterministic and probabilistic sensitivity analyses.

The model was used to estimate the costs and outcomes for patients treated with Strimvelis and to compare these estimates with the corresponding costs and outcomes of the current practice of HSCT from either a MUD or haploidentical donor. Effects are estimated as quality-adjusted life year [QALY] for each type of intervention and QALY treatment differences. The relative impact on medical costs is expressed as incremental cost-effectiveness ratios (ICERs). The analysis is conducted from an NHS perspective and uses a lifetime horizon.

The model is a cohort model, and consists of three ‘arms’ representing Strimvelis, and HSCTs from a MUD or from a haploidentical donor. The model is constructed as a combination of an initial decision tree that represents the patient pathway from the diagnosis until the immediate outcomes of an HSCT or a Strimvelis procedure. After the initial procedure (HSCT or Strimvelis), the subsequent patients’ survival, health outcomes, and costs are modelled using a Markov modelling approach, following patients in annual cycles. The decision tree captures the initial screening or waiting for Strimvelis procedure, and clinically observed outcomes of the initial procedure, whereas the Markov model describes the subsequent long-term health outcomes and costs for patients who survive the initial procedure.

The model parameters are given in Table D 5.

At the outset, patients with ADA-SCID for whom no MRD is available are assigned to HSCT treatment or to Strimvelis treatment and all patients begin receiving PEG-ADA treatment. A screening for a MUD is performed for all patients assigned to HSCT treatment. Patients assigned to Strimvelis treatment also start treatment with PEG-ADA to bridge the time between diagnosis and the Strimvelis procedure, however no donor screening is needed for Strimvelis patients.

Hence, Strimvelis patients have a significantly shorter duration of expensive PEG-ADA therapy when compared with those assigned to HSCT procedures. Time required for screening was estimated at 19 weeks [Gaspar, 2013] whereas the time between the start of PEG-ADA and Strimvelis procedure is estimated at 9 weeks as per the treatment schedule with Strimvelis. Administering PEG-ADA

prior to transplant therapy stabilizes a patient's clinical state, but it is expensive and requires weekly infusion trips to the clinical centre that disrupt the lives of patients and their caregivers. Hence, shortening the period on PEG-ADA is desirable both from a cost standpoint and from a HRQL perspective. The model accounts for the cost of PEG-ADA treatment, but not for the impact on QoL. No mortality is assumed between the start of PEG-ADA and HSCT or Strimvelis.

The entire initial sequence of events leading up to the initial transplant procedures is represented by model states labelled (1): 'PEG-ADA awaiting Strimvelis' and 'PEG-ADA and screening for a MUD.'

The period of finding a suitable donor or waiting for a Strimvelis procedure is followed by the initial transplant outcomes, which are shown in Figure 5 as three elongated ovals labelled as 'Strimvelis', 'HSCT from a MUD', and 'HSCT from a haploidentical donor'. In the model, these events are not model states; they merely reflect the point at which the costs and outcomes of the initial procedures are assigned. The initial procedure results in 1 of 3 possible immediate health outcomes: successful transplantation, labelled as model state (2) 'Success, long term survival'; failure to engraft, labelled as model state (3) 'Unsuccessful engraftment, PEG-ADA, awaiting rescue HSCT'; or post-procedure death, a transition to model state (5), 'Dead'.

The decision tree section of the model ends at the post procedure outcomes. Subsequently, a Markov approach is applied to model health outcomes and costs for patients with successful procedure, and patients with a failed initial procedure. Model states (2) and (3) are the starting states for the Markov sections of the model. The Markov trace follows 2 initial cycles of 6-month duration, and subsequently follows patients' outcomes, survival and costs on an annual cycle. A 1-year cycle length was chosen in order to be consistent with the time frame for clinical assessment.

In each model arm, patients who survive the procedure and successfully engraft (model state [2]) begin treatment with IVIG, which continues at a gradually diminishing rate until year 8. The mortality and health related quality of life of these patients is based on age-matched general population mortality and health utilities. The model follows patients' age and growth (expressed in body weight). The body weight information is needed to calculate the dose and costs of IVIG therapy since the recommended dose is expressed on a g/kg basis.

Patients that have engraftment failure either after HSCT or Strimvelis (model state [3]) commence ERT with PEG-ADA and wait for a rescue HSCT. Patients remain in state (3) until a rescue HSCT procedure is performed, with a waiting time of 2 years between initial procedure and rescue HSCT. The rescue transplant procedure is represented by the model events 'Rescue HSCT (MSD).' In the model, the rescue HSCT is assumed to be from an MSD. However, assuming a rescue MUD in the event of no new MSD by Year 3 is investigated in sensitivity analyses. Following rescue transplantation, the surviving patients enter Markov health state (4) 'Long term survival after rescue HSCT'.

Patients who receive an HSCT from a MUD or a haploidentical donor may experience graft versus host disease (GVHD). Onset of GVHD is associated with one-off costs and loss of QALY that accrue in the model during the first Markov cycle after the procedure.

The health states in the model are presented below. The structure of the tables in this report, and reported costs and health outcomes mirror the structure of the health states.

12.1.5 Provide a list of all assumptions in the model and a justification for each assumption.

Table D 2 List of key assumptions in the model

Assumption	Source
1. All patients survive from diagnosis to initial treatment with Strimvelis or HSCT with the use of PEG-ADA	PEG-ADA survival is approximately 78% at 20 years with half of the deaths on ERT occurring within the first 6 months of treatment [Gaspar, 2009]. However, for simplicity, it was conservatively assumed that survival is 100% between diagnosis and treatment.
2. The survival data after Strimvelis and after HSCT used in the model are true reflections of survival after Strimvelis and after HSCT for patients with ADA-SCID	See Section 12.2.1 for details. Survival data after HSCT from a MUD or haploidentical donor were drawn from Hassan [Hassan, 2012]; survival after Strimvelis is from Cicalese [Cicalese, 2016]. Overall 1-year survival is 100% after Strimvelis, 67% after HSCT from a MUD, and 71% after HSCT from a haploidentical donor. The cost and effect consequences of higher survival in HSCT procedures were examined in the sensitivity analyses.
3. A rescue transplant (if needed) occurs in Year 3 after Strimvelis or HSCT	No data were presented in Hassan (2012) on the timing of a rescue transplant after HSCT from a MUD or haploidentical donor [Hassan, 2012]. Rescue transplant was assumed to occur in Year 3 (2 years after the initial procedure) based on expert clinical advice.

Assumption	Source
4. Any rescue transplant required is from an MSD	Hassan reported that the 2000-2009 haploidentical donor cohort patient who failed to engraft subsequently received 2 rescue MSD HSCTs (from a newly born sibling) [Hassan, 2012]. Additionally, in the Strimvelis clinical programme, the 2 patients who received rescue transplants received their transplants from an MSD (from newly born siblings). For simplicity, 100% survival and 100% success were assumed for MSD. The possibility of using a MUD as the donor source for some rescue transplants was explored in the sensitivity analyses.
5. If a rescue transplant is required, then the patient receives PEG-ADA until a transplant takes place, and PEG-ADA commences 3 months after treatment failure	In the Integrated Population from the Strimvelis clinical programme, 3 patients had an unsuccessful response to Strimvelis, all of whom received PEG-ADA after Strimvelis. The shortest time to restarting PEG-ADA was 0.34 years, or approximately 4 months. Therefore, 3 months was chosen as the earliest point PEG-ADA would be restarted. This was confirmed with expert clinical advice.
6. Patients do not stay on long-term PEG-ADA	One patient from the Strimvelis Integrated Population had an unsuccessful response to Strimvelis, began treatment with PEG-ADA, and did not proceed to rescue transplant but instead remained on long-term PEG-ADA. In the scoping workshop, it was suggested that long term PEG-ADA is not an option considered in England. Therefore, it was assumed that all patients in England would receive a rescue transplant (HSCT from a MSD) instead.
7. All patients waiting for a rescue transplant survive until transplant	No patients in the Strimvelis Integrated Population died while waiting for rescue transplant. Hassan et al did not discuss deaths while waiting for a rescue transplant for any patients who received HSCT from a MUD or haploidentical donor. Any such deaths would have been included in the overall survival data [Hassan, 2012]. It was conservatively assumed that all patients waiting for a rescue transplant survive until transplant.

Assumption	Source
8. All Strimvelis patients with a failed engraftment have VCN testing in the period up to their rescue transplant	All Strimvelis patients will have VCN testing to monitor engraftment status. Those who fail to engraft will need additional testing while they wait for their rescue transplant procedure.
9. All patients require IVIG after intervention (Strimvelis or HSCT from a MUD or haploidentical donor): the proportion of patients receiving IVIG falls over time as per reported clinical data	In the Strimvelis clinical programme, all patients received IVIG after Strimvelis. Patients were able to discontinue IVIG over time, with more patients discontinuing IVIG use as time progressed. At Year 3, 10 of 17 patients (58.8%) were receiving IVIG. At the time of data cut (varying length of time since receipt of Strimvelis, median follow-up 6.9 years), 12 of 18 patients had discontinued IVIG [Cicalese, 2016]. Only 1 of 5 patients who had at least 8 years of follow-up was receiving IVIG in Year 8, and that patient was on long-term PEG-ADA and would probably have received rescue transplant if in England. Therefore, the IVIG use rate was taken as 0% of patients with successful engraftment at Year 8. In Hassan, 5 of 7 survivors of HSCT from a MUD with available data and all 7 of 7 survivors of HSCT from a haploidentical donor with available data had discontinued IVIG (varying length of follow-up, average for all patients 6.5 years) [Hassan, 2012]. It was conservatively assumed that IVIG use rates after HSCT from a MUD or haploidentical donor would be similar to rates observed in the Strimvelis clinical programme.
10. The average weight of an ADA-SCID patient is the 25th percentile of the weight distribution of an average child	Patients with ADA-SCID characteristically show a 'failure to thrive' [Hershfield, 2017]. Patients in the Strimvelis clinical programme continued to track along their original percentiles for growth but remained below the 50th percentile for a normal, age-matched population [Cicalese, 2016]. The effects of decreasing the average weight were explored in sensitivity analyses.

Assumption	Source
11. The rate of severe infections after Strimvelis is the same as the rate after HSCT from a MUD or haploidentical donor	The rate of severe infections in the Strimvelis Integrated Population was 0.26 from 4 months to 3 years after intervention and 0.07 for 4 years through 8 years. Similarly defined information was not available for HSCT from a MUD or haploidentical donor. In the absence of information on HSCT, the rates have been assumed to be the same, and this assumption was confirmed with an external clinical expert.
12. Life expectancy for survivors after Strimvelis or HSCT from a MUD or haploidentical donor or rescue transplant is equal to that of the general population	Kaplan-Meier overall survival curves for patients who received HSCT from a MUD or haploidentical donor, do not show deaths after approximately 1 year with a median follow-up after transplantation of 6.5 years (range 1.6 to 27.6 years) [Hassan, 2012]. No patients from the Strimvelis clinical programme have died after a median 6.9 years of follow-up (range 2.3 to 13.4 years) [Cicalese, 2016]. Clinical advice confirmed that this life expectancy assumption is reasonable.
13. In most cases, treatment and follow-up with Strimvelis would be 3.7 months and take place at the San Raffaele Hospital in Milan	Based on the clinical schedule from San Raffaele Hospital. The impact of an extra month of follow-up is explored in a sensitivity analysis.

Abbreviations: ADA-SCID=adenosine deaminase-severe combined immunodeficiency; BMT=bone marrow transplant; GSK=GlaxoSmithKline; HSCT=haematopoietic stem cell transplantation; IVIG=intravenous immunoglobulin; MUD=matched unrelated donor; NICE=National Institute for Health and Care Excellence; PEG-ADA=polyethylene glycol-modified bovine adenosine deaminase; SCID= severe combined immunodeficiency; UK=United Kingdom; VCN=vector copy number.

12.1.6 Define what the model's health states are intended to capture.

Table D 3 Model health states

Health state	Description
(1) PEG-ADA therapy represented as boxes labelled 'PEG-ADA awaiting Strimvelis' and 'PEG-ADA and screening for a MUD'	A model state describing the initial period after diagnosis for patients with ADA-SCID for whom no MRD is available. All patients in state (1) in Figure 5 receive PEG-ADA therapy. Strimvelis patients remain on PEG-ADA for 9 weeks in the base-case. A screening for a MUD donor is required for all patients assigned to HSCT treatment and they remain on PEG-ADA for 19 weeks in the base-case. State (1) is part of the decision tree part of model
(2) Represented by the boxes labelled 'Success, long term survival'	A model state describing patients who survive the initial transplant and have a successful engraftment. Patients in this Markov state experience a decreased quality of life and require high cost follow-up in the 1st post-procedure cycle. A proportion of HSCT patients in state (2) experience GVHD, with associated cost of treatment and loss of QALY. These costs are one-off in nature and are incurred at model cycle 1. Patients who receive Strimvelis treatment do not experience GVHD. Infections are observed in all patients in state (2) after their procedure. State (2) is located at the end of the decision tree part of model and the beginning of the Markov trace part of the model.

Health state	Description
(3) Represented by the boxes labelled 'Unsuccessful engraftment, PEG-ADA, awaiting rescue HSCT'	A model state describing patients who survive the initial transplant and have an engraftment failure. Patients in this Markov state experience a decreased quality of life and require high cost follow-up. A proportion of HSCT patients in state (3) experience GVHD, with associated cost of treatment and loss of QALY. These patients start PEG ADA therapy 3 months after the failed initial procedure. PEG-ADA is an expensive treatment required to bridge these patients for a rescue HSCT transplantation. In the base-case, patients remain in state (3) for 2 years post-initial implant, and no mortality is expected over that period. After 2 years (in model year 3), patients receive a rescue transplant and enter Markov state (4) 'Long term survival after rescue HSCT.' No post procedure mortality is assumed in the base-case. This state is in the Markov trace part of the model.
(4) Represented by the boxes labelled 'Long term survival after rescue HSCT'	Patients in state (4) follow a survival pathway similar to that of patients in state (2). Their costs include costs associated with IVIG use, GVHD, and infection. No subsequent costs are incurred after completion of IVIG use. State (4) is in the Markov trace part of the model.
(5) Represented by the boxes labelled 'Dead'	State (5) is the terminal health state for all patients and represents patients who have died from any cause.

Abbreviations: ADA-SCID=adenosine deaminase-severe combined immunodeficiency; GvHD=graft vs host disease; IVIG=intravenous immunoglobulin; HSCT=haematopoietic stem cell transplantation; IVIG=intravenous immunoglobulin; MRD=matched related donor; MUD=matched unrelated donor; PEG-ADA=polyethylene glycol-modified bovine adenosine deaminase; QALY=quality-adjusted life year.

12.1.7 Describe any key features of the model not previously reported.

Table D 4 Key features of model not previously reported

Factor	Chosen values	Justification	Reference
Time horizon of model	Lifetime	Strimvelis and HSCT increase the long-term survival from ADA-SCID, and the effect is assumed to be lifelong	NA
Discount rate, costs and outcomes	1.5%	Point 47 of the "Interim Process and Methods of the Highly Specialised Technologies Programme Updated to reflect 2017 changes" guidance, states: *In cases when treatment restores people who would otherwise die or have a very severely impaired life to full or near full health, and when this is sustained over a very long period (normally at least 30 years), cost-effectiveness analyses are very sensitive to the discount rate used. It is likely that application of non-reference case discounting will occur more often for highly specialised technologies and analyses that use a non-reference-case discount rate for costs and benefits may be more appropriate In line with the Guide to the Methods of Technology Appraisal, in cases when treatment restores people who would otherwise die or have a very severely impaired life to full or near full health, and when this is sustained over a very long period (normally at least 30 years), analyses that use a non-reference-case discount rate for costs and outcomes may be considered. A discount rate of 1.5% for costs and benefits may be considered by the Evaluation Committee if it is highly likely that, on the basis of the evidence presented, the*	Interim Process and Methods of the Highly Specialised Technologies Programme Updated to reflect 2017 changes [NICE, 2017a] NICE guidance document 'Eculizumab for treating atypical haemolytic uraemic syndrome' Published: 28 January 2015 Accessed: March 29 2017 Available at nice.org.uk/guidance/hst1 NICE guidance document 'Mifamurtide for the treatment of osteosarcoma' Published: 26 October 2011 Accessed: March 29 2017. Available at nice.org.uk/guidance/ta235

Factor	Chosen values	Justification	Reference
		long-term health benefits are likely to be achieved. Further, the Evaluation Committee will need to be satisfied that the introduction of the technology does not commit the NHS to significant irrecoverable costs. We have applied a discount rate of 1.5% to both costs and outcomes on this basis. Patients treated with Strimvelis are expected to have a long and sustained benefit and regain normal life expectancy. Given the minimal budget impact of Strimvelis, the introduction of the technology would not commit the NHS to significant irrecoverable costs. 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 public health programmes. The NICE Appraisal Committee accepted this same rationale as justification for using a 1.5% discount rate in the cost-consequence analyses for eculizumab for treating atypical haemolytic uraemic syndrome and mifamurtide for the treatment of osteosarcoma.	
Perspective (NHS/PSS)	NHS	NICE reference case	NA

Factor	Chosen values	Justification	Reference
Cycle length	1 year (except for first year, which consists of 2 cycles of 6 months)	The Markov model was used to project health outcomes and costs forward following the initial transplant procedure. The first year consists of 2 cycles in order to capture i) disutility post treatment in the first 6 months, and ii) 6-month survival	NA

Abbreviations: ADA-SCID=adenosine deaminase-severe combined immunodeficiency; HSCT=haematopoietic stem cell transplantation; HST=highly specialised technologies; NA=not applicable; NHS=National Health Service; NICE=National Institute for Health and Care Excellence; PSS=Prescribed Specialised Services.

12.2 Clinical parameters and variables

12.2.1 Describe how the data from the clinical evidence were used in the cost-effectiveness analysis.

When available, data from the clinical programme for Strimvelis and data from the literature on HSCT from a MUD or haploidentical donor (as historical control evidence) were used in the cost-effectiveness analysis. It is important to note that ADA-SCID is an ultra-rare disorder and therefore patient numbers are very low in the reported cohorts. Due to the small patient cohorts, a single patient can have a large impact on results.

Taking a conservative approach (as the intervention-free survival rate varied across studies), data from the Strimvelis Integrated Population were used for all inputs in the base-case where available. The impact of using data from the Pivotal Population, which had a higher intervention-free survival rate (meaning a lower expected rescue transplant rate), was explored in sensitivity analyses.

For most variables, the findings by Hassan et al were chosen as the best representation of results for HSCT from a MUD or haploidentical donor because this study contained the largest cohorts of patients specifically with ADA-SCID reported within the last 10 years. Retrospective data were collected from questionnaires distributed to all Inborn Errors Working Party members of the EBMT and to centres in North America and Saudi Arabia. Results were available for 106 children with ADA-SCID who received HSCT between August 1981 and March 2009 in 16 international transplantation centres. There were approximately equally numbers of males and females; median age at transplantation was 4 months (range 2 weeks to 7 years). Most patients (93%) had not received prior long-term PEG-ADA (longer than 3 months). Median follow-up was 6.5 years (range 1.6-27.6 years). These demographics are consistent with the patient population expected in England. In general, the patients reported in Hassan were similar to the patients in the Strimvelis Integrated Population. Exceptions were that the median age at the time of treatment was higher in the Strimvelis Integrated Population and patients in the Strimvelis Integrated Population were more likely to have failed previous treatment (previous HSCT from a haploidentical donor or long-term PEG-ADA), making them more difficult patients to treat. Of the 106 patients, 15 received HSCT from a MUD and 30 received HSCT from a haploidentical donor, which is larger than any other cohorts of patients with ADA-SCID identified in the literature search. The cohort that received HSCT from a haploidentical donor was analysed by decade of treatment (2000-2009). The cohort that received HSCT from a MUD was not analysed by decade in the publication because MUDs were only used as a donor source since 1995. Limitations of the study include the retrospective nature and the lack of detailed reporting of some key items such as adverse events. The degree of HLA-matching of MUDs and haploidentical donors was not reported. Despite these limitations, the study by Hassan et al. has been considered the most

appropriate source for clinical variables for HSCT from a MUD or haploidentical donor.

Time to treatment

Strimvelis

Time from diagnosis to treatment in a clinical trial was not considered applicable to the expected time to treatment of an approved product. Therefore, the expected 9 weeks from the clinical schedule from San Raffaele Hospital was used for the average time to treatment with Strimvelis.

HSCT from a MUD or haploidentical donor

The median time from diagnosis to transplant for patients with SCID at Great Ormond Street Hospital, London between 2000 and 2005 was 129 days (18.4 weeks) [Gaspar, 2013]. This includes transplant from all donor sources, including MSD, which would be expected to be faster, so using a value of 19 weeks for the time to transplant for HSCT from a MUD or haploidentical donor is considered a conservative approach.

Overall survival

For all treatments, the general survival curve for the England/Wales population was used to predict long-term survival after the first 3 years after successful treatment as there is no evidence to suggest a reduction in survival compared with the general population after this point.

Strimvelis

All patients from the Strimvelis clinical programme are currently alive; therefore, survival in the Integrated Population was 100% at a median follow-up of 6.9 years. Maximum follow-up in the Integrated Population was 13 years at the time of data cut [Cicalese, 2016].

HSCT from a MUD or haploidentical donor

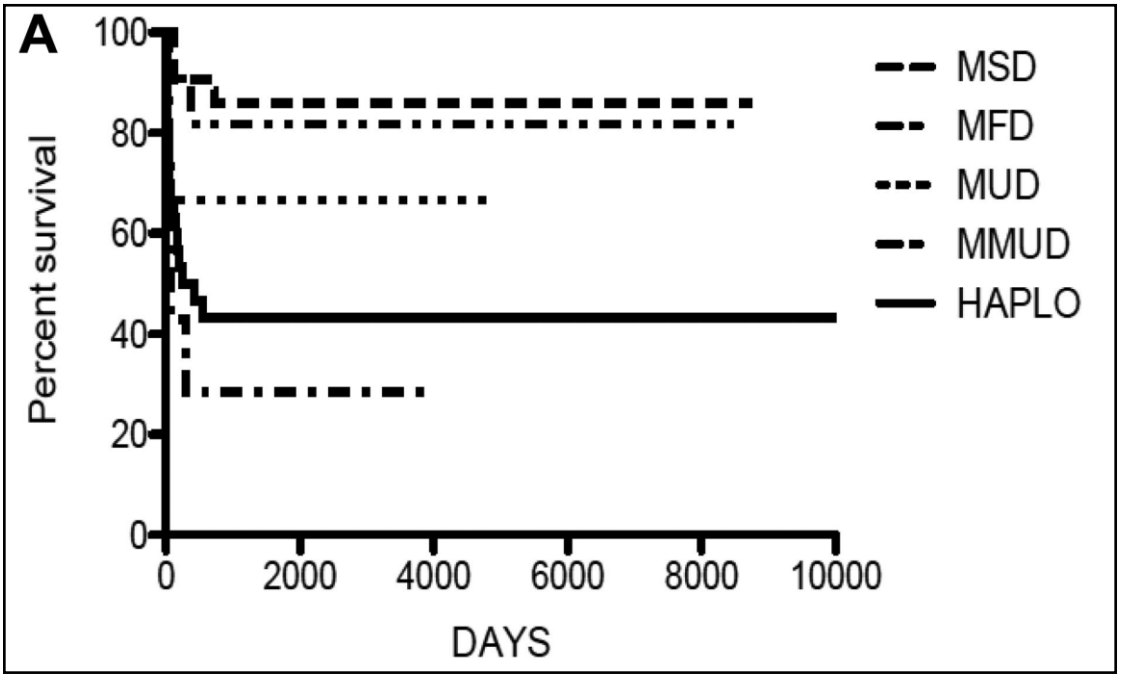
Survival data after HSCT from a MUD or haploidentical donor were drawn from the published data. The majority of deaths reported after all types of transplantations (63%; 22 of 35) were in the first 100 days after transplantation; 13 deaths occurred after 100 days (Figure 6). Hassan recorded data for only 15 HSCTs from a MUD and 30 HSCTs from a haploidentical donor [Hassan, 2012].

Hassan reported that overall survival for patients who received an HSCT from a haploidentical donor was 43% after a median all patient follow-up of 6.5 years (range 1.6-27.6 years). GSK and NICE agreed at the Highly Specialised Technologies scoping meeting that the survival data for patients who received HSCT from a haploidentical donor in the years 2000-2009 was a better representation of current practice than the overall survival reported for the whole duration of the study. In the 2000-2009 cohort, 7 patients were

treated with HSCT from a haploidentical donor, and 5 patients survived (71%). We used this figure as 1-year survival rate for patients who receive an HSCT from a haploidentical donor [Hassan, 2012].

We used the overall survival rate of 67% for estimates of survival for patients who receive an HSCT from a MUD. Hassan et al. did not analyse survival after HSCT from a MUD by decade because these procedures were first used in 1995 [Hassan, 2012].

Figure 6 Survival after HSCT [Hassan, 2012]



Abbreviations: HAPLO=haploidentical donor; HSCT=haematopoietic stem cell transplantation; MFD=matched family donor; MMUD=mismatched unrelated donor; MSD=matched sibling donor; MUD=matched unrelated donor.

IVIG use

Strimvelis

All patients in the Strimvelis Integrated Population underwent IVIG replacement therapy after receiving Strimvelis; an increasing number of patients were able to discontinue IVIG use as time progressed. At Year 3, 10 of 17 patients (58.8%) were receiving IVIG. At the time of data cut (08-May-2014, varying lengths of time since receipt of Strimvelis, median follow-up 6.9 years), 12 of 18 patients had discontinued IVIG and 6 remained on IVIG [Cicalese, 2016]. Only 1 of 5 patients who had at least 8 years of follow-up was receiving IVIG in Year 8, and that patient was on long-term PEG-ADA and would have received rescue transplant if in England. Therefore, the IVIG use rate was 0% of patients with successful engraftment at Year 8 [Cicalese, 2016; Data on file]. In the model, we used an IVIG use rate after Strimvelis of 100% at Year 1, 58.8% at Year 3, and 0% at Year 8 or later. GSK sought external expert advice on these rates, and they were considered appropriate.

HSCT from a MUD

Hassan (2012) Figure 3 appears to show that 2 out of 7 patients (28.6%) with available data were still using IVIG at the time of reporting. The mean follow-up for patients who received an HSCT from a MUD was not reported. The mean follow-up for all 55 patients with immune reconstitution data, irrespective of donor type, was 6.6 years, with a range of 1 to 22 years. The rate of IVIG use at other time points was not reported [Hassan, 2012].

In the model, it is conservatively assumed IVIG use after HSCT from a MUD would be similar to IVIG use after Strimvelis. Therefore, for modelling we used an IVIG use rate after HSCT of 100% at Year 1, 58.8% at Year 3, and 0% at Year 8 or later.

HSCT from a haploidentical donor

No IVIG use data are shown following HSCT from a haploidentical donor for the 7 patients in the 2000-2009 Hassan cohort. Data are shown for 7 patients (from the entire haploidentical cohort of 30), and none of these patients were on IVIG at data cut off [Hassan, 2012].

For modelling, we conservatively assumed IVIG use after HSCT from a haploidentical donor would be similar to IVIG use after Strimvelis. Therefore, we used an IVIG use rate after Strimvelis of 100% at Year 1, 58.8% at Year 3, and 0% at Year 8 or later in the base-case.

Rescue transplant

Strimvelis

Three patients of 17 with available data in the Strimvelis Integrated Population had an unsuccessful response to Strimvelis. Two patients subsequently received a post-gene therapy HSCT from a matched sibling donor, and 1 patient continues to receive long term PEG-ADA treatment. Following the feedback from clinical experts at the scoping workshop, we assumed that, in England, the latter patient would eventually receive a rescue transplant. Therefore, for Strimvelis, we assumed that the rescue transplant rate is 3/17 (17.6%).

HSCT from a MUD

Hassan (2012) reported that 1 patient of 15 (6.7%) required a rescue transplant; however, the timing of the rescue and the outcome were not reported [Hassan, 2012]. For HSCT from a MUD, we assumed that the rescue transplant rate is 1/15 (6.7%).

HSCT from a haploidentical donor

For the 2000-2009 cohort, Hassan (2012) reported that 1 of the 7 patients moved to rescue gene therapy and 1 patient moved to a rescue transplant. The 1 patient who required a rescue transplant received 2 rescue transplants.

If Strimvelis is not available, we assumed that 2/7 (28.6%) of patients who receive an HSCT from a haploidentical donor would require a rescue transplant. Note that for the entire cohort that received an HSCT from a haploidentical donor (n=30), 8 patients required a rescue transplant (26.7%) [Hassan, 2012].

Severe infection rates

Strimvelis

The severe infection rate between 4 months and 3 years after Strimvelis for the Integrated Population was 0.26 severe infection per person-year of observation [Cicalese, 2016]. We used this number in the base-case of the model for the severe infection rate for the first 3 years after Strimvelis. The severe infection rate between 3 years and 8 years was 0.07 [Cicalese, 2016], and this number was used in the base-case of the model for the severe infection rate for the corresponding time.

HSCT from a MUD or haploidentical donor

We did not find reported information on the rate of severe infections after HSCT from a MUD or haploidentical donor. We conservatively assumed that the severe infection rate after these procedures is the same as that observed after Strimvelis (0.26 severe infection per person-year for the first 3 years and 0.07 between 4 years and 8 years).

GvHD rates

Strimvelis

Strimvelis is an autologous therapy, so GvHD would not be expected. GvHD has not been observed in patients after Strimvelis [Cicalese, 2016].

HSCT from a MUD or haploidentical donor

Hassan (2012) reported that GvHD was the cause of 15% of all deaths, including 2 of the 13 deaths (15.4%) after 100 days. These figures were not disaggregated by donor source. No other data were reported in Hassan on the incidence of GvHD [Hassan, 2012].

We used the data for adverse events reported in the literature for patients with ADA-SCID after HSCT from a MUD or haploidentical donor as shown in Table C 28 to estimate the probability of GvHD after an HSCT from a MUD or haploidentical donor. Note that Booth 2007 was excluded from the calculation because GvHD was reported, but numbers were not provided. Additionally, the literature did not always report if a case of GvHD was acute or chronic or the grade. As these events were pulled from case reports in the literature and not a systematic reporting, it is possible that these events were underreported.

- For HSCT from a MUD, a total of 9 GvHDs were reported in 28 patients (32.1%): 4 of these GvHDs were grade III or IV, of which it appears 3

were acute and 1 was chronic. We therefore assumed that 10.7% (3/28) of patients who receive an HSCT from a MUD experience a grade III or IV acute GvHD and 3.6% (1/28) of patients who receive an HSCT from a MUD experience a grade III or IV chronic GvHD.

- For HSCT from a haploidentical donor, 3 GvHDs could be clearly determined in 9 patients (33.3%): 1 of these GvHDs was recorded as grade III (acute or chronic not reported): we conservatively assumed that this GvHD was acute. We therefore assumed that 11.1% (1/9) of patients who receive an HSCT from a haploidentical donor experience a grade III or IV acute GvHD and no patients who receive an HSCT from a haploidentical donor experience grade III or IV chronic GvHD.

12.2.2 Are costs and clinical outcomes extrapolated beyond the study follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified?

Patients in the Strimvelis clinical programme Integrated Population had a median follow-up of 6.9 years (range: 2.3 to 13.4 years) at data cut, which is a very substantial length of follow-up. Survival was 100% [Cicalese, 2016]. The mechanism of action of Strimvelis involves engraftment of CD34+ cells in the bone marrow, where they repopulate the haematopoietic system with a proportion of cells that express pharmacologically active levels of the ADA enzyme. Following successful engraftment in a patient, the effects of Strimvelis are expected to be lifelong [Strimvelis SmPC, 2016]. We therefore assumed that the yearly probability of death after 3 years for patients who receive Strimvelis is the same as that for the general England/Wales population. Clinical experts confirmed that this is a reasonable assumption.

For HSCT, a retrospective analysis analysed 106 children with ADA-SCID treated with HSCT. The median follow-up after transplantation was 6.5 years (range: 1.6 to 27.6 years). Overall survival was reported as 67%, varying from 29% after HSCT from a mismatched unrelated donor (MMUD) to 86% after HSCT from an MSD. In the overall cohort of 106 children, the mean time to death after transplant was 142 days, and the median time was 54 days (range 1 day to 2 years) [Hassan, 2012]. Analysis of the Kaplan-Meier curves appears to indicate that all deaths in patients who received an HSCT from a MUD occurred within 6 months and all deaths in patients who received an HSCT from a haploidentical donor occurred within 1 year [Hassan, 2012]. We therefore assumed that the probability of death after 3 years for patients who receive an HSCT from a MUD or a haploidentical donor is the same as the general England/Wales population.

The only costs that are incurred beyond the study follow-up period are drug and treatment costs for IVIG. The assumptions and calculations for these IVIG costs are discussed in Section 12.2.6.

12.2.3 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used and what other evidence is there to support it?

Intermediate outcome measures are not linked to final outcome measures in the model. Although intermediate outcome measures (such as vector copy number and engraftment) would be expected to correlate with final outcome measures (specifically survival), these intermediate outcome measures were not used in the model because data are available on final outcome measures over a long-term follow-up period.

12.2.4 Were adverse events included in the cost-effectiveness analysis? If appropriate, provide a rationale for the calculation of the risk of each adverse event.

GvHD is included in the model as a treatment-related AE after an HSCT from a MUD or haploidentical donor. The calculation and rationale for the estimates used for the probability of GvHD are contained in Section 12.2.1.

AEs related to conditioning regimens were not included in the cost-effectiveness analysis because no quantified data are available. This is a conservative assumption for Strimvelis because Strimvelis uses a low-dose busulfan conditioning regimen whereas some HSCT protocols use full-dose chemotherapy regimens [Hassan, 2012] and AEs may be dose-dependent [Busulfan SmPC, 2016].

12.2.5 Provide details of the process used when the sponsor's clinical advisers assessed the applicability of available or estimated clinical model parameter and inputs used in the analysis.

Clinical advice was sought from Dr. Andrew Gennery, a leading UK HSCT Transplantation expert with clinical experience of managing patients with ADA-SCID in the UK. Dr. Gennery was the only expert approached and agreed to participate in this advice seeking activity. No conflict of interest was identified on declaration. Dr. Gennery is a Clinical Reader in Paediatric Immunology and Bone Marrow Transplantation at a UK University Hospital. The advice seeking activity was a direct interview held at the hospital.

The questions asked focused on the diagnosis and management pathways of patients with ADA-SCID in England with respect to

- duration, clinical course and cost from diagnosis to interventions

- donor search pathways in England and associated cost to perform these
- proportions of patients with ADA-SCID without an MRD and management pathways used in England for these patients including cost
- validation of literature figures used in our models to reflect practice in England (eg. rates of HSCTs from haploidentical donors and MUDs, rate of rescue transplants)
- follow up management pathway and cost in England, including the need of other treatments (eg. IVIG use, PEG-ADA)
- clinical outcomes following current management pathways of ADA-SCID in England, including rates of severe infection, GVHD, and child growth

Dr. Gennery's recommendations were incorporated in the model. Any remaining uncertainty was explored using sensitivity analyses.

12.2.6 Summarise all the variables included in the cost-effectiveness analysis. Provide cross-references to other parts of the submission.

Details on the variables used in the analysis and the values selected are given in Table D 5. Where available, variables from the Strimvelis clinical programme and the literature searches previously described were used. In some cases, data were not available from the Strimvelis clinical programme or the available literature on HSCT from a MUD or haploidentical donor for the treatment of ADA-SCID.

Patients in the Strimvelis clinical programme are at various stages of follow-up, and cost data are not available in some instances. Reporting of data on some topics in the literature related to HSCT from a MUD or haploidentical donor for the treatment of ADA-SCID is incomplete and extremely limited. In these cases, we took a conservative stance using data from relevant similar medical conditions and provided the justification for using this information or assuming rates for HSCT similar to Strimvelis. Cost data were obtained from pragmatic searches for specific costs and Hettle, 2017.

Table D 5 Summary of variables applied in the cost-effectiveness model

Variable	Baseline Value	Notes
Overall Survival		
Strimvelis: first 6 months	18/18 (100%)	[Cicalese, 2016]

Variable	Baseline Value	Notes
Strimvelis: 6 months - 100 years	100% until the end of Year 3 and general population survival curve changes thereafter	No deaths were observed within a median follow-up time of 6.9 years [Cicalese, 2016].
HSCT from a MUD: first 6 months	10/15 (67%)	[Hassan, 2012]
HSCT from a MUD: 6 months - 100 years	10/15 (67)% until Year 3 and general population survival curve thereafter	Kaplan-Meier OS curves showed no deaths after approximately 1 year for patients who received an HSCT from a MUD or haploidentical donor. The median follow-up time after transplantation was 6.5 years (range 1.6 to 27.6 years) [Hassan, 2012].
HSCT from a haploidentical donor: at 6 months	5/7 (71%)	GSK and NICE agreed at the HST scoping meeting that the 71% OS after HSCT from a haploidentical donor recorded in Hassan (2012) for the 2000-2009 cohort of 7 patients is a better reflection of survival than the 43% recorded for the entire Hassan cohort (n=30) [Hassan, 2012].
HSCT from a haploidentical donor: 1 - 100 years	5/7 (71%) until the end of Year 3 and general population survival curve changes thereafter	Kaplan-Meier OS curves showed no deaths after approximately 1 year for patients who received an HSCT from a MUD or haploidentical donor. The median follow-up time after transplantation was 6.5 years (range 1.6 to 27.6 years) [Hassan, 2012].

Variable	Baseline Value	Notes
Rescue HSCT	100% first 6 months and general population survival curve changes thereafter	Based on high survival rate expected after HSCT from an MSD. The 2 patients who required a rescue transplant after Strimvelis both survived. For patients who required a rescue transplant after HSCT from a MUD or haploidentical donor, Hassan did not describe when these rescue transplants took place [Hassan, 2012]. Survival after HSCT from an MSD is likely not 100%, but survival has improved from that previously reported [Hassan, 2012]. Recent data have not been reported, so for simplicity we have set this survival rate to 100%. We explored the effects of a lower rescue transplant survival rate in the sensitivity analyses.
Clinical (Probabilities)		
Strimvelis: severe infections	26% for the first 3 years, 7% for Years 4-8	Rates are per person per year based on rates observed in the Strimvelis Integrated Population
HSCT from a MUD or haploidentical donor: severe infections	26% for the first 3 years, 7% for Years 4-8	Rates are per person per year and assumed to be the same as that observed with Strimvelis. Expert clinical advice confirmed this assumption.
Strimvelis: rescue transplant	3/17 (17.6%)	Based on patients in the Strimvelis Integrated Population who had an unsuccessful response to Strimvelis. See Section 12.2.1

Variable	Baseline Value	Notes
HSCT from a MUD: rescue transplant	1/15 (6.7%)	[Hassan, 2012]
HSCT from a haploidentical donor: rescue transplant	2/7 (28.6%)	[Hassan, 2012)] and see Section 12.2.1
Rescue transplant donor source	100% MSD	Hassan reported that the patient in the 2000-2009 haploidentical donor cohort that received rescue transplant received 2 rescue MSD HSCTs (from a newly born sibling) after failure to engraft [Hassan, 2012]. Additionally, in the Strimvelis clinical programme, 2 patients received rescue transplants from MSDs (from newly born siblings). The possibility of using a MUD as the donor source for some rescue transplants were explored in the sensitivity analyses.
Strimvelis: IVIG use after procedure	Year 1: 18/18 (100%) Year 3: 10/17 (58.8%) Year 8: 0/4 (0%) Linear interpolation between points	Based on use of IVIG in the Strimvelis Integrated Population. See Section 12.2.1
HSCT from a MUD or haploidentical donor: IVIG use after procedure	Year 1: 18/18 (100%) Year 3: 10/17 (58.8%) Year 8: 0/4 (0%) Linear interpolation between points	It was conservatively assumed that IVIG use rates after HSCT from a MUD or haploidentical donor would be similar to rates observed in the Strimvelis clinical programme.
Strimvelis: GvHD	0%	GvHD is not observed with Strimvelis.
HSCT from a MUD: severe aGvHD	3/28 (10.7%)	Based on reports in the literature. See Section 12.2.1 for detail
HSCT from a MUD: severe cGvHD	1/28 (3.6%)	Based on reports in the literature. See Section 12.2.1 for detail

Variable	Baseline Value	Notes
HSCT from a haploidentical donor: severe aGvHD	1/9 (11.1%)	Based on reports in the literature. See Section 12.2.1 for detail
HSCT from a haploidentical donor: severe cGvHD	0/9 (0%)	Based on reports in the literature. See Section 12.2.1 for detail
Timing and Duration		
Duration of PEG-ADA before Strimvelis	9 weeks	Based on clinical schedule from San Raffaele Hospital. Assumes no search for a MUD is conducted.
Duration of PEG-ADA before HSCT from a MUD	19 weeks	[Gaspar, 2013]
Duration of PEG-ADA before HSCT from a haploidentical donor	19 weeks	Assumes an unsuccessful search for a MUD was conducted before HSCT from a haploidentical donor was considered.
Timing of rescue transplant	2 years after initial Strimvelis or HSCT procedure (in Year 3).	GSK was advised by a clinical expert that rescue transplants typically occur 2 years after the initial procedure, which would be Year 3 in the model. It was assumed that patients do not receive PEG-ADA in the 3 months after the failure of the initial procedure.
Duration of PEG-ADA use in bridge to rescue transplant	1.75 years	Assumed average duration of continuous PEG-ADA use until rescue intervention was 2 years for each treatment, but no PEG-ADA administered in first 3 months.
Duration aGvHD	8 months	Clinical advice is that Grade 3-4 aGvHD episodes last between 6 and 12 months.

Variable	Baseline Value	Notes
Duration cGvHD	3 years	GSK was advised that cGvHD could last from a few months to several years, but that cGvHD cases would normally be resolved by the time of a rescue transplant. The duration of cGvHD episodes was therefore conservatively taken to be 3 years.
Dosing		
Annual number of PEG-ADA doses	52	Once per week administration
IVIG dose	0.4 g/kg every 3 weeks	The recommended dosing range is 0.2-0.8 g/kg/month [Gammagard SmPC, 2016]. A 0.4 g/kg individual dose was chosen based on clinical advice The steady state dosing regimen range is 2-4 weeks [Gammagard SmPC, 2016]. The dosing interval was assumed to be every 3 weeks, the midpoint of the 2-4-week range. 25th percentile of population growth curve used to estimate the actual dose.
Annual IVIG doses	17	The 3-week dosing interval corresponds to 17.3 doses per year.
Cost		
Price of IVIG per g	£40.10	Gammagard intravenous infusion 5 g = £200.50 [Medicines Complete, 2017]

Variable	Baseline Value	Notes
Price of PEG-ADA per week	£13,500	There is no list price for PEG-ADA in the UK, so information here is based on external expert clinical advice, which confirmed vial cost to the NHS service.
Cost of IVIG or PEG-ADA administration	£306	National Schedule of Reference Costs 2015-2016. Paediatric Clinical Immunology And Allergy Service. Currency Code WF01A Service code 255
Cost per severe infection (all comparators)	£12,143	A study of the predictors of stem-cell transplantation costs found that 15% of total hospital costs were due to severe infection costs [Lee, 2000]. We used this total hospital cost percentage and applied this to the cost of a severe infection after treatment with Strimvelis or HSCT from a MUD or haploidentical donor.
Cost of a severe GVHD episode (acute or chronic), (to be applied within one model cycle after an HSCT, primary or rescue transplant)	£29,420	A retrospective analysis of readmission rates and associated costs in 2010 in 187 consecutive allogeneic transplant patients to assess the impact of GvHD found that the mean cost of readmission in patients with Grade III/IV GvHD was £26,607 more than the cost for patients without GvHD [Dignan, 2013]. This figure was adjusted for inflation using an annual increase of prices (2010-2016) of 10.6% [PSSRU Report, 2016]. Emerging treatments for GvHD could significantly increase the cost of treatment of GvHD, but the cost-effectiveness analysis was conservatively based on historic costs.

Variable	Baseline Value	Notes
Rescue transplant	£95,516	Rescue transplant cost assumed to be the same as the cost of HSCT from a MUD. As this would be from an MSD in the base-case, no cost of searching for a donor is added. UK Reference Cost (2015-16), SA22B, Bone Marrow Transplant, Allogeneic Graft (Cord Blood), 18 years and under
Rescue transplant follow-up	£59,541	Assumed to be the same cost as follow-up for HSCT from a MUD

Variable	Baseline Value	Notes
Utilities		
Health utility in the period before HSCT or Strimvelis	0.98	For simplicity, we do not consider the potential disutility patients incur whilst waiting for Strimvelis or HSCT (e.g. due to being in isolation and receiving PEG-ADA). Given that patients receiving Strimvelis are likely to wait less than patients receiving HSCT, this is a conservative assumption
IVIG disutility	No disutility	No decrement in utility due to the use of IVIG was applied in the base-case (see Section 10.1.9). This is likely to have little impact given that we conservatively assumed the rates of IVIG use in Strimvelis and HSCT to be the same, but the consideration of disutility due to IVIG was fully explored in the sensitivity analyses.
Age-specific utilities	See Section 10.1.9	There is no literature on non-immune related disutility for ADA-SCID patients. Therefore, the model uses England EQ-5D scores by age band with values drawn from the Jones-Hughes analysis of the Health Survey for England - 2012 [Jones-Hughes, 2016] using the methodology of Ara [Ara, 2010]. This was fully explored in the sensitivity analyses.

Variable	Baseline Value	Notes
Utility decrement during the first 6 months after Strimvelis, HSCT from a MUD or haploidentical donor, or rescue transplant	0.57	No data are available for utility scores after HSCT or Strimvelis for patients with ADA-SCID. The value from Sung of a decrement of 0.57 after BMT in the study of patients with acute myeloid leukaemia [Sung, 2003] was used. This source was identified during review of the analysis by Hettle et al [Hettle, 2017].
One-off QALY loss due to a utility decrement from acute GvHD	0.41	The utility value for patients with acute GvHD and complete remission from relapsed/refractory Hodgkin lymphoma or systemic anaplastic large cell lymphoma [Swinburn, 2015] was used to calculate a utility decrement and then adjusted based on the expected average duration of an episode of acute GvHD (8 months) based on expert advice. See Section 10.1.9
One-off QALY loss due to a utility decrement from chronic GvHD	1.44	Utility value for patients with chronic GvHD and complete remission from relapsed/refractory Hodgkin lymphoma or systemic anaplastic large cell lymphoma [Swinburn, 2015] was used to calculate a utility decrement and then adjusted based on the expected duration of an episode of chronic GvHD (3 years) based on expert advice. See Section 10.1.9

Abbreviations: aGvHD=acute graft versus host disease; ADA-SCID=adenosine deaminase-severe combined immunodeficiency; cGvHD=chronic graft versus host disease; FU=follow-up; GvHD=graft versus host disease; GSK=GlaxoSmithKline; HSCT=haematopoietic stem cell transplantation; IVIG=intravenous immunoglobulin; MUD=matched unrelated donor; NA=not applicable; NICE=National Institute for Clinical Excellence; OS=overall survival; QALY=quality-adjusted life years; PEG-ADA=polyethylene glycol-modified bovine adenosine deaminase; SmPC=summary of product characteristics; UK=United Kingdom

Additional information on costs applied in the model is provided in Section 12.3.6.

Strimvelis costs by stage of treatment

Strimvelis is the transduced cell product and should not be confused with gene therapy, which is a broader term referring to all of the procedures that take place as part of delivering Strimvelis to patients. Strimvelis is registered as an advanced therapeutic medicinal product (ATMP) and was granted marketing authorisation by the EMA. There are 3 basic elements of cost associated with sending a patient to Milan for gene therapy. The first element of the cost is Strimvelis. The second element of cost is all the related hospital procedures, including screening, baseline tests, bone marrow sample, chemotherapy, infusion of Strimvelis, recovery in isolation room and outpatient follow-up. The third element of cost is the patient support, such as accommodation, food, and transport services as well as travel to/from Milan. Patient support is not included in the model.

Some of the costs of confirmation of eligibility and follow-up for Strimvelis are included in the initial hospitalisation costs (Table D 6).

After treatment in Milan, there are follow-up costs similar to the follow-up costs of HSCT.

Table D 6 Costs of Strimvelis by stage of treatment

Stage	Average Duration (Range)	Cost
Confirmation of Eligibility for Strimvelis Treatment	24 days, performed in England	[redacted]
Baseline patient preparation (CVC placement, obtain bone marrow back-up)	31 days (31-45 days), including 3 day inpatient stay	[redacted] initial hospitalisation cost; these costs exclude the cost of Strimvelis
Treatment	50 days in isolation room (may be longer if complications occur)	
Outpatient follow-up in Milan	60 days (60-90 days)	
Outpatient follow-up in England	4 months	[redacted]
	Continued for lifetime as per routine care for all patients with ADA-SCID	[redacted]

Abbreviations: CVC= central venous catheter; UK=United Kingdom; VCN=vector copy number.

Calculation of drug costs – PEG-ADA

There is no list price for PEG-ADA in the UK, so information here is based on expert clinical advice, which confirmed vial cost to the NHS service of £9,000 per vial. According to expert clinical advice, patients receive 1 to 2 vials per

week, which results in an average cost of PEG-ADA per patient of £13,500 per week.

The annual cost for PEG-ADA was then calculated from:

(Average price of PEG-ADA per week * Annual PEG-ADA doses) + (Annual PEG-ADA doses * Infusion cost for PEG-ADA)

Calculation of drug costs - IVIG

Annual costs for IVIG are based on the average weight of boys and girls in the UK (Table D 7, Figure 7) [Royal College of Paediatrics and Child Health (RCPCH), 2013)]. The 25th percentile was used.

The cost of IVIG was calculated from:

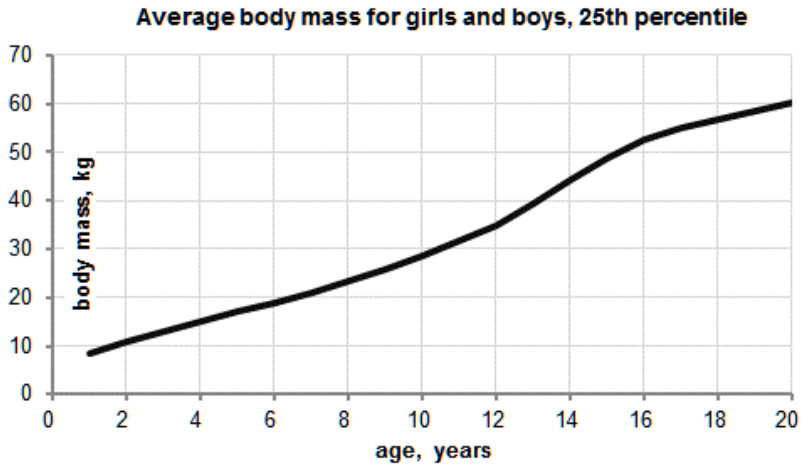
(Projected weight [from exponential curve] * IVIG monthly dose g/kg * Price of IVIG per g * 12 months/year) + (Infusion cost for IVIG * Annual IVIG doses)

Table D 7 25th percentile weight (kg) by age (years) in the United Kingdom [RCPCH, 2013]

Age	Boys	Girls	Both
1	9.00	8.20	**8.6**
2	11.20	10.50	**10.9**
3	13.20	12.70	**13.0**
4	15.15	15.00	**15.1**
5	17.20	16.90	**17.1**
6	19.10	18.70	**18.9**
7	21.10	20.90	**21.0**
8	23.30	23.40	**23.4**
9	25.70	25.80	**25.8**
10	28.30	28.80	**28.6**
11	31.20	31.90	**31.6**
12	34.20	35.60	**34.9**
13	38.30	40.50	**39.4**
14	43.70	45.00	**44.4**
15	49.30	48.30	**48.8**
16	54.40	50.50	**52.5**
17	58.40	51.80	**55.1**
18	61.00	52.70	**56.9**

An exponential curve was fitted to these data (Figure 7).

Figure 7 Line applied to United Kingdom weight data



12.3 Resource identification, measurement and valuation

NHS costs

12.3.1 Describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff.

The cost used for the initial hospitalisation for HSCT from a MUD is £95,516, which is the national average unit cost for 'Bone Marrow Transplant, Allogeneic Graft (Volunteer Unrelated Donor), 18 years and under' Currency Code SA21B. [National Schedule of Reference Costs - Year 2015 - 16 NHS trusts and NHS foundation trusts]. The corresponding cost used for HSCT from a haploidentical donor is £108,760, which is the national average unit cost for 'Bone Marrow Transplant, Allogeneic Graft (Haplo-Identical), 18 years and under' Currency Code SA23B. [National Schedule of Reference Costs - Year 2015 - 16 NHS trusts and NHS foundation trusts].

The costs used for each IVIG or PEG-ADA administration (if required) is £306 [National Schedule of Reference Costs - Year 2015-16 - NHS trusts and NHS foundation trusts - Consultant Led. Paediatric Clinical Immunology and Allergy Service. Currency Code WF01A; Service code 255].

Resource identification, measurement and valuation studies

12.3.2 Provide a systematic search of relevant resource data for the NHS in England. Include a search strategy and inclusion criteria, and consider published and unpublished studies.

Given the scarcity of published data on ADA-SCID, resource data were not included in the systematic review. A pragmatic literature review was

conducted for those resources used in patient treatment, and Hettle 2017 was used as a guide. The results are summarised in Section 12.2.6.

12.3.3 Provide details of the process used when clinical advisers assessed the applicability of the resources used in the model[2].

Clinical advice was sought from Dr. Andrew Gennery, a leading UK HSCT Transplantation expert with clinical experience of managing patients with ADA-SCID in the UK. Dr. Gennery was the only expert approached and agreed to participate in this advice seeking activity. No conflict of interest was identified on declaration. Dr. Gennery is a Clinical Reader in Paediatric Immunology and Bone Marrow Transplantation at a UK university Hospital. The advice seeking activity was a direct interview held at the hospital

The questions asked focused on the diagnosis and management pathways of patients with ADA-SCID in England with respect to

- duration, clinical course and cost from diagnosis to interventions
- donor search pathways in England and associated cost to perform these
- proportions of patients with ADA-SCID without an MRD and management pathways used in England for these patients including cost
- validation of literature figures used in our models to reflect practice in England (eg. rates of HSCTs from haploidentical donors and MUDs, rate of rescue transplants)
- follow up management pathway and cost in England, including the need of other treatments (eg. IVIG use, PEG-ADA)
- clinical outcomes following current management pathways of ADA-SCID in England, including rates of severe infection, GVHD, and child growth

Health economics advice was sought from Professor Andrew Briggs, Chair in Health Economics at the University of Glasgow, who has particular expertise in modelling techniques and assessment of uncertainty.

The advice seeking activity was conducted via a direct interview. Prof. Andrew Briggs provided extensive feedback on the structure of the model, the validity

[2] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

of the modelling approach and inputs used, ways to explore uncertainty, and the way the modelling techniques and assumptions were reported.

Prof. Andrew Briggs' recommendations were incorporated in the model. Any remaining uncertainty was explored using sensitivity analyses.

Technology and comparators' costs

12.3.4 Provide the list price for the technology.

The complete price of Strimvelis and the procedure in Milan is £505,000.

12.3.5 If the list price is not used in the de novo cost-effectiveness model, provide the alternative price and a justification.

Not applicable.

12.3.6 Summarise the annual costs associated with the technology and the comparator technology (if applicable) applied in the cost consequence model. Please consider all significant costs associated with treatment that may be of interest to commissioners.

The estimated total cost associated with the technology per patient for Strimvelis is [redacted] (Table D 8), the calculated total cost associated with the technology per patient for HSCT from a MUD is £417,371 (Table D 9), and the calculated total cost associated with the technology per patient for HSCT for a haploidentical donor is £430,615 (Table D 10). Costs have been discounted at 1.5% where appropriate (see Table D 4 for rationale). Follow-up costs have not been discounted. The costs of severe infection, IVIG, rescue transplant and its follow-up costs, GvHD, or rescue PEG-ADA are not included in the total calculated costs for the technology but are included in the model.

Table D 8 Costs per treatment/patient associated with the technology in the cost-effectiveness model

Items	Value	Source
Initial PEG-ADA, before procedure	£124,254	Calculated from the model, based on estimated duration of PEG-ADA, cost per week, and cost of administration
Price of the technology per treatment/patient	£505,000	The cost of Strimvelis in Italy is €594,000 and currency conversion for the analysis is based on the average exchange rate 1€ = £0.85 on 08 May 2017 (source www.xe.com). Please note that the San

Items	Value	Source
		Raffaele Hospital is to be paid €594,000 in euros for Strimvelis. Conversation with NHS England confirmed that they have contracts in place for another therapy to be paid in local currency so did not see this as a concern.
Confirmation of Eligibility for Strimvelis Treatment	[redacted]	
Administration cost	[redacted]	The cost of the hospital stay in Italy and any patient follow-up required during the time in Italy is [redacted]. Currency conversion is based on the average exchange rate 1€ = £0.85 on 08 May 2017 (source www.xe.com)
Follow-up costs	[redacted] per living patient[a]	UK Stem Cell Oversight committee report [redacted] Note: assumed first 2 months of follow-up are conducted in Italy so 0.3 of first 6 months' costs are included in Italian hospital charge.
Total cost per treatment/patient	[redacted]	

Abbreviations: IVIG=intravenous immunoglobulin; NHS=National Health Service; PEG-ADA=polyethylene glycol-modified bovine adenosine deaminase; UK=United Kingdom; VCN=vector copy number

[a] These are the short-term costs associated with the Strimvelis procedure. The total does not include long-term costs such as IVIG, PEG-ADA, and VCN monitoring costs.

Table D 9 Costs per treatment/patient associated with the comparator technology HSCT from a MUD in the cost-effectiveness model

Items	Value	Source
Initial PEG-ADA before procedure and screening	£262,314	Calculated from the model, based on estimated duration of PEG-ADA, cost per week, and cost of administration
Initial hospitalisation	£95,516	'Bone Marrow Transplant, Allogeneic Graft (cord blood), 18 years and under' Currency Code SA22B. [National Schedule of Reference Costs - Year 2015 - 16 NHS trusts and NHS foundation trusts]
Follow-up costs	£59,541 per living patient	[This figure is based on total follow-up estimates of €62,096 [van Agthoven, 2002], adjusted for inflation (Netherlands inflation index for category Health Expenditures [060000]), and converted to pounds (exchange rate 1€ = £0.85 on 08 May 2017 (source www.xe.com)).
Total cost per treatment/patient	**£417,371**	

Abbreviations: HSCT=haematopoietic stem cell transplantation; MUD=matched unrelated donor; NHS=National Health Service; PED-ADA=; PEG-ADA=polyethylene glycol-modified bovine adenosine deaminase; UK=United Kingdom

Table D 10 Costs per treatment/patient associated with the comparator technology HSCT from a haploidentical donor in the cost-effectiveness model

Items	Value	Source
Initial PEG-ADA before procedure and screening	£262,314	Calculated from the model, based on estimated duration of PEG-ADA, cost per week, and cost of administration
Initial hospitalisation	£108,760	'Bone Marrow Transplant, Allogeneic Graft (Haplo-Identical), 18 years and under' Currency Code SA23B [National Schedule of Reference Costs - Year 2015 - 16 NHS trusts and NHS foundation trusts]
Follow-up costs	£59,541 per living patient	Assumed to be the same cost as follow-up for HSCT from a MUD.
Total cost per treatment/patient	**£430,615**	

Abbreviations: HSCT=haematopoietic stem cell transplantation; NHS=National Health Service; PEG-ADA=; PEG-ADA=polyethylene glycol-modified bovine adenosine deaminase; UK=United Kingdom

Health-state costs

12.3.7 If the cost-effectiveness model presents health states, the costs related to each health state should be presented in Table D 11. The health states should refer to the states in Section 12.1.6. Provide a rationale for the choice of values used in the cost-effectiveness model.

Table D 11 shows the cost categories that are applied to each of the health states in the model. Section 12.2.6 shows the unit cost data used in the model, and, for those costs which are cycle dependent, shows how the values were derived. Total costs by health state are shown in Section 12.5.5.

Table D 11 List of health states and associated costs in the cost-effectiveness model

	Health state			
Cost Category	(1) 'PEG ADA awaiting Strimvelis' and 'PEG-ADA and screening for a MUD'	(2) 'Success, long term survival'	(3) 'Unsuccessful engraftment, PEG-ADA, awaiting rescue HSCT'	(4) 'Long term survival after rescue HSCT'
Product	Product cost applies to Strimvelis only and is notionally apportioned to each health state using the probability of being in each health state in Cycle 1			
Severe infection	Probability of severe infection by type of intervention (first 8 yrs only) cost of severe infection	Probability of severe infection by type of intervention (first 8 yrs only) cost of severe infection	Probability of severe infection by type of intervention (first 8 yrs only) cost of severe infection	Probability of severe infection following rescue transplant (first 8 yrs only) cost of severe infection
Rescue transplant	NA	NA	NA	Cost of rescue transplant
Rescue PEG-ADA	NA	NA	Cost of PEG-ADA (value is cycle dependent)	NA
Initial hospitalisation	Hospital cost by type of intervention	Hospital cost by type of intervention	Hospital cost by type of intervention	NA
Follow-up	Cost of follow-up	Cost of follow-up	Cost of follow-up	Cost of rescue transplant follow-up
IVIG	Cost of IVIG (value is cycle dependent)	Cost of IVIG (value is cycle dependent)	Cost of IVIG (value is cycle dependent)	Cost of IVIG (value is cycle dependent)
GvHD	Probability of GvHD by type of intervention cost of GvHD	Probability of GvHD by type of intervention cost of GvHD	Probability of GvHD by type of intervention cost of GvHD	Probability of GvHD by type of intervention after rescue transplant cost of GvHD

Abbreviations: GvHD=graft versus host disease; IVIG=intravenous immunoglobulin; NA=not applicable; PEG-ADA=polyethylene glycol-modified bovine adenosine deaminase.

Adverse-event costs

12.3.8 Provide details of the costs associated with each adverse event included in the cost-effectiveness model. Include all adverse events and complication costs, both during and after longer-term use of the technology.

The only relevant AE associated with treatment for this analysis is the risk of GvHD after HSCT from a MUD or a haploidentical donor (as the initial intervention or as a rescue transplant). Serious infections are possible, but these may be considered an outcome of the disease rather than the treatment. Treatment with either Strimvelis or HSCT decreases the incidence of serious infections.

The costs of GvHD were drawn from the UK study by Dignan et al. The authors conducted a retrospective analysis of readmission rates and associated costs in 187 consecutive allogeneic transplant patients. Higher readmission rates were associated with GvHD both in the first 100 days from transplant ($p=0.02$) and in the first year following transplant ($p<0.001$). The mean cost of readmission for patients with severe (Grade III/IV) GvHD was £26,607 more than the cost of readmission for patients without GvHD [Dignan, 2013]. This figure was adjusted for inflation using an annual increase of prices (2010-2016) of 10.6% [PSSRU Report, 2016] (the base-case value is £29,420). Given the lack of data in this area, we assumed that there are no 'on-going' GvHD costs. Note that this is a conservative assumption against Strimvelis.

Miscellaneous costs

12.3.9 Describe any additional costs and cost savings that have not been covered anywhere else (for example, PSS costs, and patient and carer costs). If none, please state.

Travel, lodging, meals, and other patient support services are not included in the price of Strimvelis. NHS England has referred GlaxoSmithKline to the commissioning policy on Proton Beam Therapy as representative of what NHS England would fund for a patient to be treated in another EU member state. The policy includes two parents (or a parent and a caregiver) to travel with the child as well as paying for accommodation during the stay in Milan. We have estimated that the total cost as €13,400, excluding the cost of public transport to and from the airport in the UK. This would include the cost of three economy class return airline tickets to a Milan airport at €900 (3*€300), accommodation in Milan for 4.5 months at €11,700 and local transport at €800. [redacted]

It should be noted that families of patients with ADA-SCID who are treated with HSCT must also usually travel to a specialty centre, where they typically

stay from diagnosis to treatment. The difference is that the travel for HSCT is within the UK.

12.3.10 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

The major advantage of Strimvelis over HSCT from a MUD or haploidentical donor is a reduction in mortality. Although we may expect reductions in the (quantified) costs of managing GvHD, no other resource savings are likely.

12.4 Approach to sensitivity analysis

12.4.1 Has the uncertainty around structural assumptions been investigated? State the types of sensitivity analysis that have been carried out in the cost-effectiveness analysis.

Yes. Structural assumptions were explored in the scenario analyses described in Section 12.4.3 to determine the impact on the results of varying these assumptions.

12.4.2 Was a deterministic and/or probabilistic sensitivity analysis undertaken? If not, why not? How were variables varied and what was the rationale for this? If relevant, the distributions and their sources should be clearly stated.

Yes. Deterministic, probabilistic, and scenario-based sensitivity analyses were undertaken. The variables used, together with the range of the variation (upper and lower values) and the method used, are summarised in Section 12.4.3.

12.4.3 Complete the tables below as appropriate to summarise the variables used in the sensitivity analysis.

Variables used in the 1-way sensitivity analysis are shown in Table D 12.

The variables used for the probabilistic sensitivity analysis are summarised in Table D 13. In general, survival probabilities, clinical probabilities, and utility inputs were sampled from beta distributions whereas costs were sampled from gamma distributions. For hospital and follow-up costs, we set the standard error to be 25% of the mean costs.

For post-intervention survival, the natural mortality curve of the population of England/Wales was used for all interventions.

Table D 12 Variables used in 1-way scenario-based deterministic sensitivity analysis

	Baseline values	Lower value	Upper value
Variation to discount rates			
Costs	1.5%	0%	3.5%
Outcomes	1.5%	0%	3.5%
Costs and outcomes at 0%	1.5%, 1.5%	0%	
Costs at 3.5%, with outcomes fixed at 1.5%	1.5%, 1.5%	1.5%, 1.5%	3.5%, 1.5%
Costs and outcomes at 3.5%	1.5%, 1.5%	3.5%	
Survival[a]			
HSCT from a MUD - survival 1st 6 months	67%	NA	83.75%
HSCT from a haploidentical donor - survival 1st 6 months	71%	NA	88.75%
Rescue HSCT	100%	67%	NA
All interventions - mean life expectancy of survivors reduced by 10%	79.9 years	71.9 years	NA
All interventions - mean life expectancy of survivors reduced by 20%	79.9 years	63.9 years	NA
Clinical (probabilities)			
Severe infection – Strimvelis first 3 years – other interventions as per baseline	26%	NA	42.9%[b]
Severe infection - HSCT from a MUD first 3 years – other interventions as per baseline	26%	NA	42.9%[b]
Severe infection - HSCT from a haploidentical donor first 3 years – other interventions as per baseline	26%	NA	42.9%[b]
Rescue transplant - Strimvelis – other interventions as per baseline	17.6%	8.3%[e]	[redacted]
Rescue transplant - HSCT from a MUD – other interventions as per baseline	6.7%	5%	8.3%

	Baseline values	Lower value	Upper value
Rescue transplant - HSCT from a haploidentical donor – other interventions as per baseline	28.6%	21.4%	35.7%
Second rescue transplant after HSCT from a haploidentical donor	0%	NA	50%
IVIG - Strimvelis (from Year 8 and onwards) – other interventions as per baseline	0%	NA	20%[d]
IVIG - HSCT from a MUD (from Year 8 and onwards) – other interventions as per baseline	0%	NA	20%[d]
IVIG - HSCT from a haploidentical donor (from Year 8 and onwards) – other interventions as per baseline	0%	NA	20%[d]
Severe acute GvHD - HSCT from a MUD – other interventions as per baseline (+/-50%)	10.7%	5.0%	16.0%
Severe acute GvHD - HSCT from a haploidentical donor (+/-50%)	11.1%	5.6%	17.0%
Severe chronic GvHD - HSCT from a MUD – other interventions as per baseline	3.6%	0%	7.2%
Severe chronic GvHD - HSCT from a haploidentical donor – other interventions as per baseline	0%	NA	3.6%[e]

	Baseline values	Lower value	Upper value
Timing and Duration			
Duration of PEG-ADA before Strimvelis – other interventions as per baseline	9 weeks	7	11
Duration of PEG-ADA before HSCT from a MUD – other interventions as per baseline	19 weeks	17	21
Duration of PEG-ADA before HSCT from a MUD – other interventions as per baseline	19 weeks	9	29
Duration of PEG-ADA before HSCT from a haploidentical donor – other interventions as per baseline	19 weeks	17	21
Timing of rescue transplant	2 years after initial Strimvelis or HSCT procedure (in Year 3).	1	3
Duration of PEG-ADA use in bridge to rescue transplant, all interventions	1.75 years	1.5	2.0
Costs			
Price of IVIG per gram (+/- 25%)	£40.10	£30.08	£50.13
Price of PEG-ADA per week	£13,500	£10,125	£16.875
Price of PEG-ADA per week, 50% of basecase	£13,500	£6,750	NA
Price of PEG-ADA per week, 25% of basecase	£13,500	£3,375	NA
Price of PEG-ADA per week, 10% of basecase	£13,500	£1,350	NA
Cost of IVIG and PEG-ADA administration	£306	£229.50	£382.50
Cost of screening for a donor for a SCT (initial transplantation)	£45,127	£33,845	£56,409
Confirmation of eligibility for Strimvelis treatment plus initial hospitalisation - Strimvelis	[redacted]	[redacted]	[redacted]

	Baseline values	Lower value	Upper value
Initial hospitalisation - HSCT from a MUD (note also impacts cost of rescue transplant)	£95,516	£71,637	£119,395
Initial hospitalisation - HSCT from a haploidentical donor	£108,760	£81,570	£135,950
Follow-up - Strimvelis	[redacted]	[redacted]	[redacted]
Follow-up - HSCT from a MUD (note - also impacts cost of rescue transplant)	£59,541	£44,656	£74,426
Follow-up - HSCT from a haploidentical donor	£59,541	£44,656	£74,426
Severe infection - all interventions	£12,143	£9,107	£15,179
Severe GvHD - all interventions	£29,420	£22,065	£36,775
Rescue transplant (note assumes cost of rescue transplant changes but cost of MUD stays as per baseline)	£95,516	£71,637	£119,395
Utilities and QALY adjustments			
Health utility in the period before HSCT or Strimvelis	0.98	0.49	1.0
Weight for IVIG disutility (with duration for 20 years)	1 (i.e., no disutility)	0.75	NA
Utilities by age band[f]	See Section 10.1.9	x 0.95 reduced	x 1.05 increased
Utility decrement during the first 6 months after Strimvelis, HSCT from a MUD or haploidentical donor, or rescue transplant (maximum variation applied)	0.57	1	0
Bereaved parent QALY loss associated with child's death	none	none	accounted for[g]
One-off QALY loss due to a utility decrement from acute GvHD (+/-25%)	0.41	0.3	0.5
One-off QALY loss due to a utility decrement from chronic GvHD (+/-25%)	1.44	1.1	1.8

Abbreviations: aGvHD=acute graft versus host disease; cGvHD=chronic graft versus host disease; GvHD=graft versus host disease; HSCT=haematopoietic stem cell transplantation; IVIG=intravenous immunoglobulin; LT=long-

term; MUD=matched unrelated donor; mths=months; NA=not applicable; PEG-ADA=polyethylene glycol modified bovine adenosine deaminase.

a. For survival (mean life expectancy for survivors), the value of 79.91 years was reduced to 71.97 (note. for HSCT from a MUD or haploidentical donor, this was achieved by first setting immediate survival to 100%, reducing mean survival time, and then resetting immediate survival to the original figure).
b. Based on data from the Strimvelis Pivotal Population.
c. The upper value for rescue transplantation after Strimvelis therapy was calculated by [redacted]Information on the Named Patient Programme is extremely limited and not well validated. These patients were included on a compassionate use basis and may not be typical of patients in England who would receive Strimvelis.[redacted]
d. In the Strimvelis Integrated Population, 1 patient with at least 8 years of follow-up remained on IVIG. The patient remained on long-term PEG-ADA. In the base-case, we assumed that this patient will receive rescue transplant in England. For the sensitivity analysis, we included this patient's use of IVIG.
e. Set to match the rate from the literature for HSCT from a MUD [Hassan, 2012].
f. Weights for utilities were increased by 25% and set at unity if the result was greater or equal to 1. Utility weights by age for the upper estimate are therefore 1.0 for all age bands except 75+ years (0.9625). Weights for lower estimate are reduced by 25%: <25 years, 0.7125; 25-34, 0.69; 35-44, 0.6675; 45-54, 0.645; 55-64, 0.63; 65-74, 0.6; 75+, 0.5775.
g. Following Christensen et al (2014), the additional quality of life-related QALY loss experienced by a bereaved family was assumed to be 9% of the child's QALY loss. The child is assumed to die in the first half year cycle (Year 0.5), and the discounted QALY loss of the child was calculated as the difference between the general population survival and the HSCT survival, integrated from Year 1 to Year 100. The child's discounted QALY losses are 23 and 20 QALYs for HSCT from a MUD or from a Haplo, respectively. The additional QALY loss experienced by the bereaved family is 9% of the child's loss: 2.1 and 1.8 QALYs for HSCT from a MUD or from a Haplo, respectively.

Multi-way sensitivity analysis was conducted. We addressed the possibility of lower long-term utility scores within this sensitivity analysis combined with the possibility of reductions to mean life expectancy. This analysis examined the combinations of reductions in mean life expectancy for survivors (MLS) (equal reductions for all treatments) with reductions in utility scores by age (equal reductions for all treatments). Both life expectancy and utility reductions are reduced by increments of 10% up to a maximum of a 20% reduction. Results for the (3*3) combinations are shown in Section 12.5.12.

Table D 13 Variables used in multi-way scenario-based sensitivity analysis

Variable	Baseline value	Notes
Survival		
Strimvelis - survival first 6 months	18/18 (100%)	Fixed value of 100%. No sampling in the multi-way sensitivity analysis
Strimvelis - survival after 6 months	normal population survival curve	Fixed - assumed normal population survival applies to post-intervention survivors
HSCT from a MUD - survival first 6 months	10/15 (67%)	Beta distribution: α = 10, β = 15, SE = 0.12
HSCT from a MUD - survival after 6 months	normal population survival curve	Fixed - assumed normal population survival applies to post-intervention survivors

Variable	Baseline value	Notes
HSCT from a haploidentical donor - survival first 6 months	5/7 (71%)	Beta distribution: α =21, β = 9, SE = 0.1
HSCT from a haploidentical donor - survival after 6 months	normal population survival curve	Fixed - assumed normal population survival applies to post-intervention survivors
Utilities		
Age-specific utility scores	See Section 10.1.9	Beta distributions. SDs from England EQ-5D scores by age: <25 (years), 0.008; 25-34, 0.006; 35-44, 0.007; 45-54, 0.012; 55-64, 0.013; 65-74, 0.012; 75+, 0.016. All SDs are from the SDs reported for the age bands in the University of York 1999 study.
First 6 months' utility score	0.43	Beta distribution. SEs set at 0.2 to return values generally within the 'plausible' range of 0.33-0.87 for Sung's baseline disutility value of 0.57 [Sung, 2003]
Weight for IVIG	1	Kept at unity (i.e., no disutility) in the PSA
Clinical (probabilities)		
IVIG - Strimvelis (at 8 years)	0/4 (0%)	No IVIG is given after year 8
IVIG - HSCT from a MUD (at 8 years)	0/4 (0%)	No IVIG is given after year 8
IVIG - HSCT from a haploidentical donor (at 8 years)	0/4 (0%)	No IVIG is given after year 8
Severe infection - Strimvelis	Years 1-3: 26% Years 4-8: 7%	Beta distribution: Years 1-3: α = 5.2, β = 14.8, SE = 0.10 Years 4-8: α = 1.4, β = 18.6, SE = 0.06
Severe infection – HSCT from a MUD	Years 1-3: 26% Years 4-8: 7%	Beta distribution: Years 1-3: α = 5.2, β = 14.8, SE = 0.10 Years 4-8: α = 1.4, β = 18.6, SE = 0.06
Severe infection – HSCT from a haploidentical donor	Years 1-3: 26% Years 4-8: 7%	Beta distribution: Years 1-3: α = 5.2, β = 14.8, SE = 0.10 Years 4-8: α = 1.4, β = 18.6, SE = 0.06

Variable	Baseline value	Notes
Rescue transplant - Strimvelis	3/17 (17.6%)	Beta distribution: α =3, β = 14, SE = 0.09
Rescue transplant - HSCT from a MUD	1/15 (6.7%)	Beta distribution: α = 1, β = 14, SE = 0.06
Rescue transplant - HSCT from a haploidentical donor	2/7 (28.6%)	Beta distribution: α = 9, β = 21, SE = 0.1
GvHD - Strimvelis	0%	Kept at 0%
GvHD (acute and chronic) - HSCT from a MUD	32.1%	Beta distribution: α = 6.4, β = 13.6, SE = 0.10
GvHD (acute and chronic) - HSCT from a haploidentical donor	33.3%	Beta distribution: α = 6.7, β = 13.3, SE = 0.10
Severe aGvHD-HSCT from a MUD	3/28 (10.7%)	Beta distribution: α = 3, β = 25, SE = 0.06
Severe aGvHD- HSCT from a haploidentical donor	1/9 (11.1%)	Beta distribution: α = 1, β = 8, SE = 0.10
Severe cGvHD - HSCT from a MUD	1/28 (3.6%)	Beta distribution: α = 1, β = 27, SE = 0.03
Severe cGvHD - HSCT from a haploidentical donor chronic	0/9 (0%)	Kept as 0% (conservative assumption for Strimvelis)
Duration of the initial treatment with PEG-ADA after diagnosis and during screening period	19 and 9 weeks in HSCT and Strimvelis procedures, respectively	Gamma distribution with SE assumed to be 25%. For 19-week duration (α = 16, β = 1.19); for 9-week duration (α = 16, β = 0.56)
Duration of rescue PEG-ADA	1.75 years	Time to rescue transplant is fixed at 2 years
Duration of IVIG	8 years	A gradual decline from an initial 100% rate to 58.8% at year 3, and to 0% at year 8; in sensitivity analysis, the year 8 IVIG use can be assumed >0%; in such case patients will continue receiving IVIG at that rate for life
Annual PEG-ADA doses	52	Fixed at weekly dose administration
IVIG dose g/kg/month	0.4	Gamma distribution, based on a mean of 0.4 and a 25% SE. (α = 16, β = 0.03)
Cost and cost-related data		

Variable	Baseline value	Notes
Severe infection	£12,143	Gamma distribution; SE set at 25% of mean (α = 16, β = 758.9). Separate calculation for each intervention
Strimvelis follow-up	[redacted]	Gamma distribution; SE set at 45% of mean (α = 16, β = 3,286). Separate calculation for each intervention
HSCT follow-up	£59,541	Gamma distribution; SE set at 25% of mean (α = 16, β = 3,721). Separate calculation for each intervention
Confirmation of eligibility for Strimvelis treatment and initial hospitalisation - Strimvelis	[redacted]	Gamma distribution; SE set at 25% of mean (α = [redacted], β = [redacted])
Initial hospitalisation – HSCT from a MUD	£95,516	Gamma distribution; SE set at 25% of mean (α = 16, β = 5,970)
Initial hospitalisation – HSCT from a haploidentical donor	£108,760	Gamma distribution; SE set at 25% of mean (α = 16, β = 6,798)
Rescue transplant	£95,516	Gamma distribution; SE set at 25% of mean (α = 16, β = 5,970)
GvHD	£29,420	Gamma distribution; SE set at 25% of mean (α = 16, β = 1839)
Cost of PEG-ADA per week	£13,500	Gamma distribution with a mean of £13,500 and SE = 1,800 (α = 56.2, β = 240)
Cost of PEG-ADA administration	£306	Gamma distribution; SE estimated at 25% of mean (α = 16, β = 19)
Price of IVIG per gram	£40.10	Known value - kept fixed in PSA
Cost of IVIG administration	£306	Gamma distribution; SE estimated at 25% of mean (α = 16, β = 19)

Abbreviations: aGvHD=acute graft versus host disease; cGvHD=chronic graft versus host disease; GvHD=graft versus host disease; HSCT=haematopoietic stem cell transplantation; IVIG=intravenous immunoglobulin; LT=long-term; MUD=matched unrelated donor; PEG-ADA=polyethylene glycol-modified bovine adenosine deaminase; PSA=probabilistic sensitivity analysis; SD=standard deviation; SE=standard error.

Two scenarios were also analysed in the sensitivity analysis.

- Scenario 1: possible death from rescue transplant.
  No patients died after rescue transplant after Strimvelis [Cicalese, 2016]. For HSCT from a MUD or haploidentical donor, it is unclear from Hassan (2012) whether deaths occurred after rescue transplant [Hassan, 2012]. The base-case model assumed that no deaths followed rescue transplant. Scenario 1 examines the impact on

incremental costs when the probability of death after rescue transplant in any type of intervention equals the probability of death after HSCT from a MUD (33%).

- Scenario 2: timing of rescue transplant.
  The base-case assumes that all rescue transplants take place in Year 3. This is based on Strimvelis data [Cicalese, 2016]. No data are available on the timing of rescue transplants after HSCT from a MUD or haploidentical donor. Scenario 2 examines the impact on incremental costs of all rescue transplants taking place in Year 2, 3, or 4.

12.4.4 If any parameters or variables listed above were omitted from the sensitivity analysis, provide the rationale.

Not applicable. All relevant parameters were included in the 1-way sensitivity analysis, multi-way sensitivity analysis, scenario sensitivity analysis, or probabilistic sensitivity analysis as described in Section 12.4.3.

The overall aim of the sensitivity analysis was to identify the critical uncertainties in the analysis. The methods outlined in Section 12.4.2 were used to evaluate the impact of varying model parameters on key economic outputs and to identify those parameters that have the largest positive or negative consequences.

12.5 Results of economic analysis

Base-case analysis

12.5.1 When presenting the results of the base-case incremental cost-effectiveness analysis in the table below, list the interventions and comparator(s) from least to most expensive. Present incremental cost-effectiveness ratios (ICERs) compared with baseline (usually standard care) and then incremental analysis ranking technologies in terms of dominance and extended dominance. If the company has formally agreed to a patient access scheme with the Department of Health, present the results of the base-case incremental cost-effectiveness analysis with the patient access scheme. A suggested format is available in the table below.

In the base-case, the ICER for Strimvelis over HSCT from a MUD is £36,360 and the ICER for Strimvelis over HSCT from a haploidentical donor is £14,645. Total and incremental per patient costs and total and incremental LYG and QALY gains are given in Table D 14.

Table D 14 Base-case results

Technologies	Total cost (£)	Total LYs gained	Total QALYs gained	Incremental costs (£)	Incremental LYG	Incremental QALY	ICER incremental (£/QALY)
Strimvelis	£1,059,425	46.1	41.4				
MUD	£565,170	31.0	27.8	£494,255	15.1	13.6	£36,360
Haplo	£888,757	33.2	29.7	£170,668	12.9	11.7	£14,645

Abbreviations: ICER=incremental cost-effectiveness ratio; LY=life years gained; MUD=matched unrelated donor; QALY=quality-adjusted life year.

12.5.2 For the outcomes highlighted in the decision problem, please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials. Discuss reasons for any differences between modelled and observed results (for example, adjustment for cross-over). Please use the following table format for each comparator with relevant outcomes included.

Not relevant. The clinical outcome assessed with the model is long term overall survival and intervention-free survival, which cannot be compared with clinical trial data.

12.5.3 Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.

Table 15 shows the probability of a patient being in one of the surviving health states or death over time.

Table D 15 Probability of a patient being in surviving health states or death over the lifetime of the model

Years after initial procedure	Dead	Success, long term survival	Unsuccessful engraftment, PEG-ADA, awaiting rescue HSCT	Long term survival after rescue HSCT
Patients who receive Strimvelis				
1 year	0.0%	82.4%	17.6%	0.0%
5 years	0.1%	82.3%	0.0%	17.6%
10 years	0.1%	82.3%	0.0%	17.6%
25 years	0.5%	82.0%	0.0%	17.5%
50 years	3.3%	79.6%	0.0%	17.1%
75 years	25.8%	61.1%	0.0%	13.1%
100 years	98.9%	0.9%	0.0%	0.2%
Patients who receive HSCT from a MUD				
1 year	33.3%	60.0%	6.7%	0.0%
5 years	33.3%	60.0%	0.0%	6.7%
10 years	33.4%	59.9%	0.0%	6.7%
25 years	33.6%	59.7%	0.0%	6.6%
50 years	35.5%	58.0%	0.0%	6.4%
75 years	50.5%	44.5%	0.0%	4.9%
100 years	99.3%	0.7%	0.0%	0.1%

Years after initial procedure	Dead	Success, long term survival	Unsuccessful engraftment, PEG-ADA, awaiting rescue HSCT	Long term survival after rescue HSCT
Patients who receive HSCT from a haploidentical donor				
1 year	28.6%	42.9%	28.6%	0.0%
5 years	28.6%	42.8%	0.0%	28.6%
10 years	28.6%	42.8%	0.0%	28.5%
25 years	28.9%	42.7%	0.0%	28.4%
50 years	30.9%	41.4%	0.0%	27.6%
75 years	47.0%	31.8%	0.0%	21.2%
100 years	99.2%	0.5%	0.0%	0.3%

Abbreviations: HSCT=haematopoietic stem cell transplantation; MUD=matched unrelated donor; PEG-ADA=polyethylene glycol modified bovine adenosine deaminase

12.5.4 Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.

Table D 16 shows QALYs accrued over time for a patient treated with Strimvelis, HSCT from a MUD, or HSCT from a haploidentical donor. Note that this is based on the probability of the patient being in each of the health states in each time period. QALYs are discounted.

Table D 16 QALYs accrued over time for a patient based on the probability of being in each health state in each time period (discounted at 1.5%)

	Success, long term survival	Unsuccessful engraftment, PEG-ADA, awaiting rescue HSCT	Long term survival after rescue HSCT	Total
Patients who receive Strimvelis				
1 year[a]	0.6	0.12	0.0	0.7
5 years	3.6	0.28	0.4	4.3
10 years	7.0	0.28	1.2	8.5
25 years	16.1	0.28	3.1	19.5
50 years	26.4	0.28	5.3	32.1
75 years	32.4	0.28	6.6	39.4
100 years	34.0	0.28	6.9	41.2
Patients who receive HSCT from a MUD				
1 year[a]	0.4	0.0	0.0	0.5
5 years	2.6	0.1	0.2	2.9
10 years	5.1	0.1	0.4	5.7
25 years	11.7	0.1	1.2	13.0
50 years	19.3	0.1	2.0	21.4
75 years	23.6	0.1	2.5	26.3
100 years	24.7	0.1	2.8	**27.5**
Patients who receive HSCT from a haploidentical donor				
1 year[a]	0.3	0.2	0.0	0.5
5 years	1.9	0.5	0.7	3.0
10 years	3.7	0.5	1.9	6.0
25 years	8.4	0.5	5.0	13.9
50 years	13.8	0.5	8.6	22.9
75 years	16.9	0.5	10.7	28.1
100 years	17.7	0.5	11.2	**29.4**

Abbreviations: HSCT=haematopoietic stem cell transplantation; MUD=matched unrelated donor; PEG-ADA=Polyethylene glycol-modified bovine adenosine deaminase; QALY=quality-adjusted life years.
These QALY figures represent the QALYs after the initial decision tree.

a Does not include pre-procedure QALYs

12.5.5 Please indicate the life years (LY) and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results.

The disaggregation of accrued LYs and QALYs is presented in Table D 17.

Table D 17 Model outputs by clinical outcomes

Strimvelis		
Outcome	**LY**	**QALY**
Pre-procedure (PEG-ADA)	0.2	0.2
Post-procedure, successful engraftment	37.8	34.0
Failure to engraft, PEG-ADA	0.3	0.3
Rescue transplant and post-transplant	7.8	6.9
Total	**46.1**	**41.4**
HSCT from a MUD		
Outcome	**LY**	**QALY**
Pre-procedure (PEG-ADA)	0.4	0.4
Post-procedure, successful engraftment	27.6	24.7
Failure to engraft, PEG-ADA	0.1	0.1
Rescue transplant and post-transplant	2.9	2.6
Total	**31.0**	**27.8**
HSCT from a haploidentical donor		
Outcome	**LY**	**QALY**
Pre-procedure (PEG-ADA)	0.4	0.4
Post-procedure, successful engraftment	19.7	17.7
Failure to engraft, PEG-ADA	0.6	0.4
Rescue transplant and post-transplant	12.6	11.2
Total	**33.2**	**29.7**

Abbreviations: HSCT=haematopoietic stem cell transplantation; LY=life years; MUD=matched unrelated donor; PEG-ADA=Polyethylene glycol-modified bovine adenosine deaminase; QALY=quality-adjusted life years.

12.5.6 Please provide details of the disaggregated incremental QALYs by health state. Suggested formats are presented below.

The disaggregation of incremental QALYs by health state are presented in Table D 18 and D 19. Strimvelis provides large incremental QALY gains: 13.6 QALYs when compared to HSCT from a MUD and 11.7 QALYs when compared to HSCT from a haploidentical donor. When compared to either HSCT procedure, more than 90% of the QALY gains delivered by Strimvelis

are due to increased survival and accrue to 2 health states: 'Success, long term survival' and 'Long term survival after rescue HSCT.'

Table D 18 Summary of QALY gain differences by health state (Strimvelis versus HSCT from a MUD)

Health state	Strimvelis QALYs	HSCT from a MUD QALYs	Increment	Absolute increment	% absolute increment
Pre-procedure PEG-ADA and screening	0.17	0.36	-0.19	0.19	1.3%
Success, long term survival	34.0	24.7	9.3	9.3	66.4%
Unsuccessful engraftment, PEG-ADA, awaiting rescue HSCT	0.3	0.1	0.2	0.2	1.3%
Long term survival after rescue HSCT	6.9	2.6	4.3	4.4	30.9%
Total	**41.4**	**27.8**	**13.6**		

Abbreviations: HSCT=haematopoietic stem cell transplantation; MUD=matched unrelated donor; PEG-ADA=Polyethylene glycol-modified bovine adenosine deaminase; QALYs=quality-adjusted life years.

Table D 19 Summary of QALY gain differences by health state (Strimvelis versus HSCT from a haploidentical donor)

Health state	Strimvelis QALYs	HSCT from a haploidentical donor QALYs	Increment	Absolute increment	% absolute increment
Pre-procedure PEG-ADA and screening	0.17	0.36	-0.19	0.19	0.9%
Success, long term survival	34.0	17.7	16.3	16.3	77.8%
Unsuccessful engraftment, PEG-ADA, awaiting rescue HSCT	0.3	0.4	-0.2	0.2	0.8%

Health state	Strimvelis QALYs	HSCT from a haploidentical donor QALYs	Increment	Absolute increment	% absolute increment
Post rescue transplant	6.9	11.2	-4.3	4.3	20.5%
Total	**41.4**	**29.7**	**11.7**		

Abbreviations: HSCT=haematopoietic stem cell transplantation; PEG-ADA=Polyethylene glycol-modified bovine adenosine deaminase; QALYs=quality-adjusted life years.

12.5.7 Please provide undiscounted incremental QALYs for the intervention compared with each comparator.

Table D 20 shows the undiscounted incremental QALYs for treatment with Strimvelis compared with HSCT from a MUD.Table D21 shows the undiscounted incremental QALYs for treatment with Strimvelis compared with HSCT from a haploidentical donor.

Table D 20 Summary of undiscounted QALY gain differences by health state (Strimvelis versus HSCT from a MUD)

Health state	Strimvelis QALYs	HSCT from a MUD QALYs	Increment	Absolute increment	% absolute increment
Pre-procedure PEG-ADA and screening	0.17	0.36	-0.19	0.19	0.8%
Success, long term survival	57.8	42.0	15.7	15.7	66.7%
Unsuccessful engraftment, PEG-ADA, awaiting rescue HSCT	0.3	0.1	0.2	0.2	0.8%
Long term survival after rescue HSCT	12.0	4.6	7.5	7.5	31.7%
Total	**70.3**	**47.1**	**23.2**		

Abbreviations: HSCT=haematopoietic stem cell transplantation; MUD=matched unrelated donor; PEG-ADA=Polyethylene glycol-modified bovine adenosine deaminase; QALYs=quality-adjusted life years.

Table D 21 Summary of undiscounted QALY gain differences by health state (Strimvelis versus HSCT from a haploidentical donor)

Health state	Strimvelis QALYs	HSCT from a haploidentical donor QALYs	Increment	Absolute increment	% absolute increment
Pre-procedure PEG-ADA and screening	0.17	0.36	-0.19	0.19	0.5%
Success, long term survival	57.8	30.1	27.7	27.7	78.0%
Unsuccessful engraftment, PEG-ADA, awaiting rescue HSCT	0.3	0.5	-0.2	0.2	0.5%
Long term survival after rescue HSCT	12.0	19.5	-7.5	7.5	21.0%
Total	**70.3**	**50.4**	**19.9**		

Abbreviations: HSCT=haematopoietic stem cell transplantation; MUD=matched unrelated donor; PEG-ADA=Polyethylene glycol-modified bovine adenosine deaminase; QALYs=quality-adjusted life years.

12.5.8 Provide details of the costs for the technology and its comparator by category of cost.

Table D 22 shows the costs for Strimvelis versus HSCT from a MUD by category of costs. Table D 23 shows the costs for Strimvelis versus HSCT from a haploidentical donor by category of costs. All costs are discounted at 1.5% (see Table D 4 for rationale).

The total lifetime difference in discounted costs for Strimvelis compared with HSCT from a MUD is an additional £494,255. The total difference in costs for Strimvelis compared with HSCT from a haploidentical donor is an additional £170,668.

Product cost is responsible for most of the increased cost of Strimvelis when compared with HSCT procedures. This is compensated to some degree by lower pre-procedure PEG-ADA costs for Strimvelis due to the shorter waiting time before the initial procedure and to the necessity of MUD screening for the HSCT procedures. It should be noted that some of the higher costs reported in Table D 22 and Table D 23 result from the increased survival of Strimvelis patients. A larger proportion of Strimvelis patients survive the initial transplant procedure and require additional clinical care.

Table D 22 Summary of costs by category of cost per patient – Strimvelis versus HSCT from a MUD

Category	Costs for Strimvelis therapy	Costs for HSCT from a MUD therapy	Difference: Strimvelis - HSCT from a MUD
Screening pre-procedure	£0	£45,127	-£45,127
Confirmation of eligibility for Strimvelis treatment	[redacted]	£0	[redacted]
PEG-ADA pre-procedure	£124,254	£262,314	-£138,060
Product	£505,000	£0	£505,000
Severe infection cost	£13,103	£8,735	£4,368
Rescue transplant cost	£16,119	£6,090	£10,030
Rescue PEG-ADA cost	£217,055	£81,999	£135,051
Hospitalisation cost	[redacted]	£95,516	[redacted]
Follow-up cost, includes VCN in Strimvelis	[redacted]	£43,027	[redacted]
GvHD	£0	£7.834	-£7,834
IVIG cost	£23,041	£14,529	£8,512
Total	**£1,059,425**	**£565,170**	**£494,255**

Abbreviations: GvHD=graft versus host disease; HSCT=haematopoietic stem cell transplantation; IVIG=intravenous immunoglobulin; MUD=matched unrelated donor; PEG-ADA=polyethylene glycol-modified bovine adenosine deaminase.
Note: All costs are discounted at 1.5%.

Table D 23 Summary of costs by category of cost per patient – Strimvelis versus HSCT from a haploidentical donor

Category	Costs for Strimvelis therapy	Costs for HSCT from a haploidentical donor therapy	Difference: Strimvelis - HSCT from a haploidentical donor
Screening pre-procedure	£0	£45,127	-£45,127
Confirmation of eligibility for Strimvelis treatment	[redacted]	£0	[redacted]
PEG-ADA pre-procedure	£124,254	£262,314	-£138,060
Product	£505,000	£0	£505,000
Severe infection cost	£13,103	£9,359	£3,744
Rescue transplant cost	£16,119	£26,098	-£9,979
Rescue PEG-ADA cost	£217,055	£351,423	-£134,367
Hospitalisation cost	[redacted]	£108,760	[redacted]
Follow-up cost	[redacted]	£58,259	[redacted]
GvHD	£0	£8,354	-£8,354
IVIG cost	£23,041	£19,063	£3,978
Total	**£1,059,425**	**£888,757**	**£170,668**

Abbreviations: GvHD=graft versus host disease; HSCT=haematopoietic stem cell transplantation; IVIG=intravenous immunoglobulin; MUD=matched unrelated donor; PEG-ADA=polyethylene glycol-modified bovine adenosine deaminase.
Note: All costs are discounted at 1.5%.

12.5.9 If appropriate, provide details of the costs for the technology and its comparator by health state.

The data are shown in Sections 12.5.5 and 12.5.6.

12.5.10 If appropriate, provide details of the costs for the technology and its comparator by adverse event.

GvHD is included in the model as a treatment-related AE after an HSCT from a MUD or haploidentical donor. The expected cost of these events is shown in Section 12.5.8. Note that rescue transplant GvHD costs are also included in these totals.

Sensitivity analysis results

12.5.11 Present results of deterministic one-way sensitivity analysis of the variables.

Results from the 1-way sensitivity analysis for the ICER are shown in Table D 24 and Table D 25.

In the base-case, the ICER for Strimvelis over HSCT from a MUD is £36,360 per QALY gained and the ICER for Strimvelis over HSCT from a haploidentical donor is £14,645 per QALY gained. In general, the results from the 1-way sensitivity analyses show that, with most variables being adjusted by +/- 25%, the ICERs are very stable and most variables have a very modest impact on the computed ICER values. Significant exceptions are discussed in Section 12.5.14. The presented ICERs should be considered in the context of the proposed criteria to automatically fund, from routine commissioning budgets, treatments for very rare conditions (highly specialised technologies) up to, in general, £100,000/QALY gained and up to £140,000/QALY gained given the magnitude of the QALY gain provided by Strimvelis over HSCT from a MUD [NICE, 2017b].

In all cases, the ICERs for Strimvelis vs either HSCT procedure remain well below the proposed maximum threshold for acceptance.

Table D 24 Strimvelis vs HSCT from a MUD, incremental cost effectiveness ratio (Base-case: £36,360 per QALY gained)

Categories and inputs	base-case	lower	upper	ICER at lower value	ICER at upper value	ICER spread
Variation in discount rates and time horizon						
Discount costs	1.5%	0%	3.5%	£36,689	£35,945	£744
Discount outcomes	1.5%	0%	3.5%	£21,271	£62,318	£41,047
Discount costs and outcomes	1.5%, 1.5%	0%, 0%	3.5%, 3.5%	£21,464	£61,607	£40,143
Time horizon 50 years	lifetime	50 years	lifetime	£46,835	£36,360	£10,475
Time horizon 20 years	lifetime	20 years	lifetime	£94,494	£36,360	£58,134
Variations in survival						
HSCT from a MUD - survival 1st 6 months	67%	67%	83.75%	£36,360	£72,766	£36,406
Clinical probabilities						
Rates of severe Infections, Years 1-3 Strimvelis	26%	26%	42.9%	£36,360	£36,800	£440
Rates of severe Infections, Years 1-3 MUD	26%	26%	42.9%	£36,360	£36.066	£36,324
IVIG - at Year 8 in Strimvelis	0%	0%	20%	£36,360	£38,536	£2,176
IVIG - at Year 8 in MUD	0%	0%	20%	£36,360	£36,127	£233

Categories and inputs	base-case	lower	upper	ICER at lower value	ICER at upper value	ICER spread
Severe acute GvHD of all patients, HSCT from a MUD	10.7%	5%	16%	£36,402	£36,321	£81
Severe chronic GvHD of all patients, HSCT from a MUD	3.6%	0%	7.1%	£36,452	£36,268	£184
Proportion of rescue transplants that are from a MUD	0%	0%	50%	£36,360	£36,534	£174
Proportion who receive a rescue transplant, Strimvelis	17.6%	8.30%	22.70%	£26,741	£41,573	£14,832
Proportion who receive a rescue transplant, HSCT from a MUD	6.70%	5.00%	8.30%	£38,081	£34,674	£3,407
Timing and duration						
Weeks on PEG-ADA before Strimvelis (+/- 2)	9	7	11	£34,424	£38,285	£3,861
Weeks on PEG-ADA before MUD (+/- 2)	19	17	21	£38,285	£34,424	£3,861
Weeks on PEG-ADA before MUD	19	9	24	£47,755	£33,452	£14,303
Timing of rescue transplant	Year 3	Year 3	Year 4	£36,360	£41,971	£5,611
Timing of rescue transplant	Year 3	Year 3	Year 5	£36,360	£47,456	£11,096
Timing of rescue transplant	Year 3	Year 2	Year 3	£30,699	£36,360	£5,661

Categories and inputs	base-case	lower	upper	ICER at lower value	ICER at upper value	ICER spread
Variations in costs						
Cost of PEG-ADA, weekly (50% of base-case)	£13,500	£6,750	£13,500	£36,468	£36,360	£108
Cost of PEG-ADA, weekly (25% of base-case)	£13,500	£3,375	£13,500	£36,522	£36,360	£162
Cost of PEG-ADA, weekly (10% of base-case)	£13,500	£1,350	£13,500	£36,554	£36,360	£194
Cost of PEG-ADA, weekly (+/- 25%)	£13,500	£10,125	£16,875	£36,414	£36,306	£108
Cost of administration of PEG-ADA (+/- 25%)	£306	£230	£383	£36,361	£36,359	£2
Price of IVIG per gram (+/- 25%)	£40.1	£30.1	£50.1	£36,299	£36,420	£121
Cost of administration of IVIG (+/- 25%)	£306	£230	£383	£36,264	£36,456	£192
Cost of screening (+/- 25%)	£45,127	£33,845	£56,409	£37,190	£35,530	£1,660
Cost of severe infection, all arms (+/- 25%)	£12,143	£9,107	£15,179	£36,279	£36,440	£161
Cost confirmation of eligibility for Strimvelis treatment and initial hospitalisation, Strimvelis (+/- 25%)	£92,217	£69,163	£115,271	£34,664	£38,056	£3,392
Cost initial hospitalisation, MUD (+/- 25%)	£95,516	£71,637	£119,395	£37,932	£34,788	£3,144

Categories and inputs	base-case	lower	upper	ICER at lower value	ICER at upper value	ICER spread
Cost of follow-up, Strimvelis (+/- 25%)	£52,578	£39,433	£65,722	£35,404	£37,316	£1,912
Cost of follow-up, MUD (+/- 25%)	£59,541	£44,656	£74,426	£36,967	£35,753	£1,214
Cost of rescue transplant, Strimvelis (+/- 25%)	£95,516	£71,637	£119,395	£36,063	£36,656	£593
Cost of rescue transplant, MUD (+/- 25%)	£95,516	£71,637	£119,395	£36,472	£36,248	£224
Cost of GVHD - all arms (+/- 25%)	£29,420	£22,065	£36,775	£36,504	£36,216	£288
Drugs dosage						
Duration of PEG-ADA use in bridge to rescue transplant	1.75 years	1.5 years	2 years	£34,910	£37,810	£2,900
Cost of IVIG based on average dose years 0-8	weight	weight	average	£36,360	£36,439	£79
Utilities						
Health utility in the period before HSCT or Strimvelis	0.98	0.49	1	£36,110	£36,371	£261
QALY loss due to an aGvHD, MUD (+/- 25%)	0.41	0.3	0.5	£36,379	£35,340	£1,039
QALY loss due to a cGvHD, MUD (+/- 25%)	1.44	1.1	1.8	£36,383	£36,337	£46

Categories and inputs	base-case	lower	upper	ICER at lower value	ICER at upper value	ICER spread
Utilities by age band	General population.	x 0.95	x 1.05	£38,278	£34,625	£3,653
Utilities by age band @0.90 general population	General population.	x 0.90	General population.	£40,410	£36,360	£4,050
Utilities by age band @0.85 general population	General population.	x 0.85	General population.	£41,793	£36,360	£5,433
Utilities by age band @0.80 general population	General population.	x 0.80	General population.	£45,475	£36,360	£9,115
Weight for IVIG disutility	1.00	0.75	1.00	£37,158	£36,360	£798
Utility decrement 6 months (Strimvelis and MUD)	0.57	none	1.00	£36,029	£36,614	£585
Carer's QALY loss due to premature death of child[a]	none	none	accounted for	£36,360	£33,201	£3,159

Abbreviations: aGvHD=acute graft versus host disease; cGvHD=chronic graft versus host disease; GvHD=graft versus host disease; HSCT=haematopoietic stem cell transplantation; ICER=incremental cost-effectiveness ratio; IVIG=intravenous immunoglobulin; LT=long-term; mths=months; MUD=matched unrelated donor; NA=not applicable; PEG-ADA=polyethylene glycol-modified bovine adenosine deaminase; U=unit.

[a]. Following Christensen et al (2014), the additional quality of life-related QALY loss experienced by a bereaved family was assumed to be 9% of the child's QALY loss. The child is assumed to die in the first half year cycle (Year 0.5), and the discounted QALY loss of the child was calculated as the difference between the general population survival and the HSCT survival, integrated

from Year 1 to Year 100. The child's discounted QALY losses are 23 and 20 QALY for HSCT from a MUD or from a Haplo, respectively. The additional QALY loss experienced by the bereaved family is 9% of the child's loss: 2.1 and 1.8 QALYs for HSCT from a MUD or from a Haplo, respectively.

Table D 25 Strimvelis vs HSCT from a haploidentical donor, incremental cost effectiveness ratio (Base-case: £14,645 per QALY gained)

	base-case	lower	upper	ICER at lower value	ICER at upper value	ICER spread
Variation in discount rates and time horizon						
Discount costs	1.5%	0%	3.5%	£14,373	£14,989	£616
Discount outcomes	1.5%	0%	3.5%	£8,567	£25,107	£16,540
Discount costs and outcomes	1.5%, 1.5%	0%, 0%	3.5%, 3.5%	£8,408	£25,697	£17,289
Time horizon 50 years	lifetime	50 years	lifetime	£18,863	£14,645	£4,218
Time horizon 20 years	lifetime	20 years	lifetime	£38,047	£14,645	£23,402
Variations in survival						
HSCT from a Haplo - survival 1st 6 months	71.4%	71.4%	80%	£14,645	£19,987	£5,342
Clinical probabilities						
Rates of severe Infections, Years 1-3 Strimvelis	26%	26%	42.9%	£14,645	£15,159	£514

	base-case	lower	upper	ICER at lower value	ICER at upper value	ICER spread
Rates of severe Infections, Years 1-3 Haplo	26%	26%	42.9%	£14,645	£14,277	£368
IVIG - at Year 8 in Strimvelis	0%	0%	20%	£14,645	£17,183	£2,538
IVIG - at Year 8 in Haplo	0%	0%	20%	£14,645	£13,316	£1,329
Severe acute GvHD of all patients, HSCT from a haploidentical donor	11.1%	5.6%	17%	£14,665	£16,624	£1,959
Severe chronic GvHD of all patients, HSCT from a haploidentical donor	0.0%	0%	3.6%	£14,645	£14,599	£46
Proportion of rescue transplants that are from a MUD	0%	0%	50%	£14,645	£14,442	£203
Proportion who receive a rescue transplant, Strimvelis	17.6%	8.30%	22.70%	£3,473	£20,703	£17,230
Proportion who receive a rescue transplant, HSCT from a haploidentical donor	28.6%	21.40%	35.70%	£23,261	£6,106	£17,155
Rates of severe Infections, Years 1-3 Strimvelis	26%	26%	42.9%	£14,645	£15,159	£514
Rates of severe Infections, Years 1-3 HSCT from a haploidentical donor	26%	26%	42.9%	£14,645	£14,277	£368

	base-case	lower	upper	ICER at lower value	ICER at upper value	ICER spread
IVIG - at Year 8 in Strimvelis	0.0%	0.0%	20.0%	£14,645	£17,183	£2,538
IVIG - at Year 8 in HSCT from a haploidentical donor	0.0%	0.0%	20.0%	£14,645	£13,316	£1,329
Timing and duration						
Weeks on PEG-ADA before Strimvelis (+/- 2)	9	7	11	£12,315	£16,959	£4,644
Weeks on PEG-ADA before Haplo (+/- 2)	19	17	21	£16,959	£12,315	£4,644
Weeks on PEG-ADA before Haplo	19	9	24	£26,071	£8,792	£17,279
Timing of rescue transplant	Year 3	Year 3	Year 4	£14,645	£8,414	£6,231
Timing of rescue transplant	Year 3	Year 3	Year 5	£14,645	£2,147	£12,498
Timing of rescue transplant	Year 3	Year 2	Year 3	£20,822	£14,645	£6,177
Variations in costs						
Cost of PEG-ADA, weekly (50% of base-case)	£13,500	£6,750	£13,500	£26,074	£14,645	£11,429
Cost of PEG-ADA, weekly (25% of base-case)	£13,500	£3,375	£13,500	£31,788	£14,645	£17,143
Cost of PEG-ADA, weekly (10% of base-case)	£13,500	£1,350	£13,500	£35,217	£14,645	£20,572
Cost of PEG-ADA, weekly (+/- 25%)	£13,500	£10,125	£16,875	£20,359	£8,930	£11,429

	base-case	lower	upper	ICER at lower value	ICER at upper value	ICER spread
Cost of administration of PEG-ADA (+/- 25%)	£306	£230	£383	£14,774	£14,515	£259
Price of IVIG per gram (+/- 25%)	£40.1	£30.1	£50.1	£14,608	£14,681	£73
Cost of administration of IVIG (+/- 25%)	£306	£230	£383	£14,596	£14,693	£97
Cost of screening (+/- 25%)	£45,127	£33,845	£56,409	£15,613	£13,677	£1,936
Cost of severe infection, all arms (+/- 25%)	£12,143	£9,107	£15,179	£14,564	£14,725	£161
Cost confirmation of eligibility for Strimvelis treatment and initial hospitalisation, Strimvelis (+/- 25%)	£92,217	£69,163	£115,271	£12,666	£16,623	£3,957
Cost initial hospitalisation, Haplo (+/- 25%)	£108,760	£81,570	£135,950	£16,978	£12,312	£4,666
Cost of follow-up, Strimvelis (+/- 25%)	£52,578	£39,433	£65,722	£13,530	£15,760	£2,230
Cost of follow-up, Haplo (+/- 25%)	£59,541	£44,656	£74,426	£15,547	£13,743	£1,804
Cost of rescue transplant, Strimvelis (+/- 25%)	£95,516	£71,637	£119,395	£14,299	£14,990	£691
Cost of rescue transplant, HSCT from a haploidentical donor (+/- 25%)	£95,516	£71,637	£119,395	£15,205	£14,085	£1,120
Cost of GVHD, all interventions (+/- 25%)	£29,420	£22,065	£36,775	£14,824	£14,465	£359

	base-case	lower	upper	ICER at lower value	ICER at upper value	ICER spread
Drugs dosage						
Duration of PEG-ADA use in bridge to rescue transplant (no change in time to rescue transplant)	1.75 years	1.5 years	2 years	£16,327	£12,962	£3,365
Cost of IVIG based on average dose years 0-8	weight	weight	average	£14,645	£14,662	£17
Utilities						
Health utility in the period before HSCT or Strimvelis	0.98	0.49	1.0	£14,527	£14,650	£123
One-off QALY loss due to a utility decrement from acute GvHD (+/- 25%)	0.41	0.31	0.51	£14,665	£14,634	£31
One-off QALY loss due to a utility decrement from chronic GvHD (+/- 25%)	1.44	1.08	1.80	£14,645	£14,645	£0
Utilities by age band	General population.	x 0.95	x 1.05	£15,424	£13,941	£1,483
Utilities by age band @0.90 general population	General population.	x 0.90	General population.	£16,290	£14,645	£1,645
Utilities by age band @0.85 general population	General population.	x 0.85	General population.	£17,260	£14,645	£2,615
Utilities by age band @0.80 general population	General population.	x 0.80	General population.	£18,356	£14,645	£3,711

	base-case	lower	upper	ICER at lower value	ICER at upper value	ICER spread
Utility weight for IVIG	1.00	0.75	1.00	£14,865	£14,645	£220
Utility decrement 6 months (Strimvelis and MUD)	0.57	none	1.00	£14,580	£14,694	£114
Carer's QALY loss due to premature death of child[a]	none	none	accounted for	£14,645	£13,373	£1,272

Abbreviations: aGvHD=acute graft versus host disease; cGvHD=chronic graft versus host disease; GvHD=graft versus host disease; Haplo=haploidentical donor; HSCT=haematopoietic stem cell transplantation; ICER=incremental cost-effectiveness ratio; IVIG=intravenous immunoglobulin; LT=long-term; mths=months; MUD=matched unrelated donor; NA=not applicable; PEG-ADA=polyethylene glycol-modified bovine adenosine deaminase; U=unit.

[a]. Following Christensen et al (2014), the additional quality of life-related QALY loss experienced by a bereaved family was assumed to be 9% of the child's QALY loss. The child is assumed to die in the first half year cycle (Year 0.5), and the discounted QALY loss of the child was calculated as the difference between the general population survival and the HSCT survival, integrated from Year 1 to Year 100. The child's discounted QALY losses are 23 and 20 QALY for HSCT from a MUD or from a Haplo, respectively. The additional QALY loss experienced by the bereaved family is 9% of the child's loss: 2.1 and 1.8 QALYs for HSCT from a MUD or from a Haplo, respectively.

12.5.12 Present results of deterministic multi-way scenario sensitivity analysis described in Table D 13.

Results for the multi-way scenario analysis are shown in Table D 26. In the base-case, the ICER for Strimvelis over HSCT from a MUD is £36,360/QALY gained and the ICER for Strimvelis over HSCT from a haploidentical donor is £14,645/QALY gained. The multi-way analysis examined the combinations of reductions in MLS (equal reductions for all treatments) with reductions in utility scores by age (equal reductions for all treatments). In the analysis, the life expectancy and utility reductions were reduced by increments of 10% up to a maximum of a 20% reduction: a total of 9 individual scenarios were examined including the base-case. The other variables used for the ICER analysis for Strimvelis over HSCT from a MUD and Strimvelis over HSCT from a haploidentical donor are presented in Table D 13 and the results are discussed in Section 12.5.15.

Table D 26 Results from the multi-way scenario-based sensitivity analysis: ICER for Strimvelis over HSCT from a MUD or haploidentical donor

	MLS*1 (79.9 yrs)	**MLS*0.9 (71.9 yrs)**	**MLS*0.8 (63.9 yrs)**
Strimvelis vs HSCT from a MUD			
Utility Score by Age * 1	£36,360	£38,375	£40,987
Utility Score by Age * 0.9	£40,410	£42,650	£45,554
Utility Score by Age * 0.8	£45,475	£47,997	£51,266
Strimvelis vs HSCT from a Haploidentical donor			
Utility Score by Age * 1	£14,645	£15,456	£16,508
Utility Score by Age * 0.9	£16,290	£17,194	£18,366
Utility Score by Age * 0.8	£18,352	£19,371	£20,694

Abbreviations: HSCT=haematopoietic stem cell transplantation; ICER=incremental cost-effectiveness ratio; MLS=mean life expectancy for survivors; MUD=matched unrelated donor.

Two additional one-way sensitivity analyses were performed to examine uncertainties associated with time of rescue transplant and the probability of death after a rescue transplant.

i) In the base-case, all rescue transplants occur in Year 3. We examined the consequences of assuming the rescue transplants occur in Years 2, 4, and 5. The effects are modest. The ICERs for Strimvelis over HSCT from a MUD are £30,699/QALY gained (rescue transplant in Year 2), £36,360/QALY gained (rescue transplant in Year 3, base-case), to £41,971/QALY gained (rescue transplant in Year 4), and

£47,456/QALY gained (rescue transplant in Year 5). The ICERs for Strimvelis over HSCT from a haploidentical donor are £20,822 (rescue transplant in Year 2), £14,645/QALY gained (rescue transplant in Year 3, base-case), to £8,414/QALY gained (rescue transplant in Year 4), and Strimvelis dominates if the rescue transplant occurs in Year 5.I

ii) In the base-case, it was assumed that no deaths occur after rescue transplant based on results obtained for Strimvelis patients [Cicalese, 2016]. However, there are no literature data on likelihood of death after rescue transplant for patients who receive HSCT from a MUD or haploidentical donor [Hassan, 2012]. In the conservative base-case model it was assumed that no deaths followed rescue transplant in such cases. To explore this assumption, the probability of death after a rescue transplant from a MUD or haploidentical donor was taken to be 33%, which is the probability of death after an initial HSCT from a MUD. In such a scenario, the ICER for Strimvelis over HSCT from a MUD rises from £36,360/QALY gained to £40,413/QALY gained, while the ICER for Strimvelis over HSCT from a haploidentical donor falls from £14,645/QALY gained to £13,279 /QALY gained.

Finally, an additional small set of 1-way ICER sensitivity analyses for variations in discount rate are presented in Appendix 8 for completeness.

12.5.13 Threshold analysis

In the 1-way sensitivity analysis, we identified a small set of important parameters that most influence the predicted ICER values. These parameters fall into 3 categories:

- Post-procedure survival in Strimvelis and HSCT procedures
- The price of the Strimvelis procedure
- The long-term post-procedure utility values for Strimvelis and HSCT procedures

We performed a threshold analysis to determine the range of values for these important parameters that will produce ICERs above £140,000/QALY gained (for Strimvelis vs HSCT from a MUD) or above £120,000/QALY gained (for Strimvelis vs HSCT from a haploidentical donor).

Post-procedure survival (Strimvelis vs HSCT from a MUD)

The model produces ICERs >£140,000/QALY gained if:

- the survival for HSCT from a MUD is >92%
- or, the survival in Strimvelis is <74%.

Post-procedure survival (Strimvelis vs HSCT from a haploidentical donor)

The model produces ICERs >£120,000/QALY gained if:

- the survival for HSCT from a haploidentical donor is >97%
- or, the survival in Strimvelis is <73%

The base-line survival rates are 100% (Strimvelis), 66.7% (HSCT from a MUD), and 71.4% (HSCT from a haploidentical donor). Post-procedure survival rates in the ranges necessary to exceed the ICER thresholds are not expected to occur given the information available.

Price of Strimvelis (Strimvelis vs HSCT from a MUD)

The model produces ICERs >£140,000/QALY gained if:

- the price of the Strimvelis procedure is >£1,913,831

Price of Strimvelis (Strimvelis vs HSCT from a haploidentical donor)

The model produces ICERs >£120,000/QALY gained if:

- the price of the Strimvelis procedure is >£1,732,803

Long-term post-procedure utility values

For the base-case QALY gain calculation, we assume that long-term survivors of Strimvelis or HSCT procedures have the same age-based utility values as the general population. Simultaneous reduction of the utilities for Strimvelis and HSCT, by applying a multiplicative utility weight to the general population utilities, results in the following conclusions.

For Strimvelis vs HSCT from a MUD, model ICERs >£140,000/QALY gained are produced if, and only if:

- the utility weight is <0.26

For Strimvelis vs HSCT from a haploidentical donor, ICERs >£120,000/QALY gained are produced if, and only if:

- the utility weight is <0.13

Utilities in these ranges are not expected to be realistic.

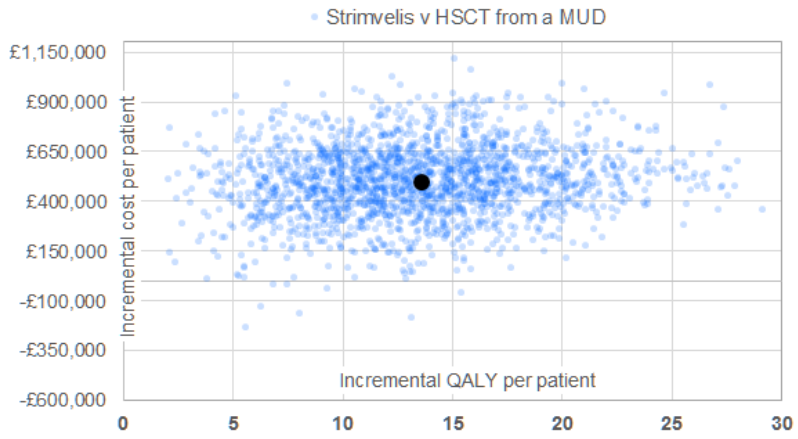
12.5.14 Present results of the probabilistic sensitivity analysis.

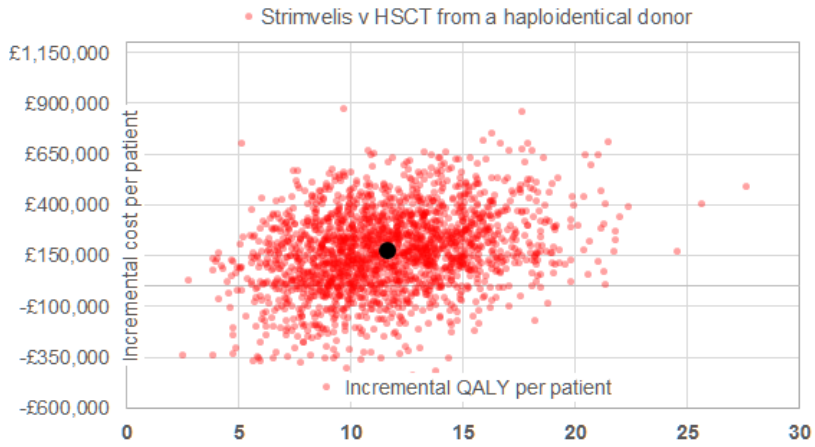
Figure 8 shows the scatter plots of the differences in costs and the differences in effects for 1,000 model runs.

When Strimvelis was compared with HSCT from a MUD, almost all the results (>99%) fell into the northeast quadrant, indicating that Strimvelis is both more expensive and generates more QALYs than HSCT from a MUD. Two percent of the model runs resulted in an ICER greater than £100,000/QALY gained, with results showing that the ICER ranges between dominance for Strimvelis and £189,235/QALY gained, with a median value of £35,642/QALY gained.

When Strimvelis was compared with HSCT from a haploidentical donor most of the results (74%) fell in the northeast quadrant, indicating that Strimvelis is both more expensive and generates more QALYs than HSCT from a haploidentical donor; 26% of the results fell into the southeast quadrant, indicating the dominance of Strimvelis. Three percent of the model runs resulted in an ICER greater than £100,000/QALY gained, with results showing that the ICER ranges between dominance for Strimvelis (for PSA runs in the southeast quadrant) and £279,491/QALY gained. The median ICER value was £14,856/QALY gained.

Figure 8 Scatter plots of differences in costs and outcomes of Strimvelis versus HSCT from a MUD or haploidentical donor





Abbreviations: HSCT=haematopoietic stem cell transplantation; MUD=matched unrelated donor; QALY=quality-adjusted life years

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Table D 27 shows the mean differences in outcomes and costs from the probabilistic sensitivity analysis (PSA) and the minimum, maximum, mean, and median ICER results for Strimvelis versus HSCT from a MUD.

In the PSA incremental costs range between -£235,770 and £1,115,559, incremental QALY ranges between 2.1 and 32.6, and incremental cost effectiveness from dominance for Strimvelis to £361,272 per QALY gained.

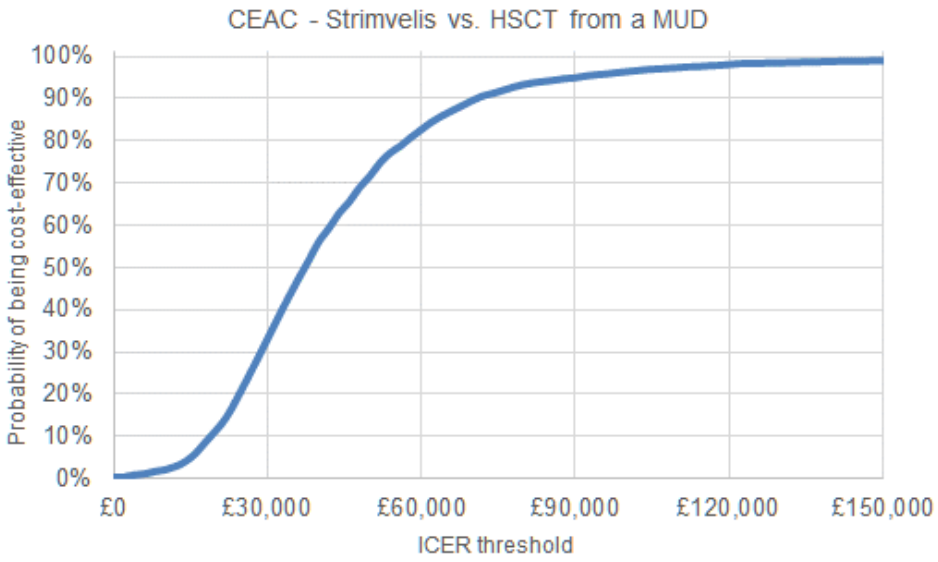
Table D 27 Results from the probabilistic sensitivity analysis - Strimvelis versus HSCT from a MUD

Strimvelis vs MUD	Min	Max	Median	Mean
Incremental cost	-£235,770	£1,115,559	£500,878	£500,422
Incremental QALY	2.1	32.6	13.2	13.5
ICER	dominant	£361,272	£37,269	£42,863
CE Plane (Strimvelis vs MUD)				**%**
Incr. cost >0, Incr. QALY <0 (dominated)				0.0%
Incr. cost <0, Incr. QALY >0 (dominant)				0.4%
Incr. cost >0, Incr. QALY >0, ICER <100K/QALY gained				96.1%
Incr. cost >0, Incr. QALY >0, ICER >100K/QALY gained				3.5%
Incr. cost <0, Incr. QALY <0				0.0%

Abbreviations: HSCT=haematopoietic stem cell transplantation; ICER=incremental cost-effectiveness ratio; Max=maximum; Min=minimum; MUD=matched unrelated donor; QALY=quality adjusted life year.

Figure 9 shows the cost effectiveness acceptability curve (CEAC) where the percentages of simulations below each possible willingness-to-pay threshold are shown. At an ICER threshold of £30,000, the probability of being cost effective is 33%; at £40,000, the probability of being cost effective is 56%; at £50,000, the probability is 72%; at £100,000, the probability is 97%; and at £140,000, the probability is 99%.

Figure 9 Cost effectiveness acceptability curve for Strimvelis versus HSCT from a MUD



Abbreviations: CEAC=cost effectiveness acceptability curve; HSCT=haematopoietic stem cell transplantation; MUD=matched unrelated donor; QALY=quality-adjusted life years.

Table D 28 shows the mean differences in outcomes and costs from the PSA and the minimum, maximum, mean, and median ICER results for Strimvelis versus HSCT from a haploidentical donor.

In PSA incremental costs range between - £640,284 and £872,039, the incremental QALY ranges between 2.5 and 27.6, and the incremental cost effectiveness from dominance for Strimvelis to £135,814 per QALY gained.

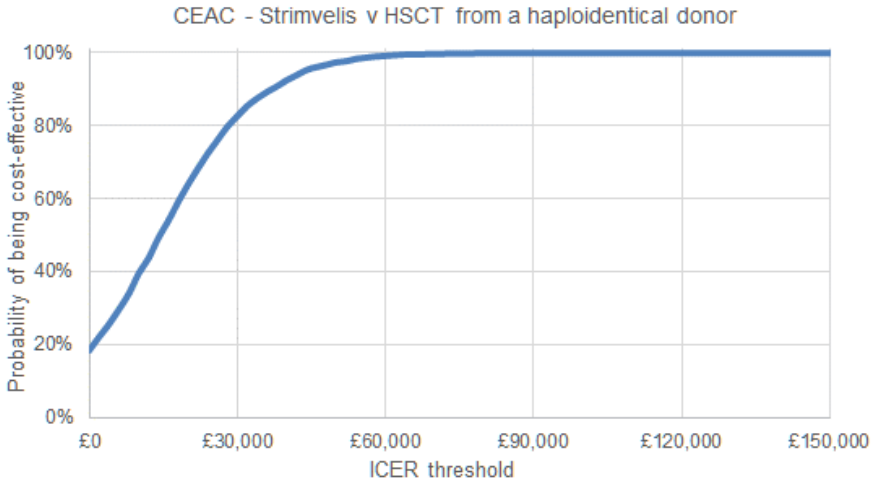
Table D 28 Results from the PSA – Strimvelis versus HSCT from a haploidentical donor

Strimvelis vs haploidentical donor	Min	Max	Median	Mean
Incremental cost	-£640,284	£872,039	£167,487	£168,197
Incremental QALY	2.5	27.6	11.5	11.7
ICER	Dominant	£135,814	£14,341	£13,979
CE Plane (Strimvelis vs Haplo)				**%**
Incr. cost >0, Incr. QALY <0 (dominated)				0%
Incr. cost <0, Incr. QALY >0 (dominant)				18.4%
Incr. cost >0, Incr. QALY >0, ICER <100K/QALY gained				81.6%
Incr. cost >0, Incr. QALY >0, ICER >100K/QALY gained				0.1%
Incr. cost <0, Incr. QALY <0				0%

Abbreviations: Haplo = haploidentical donor; HSCT= HSCT=haematopoietic stem cell transplantation; ICER=incremental cost-effectiveness ratio; Max=maximum; Min=minimum; MUD=matched unrelated donor; PSA=probabilistic sensitivity analysis; QALY=quality adjusted life year.

Figure 10 shows the CEAC where the percentages of simulations below each possible willingness-to-pay threshold are shown. At a threshold of £30,000, the probability of being cost-effective is 83%; at £40,000, the probability is 93%; at £60,000, the probability is 99%; at £100,000 per QALY gained the probability is 100%.

Figure 10 CEAC for Strimvelis versus HSCT from a haploidentical donor



Abbreviations: CEAC=cost effectiveness acceptability curve; haplo=HSCT from a haploidentical donor; HSCT=haematopoietic stem cell transplantation; QALY=quality-adjusted life years.

12.5.15 What were the main findings of each of the sensitivity analyses?

The detailed analysis is given in Section 12.5.11 and Appendix 8. In general, the results from the 1-way sensitivity analyses show that, with most variables

being adjusted by +/- 25%, the ICERs are very stable and most variables have very modest impact on the computed ICER values. Even where the variation in ICERs was greater, the cost-effectiveness verdict for all but 1 case would be the same because ICERs fall well below the criteria to automatically fund treatments for very rare conditions (appraised under the Highly Specialised Technologies programme) of, in general, £100,000/QALY gained and up to £140,000 or £120,000 per QALY gained given the magnitude of the QALY gain provided by Strimvelis when compared to MUD (13.6) and Haplo (11.7), respectively. Examples of variable changes that resulted in a greater variation in the ICERs include:

- the discount rate employed (especially the discount rate for outcomes)
- rescue transplant rates for Strimvelis and HSCT from a haploidentical donor

and,

- the initial post-intervention survival rates

The discount rate: When a 3.5% discount rate is used for both costs and outcomes, then the ICER for Strimvelis vs HSCT from a MUD rises from £36,360 to £61,607. If costs are discounted at 3.5% and outcomes at 1.5%, then the ICER for Strimvelis vs HSCT from a MUD falls slightly from £36,360 to £35,945 (a decrease of <1%). Applying no discounting to costs and outcomes reduces the Strimvelis ICER vs HSCT from a MUD to £21,312.

When a 3.5% discount rate is used for both costs and outcomes, then the ICER for Strimvelis versus HSCT from a haploidentical donor rises from £14,645 to £25,697. If costs are discounted at 3.5% and outcomes at 1.5%, then the ICER for Strimvelis vs HSCT from a haploidentical donor increases slightly from £14,645 to £15,294. Applying no discounting reduces the Strimvelis ICER vs HSCT from a haploidentical donor to £8,278.

In all these cases, the ICERs for Strimvelis vs either HSCT procedure remain well below the criteria to automatically fund treatments for very rare conditions (highly specialised technologies) up to, in general, £100,000/QALY gained and up to £140,000/QALY gained given the magnitude of the QALY gain (13.6) provided by Strimvelis compared with HSCT from a MUD [NICE, 2017b].

Rescue transplant rates: Reducing the probability of a rescue transplant being required after Strimvelis from the baseline 17.6% to 8.3% reduces the ICER for Strimvelis versus HSCT from a MUD and HSCT from a haploidentical donor to £25,881 and £3,626, respectively. Increasing the probability of a rescue transplant being required after Strimvelis to 22.7% increases the ICER for HSCT from a MUD and HSCT from a haploidentical donor to £40,483 and £20,214, respectively. Once again, the ICERs for Strimvelis vs either HSCT procedure remain well below the £100,000/QALY gained and up to £120,000/QALY gained (for QALY gains of 11.7) criteria.

The initial post-intervention survival rates: Increasing the HSCT from a MUD survival rate from 67% to 83.75% substantially increases the ICER for Strimvelis vs HSCT from a MUD from £36,360 to £67,403, which is still considerably below the £100,000/QALY gained and up to £140,000/QALY gained criteria

In summary, none of the extensive 1-way deterministic sensitivity analyses results in an ICER above £100,000 per QALY.

In the multi-way sensitivity analysis, the impact on the ICERs of varying both the mean life expectancy of survivors and the quality of life of these survivors is relatively modest.

These results were consistent with the probabilistic sensitivity analysis, the ICERs/QALY gained range between dominance for Strimvelis and £361,272/QALY with a median value of £37,269/QALY gained for HSCT from a MUD; and between dominance for Strimvelis and £135,814 for HSCT from a haploidentical donor with a median value of £14,341/QALY gained. Although the sensitivity analysis produced some instances where the ICER exceeded the £100,000/QALY gained threshold, such instances were rare: the probability that the ICER met the threshold is 96%.

In summary, GSK has performed a detailed and comprehensive sensitivity analysis that confirmed the primary conclusion of the base-case analysis: Strimvelis is a highly effective treatment vs HSCT and, in almost all cases, easily meets the new HST ICER cost-effectiveness criteria for automatic funding of treatments for ultra-rare conditions.

12.5.16 What are the key drivers of the cost results?

Table D 29 shows the percentage of total costs for each cost category for each of the three interventions.

Table D 29 Percentage of total costs by cost category

Cost category	Costs for Strimvelis therapy	HSCT from a MUD	HSCT from a haploidentical donor
Screening pre-procedure	0.0%	8.0%	5.1%
Confirmation of eligibility for Strimvelis treatment	[redacted]	0.0%	0.0%
PEG-ADA pre-procedure	11.7%	46.4%	29.5%
Product	47.7%	0.0%	0.0%
Severe infection cost	1.2%	1.5%	1.1%
Rescue transplant cost	1.5%	1.1%	2.9%

Cost category	Costs for Strimvelis therapy	HSCT from a MUD	HSCT from a haploidentical donor
Rescue PEG-ADA cost	20.5%	14.5%	39.5%
Hospitalisation cost	[redacted]	16.9%	12.2%
Follow-up cost	[redacted]	7.6%	6.6%
GvHD	0.0%	1.4%	0.9%
IVIG cost	2.2%	2.6%	2.1%
Total	**100%**	**100%**	**100%**

Abbreviations: HSCT= HSCT=haematopoietic stem cell transplantation; GvHD=graft-versus-host disease; IVIG=intravenous immunoglobulin; MUD=matched unrelated donor; PEG-ADA=polyethylene glycol-modified bovine adenosine deaminase.
Note: All percentages are calculated using costs discounted at 1.5%.

The cost of the Strimvelis product is the major cost component of total Strimvelis costs followed by rescue PEG-ADA costs. PEG-ADA pre-procedure costs are the major cost component of total HSCT from a MUD followed by hospitalisation costs. Rescue PEG-ADA costs are the major cost component of total HSCT from a haploidentical donor followed by PEG-ADA pre-procedure costs.

The 2 major drivers of cost are the probabilities of survival after intervention and probability of requiring a rescue transplant. Survival generates potential additional severe infection, rescue transplant, associated PEG-ADA, follow-up, GvHD (for HSCT), and IVIG costs. Increasing the probability of a rescue transplant being required increases severe infection, further rescue transplant, associated PEG-ADA, hospitalisation, follow-up GvHD, and IVIG costs.

Miscellaneous results

12.5.17 Describe any additional results that have not been specifically requested in this template. If none, please state.

Using the same baseline assumptions as discussed earlier, the cost per life year gained for Strimvelis versus HSCT from a MUD is £31,629. The cost per Life Year gained for Strimvelis versus HSCT from a haploidentical donor is £12,959.

12.6 Subgroup analysis

12.6.1 Specify whether analysis of subgroups was undertaken and how these subgroups were identified. Cross-reference the response to the decision problem in table A1.

In line with the decision problem, subgroup analyses were not undertaken due to the small number of patients in each treatment group. Further dividing the

small patient numbers in analyses are unlikely to provide clinically meaningful information.

12.6.2 Define the characteristics of patients in the subgroup(s).

Not applicable.

12.6.3 Describe how the subgroups were included in the cost-effectiveness analysis.

Not applicable.

12.6.4 What were the results of the subgroup analysis/analyses, if conducted? The results should be presented in a table similar to that in section 12.5.6 (base-case analysis). Please also present the undiscounted incremental QALYs consistent with Section 12.5.7.

Not applicable.

12.6.5 Were any subgroups not included in the submission? If so, which ones, and why were they not considered?

Not applicable.

12.7 Validation

12.7.1 Describe the methods used to validate and cross-validate (for example with external evidence sources) and quality-assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical and resources sections.

Given the scarcity of long-term studies on the progression of patients with ADA-SCID after a successful intervention, data validation using literature sources was not possible. Economic modelling was validated with Professor Andrew Briggs, Chair in Health Economics at the University of Glasgow.

12.8 Interpretation of economic evidence

12.8.1 Are the results from this cost-effectiveness analysis consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

A systematic literature search identified no published economic literature on treatments for ADA-SCID, so this could not be ascertained. However,

improvements in clinical outcomes including survival are reflected in the fact that gene therapy is now considered to be the first option for the treatment of ADA-SCID for patients without a matched related donor in European guidelines [ESID/EBT Guideline, 2017].

12.8.2 Is the cost-effectiveness analysis relevant to all groups of patients and specialised services in England that could potentially use the technology as identified in the scope?

Yes, the analysis is relevant to all patients with ADA-SCID likely to present at the two specialist bone marrow transplant centres in England for whom a suitable matched related stem cell donor is not available, in accordance with the marketing authorisation for Strimvelis.

12.8.3 What are the main strengths and weaknesses of the analysis? How might these affect the interpretation of the results?

The model is complete in scope and in content. It includes all the clinical stages for ADA-SCID patients that are seen in clinical practice and the model parameters are drawn from clinical studies, peer-reviewed literature, clinical practice, and expert advice. Reasonable assumptions were made for the base-case analysis when data were not available and the basis for these assumptions is clearly provided in this report. When data were missing, dated, or uncertain, we explored the consequences of data uncertainties with extensive deterministic and probabilistic sensitivity analyses. The primary results of the modelling and the main cost-benefit conclusions are very robust under reasonable sensitivity parameter variation. In all non-extreme scenarios, Strimvelis treatment gives significant QALY gains when compared to HSCT from a MUD or from a haploidentical donor and, these gains are achieved with ICERs well under £100,000 per QALY gained.

Modelling is an attempt to simplify reality. Relative to other diseases, clinical and natural history data for patients with ADA-SCID are scarce. For example, data for Strimvelis are based on integrated studies of 18 patients. A detailed and thorough search of the scientific literature was performed and the model incorporates the latest data available. Despite this, data gaps exist and, in such cases, we have used sensitivity analyses to identify and quantify key uncertainties. Some literature data, e.g., those reported by Hassan (2012), cover a long time period over which clinical practice was evolving, and these temporal changes may increase uncertainties, but we have addressed this to take a conservative view when in doubt. The results in these studies are not comprehensively reported, and a number of assumptions have been made to address these data gaps.

The impact (cost or outcomes) of cognitive or neurodevelopmental deficits (e.g., deafness) was not included in the analysis. This is not necessarily a concern since no available treatment (Strimvelis, HSCT, or PEG-ADA) is thought to improve the neurological deficits observed in patients with ADA-SCID. Nevertheless, the evidence indicates that Strimvelis increases overall survival, which will increase the number of patients who suffer from such

deficits. If these patients incur higher health care costs than patients without such deficits, total costs would be greater in the Strimvelis surviving population. However, given the very small number of patients that would likely fall in this category, the aggregate cost burden would be extremely low.

12.8.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

Given the summary and incomplete nature of the published clinical evidence for HSCT from a MUD or haploidentical donor for the treatment of ADA-SCID and the limited experience with Strimvelis, the preceding analysis includes a number of assumptions. These assumptions naturally lead to uncertainties in the model. We have addressed the main uncertainties within the various sensitivity analyses that have been conducted. It is expected that the ongoing follow up of current and future patients with ADA-SCID who receive Strimvelis through the patient registry will be sufficient to address any remaining minor uncertainties and support the demonstrated high cost-effectiveness of Strimvelis in this submission.

13 Cost to the NHS and Personal Social Services

Summary

- Over 5 years, the cumulative budget impact of treating 1 patient with Strimvelis every year (rather than 1 patient with HSCT from a MUD per year) is estimated to be £2,339,257.

13.1 How many patients are eligible for treatment in England? Present results for the full marketing authorisation and for any subgroups considered. Also present results for the subsequent 5 years.

The incidence of ADA-SCID in the UK has not been specifically studied, but this information can be extrapolated from available data. According to the 2012 Screening for Severe Combined Immunodeficiency: External Review Against Programme Appraisal Criteria for the UK National Screening Committee, 20 children per year presented with SCID to the 2 UK centres for care (Great Ormond Street Hospital and Newcastle Great North Children's Hospital), which suggests an incidence for SCID of approximately 2.86 infants per 100,000 [UK National Screening Committee, 2012]. Using an estimate quoted in that report that ADA-SCID accounts for 14.8% of all patients with SCID yields an incidence of ADA-SCID in the UK of 2.96 patients per year. In another report, the percent of patients with SCID in the UK with ADA-SCID has been noted to be as high as 20% [Adams, 2015], which would yield an incidence of 4 patients per year in the UK. Therefore, 3 to 4 children per year would be likely to be diagnosed with ADA-SCID in the UK per year. The number of patients diagnosed with the condition per year in England would be a portion of the patients diagnosed per year in the UK. The exact proportion is unknown, but less than 4 patients per year in England would be expected.

Strimvelis is indicated for patients with ADA-SCID who do not have a matched related donor. Of the incident cases of 3 to 4 patients per year in the UK, 75-80% of patients will not have a suitable HLA-matched related stem cell donor available [Ferrua, 2010; Hirschorn, 2014], so only 2 to 3 patients per year from the UK are likely to be eligible for Strimvelis. The number of eligible patients from England would be expected to be smaller, and this number would be expected to be consistently within that range over the next 5 years.

13.2 Describe the expected uptake of the technology and the changes in its demand over the next five years.

Market growth information in other countries is not yet available. Uptake is not expected to be 100% of eligible patients. Strimvelis therapy requires patients to travel to and stay in Italy for 4.5 months. It is anticipated that some families will not be willing to make this trip and will seek alternatives that can be provided in England. Therefore, it is likely that only 1 patient per year from England, or potentially even less than 1 patient per year, will receive Strimvelis. This demand would be expected to be consistently within that range over the next 5 years.

13.3 In addition to technology costs, please describe other significant costs associated with treatment that may be of interest to NHS England (for example, additional procedures etc).

Not applicable.

13.4 Describe any estimates of resource savings associated with the use of the technology.

Section 12.5.8 summarises the changes in cost by cost category of moving from treatment with HSCT from either a MUD or haploidentical donor to Strimvelis.

The use of Strimvelis in place of HSCT from a MUD or haploidentical donor offers an opportunity for resource savings in several areas. With Strimvelis, there is no search for a MUD or the associated cost for that search. This also means the time to treatment is shorter for Strimvelis (9 weeks versus 19 weeks on average). Patients will require supportive care, including expensive PEG-ADA for a shorter period of time before treatment. The cost of hospitalisation is lower for Strimvelis. Additionally, there are no costs to treat GvHD as there may be with HSCT from a MUD or haploidentical donor because GvHD does not occur in patients treated with Strimvelis.

If Strimvelis is used instead of HSCT from a MUD, the net increase in costs per patient (lifetime and not discounted) is expected to be £498,735. This value is after including an expected savings of £194,366 (savings of £45,127 for screening for a MUD, £138,060 for PEG-ADA before the procedure, [redacted] for hospitalisation, and £7,880 for reductions in treating GvHD).

If Strimvelis is used instead of HSCT from a haploidentical donor, the net increase in costs per patient (lifetime and not discounted) is expected to be £167,502. This value is after including expected savings of £355,818 (savings of £45,127 for screening for HSCT, £138,060 for PEG-ADA before the procedure, £10,435 for rescue transplant, £137,248 for rescue PEG-ADA, [redacted] for hospitalisation and £8,406 for reductions in treating GvHD).

13.5 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

None applicable.

13.6 Describe any costs or savings associated with the technology that are incurred outside of the NHS and PSS.

Travel, lodging, meals, and other patient support services are not included in the price of Strimvelis. NHS England has referred GlaxoSmithKline to the commissioning policy on Proton Beam Therapy as representative of what NHS England would fund for a patient to be treated in another EU member state. The policy includes two parents (or a parent and a caregiver) to travel with the child as well as paying for accommodation during the stay in Milan. We have estimated that the total cost as €13,400, excluding the cost of public transport to and from the airport in the UK. This would include the cost of three economy class return airline tickets to a Milan airport at €900 (3*€300), accommodation in Milan for 4.5 months at €11,700 and local transport at €800. [redacted]

It should be noted that families of patients with ADA-SCID who are treated with HSCT must also usually travel to a specialty centre, where they typically stay from diagnosis to treatment. The difference is that the travel for HSCT is within the UK.

13.7 What is the estimated budget impact for the NHS and PSS over the first year of uptake of the technology, and over the next 5 years?

The budget impact model is constructed as a module within the cost-effectiveness model. The numbers of patients who would be eligible for treatment within each year of a 5-year period and the current treatment options that Strimvelis would replace for each year are selected.

All cost data for the analysis are drawn from the cost-effectiveness model. Discounting is not applied within the budget impact model.

For the current situation, the model calculates the total cost of treatment for patients treated through Years 1 to 5 inclusive by reference to the model underlying the cost-effectiveness analysis. If a patient were to join in Year 2, then the model would begin calculation from the model, again, from Year 1, but the Year 1 data for this patient are added to the Year 2 data for the first

patient. Similarly, the Year 2 data for the second year patient are added to the Year 3 data for the patient who joined in Year 1.

Since the incidence rate of ADA-SCID in the UK and the exact proportion of patients who could be treated by an MRD are uncertain, we present the budget impact results by first showing the budget impact of Strimvelis replacing a single HSCT from a MUD or haploidentical donor. We then calculate the anticipated total number of patients over the next 5 years. We have assumed that 3 patients in England will be diagnosed with ADA-SCID per year and that 1 of those 3 patients will receive HSCT from an MRD. Therefore 2 patients per year will be eligible to receive Strimvelis. Uptake is not expected to be 100% given the travel requirements; therefore, we have assumed that 1 patient per year will receive Strimvelis. We have assumed that Strimvelis will be replacing 1 HSCT from a MUD based on clinical expert explanation that HSCT from a haploidentical donor has not been performed in England in the last 15 years.

Table D 30, Table D 31, and Table D 32 show the annual cost per year for up to 5 years of 1 patient treated by an HSCT from a MUD, 1 patient treated by an HSCT from a haploidentical donor, and 1 patient treated with Strimvelis, respectively.

Table D 30 Cost per year of a patient being treated with HSCT from a MUD (undiscounted)

Cost category	Year 1	Year 2	Year 3	Year 4	Year 5	Total	% Total
Screening	£45,127	£0	£0	£0	£0	£45,127	8.0%
PEG-ADA pre-procedure	£262,314	£0	£0	£0	£0	£262,314	46.3%
Product	£0	£0	£0	£0	£0	£0	0.0%
Severe infection cost	£2,105	£2,105	£2,105	£566	£566	£7,447	1.3%
Rescue transplant cost	£0	£0	£6,368	£0	£0	£6,368	1.1%
Rescue PEG-ADA cost	£35,896	£47,861	£0	£0	£0	£83,756	14.8%
Hospitalisation cost	£95,516	£0	£0	£0	£0	£95,516	16.9%
Follow-up cost	£30,564	£9,130	£3,056	£912	£0	£43,663	7.7%
GvHD	£7,880	£0	£0	£0	£0	£7,880	1.4%
IVIG cost	£5,236	£3,766	£2,435	£1,739	£1,045	£14,220	2.5%
Total` Cost	**£484,638**	**£62,861**	**£13,964**	**£3,218**	**£1,611**	**£566,292**	**100.0%**
Cumulative	**£484,638**	**£547,499**	**£561,463**	**£564,681**	**£566,292**		

Abbreviations: GvHD=graft-versus-host disease; IVIG=intravenous immunoglobulin; PEG-ADA=polyethylene glycol-modified bovine adenosine deaminase.

Table D 31 Cost per year of a patient being treated with HSCT from a haploidentical donor (undiscounted)

Cost category	Year 1	Year 2	Year 3	Year 4	Year 5	Total	% Total
Screening	£45,127	£0	£0	£0	£0	£45,127	5.1%
PEG-ADA pre-procedure	£262,314	£0	£0	£0	£0	£262,314	29.3%
Product	£0	£0	£0	£0	£0	£0	0.0%
Severe infection cost	£2,255	£2,255	£2,255	£607	£607	£7,979	0.9%
Rescue transplant cost	£0	£0	£27,290	£0	£0	£27,290	3.0%
Rescue PEG-ADA cost	£153,838	£205,118	£0	£0	£0	£358,956	40.0%
Hospitalisation cost	£108,760	£0	£0	£0	£0	£108,760	12.1%
Follow-up cost	£32,748	£9,782	£13,099	£3,911	£0	£59,539	6.6%
GvHD	£8,406	£0	£0	£0	£0	£8,406	0.9%
IVIG cost	£5,610	£4,341	£3,536	£2,784	£1,716	£17,987	2.0%
Total Cost	**£619,058**	**£221,495**	**£46,181**	**£7,302**	**£2,323**	**£896,358**	**100.0%**
Cumulative	**£619,058**	**£840,553**	**£886,734**	**£894,035**	**£896,358**		

Abbreviations: GvHD=graft-versus-host disease; IVIG=intravenous immunoglobulin; PEG-ADA=polyethylene glycol-modified bovine adenosine deaminase.

Table D 32 Cost per year of a patient being treated with Strimvelis (undiscounted)

Cost category	Year 1	Year 2	Year 3	Year 4	Year 5	**Total**	**% Total**
Screening	£0	£0	£0	£0	£0	£0	0.0%
Confirmation of eligibility for Strimvelis treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PEG-ADA pre-procedure	£124,254	£0	£0	£0	£0	£124,254	11.7%
Product	£505,000	£0	£0	£0	£0	£505,000	47.5%
Severe infection cost	£3,157	£3,157	£3,157	£850	£850	£11,171	1.1%
Rescue transplant cost	£0	£0	£16,856	£0	£0	£16,856	1.6%
Rescue PEG-ADA cost	£95,018	£126,690	£0	£0	£0	£221,708	20.8%
Hospitalisation cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Follow-up cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GvHD	£0	£0	£0	£0	£0	£0	0.0%
IVIG cost	£7,854	£5,758	£3,983	£2,937	£1,703	£22,312	2.1%
Total Cost	**£870,399**	**£150,112**	**£34,075**	**£6,202**	**£2,629**	**£1,063,417**	**100.0%**
Cumulative	**£870,399**	**£1,020,511**	**£1,054,586**	**£1,060,788**	**£1,063,417**		

Abbreviations: GvHD=graft-versus-host disease; IVIG=intravenous immunoglobulin; PEG-ADA=polyethylene glycol-modified bovine adenosine deaminase; TC=total cost.

From the 1-year perspective, the budget impact per patient of Strimvelis replacing an HSCT from a MUD is estimated to be £385,761 (£870,399 - £484,638). From the 5-year perspective, the budget impact per patient is £497,125 (£1,063,417 - £566,292).

From the 1-year perspective, the budget impact per patient of Strimvelis replacing an HSCT from a haploidentical donor is estimated to be £251,341 (£870,399 - £619,058). From the 5-year perspective, the budget impact per patient is £167,059 (£1,063,417 - £896,358).

Median and mean hospital stay after the procedure in the Strimvelis integrated population was 45 days and 53 days, respectively. Minimum stay after the procedure was 34 days, whilst one patient stayed hospitalised for the maximum of 110 days. In the extreme case in which a particular patient needed to stay in hospital longer 110 days the budget impact of Strimvelis replacing an HSCT from a MUD is estimated to increase by €53,138 (approximately £45,167), going up to £430,928 and £542,293 per patient from 1-year and 5-year perspectives, respectively.

Table D 33 shows the cost per year and over 5 years of the expected current treatment of HSCT from a MUD for 1 patient per year in England over the next 5 years (‘current situation’).

Table D 33 Cumulative cost of treating 1 patient per year for 5 years with HSCT from a MUD

Cost category	Year 1	Year 2	Year 3	Year 4	Year 5	Total	% Total
Screening	£45,127	£45,127	£45,127	£45,127	£45,127	£225,635	8.3%
PEG-ADA pre-procedure	£262,314	£262,314	£262,314	£262,314	£262,314	£1,311,570	48.1%
Product	£0	£0	£0	£0	£0	£0	0.0%
Severe infection cost	£2,105	£4,210	£6,314	£6,881	£7,447	£26,957	1.0%
Rescue transplant cost	£0	£0	£6,368	£6,368	£6,368	£19,103	0.7%
Rescue PEG-ADA cost	£35,896	£83,756	£83,756	£83,756	£83,756	£370,921	13.6%
Hospitalisation cost	£95,516	£95,516	£95,516	£95,516	£95,516	£477,580	17.5%
Follow-up cost	£30,564	£39,694	£42,750	£43,663	£43,663	£200,335	7.4%
GvHD	£7,880	£7,880	£7,880	£7,880	£7,880	£39,402	1.4%
IVIG cost	£5,236	£9,002	£11,437	£13,176	£14,220	£53,070	1.9%
Total Cost	**£484,638**	**£547,499**	**£561,463**	**£564,681**	**£566,292**	**£2,724,572**	**100.0%**
Cumulative	**£484,638**	**£1,032,137**	**£1,593,600**	**£2,158,281**	**£2,724,572**		

Abbreviations: GvHD=graft-versus-host disease; HSCT=haematopoietic stem cell transplantation; IVIG=intravenous immunoglobulin; MUD=matched unrelated donor; PEG-ADA=polyethylene glycol-modified bovine adenosine deaminase; TC=total cost.

Table D 34 shows the cost per year over 5 years of treating 1 patient per year with Strimvelis ('new situation').

Table D 34 Cumulative cost of treating 1 patient per year for 5 years with Strimvelis

Cost category	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Total**	% Total
Screening	£0	£0	£0	£0	£0	£0	0.0%
Confirmation of eligibility for Strimvelis Treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PEG-ADA pre-procedure	£124,254	£124,254	£124,254	£124,254	£124,254	£621,270	12.3%
Product (Strimvelis)	£505,000	£505,000	£505,000	£505,000	£505,000	£2,525,000	49.8%
Severe infection cost	£3,157	£6,314	£9,472	£10,321	£11,171	£40,435	0.8%
Rescue transplant cost	£0	£0	£16,856	£16,856	£16,856	£50,567	1.0%
Rescue PEG-ADA cost	£95,018	£221,708	£221,708	£221,708	£221,708	£981,850	19.4%
Hospitalisation cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Follow-up cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GvHD	£0	£0	£0	£0	£0	£0	0.0%
IVIG cost	£7,854	£13,612	£17,595	£20,532	£22,312	£81,905	1.6%
Total Cost	**£870,399**	**£1,020,511**	**£1,054,586**	**£1,060,788**	**£1,063,417**	**£5,069,700**	**100.0%**
Cumulative	**£870,399**	**£1,890,909**	**£2,945,495**	**£4,006,283**	**£5,069,700**		

Abbreviations: GvHD=graft-versus-host disease; IVIG=intravenous immunoglobulin; PEG-ADA=polyethylene glycol-modified bovine adenosine deaminase; TC=total cost.

Over the first year of uptake, the budget increase (from treating 1 patient with Strimvelis rather than HSCT from a MUD) is £385,761 (£870,399 - £484,638). Over 5 years, the cumulative budget impact of treating 1 patient with Strimvelis each year (rather than 1 patient with HSCT from a MUD each year) is £2,345,128 (£5,069,700 - £2,724,572).

Table D 35 shows the difference in costs for each year for the ‘new situation’ replacing the ‘current situation’. This represents a very low budget impact, particularly for a totally innovative therapy that is addressing a very high unmet need in children diagnosed with ADA-SCID.

Table D 35 Difference in cost of Strimvelis replacing 1 HSCT from a MUD per year for 5 years

Cost category	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Screening	-£45,127	-£45,127	-£45,127	-£45,127	-£45,127	-£225,635
Confirmation of eligibility for Strimvelis Treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PEG-ADA pre-procedure	-£138,060	-£138,060	-£138,060	-£138,060	-£138,060	-£690,300
Product	£505,000	£505,000	£505,000	£505,000	£505,000	£2,525,000
Severe infection cost	£1,052	£2,105	£3,157	£3,440	£3,724	£13,478
Rescue transplant cost	£0	£0	£10,488	£10,488	£10,488	£31,464
Rescue PEG-ADA cost	£59,122	£137,952	£137,952	£137,952	£137,951	£610,929
Hospitalisation cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Follow-up cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GvHD	-£7,880	-£7,880	-£7,880	-£7,880	-£7,880	-£39,402
IVIG cost	£2,618	£4,610	£6,158	£7,357	£8,092	£28,835
Total Cost	£385,761	£473,012	£493,123	£496,107	£497,125	£2,345,128
Cumulative	£385,761	£858,772	£1,351,895	£1,848,002	£2,345,128	

Abbreviations: GvHD=graft-versus-host disease; HSCT=haematopoietic stem cell transplantation; IVIG=intravenous immunoglobulin; MUD=matched unrelated donor; PEG-ADA=polyethylene glycol-modified bovine adenosine deaminase; TC=total cost.

13.8 Describe the main limitations within the budget impact analysis (for example quality of data inputs and sources and analysis etc.).

Section 12.8.3 details the limitations of the cost-effectiveness analysis. The limitations relating to the availability of the underlying data also apply to the budget impact analysis. In addition, small variations in the total number of patients treated per year may have a significant effect on the total budget impact. If 2 patients per year were eligible for Strimvelis, the 5-year budget impact would increase from £2,345,128 to £4,690,256.

Section E – Impact of the technology beyond direct health benefits

14 Impact of the technology beyond direct health benefits

14.1 Describe whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal social services, or are associated with significant benefits other than health.

There are benefits to treating patients with ADA-SCID beyond simple costs or improved health. ADA-SCID is a fatal disease that takes a toll on the quality of life of not only the patient but also the patient's carers and family. There were no deaths in the Strimvelis clinical programme or in any of the gene therapy studies identified in the literature search in Section 9, while the expected survival rate after HSCT from a MUD is 67% and from a haploidentical donor is 71%. The decision to treat a child with a therapy with a survival rate of 67% or 71% would be expected to cause the patient's parents a considerable amount of anxiety. Patients from the Strimvelis clinical programme have been able to participate in age-appropriate activities such as school and would be expected to become functioning adult members of society. Their value to society should not be undervalued.

14.2 List the costs (or cost savings) to government bodies other than the NHS.

None applicable

14.3 List the costs borne by patients that are not reimbursed by the NHS.

Some costs due to travel may not reimbursed by the NHS, but the patients and carers would likely incur these costs regardless of the treatment selected. [redacted] There is also the potential for lost income of carers who travel to Milan with their children and during the immediate follow-up period. It is important to note that in telephone interviews conducted for GSK research, [redacted] some carers reported that [redacted] [Data on file].

14.4 Provide estimates of time spent by family members of providing care. Describe and justify the valuation methods used.

In an effort to better understand the family impact of ADA-SCID, GSK conducted research through telephone interviews of carers of patients with ADA-SCID. Carers reported that [redacted] [Data on file].

14.5 Describe the impact of the technology on strengthening the evidence base on the clinical effectiveness of the treatment or disease area. If any research initiatives relating to the treatment or disease area are planned or ongoing, please provide details.

Strimvelis is, to date, the only ex vivo gene therapy to gain marketing authorisation from the EMA. It is a one-time treatment with a potential for lifelong benefits and represents an absolute step-change for the treatment of patients with ADA-SCID with no suitable HLA matched related stem cell donor. The impact of Strimvelis has been recognised by the EBMT guidelines for the treatment of ADA-SCID. The updated EBMT guidelines recommend an approved gene therapy as the first-line treatment for patients with ADA-SCID who do not have a matched related donor available [EBMT/ESID Guidelines, 2017]. This positioning demonstrates the high unmet need of patients with ADA-SCID who do not have a matched related donor and also recognises the clinical evidence and benefit risk of Strimvelis gene therapy for this specified population.

The long-term efficacy, tolerability, and safety outcomes will continue to be monitored and assessed via the Strimvelis Registry Study, a non-interventional, prospective Post-Authorisation Safety Study (PASS) of patients with ADA-SCID treated with Strimvelis as described in Section 14.7. This registry, as well as existing registries from established communities (e.g., EBMT and ESID), will provide more information to strengthen the evidence available for this disease and associated treatments. GSK is exploring opportunities to integrate long-term follow-up data from Strimvelis with existing immunodeficiency registries.

The approval of Strimvelis represents the culmination of more than 20 years of research by HSR-TIGET and a critical strategic collaboration between HSR-TIGET and GSK to overcome the regulatory challenges for a novel gene-therapy advanced therapy medicinal product. As Strimvelis is the first ex-vivo gene therapy to be approved, bringing Strimvelis to the market has paved the regulatory pathway for future gene therapies.

14.6 Describe the anticipated impact of the technology on innovation in the UK.

Strimvelis is the first ex-vivo gene therapy approved by the European Medicines Agency and would be the first ex-vivo gene therapy approved for use in the UK. Strimvelis is a step-change in the management of ADA-SCID because it corrects the underlying cause of the disease using the patients' own cells circumventing the need for a stem cell donor search and the risk of immune rejection (GvHD). In patients with ADA-SCID with no suitable MRD, Strimvelis can offer improved survival rates over HSCT, when compared indirectly. This innovative step-change is reflected in the change in EBMT/ESID guidelines [EBMT/ESID Guidelines, 2017].

Advanced therapies form an important part of the UK Life Sciences strategy. The UK aspires to position itself as a global hub for researching, developing, manufacturing, and adopting advanced therapies. Today, the UK is recognized for a leading position in advanced therapies medical research. However, investors will be most attracted to those countries and health systems that are also ready to 'pull' through these products for early reimbursement and adopt these innovative therapies for the benefit of appropriate patients. A NICE approval will signal to investors that cell and gene therapy products can secure reimbursement in the UK and contribute to increased investment in innovation in the UK.

In summary, besides being an innovative medicine which will transform the way ADA-SCID is treated, Strimvelis will contribute to build the environment in the UK to attract investment and bring future innovation to the UK.

14.7 Describe any plans for the creation of a patient registry (if one does not currently exist) or the collection of clinical effectiveness data to evaluate the benefits of the technology over the next 5 years.

The long-term efficacy, tolerability, and safety outcomes will continue to be monitored and assessed via the Strimvelis Registry Study, a non-interventional, prospective Post-Authorisation Safety Study (PASS) of patients with ADA-SCID treated with Strimvelis. The primary objective of this study is to characterise the long-term safety and effectiveness of Strimvelis over a 15-year post treatment period in up to 50 patients treated. Participation in the registry is not mandatory since it is considered unethical to obligate any patient to participate in a registry as a pre-requisite for receipt of a life-saving treatment. However, participation will be strongly encouraged since long-term data on Strimvelis are limited and it is in the patient's own interest to continue receiving this monitoring in addition to their regular health monitoring. This registry, as well as existing registries from established communities (e.g., EBMT and ESID), will provide more information to strengthen the evidence available for this disease and associated treatments. GSK is exploring opportunities to integrate long-term follow-up data from Strimvelis with existing immunodeficiency registries.

14.8 Describe any plans on how the clinical effectiveness of the technology will be reviewed.

If the patient agrees to be part of the observational patient registry, the effectiveness of Strimvelis will be assessed by the survival rate, intervention-free survival, immune reconstitution (an increase in T lymphocytes [CD3+]), growth, the percentage of treatment failures, systemic metabolite detoxification, and vector copy number; paediatric development and quality-of-life data will also be collected, where assessed. The safety of Strimvelis will be assessed by AEs and SAEs (including infections), risks related to medical or surgical procedures, non-immunological manifestations (e.g., hepatic steatosis, cognitive defects, behavioural abnormalities, hearing impairment),

immune reactions (e.g., hypersensitivity, autoimmunity), oncogenesis, laboratory parameters, thyroid stimulating hormone levels, replication competent recombinant retrovirus testing, and retroviral insertion site analysis, if performed.

14.9 What level of expertise in the relevant disease area is required to ensure safe and effective use of the technology?

As treatment will only occur in Italy, expertise in administering gene therapy is not required. However, specialists may require access to gene therapy-specific diagnostic tests for long-term monitoring (see Section 8.7).

For all treatments for ADA-SCID, a sophisticated infrastructure is needed to rapidly diagnose patients with ADA-SCID and refer them to specialists with expertise in managing the initial presentation and complications of ADA-SCID.

14.10 Would any additional infrastructure be required to ensure the safe and effective use of the technology and equitable access for all eligible patients?

No.

Section F – Managed Access Arrangements (please see Sections 55-59 of the HST methods guide)

15 Managed Access Arrangement

15.1 Describe the gaps identified in the evidence base, and the level of engagement with clinical and patient groups to develop the managed access arrangement (MAA)

Given the low ICERs and budget impact, GSK does not believe that a formal MAA is required. Moreover, elements often observed in MAAs are already naturally in place for Strimvelis. Not all patients with ADA-SCID are eligible for Strimvelis. Strimvelis is only indicated for patients with ADA-SCID without an MRD; therefore, eligibility is already restricted to those patients that can benefit the most. In addition, GSK will only expect referrals from 2 specialist hospitals, which are the major paediatric immune disease centres in England. This further ensures that Strimvelis will only be given to patients for whom the treatment is fully appropriate. Data collection to monitor outcomes is already in place through the Strimvelis registry, and these data can be shared with the NHS in the form of periodic benefit risk evaluation reports that are mandated by the EMA as they become available.

Irrespectively of this, Strimvelis is a single-dose treatment with benefits that are expected to be lifelong offered at a price considerably lower than the lifetime cost of other chronic and long-term therapies. There is a significant QALY gain with Strimvelis compared with HSCT from a MUD or haploidentical donor. The cost-effectiveness estimated for Strimvelis is considerably below the acceptability threshold even when assuming conservative unsuccessful engraftment rates for Strimvelis and comparators. Any uncertainty was extensively explored in sensitivity analyses, and it is clear that the ICER estimates are extremely robust. In addition, the estimated budget impact is small for such a considerable benefit in an ultra-rare disease. For all these reasons, GSK does not believe a formal MAA is required.

15.2 Describe the specifics of the MAA proposal, including:

- *The duration of the arrangement, with a rationale*
- *What evidence will be collected to reduce uncertainty*
- *How this evidence will be collected and analysed*
- *The clinical criteria to identify patients eligible to participate in the MAA, and criteria for continuing or stopping treatment during the MAA*
- *Any additional infrastructure requirements to deliver the MAA (e.g. databases or staffing)*
- *Funding arrangement, including any commercial proposals or financial risk management plans*
- *The roles and responsibilities of clinical and patient groups during the MAA*
- *What will happen to patients receiving treatment who are no longer eligible for treatment if a more restricted or negative recommendation is issued after the guidance has been reviewed*

Not applicable.

15.3 Describe the effect the MAA proposal will have on value for money; if possible, include the results of economic analyses based on the MAA

Not applicable.

16 References

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Highly Specialised Technology Evaluation

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

Dear Angela

The Evidence Review Group, Centre for Reviews & Dissemination – York (CRD), and the technical team at NICE have looked at the submission received on 05 July 2017 by GSK. In general terms they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification relating to some of the data (see questions listed at the end of the letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide a written response to the clarification questions by **5pm on 4 August 2017.** Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, and all information submitted under 'academic in confidence' in yellow.

If you present data that is not already referenced in the main body of your submission and that data is seen to be academic/commercial in confidence information, please complete the attached checklist for in confidence information.

Please do not 'embed' documents (i.e. PDFs, spreadsheets) in your response as this may result in your information being displaced or unreadable.

If you have any further queries on the technical issues raised in this letter then please contact Thomas Strong, Technical Lead (Thomas.strong@nice.org.uk). Any procedural questions should be addressed to Jenna Dilkes, Project Manager (jenna.dilkes@nice.org.uk).

Yours sincerely

Sheela Upadhyaya
Associate Director – Highly Specialised Technologies
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Encl. checklist for in confidence information

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Section A: Clarification on effectiveness data

Patient characteristics table and Information on Screening and Exclusion to Trial

A1. For the integrated analysis population (n=18) please provide the proportion of patients with viral infection at baseline.

A2. **Priority question**. Please provide details on number of patients screened for eligibility to the pilot and pivotal studies and numbers of patients excluded (with reasons).

Named Patient Programme data

A3. **Priority question**. The ERG appreciates that the data from the Named Patient Programme (NPP) is distinct from the Strimvelis Integrated Population, and that the company does not have as much access to this data. However, based on the data available, please could you provide similar information for this cohort of 4 patients in the format of Table 1 (page 23) of the Cicalese et al. 2016 paper? If available, please also provide the proportion of patients with viral infection at baseline for the NPP patients.

A4. **Priority question**. Please provide a narrative summary of the data (e.g. in terms of overall survival, intervention-free survival, adverse events etc.) available from the named patient programme using the same format as in the main clinical effectiveness section on the Strimvelis Integrated Population. Though the details are provided in Appendix 6 it would be helpful to compare and contrast these data.

A5. **Priority question**. In Appendix 6 of the submission it states that [redacted] patients who received Strimvelis in the Named Patient Programme (NPP) had unsuccessful responses to gene therapy. Due to the removal of patient numbers from the text it is difficult to decipher the information provided. Please clarify whether or not these are the [redacted] patients who received PEG-ADA post- Strimvelis and if this is counted as an intervention (i.e. >3months). Did either of the other [redacted] NPP patients require post-Strimvelis intervention? Please also provide the totals for post-Strimvelis PEG-ADA and post-Strimvelis HSCT in the NPP.

Clarification about delivery of Strimvelis

A6. **Priority Question**: Please clarify the process for determining whether patients are able to donate adequate CD34+ cells, to deliver a minimum of 4 million purified CD34+ cells/kg, required for the manufacture of Strimvelis. What proportion of the relevant patient population (ADA-SCID, for whom no suitable HLA-matched related stem cell donor is available) would be able to deliver this minimum?

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A 7. Prior to treatment, patients are required to donate and have stored a 'back up' bone marrow transplant that could be used in the event of a failed manufacturing run or other complications. In what proportion of the 18 integrated analysis patients was this back-up used? In what proportion of the NPP patients was it used?

Clarification of specific data

A8. **Priority question**. It is stated in the European public assessment report associated with GSK2696273 that evaluating the changes in quality of life over time in ADA-SCID is a key objective of the pivotal study (AD1115611). Please provide the quality of life data collected in patients who have received Strimvelis. If possible, please analyse this data according to whether or not the patient:

(i) Experiences neurological deficits observed in patients with ADA-SCID.

(ii) Is receiving Intravenous Immunoglobulin (IVIG)

A9. Due to the removal of patient numbers from the text, the information provided on IVIG is difficult to decipher. Please provide the duration of post-Strimvelis use across all 18 patients: number who stopped use within 3 years; and median duration of use (minimum and maximum).

A10. Please clarify if the patients whose initial drug product was contaminated (see EPAR, p61) were classified as successful or unsuccessful for the intervention-free survival outcome and which patient numbers these were in the Cicalese et al 2016 paper?

A11. **Priority question**. Please clarify the data provided in Table D.12 footnote c (page 183, company submission; [redacted]). Is the total patient number the Strimvelis integrated population (n=18) and the Named Patient Programme ([redacted])? Please could you clarify, is the patient excluded from the integrated population in the long term follow up study (due to a lack of available data on PEG-ADA use) included here as experiencing intervention-free survival? Similarly, is [redacted] counted as experiencing intervention-free survival?

A12. **Priority question**. The most recent data provided from study AD1115611 LTFU is from May 2014. Is more recent follow up data available? If so, please provide this data.

Data on Hematopoietic stem cell transplantation (HSCT) from a Matched Unrelated Donor (MUD)

A13 Although the ERG agrees this is the best available data for a historical comparison with the Strimvelis data, it would be helpful to include further discussion of the extent

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to which the company considers that the data in Hassan 2012 reflects current overall survival rates for HSCT.

Impact on families and carers

A14. **Priority question:** Please clarify whether the company assessed the impact on families and carers of patients receiving treatment for up to three and half months overseas.

External Validity

A15. On page 113 data on adverse events associated with other forms of gene therapy are presented. Can the company provide further information regarding how directly relevant these are for Strimvelis, and the justification for this.

Section B: Clarification on cost model and value for money

B1. **Priority question:** The model includes an expected wait time of 19 weeks between time of diagnosis and HSCT from a matched unrelated donor or a haploidentical donor. The ERG have seen a presentation on the UK Stem Cell Strategic Forum Recommendations which state the wait time from diagnosis to transplant is 6 to 8 weeks, and other sources estimate the average search time at 50 days (7.1 weeks) for bone marrow and 13.5 days (1.9 weeks) for cord blood. Please justify the selection of Gaspar 2013 to inform wait time. Please provide further information on the expected duration of screening for suitable donors for transplant to ADA-SCID patients separately for:

i) a cord blood match;

ii) a matched unrelated donor for bone marrow transplant;

iii) a haploidentical donor for bone marrow transplant.

Please also provide information on the proportion of patients with ADA-SCID for whom a cord blood match is expected.

B2. **Priority question:** The model includes a cost of screening for matched unrelated donor and haploidentical donors of £45,127. Please explain the rationale for this cost, a breakdown of what is included, and the sources used to inform this cost.

B3. **Priority question:** The model assumes that no costs of searching for matched unrelated donor are incurred for patients allocated to Strimvelis. Please clarify whether the decision to use Strimvelis is expected to be made in the absence of knowledge regarding whether the patient has a cord blood match and/or potentially suitable adult donor in the registry. Please clarify whether a decision to use Strimvelis

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may be taken after a search for matched unrelated donor has failed to identify a suitable donor.

B4. Please provide the rationale behind the choice of NHS reference cost for each administration of IVIG or PEG-ADA (£306). Please clarify whether the costs incurred for administration, and the price of IVIG and PEG-ADA, are expected to differ for patients receiving those therapies whilst in Milan.

B5. **Priority question:** The model includes a cost of [redacted] for the initial hospitalisation for Strimvelis, [redacted] of which is assumed to occur in the UK prior to travel and the remaining [redacted] assumed to occur in Milan.

i) Please provide a breakdown of what is included in the [redacted] for confirming eligibility for Strimvelis and the sources used to inform this cost.

ii) Please provide a breakdown of the [redacted], the sources for the unit costs, and how payment from the UK NHS to Milan is expected to be made for these costs.

B6. **Priority question:** Please clarify whether the estimated technology cost of £505,000 and the initial hospitalisation cost of [redacted] are fixed payments for all patients treated with Strimvelis. Please confirm whether these costs would apply in the following circumstances (and if relevant provide alternative costing estimates):

i) extended hospitalisation resulting from severe infection;

ii) patients for whom the product contains less than 2 million $CD34^+$ cells/kg;

iii) other cases of product failure e.g. contamination;

iv) cases of transplant failure, or prolonged bone marrow aplasia after treatment with Strimvelis which require the use of the rescue product.

B7. The model includes an expected wait time of 9 weeks for Strimvelis based on the 'clinical schedule from San Raffaele Hospital'. Table D6 (page 168, company submission) presents the average durations of baseline patient preparation and confirmation of eligibility for Strimvelis, but it is not clear how or whether these relate to the 9 week wait period. Please provide further information on the clinical schedule, providing a reference if possible. Please provide a breakdown of the expected duration of time and events between:

i) Decision to use Strimvelis (i.e. meeting of multidisciplinary team to determine next treatment step after failure to find a matched related donor) and travel to Milan

ii) Arrival in Milan and commencement of treatment with Strimvelis

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B8. Please provide further justification for why time from diagnosis to treatment in the clinical trial was not considered applicable to the expected time to treatment with Strimvelis (AD1115611 – average duration of the pre-treatment phase was 5.7 months, range 10 days – 1.1 years), and how this would be expected to differ outside of a clinical trial setting.

B9. The travel arrangements that the NHS may support for families receiving Strimvelis proposed in this submission includes three economy class return airline tickets to a Milan airport and public transport to and from the airport. Please justify why these NHS supported travel costs are not included in the economic model.

B10. **Priority question:** Clinical advice to the ERG suggested that patients may require transfers by ambulance or air ambulance given their clinical condition. Please clarify from what locations patients travelled to receive treatment, and the method of transport (e.g. train, commercial airline, air ambulance ambulance). Please provide an estimated cost for ambulance transfer to and from airports, and by air ambulance from the UK to Milan.

B11. After Strimvelis gene therapy, the cost of follow-up was assumed similar to that post-HSCT. Clinical advice received by the ERG suggests additional blood tests are required after gene therapy to assess oncogenesis and vector copy numbers. Please provide further information on the type of tests required for monitoring after receipt of gene therapy, the frequency of the tests, the expected cost of each test and the length of follow-up over which the tests are indicated.

B12. Please provide a copy of 'The UK Stem Cell Strategy Oversight Committee Report on unrelated donor stem cell transplantation in the UK: effective affordable sustainable November 2014'.

B13. Please clarify whether the follow up costs in Tables D8 & D9 (page 172-174, company submission; reference to the UK Stem Cell Oversight committee and van Agthoven respectively) are based on the same source.

B14. **Priority question:** Please update the economic analysis and model with dosage and costs of PEG-ADA based on weight as was undertaken for IVIG. Please provide further justification for assuming the average weight of an ADA-SCID patient in the 25th percentile of the weight distribution of an average child.

B15. **Priority question:** The time horizon in the model is 10 weeks shorter for patients treated with Strimvelis (such that when survival from matched unrelated donor and haploidentical donor are set to 100% the predicted life years gained is 46.3 with these strategies versus 46.1 years with Strimvelis). Please provide an updated model that assesses all treatments over a common time horizon.

B16. **Priority question:** The model structure assumes no searching for a matched unrelated donor or a haploidentical donor is ever undertaken for patients allocated to receive Strimvelis, even after failure of Strimvelis. Please provide a scenario analysis

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in which the rescue transplant following Strimvelis is based on use of a matched unrelated donor or a haploidentical donor using the same search costs and survival rates as those for patients initially allocated to a matched unrelated donor in the economic model.

B17. **Priority question:** In the base case there is no procedural or disease related mortality in patients allocated to Strimvelis (as survival after Strimvelis and rescue therapy with a matched sibling donor is assumed to be 100%). As there are so few patients that have received Strimvelis, any mortality observed in the next few patients to receive treatment could significantly reduce survival rates. Please provide a scenario in which the survival after 6 months with Strimvelis is reduced from 100% (18/18) to 95% (18/19) and to 90% (18/20).

B18. **Priority question:** Please clarify whether the threshold analysis for the 'price of the Strimvelis procedure' (page 215, company submission) refers to varying the £505,000 acquisition cost of Strimvelis treatment.

B19. **Priority question:** matched unrelated donor Section 12.5.13 provides some threshold analyses with thresholds determined by the incremental QALY gain of Strimvelis at a discount rate of 1.5% (that is a threshold of £140,000 per QALY and £120,000 per QALY for Strimvelis vs matched unrelated donor and haploidentical donor respectively). Please repeat the same threshold matched unrelated donor analyses at

i) Thresholds of £100,000 per QALY.

ii) At threshold levels determined by the incremental QALY gain with Strimvelis at a discount rate of 0% (i.e. undiscounted QALYs).

B20. **Priority question:** The mean ICER from the probabilistic sensitivity analysis (PSA) is the ERG's preferred ICER. This ICER estimated from the PSA is estimated to be 18% higher than the deterministic ICER from Strimvelis compared to a matched unrelated donor (£42,863 compared to £36,360). The corresponding ICER for Strimvelis versus haploidentical donor is assumed to be lower based on the PSA compared to the deterministic model. Please report all results and sensitivity analyses based on the mean ICER from the PSA.

B21. Please provide an estimate of the long-term health service resource use associated with neurological deficits observed in patients with ADA-SCID.

B22. The company submission notes clinical advice stating that chronic graft-versus-host disease (cGvHD) could last from a few months to several years, but that cGvHD cases would normally be resolved by the time of a rescue transplant (p167, company submission). Please provide the rationale for the modelled duration of cGvHD episodes (3 years) extending beyond the assumed time until a rescue transplant (2 years).

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B23. Table D.24 and D.25 (page 203-208) of the company submission provide results of one-way deterministic sensitivity analyses for Strimvelis vs matched unrelated donor and haploidentical donor respectively. Please provide the results of these analyses in the format of a tornado diagram.

B24. Clinical advice to the ERG is that survival rates with HSCT are continually improving, especially with modern techniques for achieving good matches, and that current survival rates may be as high as 90% both for matched unrelated donor and haploidentical donor. Please repeat the one-way sensitivity analyses and produce a tornado diagram which assumes:

i) The upper bound for survival after 6 months for both matched unrelated donor and haploidentical donor is 90%, and

ii) The lower bound for survival after 6 months with Strimvelis is 90% (see question B17)

Section C: Textual clarifications and additional points

Search strategy

C1. Why was Strimvelis not included in the EMBASE search strategy for clinical data in Appendix 1, section 17.2.4, page 263?

C2. Why was the EMTREE term adenosine deaminase deficiency/ not included in the clinical data EMBASE search strategy (Appendix 1, section 17.2.4, page 263) and the economic data EMBASE search strategy (Appendix 3, section 17.3.4, page 269)?

C3. Is there a specific reason why truncation has not been used in any of the EMBASE search strategies in Appendices 1, 3, and 5?

Confidentiality marking

C4. **Priority question:** NICE considers it essential that evidence on which the Evaluation Committee's decisions are based is publicly available. NICE have noted that some of the confidentiality marking is not in line with the instructions sent with the invitation to submit. Specifically, NICE believes that the following data that has been redacted or marked as commercial in confidence is publically available:

i) Individual patient numbers, individual demographics, and data on each specific patient (page 57, 60, 65, 69, 70, 71, 74, 75, 76, 77, 78, 79, 80, 81, 85, 86, 94, 96, 102, 103, 112, 281, 285):
Within the original submission, this data was marked as ‘commercial in

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confidence' (CiC). Following GSK's concern over sharing potentially patient identifiable information with the committee, NICE agreed that this data could be redacted from the submission. The ERG have highlighted that much of the data is publically available, for example in the European public assessment report and the paper by Cicalese (2016). NICE therefore considers that this redacted information must be shared with committee, and further that all data that is publically available cannot be considered confidential. Please reconsider the marking of any of the remaining data that is not yet publically available, given that the rationale for its marking was that it could be used to identify patients.

ii) The acquisition cost of Strimvelis (page 16, 172, 200, 201, 233, 236, 238):
The submission marks this data as CiC. However the European acquisition cost used in this submission is publically available from numerous sources, and therefore cannot be considered confidential.

iii) Other data, for which the rationale given for confidentiality is that it could be used to back-calculate the acquisition cost:
Given that the acquisition cost of Strimvelis is publically available and cannot be marked as confidential, please remove the confidentiality marking of all data for which the only rationale given for confidential status is that it can be used to back-calculate the acquisition cost of Strimvelis.

Please resubmit two versions of your submission and include a revised and fully completed Checklist of Confidential Information stating, for each piece of information, the rationale for treating it as confidential and the expiry date of that confidentiality. When remarking the submission, please consider that large blocks of texts cannot be considered confidential, and that the confidential data must be marked individually.

One version of your submission should contain the remaining confidential information clearly marked. Please therefore underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. The second version of your submission should have that information redacted, any 'academic in confidence' or 'commercial in confidence' information should be replaced with asterisks and then highlighted in black. The revised documents should be consistent with the guidance in the invitation to participate document 'Appendix E: Confidential information checklist & guidance note'.

A1. For the integrated analysis population (n=18) please provide the proportion of patients with viral infection at baseline.

Data on viral infection status at baseline are not available, but no patients in the integrated analysis population had a confirmed active viral infection at screening. One subject had diarrhoea at screening; the cause is unknown.

A2. **Priority question.** Please provide details on number of patients screened for eligibility to the pilot and pivotal studies and numbers of patients excluded (with reasons).

There is no information available on the number of patients screened or excluded in the pilot studies. Twelve patients were screened for eligibility for the Pivotal Study, and no patients were excluded.

A3. **Priority question**. The ERG appreciates that the data from the Named Patient Programme (NPP) is distinct from the Strimvelis Integrated Population, and that the company does not have as much access to this data. However, based on the data available, please could you provide similar information for this cohort of 4 patients in the format of Table 1 (page 23) of the Cicalese et al. 2016 paper? If available, please also provide the proportion of patients with viral infection at baseline for the NPP patients.

Table 1 contains the requested information, as available, for patients in the NPP. Data on the proportion of patients with viral infection at baseline are not available. As the ERG has noted, the NPP is not run by GSK, which limits access to data and as such it is difficult to speculate on wider applicability of these immature and incomplete data. The programme is ongoing and data are not scheduled for formal analysis until all patients have reached 3 years of follow-up.

Table 1 Summary of Subjects Treated in the NPP

Subject	GSK study	Sex	Race	Country of origin at diagnosis	Prior SCT or PEG-ADA, duration	Age at gene therapy, yrs	GSK2696273 treatment date	GSK2696273 dose, CD34+ cells x10^6/kg	VCN of product
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted] [redacted]	4.6 (fresh)[a] 2.2 (frozen)[a]	0.6 0.4
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	16.9	1.1
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	4.6	2.0
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Not available	2.0

Abbreviations: F = female; M = male; PEG-ADA = polyethylene glycol adenine deaminase; VCN = vector copy number.

[redacted]

A4. **Priority question**. Please provide a narrative summary of the data (e.g. in terms of overall survival, intervention-free survival, adverse events etc.) available from the named patient programme using the same format as in the main clinical effectiveness section on the Strimvelis Integrated Population. Though the details are provided in Appendix 6 it would be helpful to compare and contrast these data.

An investigator-initiated Named Patient Programme was initiated in 2014. Formal analyses will not be conducted until all subjects reach 3 years of follow-up. However, preliminary data are available from in-stream reviews and safety monitoring. [redacted]

A5. In Appendix 6 of the submission it states that [redacted] patients who received Strimvelis in the Named Patient Programme (NPP) had unsuccessful responses to gene therapy. Due to the removal of patient numbers from the text it is difficult to decipher the information provided. Please clarify whether or not these are the [redacted] patients who received PEG-ADA post- Strimvelis and if this is counted as an intervention (i.e. >3months). Did either of the other [redacted] NPP patients require post-Strimvelis intervention? Please also provide the totals for post-Strimvelis PEG-ADA and post-Strimvelis HSCT in the NPP

[redacted] To the best of our knowledge, these represent the extent of post-Strimvelis interventions (PEG-ADA or further HSCT) in the NPP. However, GSK is not the sponsor of this programme and therefore data are limited. Full analysis of data from this program is planned when all subjects reach 3 years of follow-up.

A6. **Priority question.** Please clarify the process for determining whether patients are able to donate adequate CD34+ cells, to deliver a minimum of 4 million purified CD34+ cells/kg, required for the manufacture of Strimvelis. What proportion of the relevant patient population (ADA-SCID, for whom no suitable HLA-matched related stem cell donor is available) would be able to deliver this minimum?

Patients undergo a bone marrow biopsy to determine their ability to donate adequate CD34+ cells. This procedure is currently performed in Milan, but it can be performed in England.

The goal of the cell harvest procedure is to obtain sufficient CD34+ cells to permit manufacture of the Strimvelis product; this goal is encapsulated as the stated threshold of a minimum of 4 million purified CD34+ cells/kg.

Cellularity typically decreases with increasing age, and patients with lower cellularity may be unable to deliver the minimum amount of cells required. In the clinical trials, patients aged from 6 months to 6 years 1 month were able to deliver this minimum amount.

There are no data on the number of cells that were harvested, but data do exist for the Strimvelis doses that were administered in each Strimvelis procedure. The recommended dose range is between 2 and 20 million purified CD34+ cells/kg. For details of the administered doses given in the clinical programme, please refer to Table C21 in the original submission.

One subject in an early pilot study received a lower than recommended dose in their first Strimvelis procedure. On this basis, it can be said that 1 (6%) of 18 integrated population patients were unable to deliver the minimum purified CD34+ cells/kg to manufacture Strimvelis in the recommended dose range. This subject received Strimvelis before the recommended dose of Strimvelis was determined. If this were a patient from England today, the bone marrow biopsy that is now in place to determine ability to donate adequate CD34+ cells would identify that the patient is not a candidate for Strimvelis before travel to Italy.

A7. Prior to treatment, patients are required to donate and have stored a ‘back up’ bone marrow transplant that could be used in the event of a failed manufacturing run or other complications. In what proportion of the 18 integrated analysis patients was this back-up used? In what proportion of the NPP patients was it used?

In the integrated population, 1 subject (6%) received back up bone marrow cells because the subject was unable to receive the scheduled infusion of Strimvelis at the first attempt due to contamination, and 3 subjects (17%) received stored back up of unmanipulated bone marrow cells due to events after Strimvelis. [redacted] There is no further information on the use of back up bone marrow in the available NPP data.

A8. **Priority question.** It is stated in the European public assessment report associated with GSK2696273 that evaluating the changes in quality of life over time in ADA-SCID is a key objective of the pivotal study (AD1115611). Please provide the quality of life data collected in patients who have received Strimvelis. If possible, please analyse this data according to whether or not the patient: (i) Experiences neurological deficits observed in patients with ADA-SCID (ii) Is receiving Intravenous Immunoglobulin (IVIG)

An objective of Study AD1115611 was to evaluate the change in quality of life over time in subjects with ADA-SCID following treatment with Strimvelis. This objective applied to the long-term follow-up (LTFU, 4 to 8 years after gene therapy) only. The data-cut for the LTFU report was 08 May 2014. The endpoints evaluated were the Paediatric Quality of Life Inventory (PedsQL) and Lansky Performance status index. This information is provided in the submission in Section 10.1.3 and is repeated below.

An interim clinical study report for the LTFU dated 14-April 2015 presents post-baseline data on Lansky performance index for subjects with available data (n=8 at Year 4; n=9 at Year 5; n=6 at Year 6; n=6 at Year 7; n=1 at Year 9; n=1 at Year 13). All patients were reported as 'fully active, normal' during LTFU, with 1 exception, who had minor restrictions in strenuous physical activity recorded at Year 7 [Cicalese, 2016]. The patient with minor restrictions in strenuous physical activity was not receiving IVIG at the time of the restrictions and did not experience neurological deficits during the LTFU but was noted to have a foot deformity and muscle atrophy. Further information on IVIG use in the population as a whole is available in the response to question A9.

[redacted]completed the PedsQL questionnaire for the patient's age, at the Year 13 visit. The totality of [redacted] score, including the score by question and dimension, was as expected in an average healthy adolescent of the patient's age, based on a paediatric assessment. This patient did not experience neurological deficits and was not receiving IVIG at the time of the assessment.

Additionally, non-standardised and informal paediatric quality-of-life assessments were made in the LTFU study AD1115611 by means of patient status updates at annual follow-up visits. These assessments included attendance at school, participation in sports, eating habits, and receipt of childhood vaccinations. These LTFU assessments were not pre-specified as efficacy endpoints, and baseline assessments were not collected; however, they provide some indication of the clinical benefit of Strimvelis at LTFU time points with regard to overall well-being and daily function. The majority of patients across all studies who had available LTFU data (which includes patients from pivotal and supportive studies) reported on-time vaccinations, attendance at school or pre-school as appropriate for the patient's age (12 out of 14 patients [86%]), and eating

well with a varied and adequate diet. Most patients did not report participating in sports during the LTFU, primarily due to their parents' choice.

A9. Due to the removal of patient numbers from the text, the information provided on IVIG is difficult to decipher. Please provide the duration of post-Strimvelis use across all 18 patients: number who stopped use within 3 years; and median duration of use (minimum and maximum).

In the pivotal population, 7 (58%) of 12 patients discontinued use of IVIG within 3 years of follow-up. Further details of IVIG use after therapy with Strimvelis across all 18 patients treated in the integrated population, excluding one subject ([redacted]), are provided in Table 2. It is difficult to provide complete data on the duration of IVIG use, especially for maximum and median values, due to intermittent use, study withdrawals, rescue transplants, and ongoing therapy at the time of data cutoff (8 May 2014). The minimum duration of IVIG use after Strimvelis was 4 months.

Table 2 Post-Strimvelis use of IVIG in the Integrated population

Strimvelis Outcome	IVIG use for subjects with successful Strimvelis outcome	Subject numbers	n	Proportion of subjects[a] (%)	
				Proportion of subjects (%) N=17[c]	Proportion of subjects (%) N=14[d]
Unsuccessful[b]		[redacted]	3	18	
Successful	Permanently stopped IVIG within 3 yrs follow up	[redacted]	8	47	57
	Stopped IVIG within 3 yrs follow up, restarted during LTFU, stopped before data cutoff[e]	[redacted]	1	6	7
	Continued IVIG beyond 3 years, stopped before data cutoff	[redacted]	2	12	14
	Continued IVIG beyond 3 years, ongoing at data cutoff	[redacted]	3	18	21

Abbreviations: GT = gene therapy; IVIG = Intravenous immunoglobulin; LTFU = long-term follow up; n = number of patients; N = total number of patients.

a. Both columns exclude [redacted].
b. Two subjects ([redacted])were continuing IVIG at data cut; One subject ([redacted]) received IVIG replacement until withdrawal from the study to receive a sibling donor SCT
c. Includes all subjects independent of outcome of Strimvelis therapy. Excludes [redacted].
d. Includes only subjects who had a successful response to Strimvelis. Excludes unsuccessful responses and [redacted].
e. One subject ([redacted]) discontinued IVIG during 0–3 year follow-up, restarted in Year 4, and discontinued before data cutoff. The LTFU data cutoff was 08 May 2014.

A10. Please clarify if the patients whose initial drug product was contaminated (see EPAR, p61) were classified as successful or unsuccessful for the intervention-free survival outcome and which patient numbers these were in the Cicalese et al 2016 paper?

There were 2 patients whose initial drug product was contaminated. They correspond to subjects [redacted] and [redacted] in the Cicalese et al 2016 paper. Both patients had successful responses to gene therapy.

A11. **Priority question.** Please clarify the data provided in Table D.12 footnote c (page 183, company submission; [redacted]). Is the total patient number the Strimvelis integrated population (n=18) and the Named Patient Programme ([redacted])? Please could you clarify, is the patient excluded from the integrated population in the long term follow up study (due to a lack of available data on PEG-ADA use) included here as experiencing intervention-free survival? Similarly, is [redacted] counted as experiencing intervention-free survival?

Yes, the total patient number for the integrated population is n=18, and the total number for the NPP is [redacted]. However, [redacted] from Pilot Study 1 was enrolled into the AD1115611 LTFU study [redacted] and contributes only SAE data after [redacted] and the date of gene therapy to integrated analyses of duration of follow up and survival. Three (18%) of 17 patients in the integrated population did not experience intervention-free survival, which provides the 82% (14/17) intervention-free survival presented in the submission. Formal analyses of the NPP will not be conducted until all subjects reach 3 years of follow-up. However, preliminary data available from in-stream reviews and safety monitoring indicate that [redacted].

The patient from Pilot Study 1 was excluded from the intervention-free survival analysis presented in the clinical section due to a lack of available data on PEG-ADA. However, for the purposes of the economic analysis, GSK included all patients who have participated in the Strimvelis clinical programme, even those with limited data. [redacted]

A12. The most recent data provided from study AD1115611 LTFU is from May 2014. Is more recent follow up data available? If so, please provide this data.

The most recent data-cut and analysis from study AD1115611 LTFU is from May 2014. This information was provided in the submission and was published last year [Cicalese, 2016].

A13. Although the ERG agrees this is the best available data for a historical comparison with the Strimvelis data, it would be helpful to include further discussion of the extent to which the company considers that the data in Hassan 2012 reflects current overall survival rates for HSCT.

For a large cohort of patients specifically with ADA-SCID, Hassan provides the most up-to-date peer reviewed data. ADA-SCID is an ultra-rare condition, and evidence on treatment improvements accumulates slowly. We have made a concerted effort to incorporate all the latest peer reviewed and clinical advice data into the economic model.

As was noted in the original submission, it is likely that outcomes for HSCT from a MUD procedures have improved since the Hassan paper, but it is not possible to establish the extent to which this has happened from the available literature. Baseline overall survival in the economic model is 67%, which is the value given in Hassan. Clinical advice was that overall survival in MUD procedures might eventually become as high as 80%. Even though there is no data to support this improvement, we explored survival rates up to 83.75% in the sensitivity analyses in the submission and found that ICERs remained comfortably below the published acceptability threshold for the HST Evaluation Programme.

Likewise, it is reasonable to assume that accumulating experience and clinical advances have increased overall survival rates in HSCT from a haploidentical donor. Baseline overall survival in the economic model is 71%, which is the value given in Hassan for the cohort of 7 patients who received treatment in the last reported decade (2000-2009). HSCT using a haploidentical donor is uncommon and noted as a fourth line option in clinical guidelines for ADA-SCID. In line with this, clinical advice received suggested that no HSCT from a haploidentical donor procedures have been performed in England in the last 15 years for ADA-SCID. Overall survival rates up to 88.75% were included in the sensitivity analyses in the submission and again the ICERs were still well within the cost-effectiveness range determined by the HST threshold.

In all considerations of overall survival with different types of HSCT (MUD or haploidentical), it is important to understand whether the clinical advice provided for these survival data relate to SCID in general or specifically to ADA-SCID. ADA-SCID differs considerably from other forms of SCID. Unlike other primary immunodeficiencies caused by defects in lymphocyte signalling pathways, ADA deficiency is a systemic metabolic disorder, and the clinical management pathway for ADA-SCID differs from the pathways for other types of SCID. Since ADA-SCID is distinct from other SCIDs, it is inappropriate to generalise overall survival following HSCTs for all forms of SCID to ADA-SCID. For example, overall survival in haploidentical HSCTs has improved in recent years and these procedures are used to treat other forms of SCID, but they are

not used for ADA-SCID patients in the UK. It would be inappropriate to use overall survival data for haploidentical HSCT for SCIDs in general in an economic model specific to ADA-SCID.

After Hassan, clinical experts have advised GSK that they will follow the ESID/EBMT recommended guidelines for the treatment of ADA-SCID. The scientific and clinical experts committee at ESID and EBMT have pooled their experience and knowledge and concluded that, in the absence of a MRD for ADA-SCID, the next best available treatment from their view is gene therapy. If gene therapy is not available, the next treatment is HSCT from a MUD. Of note, the committee included clinical experts from England such as Dr. Andrew Gennery and Prof. Bobby Gaspar. The publication of the ESID/EBMT guideline is a very important event because the guideline is specific to ADA-SCID and considers the collective experience of treating ADA-SCID rather than the perspective one single expert may have on a extremely small sample. The committee members have detailed knowledge of the possible treatment options and the ways in which ADA-SCID differs from other forms of SCID. Their recommendation of gene therapy over HSCT from a MUD should therefore be afforded great weight.

A14. **Priority question:** Please clarify whether the company assessed the impact on families and carers of patients receiving treatment for up to three and half months overseas.

GSK has not performed an assessment of the impact of stays abroad on families and carers of patients who have received Strimvelis in Milan.

However, the Telethon Foundation, the charity responsible for providing the care services at Milan for patients who undergo gene therapy, started an anonymous formal assessment in July 2017. Areas assessed included patient/parent satisfaction and quality of care support provided, logistical and practical support services, travel and accommodations, emotional support and guidance provided by their care coordinator, clinical research nurses, clinicians and psychologists.

The preliminary results of this assessment showed that patients and parents were very satisfied overall with the support provided by the Telethon Foundation. As an example, a parent described their family's 3.5 months stay in Milan with the phrase "It was just like home."

In addition to the formal assessment, the Telethon Foundation collects ongoing feedback from patients and relatives as part of a continual assessment to support performance. Spontaneous and unsolicited feedback contributes to the foundation's understanding of the kind of support that makes a difference in a family's experience in Milan. Here are some examples of the spontaneous feedback that was provided to GSK: "The biggest help was to find a babysitter for my daughter. It was a wonderful evening and we were really happy to go out together"; "We are so grateful for all that you did for us. We really felt welcomed by friends. We would never have imagined to receive all this. Now we only hope that all will be good for our son"; "Me and my family did not thank you enough for all the things you brought to us, it was too much and it helped us a lot, so thank you so much for everything."

Finally, we note that there are only 2 centres in the UK that perform paediatric HSCT procedures: Great Ormond Street Hospital in London and the Great North Children's Hospital in Newcastle. As a result, families and carers of children who receive HSCT procedure in England may therefore still face lengthy treatments far from home.

A15. On page 113 data on adverse events associated with other forms of gene therapy are presented. Can the company provide further information regarding how directly relevant these are for Strimvelis, and the justification for this.

The page 113 data on adverse events associated with other forms of gene therapy for ADA-SCID help to provide the overall safety context for gene therapy treatments for ADA-SCID.

Since 2000, 60 patients have received gene therapy for the treatment of ADA-SCID: Strimvelis (N=18), other comparable gamma-retroviral vectors (N=22), and lentiviral vectors (N=20) [Farinelli, 2014; Gaspar, 2015; Cicalese, 2016] (see Appendix 7 of the original submission for the full list of individual publications). There have been no incidences of leukaemia or myelodysplasia reported following gene therapy for ADA-SCID. The Strimvelis length of follow-up median is 6.9 years (maximum 13 years).

Haematological malignancies have been reported during trials for X-linked SCID, chronic granulomatous disease, and Wiskott-Aldrich syndrome that used MLV-like vectors with slightly differing envelope proteins and/or gene expression systems, but no cases have ever been reported for ADA-SCID.

Multiple references in the scientific literature hypothesise that leukaemia risk after retroviral gene therapy is multifactorial. The background disease of ADA-SCID may play some role in the safety record to date, as ADA is known as a ‘house-keeping’ protein.

Strimvelis continues to have additional monitoring by the European Medicines Agency (EMA) through mandated pharmacovigilance reporting (Periodic Benefit-Risk Evaluation Reports [PBRERs], Periodic Safety Update Reports [PSURs] and Drug Safety Update Reports [DSURs]) and Risk Management Plans (RMP). To date, the EMA has granted that Strimvelis continues to have a positive benefit:risk profile for patients with ADA-SCID who do not have an HLA-matched related donor available.

The data from other forms of gene therapy in ADA-SCID therefore do supplement and give additional assurance that gene therapy modalities are generally well tolerated in patients with ADA-SCID.

B1. **Priority question:** The model includes an expected wait time of 19 weeks between time of diagnosis and HSCT from a matched unrelated donor or a haploidentical donor. The ERG have seen a presentation on the UK Stem Cell Strategic Forum Recommendations which state the wait time from diagnosis to transplant is 6 to 8 weeks, and other sources estimate the average search time at 50 days (7.1 weeks) for bone marrow and 13.5 days (1.9 weeks) for cord blood. Please justify the selection of Gaspar 2013 to inform wait time. Please provide further information on the expected duration of screening for suitable donors for transplant to ADA-SCID patients separately for:

i. a cord blood match;

ii. a matched unrelated donor for bone marrow transplant;

iii. a haploidentical donor for bone marrow transplant.

To our knowledge the requested information on specific times of screening for different donors is not available in the literature. The information used in the economic model is based on published data focusing on the comparators included in the scope, with a focus on the donor type most relevant in terms of the clinical practice in England, ie, MUD. Clinical advice received by GSK suggested that no HSCT from a haploidentical donor have been performed in England in the last 15 years. The 19 week timing reported by Gaspar does appear to include all sources of donors, but no specific information on using umbilical cord blood was obtained because cord blood transplantation is outside of the scope defined by NICE, which referred to bone marrow transplant only. However, based on the clinical advice received, GSK believes cord blood transplant would be expected to be similar to MUD from bone marrow in terms of timing and costs.

The 6 to 8 week wait time mentioned in the question is a general recommendation for patients who are eligible to receive a transplant, whilst the wait times in Gaspar 2013 are based on the wait times recorded specifically for patients with ADA-SCID at 1 of the only 2 centres providing HSCT in the UK. Therefore, we would expect these wait times to represent the reality of UK clinical practice for ADA-SCID, particularly for HSCT from a MUD. The author of Gaspar 2013 provides a justification for the reported wait times, noting they are "... probably due to our willingness to wait for a suitable donor to be identified through donor registries or through extended family searches, even if this may take longer than the currently recommended 6 to 8 weeks for the diagnosis-to-transplant time period."

As noted above, this includes transplant from all donor sources, including MSD, which would be expected to be faster, so using a value of 19 weeks for the time to transplant

for HSCT from a MUD or haploidentical donor is considered a conservative approach.In addition, it should be noted that patients with ADA-SCID need to be stable and clinically well before they receive treatment, and the time to achieve such a state is not necessarily comparable across diseases. Thus, other sources for estimated time from diagnosis to transplant may not be directly transferrable to what is observed in clinical practice for ADA-SCID. Relevant to the impact of this assumption, it should be noted that PEG-ADA is usually stopped 20 days before infusion of Strimvelis, which was conservatively overlooked in the model for the sake of simplicity.

B2. **Priority question:** The model includes a cost of screening for matched unrelated donor and haploidentical donors of £45,127. Please explain the rationale for this cost, a breakdown of what is included, and the sources used to inform this cost.

First, we should note an oversight on our part: the £45,127 baseline cost of screening was included in the economic model, but was omitted from Table D5 of the submission.

This cost covers all expenditures associated with the screening for a MUD or a haploidentical donor. It is not based directly on an NHS England reference cost, rather it comes from the published literature. Van Agthoven (2002) reported a 1999 screening cost for a MUD transplant of €47,063. A breakdown of the costs by cost component is provided in Table 3. These numbers are based in the health costs observed in the Netherlands, and GSK considered it reasonable to assume that they would be broadly transferable to the English reality. As stated in the original submission, we used the same cost value for screening for a haploidentical donor.

The reported 1999 cost was inflated to a 2016 value of €53,090 using a health inflation adjustment of 12.8% reported by Statistics Netherlands (http://statline.cbs.nl) and converted to British pounds using an exchange rate of 1€ = £0.85 on 08 May 2017 (source:www.xe.com).

Table 3 Cost Components from Van Agthoven

Cost Component	**Cost (€)**
Family HLA typing	6,842
Requesting blood samples	5,506
Sample typing	12,232
Requesting donor graft	15,971
Europdonor intermediation	1,920
CD34 selection/T cell depletion	4,592
Total costs (excluding personnel costs)	47,063

B3. **Priority question:** The model assumes that no costs of searching for matched unrelated donor are incurred for patients allocated to Strimvelis. Please clarify whether the decision to use Strimvelis is expected to be made in the absence of knowledge regarding whether the patient has a cord blood match and/or potentially suitable adult donor in the registry.

The scientific and clinical experts committee at ESID and EBMT have developed clinical guidelines for the treatment of ADA-SCID. The guidelines recommend that, in the absence of an MRD, the next best available treatment is gene therapy. GSK has received clinical advice that this recommendation will be followed in England. Hence, we believe there would be no clinical reason for a non-MRD donor to be prioritised over Strimvelis and, therefore, no need to perform a search for a MUD ahead of being treated with gene therapy.

B4. Please provide the rationale behind the choice of NHS reference cost for each administration of IVIG or PEG-ADA (£306). Please clarify whether the costs incurred for administration, and the price of IVIG and PEG-ADA, are expected to differ for patients receiving those therapies whilst in Milan.

The costs of administering IVIG or PED-ADA whilst in Milan would already be included in agreed treatment cost as this is based on the local transplant DRG. That said, in the model these were included again in the Strimvelis arm for simplicity, conservatively overestimating the impact of administration costs.

The cost section for the NHS reference code used to inform the model is HCD. This is for high-cost drugs and was therefore deemed appropriate for both IVIG and PEG-ADA treatments. The choice of the actual cost code was somewhat arbitrary; it was chosen primarily because it is a conservative and moderate cost figure.

The sensitivity analysis provided in the original submission showed that the computed ICER values are insensitive to the cost of administration of IVIG and PEG-ADA. This makes sense since the cost of the drugs themselves far exceeds any reasonable cost of administration. Changes in the ICER for Strimvelis versus HSCT from a MUD are presented in Table 24 of the original submission. Varying the cost of administering IVIG and PEG-ADA by +/- 25% (from £383 to £230) produced ICER spreads of £138 (IVIG) and £2 (PEG-ADA).

An alternative estimate of administration cost for IVIG and PEG-ADA was investigated as an additional sensitivity analysis to illustrate the low impact of this input. This estimate was based on hourly nurse time of a Grade 6 hospital nurse (£108) from PSSRU 2016 (Personal Social Service Research Unit, PSSRU, pssru.ac.uk/project-pages/unit-costs/2016/)). As IVIG is administered by a 30-minute infusion, we assumed two hours of nurse time to include 30 minutes preparation time and one-hour post infusion monitoring, giving a total costs of £216. PEG-ADA is given as an intramuscular injection, so we assumed 30 mins nurse time to prepare the patient and observe the patient after the injection, giving a total admin cost of £54. Using these values in the sensitivity analyses showed a marginally small impact on the ICERs yielded (£36,251/QALY vs HSCT from a MUD and £15,014/QALY vs HSCT from a haploidentical donor).

B5. **Priority question:** The model includes a cost of [redacted] for the initial hospitalisation for Strimvelis, [redacted] of which is assumed to occur in the UK prior to travel and the remaining [redacted] assumed to occur in Milan.

i. Please provide a breakdown of what is included in the [redacted] for confirming eligibility for Strimvelis and the sources used to inform this cost.

ii. Please provide a breakdown of the [redacted], the sources for the unit costs, and how payment from the UK NHS to Milan is expected to be made for these costs.".

The [redacted] cost and its breakdown into [redacted] and [redacted] used in the model is derived from the schedule of payments (denominated in Euros) that was provided by Ospedale San Raffaele, Milan (OSR). These are based on the tariff/DRG applied for Italian statutory patients and OSR has said that these costs in the schedule of payments would be the same for patients that are not Italian statutory patients as well. GSK does not have any fully detailed cost breakdown but provide additional information below. The costs were converted to UK Pounds based on the average exchange rate 1€ = £0.85 on 08 May 2017 (source www.xe.com).

Table 4 **Schedule of Payments provided by Ospedale San Raffaele**

ADA SCID - Patient's Procedural Phases and Reimbursement	
SCREENING	[redacted]
BASELINE	[redacted]
TREATMENT	[redacted]
FOLLOW-UP, month 1 and 2 from discharge	[redacted]
Total	[redacted]

Abbreviations: BAEP = brainstem auditory evoked response; CT = computed tomography; echo = echocardiogram; EEG = electroencephalogram; MRI = magnetic resonance imaging; OSR = Ospedale San Raffaele; VEP = visual evoked response.
Notes: The SCREENING and FOLLOW- UP phases include: Laboratory tests (routine, micro-biology, immunology, virology,etc.), Imaging and Instrumental tests (CT, MRI, X-ray, audiometric test, EEG, Echo, VEPs, BAEPs, etc) , drugs (immunoglobulin therapy, etc) , clinical tests and specialist consultings. The BASELINE phase includes all costs related to testing, release and cryopreservation of back-up

The [redacted] cost is the per patient cost for confirming eligibility for Strimvelis treatment. It covers expenses incurred in England prior to travel to Italy. According to information received from the San Raffaele Telethon Institute for

Gene Therapy (SR-TIGET), the screening cost generally covers the following items:

- Outpatient: signature of informed consent; clinical and laboratory tests
- Day Hospital: diagnostic bone marrow aspirate

Per SR-TIGET, the remaining [redacted] cost is the per patient cost for the hospital stay including baseline, treatment and 2 months follow up during the time in Italy.

The baseline cost covers all costs related to testing, release and cryopreservation of back-up, and in total cover an average duration of 31 days:

- 7 days outpatient: signature of informed consent (if screening exams not done at OSR); clinics and laboratory tests and imaging; administration of IVIG
- 3 days hospitalization for placement of central venous catheter (CVC)
- 3 weeks to wait for bone marrow back sterility testing (minimum of 5 days) and CVC healing - this may be reduced to 2 weeks based on recent experience (cutting the average duration to 24 days)
- Note: PEG-ADA is given during this time, but usually stopped 20 days before the infusion of Strimvelis – this cost-saving was conservatively overlooked in the model for the sake of simplicity

The treatment stage includes:

- Hospitalization for gene therapy: drugs, laboratory tests, imaging, consultants, isolation room, personnel, administrative and structural costs
- Specific disease/Gene therapy tests

And the follow up costs for the first two months would generally include:

- Outpatient: clinics and laboratory tests, imaging
- Day Hospital: diagnostic bone marrow aspiration
- Specific disease/gene therapy tests

The process for payment depends on if the UK patient with S2 form approved (they would be treated as an Italian statutory patient) or if the UK patient is arriving without the S2 form. NHS England has indicated that patients would not arrive with an S2 form. In the case of UK patients, which would not arrive with an S2 form approved, the NHS would pay the San Raffaele hospital directly for the treatment of the patient.

Please note that the price of the Strimvelis product and all the hospital procedure costs will be invoiced in Euros. We have provided the Euro costs in Table 4 above and, for the purposes of the NICE evaluation, we converted the prices to Pound Sterling at the defined exchange rate. At the time of payment, the NHS will need to pay in Euros based on the Euro costs provided; the cost in Pound Steriling may differ that what we have

provided in the submission due to exchange rate fluctuation. NHS England have confirmed that they are not concerned about the potential for currency fluctuation due to payment based in local currency and that they are currently paying for proton beam therapy outside the UK in local currency.

B6. Priority question: Please clarify whether the estimated technology cost of £505,000 and the initial hospitalisation cost of [redacted] are fixed payments for all patients treated with Strimvelis. Please confirm whether these costs would apply in the following circumstances (and if relevant provide alternative costing estimates):

i. extended hospitalisation resulting from severe infection;

ii. patients for whom the product contains less than 2 million CD34+ cells/kg;

iii. other cases of product failure e.g. contamination;

iv. cases of transplant failure, or prolonged bone marrow aplasia after treatment with Strimvelis which require the use of the rescue product.

The payment price for the Strimvelis product is fixed at €594,000 (£505,000 at exchange rate of 0.85£/€) and would be paid directly to OSR. GSK has discussed a fixed price in local currency for Strimvelis with NHS England, who have said this is how they have contracted with countries outside the UK for proton beam therapy.

The initial hospitalisation cost of [redacted] is fixed. This is the total payment paid to OSR for the initial hospitalisation if the patient goes on to receive Strimvelis. As noted in the response to answer B5, this sum is comprised of costs for baseline [redacted], treatment [redacted], and follow-up month 1 and 2 from discharge [redacted].

These costs would be expected to apply for the majority of cases, specifically in all cases where the procedure went as planned, and the patients did not experience major complications. In the exceptional cases referred to in the question, additional costs would be expected:

i. Extended hospitalisation resulting from severe infection: Strimvelis product cost of €594,000 (£505,000) and the initial hospitalisation cost of [redacted] would apply in this case. Additional days in the hospital beyond the assumed clinical schedule (i.e., > 55/days standard stay) would be charged at [redacted] per day for Italian statutory patients. If the patient does not come with an approved S2 form, then they would be charged for each procedure conducted during that period.

ii. Patients for whom the product contains less than 2 million CD34+ cells/kg: Please note that although iii. asks for other cases of product failure (implying that ii. would be considered a product failure), in actuality, if the Strimvelis product contains less than 2 million CD34+ cells/kg, that would not be defined as a product failure. Estimated Strimvelis product cost of €594,000 (£505,000) and the initial hospitalisation cost of [redacted] would not apply in this case in this case if Strimvelis was not administered. In the case that the Strimvelis product contains

less than 2 million CD34+ cells/kg, the patient may receive its own back-up as rescue therapy as he/she has already received chemotherapy. In this scenario,

a. If the patient is supported through an S2 Form (i.e. the patient would be treated as an Italian statutory patient), the administration of the back-up will fall under the autologous transplantation and the tariff/DRG for the autologous transplantation will be charged to the NHS (i.e., [redacted]; DRG 481, Oct 2016).
b. If the patient does not come with an approved S2 form, the administration of the back-up would fall under the autologous transplantation, but in this case, any clinical service paid in advance and not provided will be reimbursed after the patient is discharged.

iii. Other cases of product failure e.g. contamination**:** Strimvelis product cost of €594,000 (£505,000) and the initial hospitalisation cost of [redacted] would not apply in this case in this case if Strimvelis was not administered. In the case of Strimvelis product being contaminated, the patient may receive its own back-up as rescue therapy as he/she has already received chemotherapy. In this scenario,

a. If the patient is supported through an S2 Form (i.e. the patient would be treated as an Italian statutory patient), the administration of the back-up will fall under the autologous transplantation and the tariff/DRG for the autologous transplantation will be charged to the NHS (i.e., [redacted]; DRG 481, Oct 2016).
b. If the patient does not come with an approved S2 form, the administration of the back-up would fall under the autologous transplantation, but in this case, any clinical service paid in advance and not provided will be reimbursed after the patient is discharged.

iv. Cases of transplant failure, or prolonged bone marrow aplasia after treatment with Strimvelis which require the use of the rescue product:
Estimated technology cost of €594,000 (£505,000) and the initial hospitalisation cost of €105,219 (£89,482) would apply in this case. In the case of treatment failure, if the back-up bone marrow is used to facilitate hematopoietic recovery, then this cost is covered by the initial hospitalisation cost up to 55/days standard stay. Additional days in the hospital beyond the assumed clinical schedule (i.e., > 55/days standard stay) would be charged as described in response (i.)

B7. The model includes an expected wait time of 9 weeks for Strimvelis based on the 'clinical schedule from San Raffaele Hospital'. Table D6 (page 168, company submission) presents the average durations of baseline patient preparation and confirmation of eligibility for Strimvelis, but it is not clear how or whether these relate to the 9 week wait period. Please provide further information on the clinical schedule, providing a reference if possible. Please provide a breakdown of the expected duration of time and events between:

i. Decision to use Strimvelis (i.e. meeting of multidisciplinary team to determine next treatment step after failure to find a matched related donor) and travel to Milan
ii. Arrival in Milan and commencement of treatment with Strimvelis.

The clinical schedule is not in the general public domain, but was provided to us by the San Raffaele Telethon Institute for Gene Therapy (SR-TIGET) and presented in Table D6 of the original submission. We are not able to provide the requested breakdown of expected duration of events beyond what is presented in the answer to Question B5. However, in practice, the individual components in the baseline patient preparation and confirmation are expected to be continuous and overlapping in time.

SR-TIGET indicated that, in practice, confirmation for eligibility for Strimvelis and baseline patient preparation together take between 55 days (approximately 8 weeks) and 69 days (approximately 10 weeks), with the decision to use Strimvelis and travel to Milan taking approximately 24 days and the arrival in Milan and commencement of treatment with Strimvelis taking between 31 and 45 days. We used the midpoint of 9 weeks as the total wait period (i.e. the waiting time from decision to treat to date of treatment) in our economic model base case calculations.

For context, Gaspar et al suggest that the waiting time from decision to treat to date of treatment for a matched unrelated donor stem cell transplant in England is approximately 19 weeks for a patient with ADA-SCID. GSK received expert advice that, in England, the waiting time for HSCT is variable depending on the condition of the patient, the place of treatment, and other variables. For example, waiting times are usually longer if the patient is diagnosed in the winter.

B8. Please provide further justification for why time from diagnosis to treatment in the clinical trial was not considered applicable to the expected time to treatment with Strimvelis (AD1115611 – average duration of the pre-treatment phase was 5.7 months, range 10 days – 1.1 years), and how this would be expected to differ outside of a clinical trial setting.

The average duration from diagnosis to treatment in a clinical trial and in real world clinical practice naturally differ significantly. Health authorities have differing requirements on consent procedures, arrangements for travel, and other elements of the registration of a patient for treatment in a trial of an unlicensed investigational medical product. The differing requirements result in a spectrum of pre-treatment phase wait times. The range quoted in the question of 10 days to 1.1 years, which comes from Section 5.1 of the Pivotal study CSR, illustrates such a spectrum.

We note that most of the information on time to treatment in the Strimvelis development programme is quite old. The pivotal study treated its first patient in October 2002 and its last patient in June 2008. Time to treatment will be shorter now post-authorisation as the need for ethical approval and other such delays will be eliminated. If Strimvelis receives a positive approval from NICE, then NHS England will be obliged to provide funding so that there will be no need for further approvals in order to refer a patient to Milan for treatment with Strimvelis .Strimvelis has been appraised by regulators and clinical scientific bodies, and treatment guidelines for the use of gene therapy for ADA-SCID in the absence of a matched related donor are now available. In addition, the growth in cell and gene therapy, the growing understanding of disparities in outcomes in HSCT, seminal publications in NEJM and Blood, and the experience gained in the programme at TIGET means that it is extremely likely that referral and treatment will be significantly more streamlined than it was for the recruitment period, over at least ten years ago.

We are confident that the schedule provided by the San Raffaele Telethon Institute for Gene Therapy (SR-TIGET) reflects the normal expectation for a typical patient. See the response for Question B5 for information provided to GSK. Indeed, it is expected that the time from diagnosis to treatment will diminish further with time. As an example, SR-TIGET noted in or last communciations that the average time in Italy for the baseline phase of the Strimvelis procedure may have already been reduced by about a week for more recent patients.

B9. The travel arrangements that the NHS may support for families receiving Strimvelis proposed in this submission includes three economy class return airline tickets to a Milan airport and public transport to and from the airport. Please justify why these NHS supported travel costs are not included in the economic model.

GSK first became aware of the possible availability of travel support after our last telephone conversation with NHS England. This occurred immediately before the Strimvelis submission was due to take place, so there was not an opportunity to include travel support in the model; it was anticipated that support for these costs would have little impact on the assessment of cost-effectiveness.

As a scenario analysis, we have now estimated that the net cost of 3 economy class return tickets plus taxi to and from the airport would not to be expected to exceed £800. In the unlikely event that ambulance services were needed to and from airports, additional costs would be incurred. Assuming the most conservative estimates, the cost of the ambulance service would be £236 x 2 = £472 in the UK (this is based on UK NHS reference cost, 2016; Section “Ambulance”, code ASS02, the national average £236) and €200 x 2 ambulance trips = €400 or £340 at the exchange rate of 1€ = £0.85 used in the submission (the quote for one-way ambulance trip from San Raffaele Hospital was provided by SR-TIGET at GSK’s request, the value was €170, that we rounded to €200). A return flight for a family of 3 to Milan was estimated at £200 per person (£600 total). When including these costs for the whole Strimvelis cohort in the model, the ICER for Strimvelis varies by only £104 when compared with HSCT from a MUD and £121 when compared with HSCT from a haploidentical donor.

B10. **Priority question:** Clinical advice to the ERG suggested that patients may require transfers by ambulance or air ambulance given their clinical condition. Please clarify from what locations patients travelled to receive treatment, and the method of transport (e.g. train, commercial airline, air ambulance ambulance). Please provide an estimated cost for ambulance transfer to and from airports, and by air ambulance from the UK to Milan.

According to the San Raffaele Telethon Institute for Gene Therapy (SR-TIGET), patients arrive by car or train. Commercial air travellers connect through the Linate or Milan-Malpensa airports. No Strimvelis patients have required air ambulance services and 1 Strimvelis patient required an ambulance.

Per SR-TIGET, the estimated costs for an ambulance between the airports and Ospedale San Raffaele (OSR) are as follows:

Cost without a physician on board:

- Linate to OSR(1 way): €60
- Milan-Malpensa to OSR: €170

Cost with a physician on board:

- Linate to OSR(1 way): €70
- Milan-Malpensa to OSR: €200

These costs would be double for a round trip. These modest costs do not have significant impact on the cost-effectiveness analysis for Strimvelis.

Although no patients have required an air ambulance or are expected to need it in the future, we have gathered information to support your request. SR-TIGET estimated the cost of an air ambulance with respiratory assistance from OSR to London would lie in the range of €11,000 to €17,500. This is a 1-way cost, but SR-TIGET believe the same cost would apply for the outbound London to OSR trip.

The estimated air ambulance costs are relatively high, but the likelihood of an air ambulance being needed is small as patients are always stabilised before they travel. Given this, ambulance requirements would not be expected to have a significant impact on the cost-effectiveness of Strimvelis.

B11. After Strimvelis gene therapy, the cost of follow-up was assumed similar to that post-HSCT. Clinical advice received by the ERG suggests additional blood tests are required after gene therapy to assess oncogenesis and vector copy numbers. Please provide further information on the type of tests required for monitoring after receipt of gene therapy, the frequency of the tests, the expected cost of each test and the length of follow-up over which the tests are indicated.

It was noted in Table D6 of the submission that outpatient follow-up in England is similar to HSCT with one exception. Strimvelis requires vector copy number (VCN) testing and the cost of this test was included in our economic model in the original submission.

VCN testing is recommended to be performed every 6 months for the first 3 years. Cost information is given in Table 5. If the recommended testing regimen is followed, the total cost is 6 X £1,199 = £7,194

Table 5 VCN Testing Cost Information

Cost item	Unit cost (€)	Unit cost (£)	Testing regimen	Total tests
VCN test	1,420	1,199	Every 6 months for 3 years	6

Retroviral insertion site testing (expected to cost approximately €7,299 per the contract with the laboratory that would perform this testing) and replication competent retrovirus testing (expected to cost approximately €1,420 per the contract with the laboratory that would perform this testing) would only be performed in the event of a leukemic adverse event; no patients in the Strimvelis clinical programme experienced such an event. Therefore, the only additional test expected for Strimvelis is vector copy number.

B12. Please provide a copy of 'The UK Stem Cell Strategy Oversight Committee Report on unrelated donor stem cell transplantation in the UK: effective affordable sustainable November 2014'.

A copy of the report will be attached to this response.

B13. Please clarify whether the follow up costs in Tables D8 & D9 (page 172-174, company submission; reference to the UK Stem Cell Oversight committee and van Agthoven respectively) are based on the same source.

GSK confirms that the follow up costs in Tables D8 and D9 were derived from the same source. The follow-up costs in the Strimvelis arm were taken from the UK Stem Cell Oversight committee report, which extrapolated them from van Agthoven (2002). The follow-up costs in the HSCT from a MUD arm were derived directly from that same van Agthoven (2002) source.

Details on the approach taken are provided in the tables below.

Table 6 Costs per treatment/patient associated with the technology in the cost-effectiveness model

Follow-up costs – Strimvelis	[redacted]	[redacted]

*Source: UK Oversight Committee Report: "Table 16: Summary of transplant costs per patient (extrapolated from van Agthoven et al. (2002)"

The cost components are as follows [redacted] which covers the period from 12 to 24 months after transplantation.

Table 7 Costs per treatment/patient associated with the comparator technology HSCT from a MUD or haploidnetical donor in the cost-effectiveness model

Follow-up costs	**£59,541** per living patient	This figure is based on total follow up estimates of €62,096 * [van Agthoven, 2002], adjusted for inflation (Netherlands inflation index for category Health Expenditures [060000]), and converted to pounds (exchange rate 1€ = £0.85 on 08 May 2017 (source www.xe.com)).

*Source: van Agthoven, Groot MT, Verdonck LF, Löwenberg B, et al. "Cost analysis of HLA-identical sibling and voluntary unrelated allogeneic bone marrow and peripheral blood stem cell transplantation in adults with acute myelocytic leukaemia or acute lymphoblastic leukaemia.", Bone Marrow Transplant. 2002 Aug;30(4):243-51.

The follow up cost of €62,096 in the van Agthoven paper can be derived from Table 7, column MUD, Average cost per living patient as the sum of "Follow up 1", "Follow up 2", and "Follow up 3" (€30,292 + €18,473 + €13,331)

The rationale for using 2 different approaches is mostly related to the fact that van Agthoven specifically considers transplants from MUD, whilst the UK Oversight Committee Report adjusts it to the cost of other types of transplant. By using the figures

reported by the UK Oversight Committee, which estimates a total [redacted] versus the £59,541 derived directly from van Agthoven et al, [redacted]

B14. Priority question: Please update the economic analysis and model with dosage and costs of PEG-ADA based on weight as was undertaken for IVIG. Please provide further justification for assuming the average weight of an ADA-SCID patient in the 25th percentile of the weight distribution of an average child.

PEG-ADA is not registered in the UK, and there is no list price available. Costing and usage of PEG-ADA was therefore based on expert consultation, according to whom the cost of 1 vial of PEG-ADA to the hospital was £9,000 and the use of PEG-ADA per patient was estimated between 1 and 2 vials per week (£9,000-£18,000), depending on the weight of the patient. In the model we assumed the mean of these values, i.e. £13,500 per patient per week and applied it directly.

Patients with ADA-SCID typically experience failure to thrive, and are therefore unlikely to be at the 50th percentile for weight by age. We selected the 25th percentile as a reasonable estimate of the average weight of patients with ADA-SCID and confirmed this assumption with external expert clinical advice.

In sensitivity analysis presented in the original submission we explored using just 1 vial and using 2 full vials and observed a moderate impact in absolute terms for HSCT from a haploidentical donor [ICERs: £22,264 at 1 vial per week, and £7,025 at 2 vials per week] but not significant for MUD [ICERs: £36,432 at 1 vial per week, and £36,288 at 2 vials per week]. In each of those cases, the ICERs remained well below the thresholds usually applied.

In order to answer directly the request on question B14, we changed the initial estimate of £13,500 for the weekly cost of PEG-ADA and estimated a weight-based dosage of PEG-ADA per week assuming the patient average weight to be on the 25th percentile (Table 8).

Table 8 Weekly cost of PEG-ADA based on weight

Age	Weight * (25th percentile)	Units per patient per week **	Vials per patient per week ***	Vials rounded	Weekly cost of PEG-ADA
1 year	8.6 kg	258	0.69	1.0	£9000
2 years	10.9 kg	326	0.87	1.0	£9000
3 years	13.0 kg	389	1.04	1.0	£9000

* Boys & girls averaged, WHO Growth Charts, source RCPCH (Royal College of Paediatric and Child Health, rcpch.ac.uk), we used only the 1st three years, the age within which PEG-ADA may be required – for pre-procedure treatment and for patients awaiting a second (rescue) HSCT; ** Estimated based on the dose of 30 units per kg (*adagen.com/pdf/Adagen_Monograph_Final.pdf*, 30 units/kg was quoted as a maximum

dose that should not be exceeded); *** The minimum vial needed was estimated from the weekly dose and vial size ("Each vial contains 250 units/mL and is supplied as a 1.5 mL single-use vial", *adagen.com/pdf/Adagen_Monograph_Final.pdf*)

When the above assumption was tested in a sensitivity analysis, the ICERs were similar to the sensitivity analysis presented for using just one vial. As reported above, for Strimvelis compared with HSCT from a MUD, the ICER became £36,432 (a small difference of £70 from base case); and for Strimvelis compared with HSCT from a haploidentical donor, the ICER became £22,264 (a difference of £7.6K). It should be noted that this estimate is the lowest estimate of the dose needed as the 25th percentile most likely represents the lower range of patient weight, and expert consultation suggests that 2 vials may be needed for some patients. In any case, as before, ICERs remain comfortably below the thresholds normally used for the HST Evaluation Programme.

B15. **Priority question:** The time horizon in the model is 10 weeks shorter for patients treated with Strimvelis (such that when survival from matched unrelated donor and haploidentical donor are set to 100% the predicted life years gained is 46.3 with these strategies versus 46.1 years with Strimvelis). Please provide an updated model that assesses all treatments over a common time horizon.

Although it is not explicitly stated in the submission, the 10-week difference noted by the ERG is due to differing assumed durations from the time of diagnosis to the timing of the procedure and not due to any modelling malfunction.

The economic model is comprised of two separate parts: the first describing the process of preparation for treatment (including screening for eligibility), and the second describing the procedure itself and all subsequent events.

The time horizon for the second part of the model is lifetime for patients in the Strimvelis and in both HSCT arms, i.e., the model follows the average patient over the entire care pathway for life, until the entire modelled cohort dies. However, the difference in the initial screening steps in the model – 19 weeks and 9 weeks for either HSCT or Strimvelis, respectively – does result in a small difference observed in total life expectancy.

As a result, the total time horizon is indeed shorter in the Strimvelis arm by 10 weeks. This, however, is a conservative anomaly expected to benefit the HSCT arms. In addition, given that this small difference in life expectancy is only realised at the end of the patients' life, we would expect these 10 weeks would be reduced to insignificance through discounting. Given this, and the fact we believe that making artificial adjustments to equalise total life expectancy might not be appropriate and that adjusting survival curves by 10 weeks would involve a great degree of complexity, we suggest that there is no need to align life expectancies.

B16. Priority question: The model structure assumes no searching for a matched unrelated donor or a haploidentical donor is ever undertaken for patients allocated to receive Strimvelis, even after failure of Strimvelis. Please provide a scenario analysis in which the rescue transplant following Strimvelis is based on use of a matched unrelated donor or a haploidentical donor using the same search costs and survival rates as those for patients initially allocated to a matched unrelated donor in the economic model..

In the base case presented in the original submission, we considered that all rescue transplants were from a matched sibling donor because that was what was observed in the patients included in the Strimvelis clinical programme that went on to receive a rescue transplant. The scenario where the case that the rescue transplant following Strimvelis is from a matched unrelated donor is already included in the sensitivity analyses presented in the original submission Section 12.5.11 Table D24. According to expert advice, no HSCT from a haploidentical donor for a patient with ADA-SCID has been performed in England in the last 15 years. Therefore, a scenario using a haplo donor for a rescue transplant was not considered, but one would not expect the impact to be much different from using a HSCT from a MUD as rescue.

B17. **Priority question**: In the base case there is no procedural or disease related mortality in patients allocated to Strimvelis (as survival after Strimvelis and rescue therapy with a matched sibling donor is assumed to be 100%). As there are so few patients that have received Strimvelis, any mortality observed in the next few patients to receive treatment could significantly reduce survival rates. Please provide a scenario in which the survival after 6 months with Strimvelis is reduced from 100% (18/18) to 95% (18/19) and to 90% (18/20).

GSK believes that it is not appropriate to consider anything other than 100% survival after Strimvelis. NICE decisions should be based on the available evidence. It is important to avoid deviating from the parameters of published and properly scrutinized data. All available evidence shows 100% survival after Strimvelis (N=18) with a median follow-up of 6.9 years [Cicalese, 2016] and after all 60 gene therapy procedures for ADA-SCID since 2000, which includes the 18 patients from the Strimvelis program, 22 patients treated with other comparable gamma-retroviral vectors, and 20 patients treated with lentiviral vectors [Farinelli, 2014; Gaspar, 2015; Cicalese, 2016] (see Appendix 7 of the original submission for each individual publication confirming these results).

There is no clinical reason to believe that survival after Strimvelis would be anything other than 100%. The death of the next 2 patients is extremely unlikely given that none of the previous 60 patients treated with gene therapy for ADA-SCID have died. GSK does not agree with developing a scenario that has no basis in evidence. Creating a precedent to model lower results in light of the patient size will unfairly penalise ultra-rare disease medicines where clinical trial populations are small by necessity.

However, GSK is willing to provide the information requested despite not agreeing that this analysis is appropriate. ICERs remain comfortably below the threshold of acceptability, even before adjusting for the incremental QALY gain, when a 95% survival rate (Table 10) or a 90% survival rate (Table 11) is used in modeling of Strimvelis.

Table 9 Base case (100% survival for Strimvelis)

Technologies	Total cost (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALY	ICER incremental (£/QALY)
Strimvelis	£1,059,425	46.1	41.4				
MUD	£565,170	31.0	27.8	£494,255	15.1	13.6	£36,360
Haplo	£888,757	33.2	29.7	£170,668	12.9	11.7	£14,645

Table 10 Scenario 1 (95% survival for Strimvelis)

Technologies	Total cost (£)	Total LYG	Total QALYs	Incremental costsa (£)	Incremental LYGb	Incremental QALYc	ICER incremental (£/QALY)
Strimvelis	£1,042,527	43.8	39.3				
MUD	£565,170	31.0	27.8	£477,357	12.8	11.5	£41,387
Haplo	£888,757	33.2	29.7	£153,770	10.6	9.6	£16,027

Table 11 Scenario 2 (90% survival for Strimvelis)

Technologies	Total cost (£)	Total LYG	Total QALYs	Incremental costsa (£)	Incremental LYGb	Incremental QALYc	ICER incremental (£/QALY)
Strimvelis	£1,025,630	41.5	37.2				
MUD	£565,170	31.0	27.8	£460,460	10.5	9.5	£48,601
Haplo	£888,757	33.2	29.7	£136,873	8.3	7.5	£18,166

B18. Priority question: Please clarify whether the threshold analysis for the 'price of the Strimvelis procedure' (page 215, company submission) refers to varying the £505,000 acquisition cost of Strimvelis treatment.

This is correct, it relates to the acquisition costs of Strimvelis product.

B19. **Priority question**: matched unrelated donor Section 12.5.13 provides some threshold analyses with thresholds determined by the incremental QALY gain of Strimvelis at a discount rate of 1.5% (that is a threshold of £140,000 per QALY and £120,000 per QALY for Strimvelis vs matched unrelated donor and haploidentical donor respectively). Please repeat the same threshold matched unrelated donor analyses at

i) Thresholds of £100,000 per QALY

ii) At threshold levels determined by the incremental QALY gain with Strimvelis at a discount rate of 0% (i.e. undiscounted QALYs).

i) At the the threshold value of £100,000 per QALY, the ICER for Strimvelis vs MUD would be >£100K vs HSCT from a MUD if the survival for HSCT from a MUD is greater than 88%, or if the survival after Strimvelis is less than 77%. The ICER of >£100K/QALY can be achieved at the price of Strimvelis >£1,370,092. The ICER of >£100K/QALY for Strimvelis vs HSCT from a MUD can be achieved if the utility weight (a weight applied to general population utility - post procedure long term utility) is <0.37.

ii) At the discount rate of 0% (the undiscounted QALY), the estimated QALY difference between Strimvelis and HSCT from a MUD will be 23.2, and the respective ICER threshold is £230,000 per QALY gained. The ICER for Strimvelis vs MUD would be >£230K vs HSCT from a MUD if the survival for HSCT from a MUD is greater than 95%, or if the survival after Strimvelis is less than 71%. The ICER of >£230K /QALY can be achieved at the price of Strimvelis >£3,137,243. The ICER of >£230K /QALY for Strimvelis vs HSCT from a MUD can be achieved if the utility weight is <0.16.

As with the scenario threshold analysis presented in the original submission, post-procedure survival rates in the ranges necessary to exceed the above ICER thresholds are not expected to occur given the information available. The long term utilities suggested in these ranges are also not expected to be realistic.

B20. **Priority question**: The mean ICER from the probabilistic sensitivity analysis (PSA) is the ERG's preferred ICER. This ICER estimated from the PSA is estimated to be 18% higher than the deterministic ICER from Strimvelis compared to a matched unrelated donor (£42,863 compared to £36,360). The corresponding ICER for Strimvelis versus haploidentical donor is assumed to be lower based on the PSA compared to the deterministic model. Please report all results and sensitivity analyses based on the mean ICER from the PSA.

The variation observed between the deterministic and the mean of the PSA ICERs results from the small sample determining the distributions applied to the inputs that drive uncertainties in model outputs. The fitting of distributions with such small samples is naturally more complex and less precise with very reduced number of data points available, resulting at times in draws from distributions for certain inputs falling in ranges considered to be implausible. This, in effect, means the variance on the PSA ICERs is compounded by the methodology itself and not strictly just a result of the uncertainty around the tested parameters. This is illustrative of ADA-SCID being an ultra-rare disease and cannot realistically be resolved through gathering more information any time soon.

In addition, whilst it is important for the Appraisal Committee to understand the uncertainties associated with clinical and cost-effectiveness information provided, there are strong arguments for basing decisions about resource allocation on expected cost-effectiveness rather than the traditional and arbitrary rules of inference [Claxton, 1999]. Therefore, PSA and other measures of uncertainty should still be considered as an instrument to assess the uncertainty surrounding the decision in this appraisal, but should not be used itself as the primary output on which to base a decision. As a result, although the conclusions are not likely to change given that the mean of the PSA ICERs remain well below the threshold commonly applied in the HST Evaluation Programme, we believe it is not appropriate to report the mean of the PSA ICERs as the main output of the cost effectiveness model.

The ERG has in the meantime suggested that they were interested in the ratio of the mean costs and mean QALYs derived from the PSA simulations. This is £36,161/QALY for the analyses versus HSCT from a MUD and £14,964/QALY for the analyses against HSCT from a haploidentical donor. These are comparable to the deterministic ICERs (£36,360/QALY for HSCT from a MUD and £14,645/QALY for HSCT from a haploidentical donor, respectively) and we, therefore, believe this issue to be resolved.

Reference

Claxton K. The irrelevance of inference: a decision-making approach to the stochastic evaluation of health care technologies. J Health Econ 1999; 18: 341–364.

B21. Please provide an estimate of the long-term health service resource use associated with neurological deficits observed in patients with ADA-SCID.

There is no information in the published literature on the impact neurological deficits observed in patients with ADA-SCID may have on resource use. In addition, because there is no clarity on the extent of these effects, it is speculative at best to estimate what associated costs may be.

The neurological events present at baseline and observed in LTFU in the Strimvelis programme are similar to those observed in patients treated with bone marrow transplant. Given that, to date, neither therapy has demonstrated any impact on the onset and progression of neurological events, it can be assumed that the costs are at least similar for both HSCT and Strimvelis treatments. In any case, the sensitivity analyses testing a reasonable increase in costs presented in the original submission have shown that the impact is not expected to be significant.

B22. The company submission notes clinical advice stating that chronic graft-versus-host disease (cGvHD) could last from a few months to several years, but that cGvHD cases would normally be resolved by the time of a rescue transplant (p167, company submission). Please provide the rationale for the modelled duration of cGvHD episodes (3 years) extending beyond the assumed time until a rescue transplant (2 years).

Clinical advice suggested that a rescue transplant would only be performed after cGvHD has resolved since the patient needs to be stable. Gene therapy does not carry a risk of GvHD so, in principle, the time to rescue transplant might be shorter for Strimvelis treatment as compared with HSCT.

Due to the lack of data on the time to rescue transplant in HSCT, we have conservatively assumed that the time to rescue transplant would be what was observed in the Strimvelis programme for both the Strimvelis and HSCT arms. Shorter and longer time to rescue transplant were tested as sensitivity analysies and presented in the original submission. For Strimvelis compared with HSCT from a MUD, rescue transplant at year 2 resulted in an ICER of £30,699; rescue transplant in years 4 and 5 resulted in ICERs that were £41,971 and £47,456, respectively. For Strimvelis versus HSCT from a haploidentical donor, the ICER for rescue transplantation at year 2 was £20,822/QALY and for rescue transplantation at years 4 and 5 were £8,414 and £2,147, respectively.

If we were to reduce the average time of cGvHD to 2 years, the impact on the cost-effectiveness would be minimal (Strimvelis vs HSCT from a MUD: ICER = £36,421/QALY; Strimvelis vs HSCT from a Haplo ICER = £14,645/QALY).

B23. Table D.24 and D.25 (page 203-208) of the company submission provide results of one-way deterministic sensitivity analyses for Strimvelis vs matched unrelated donor and haploidentical donor respectively. Please provide the results of these analyses in the format of a tornado diagram.

We have prepared tornado diagrams for the comparisons of Strimvelis vs HSCT from a matched unrelated donor and Strimvelis vs HSCT from a haploidentical donor. The tornado diagrams for the 25 largest ICER ranges are presented in Figure 1 and Figure 2 below.

Figure 1 **Tornado diagram (for Table D24) Strimvelis vs HSCT from a MUD, incremental cost effectiveness ratio (Base-case: £36,360 per QALY gained) – top 25**

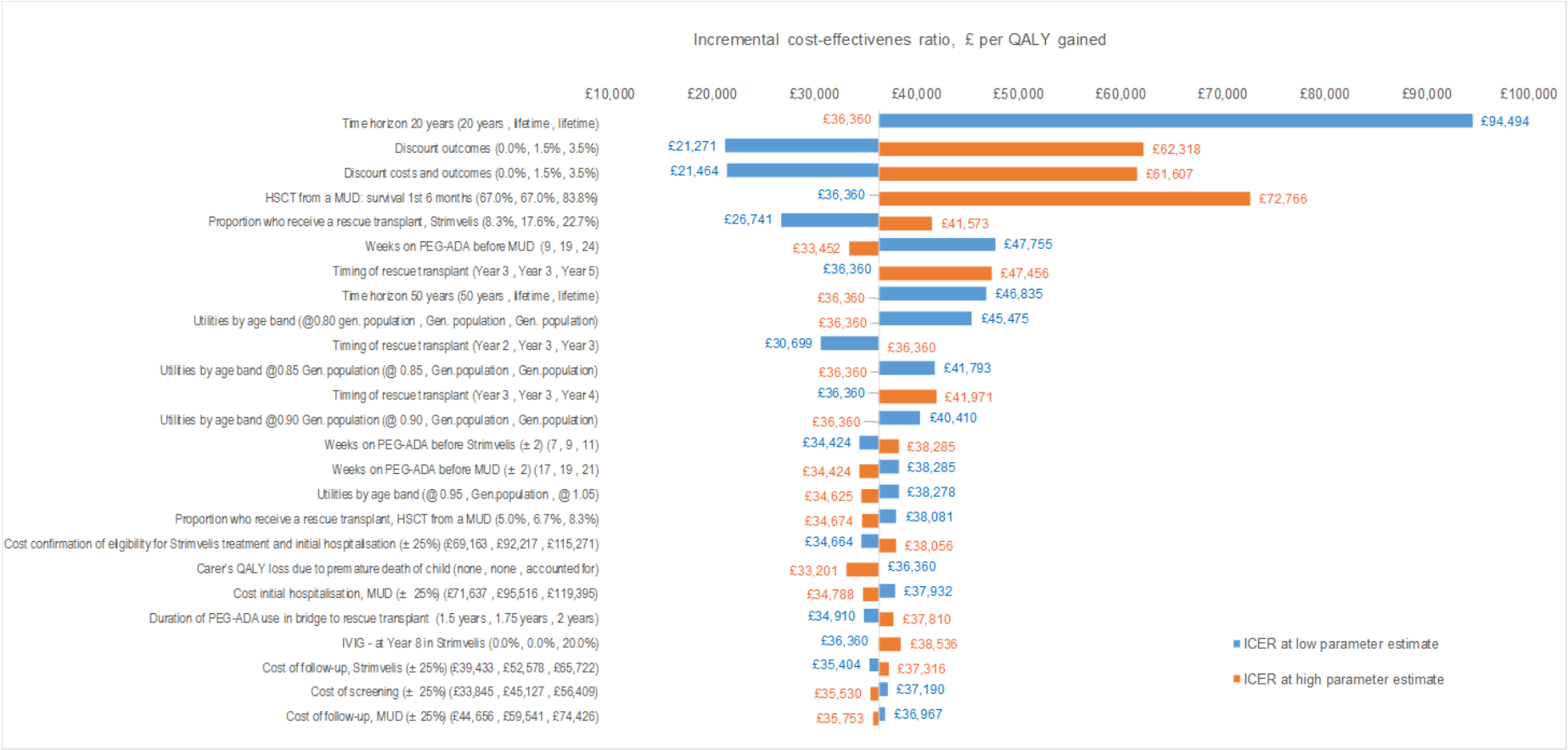
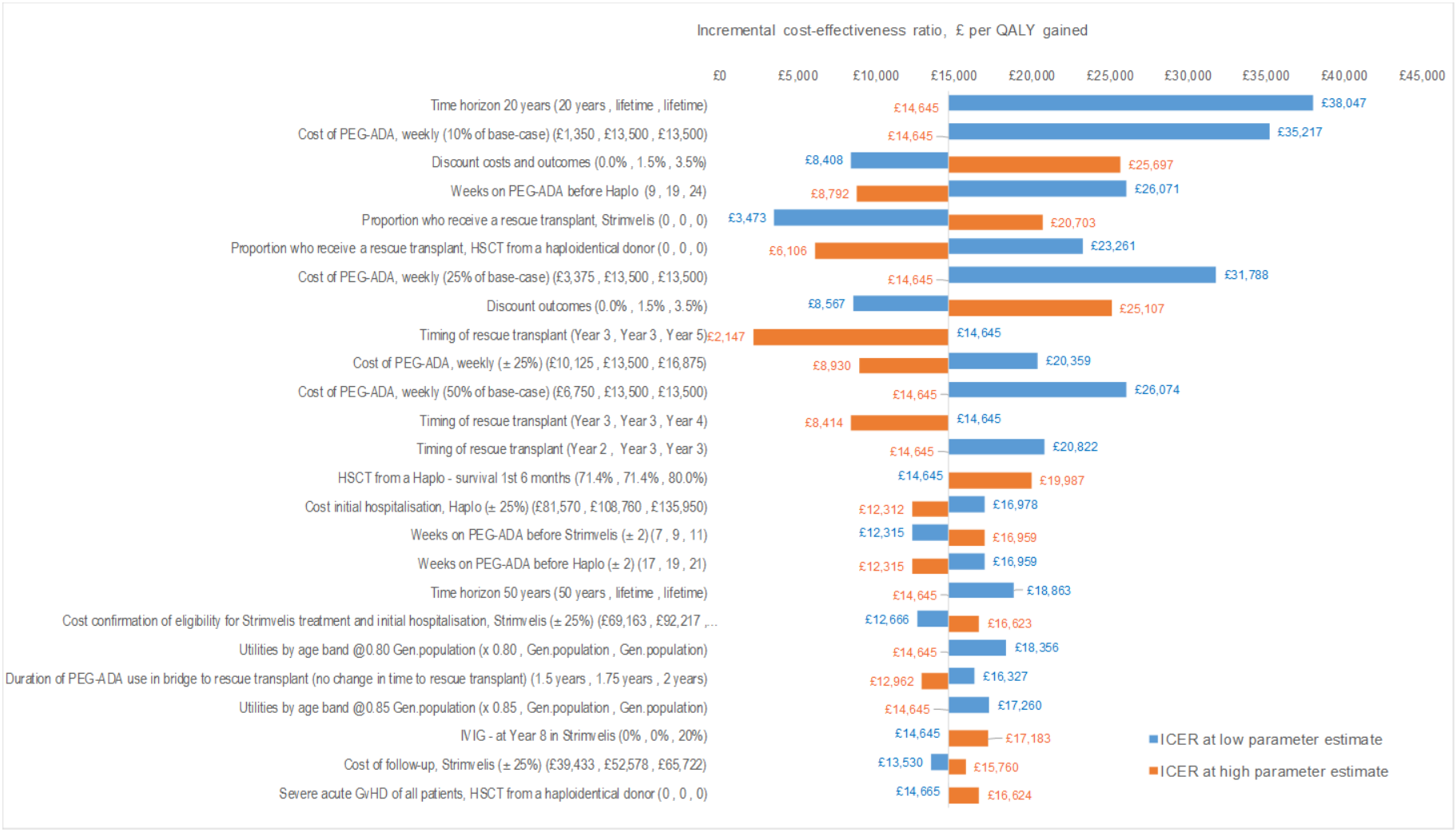


Figure 2 **Tornado diagram (for Table D25) Strimvelis vs HSCT from a haploidentical donor, incremental cost effectiveness ratio (Base-case: £14,645 per QALY gained) – top 25**



B24. Clinical advice to the ERG is that survival rates with HSCT are continually improving, especially with modern techniques for achieving good matches, and that current survival rates may be as high as 90% both for matched unrelated donor and haploidentical donor. Please repeat the one-way sensitivity analyses and produce a tornado diagram which assumes:

i) The upper bound for survival after 6 months for both matched unrelated donor and haploidentical donor is 90%, and
ii) The lower bound for survival after 6 months with Strimvelis is 90% (see question B17)

GSK believes these conditions represent an extreme and unrealistic scenario that is not supported by available data or current clinical practice in England.

The clinical data from the Strimvelis program show a 100% survival rate, with a median follow-up time of 6.9 years. As noted in the response to Question B17, it would be inappropriate to consider such a diminished post-procedure survival rate given that no deaths have occurred in the Strimvelis program or any other ADA-SCID gene therapy program to date, including 60 patients treated since 2000 [Farinelli, 2014; Gaspar, 2015; Cicalese, 2016] (see Appendix 7 of the original submission for the full list of individual publications).

In addition, to our knowledge, there are no data suggesting that survival rates for HSCT could be as high as 90% in patients with ADA-SCID. Our external expert clinical advice indicated that the survival rate following HSCT from a MUD might eventually reach 80%, and that HSCT from a haploidentical donor is not currently conducted in England. HSCT from a haploidentical donor using alpha-beta T-cell depleted haploidentical transplantation is being explored in other diseases, but is not being considered for patients with ADA-SCID in England. Given the complex nature of ADA-SCID, it is not appropriate to extrapolate results from other conditions (other types of SCID) to the current analysis.

The clinical benefits of Strimvelis over HSCT from either a MUD or a haploidentical donor include a significant improvement in survival, avoidance of the cost and burden of GvHD, and reductions in screening costs. These advantages are reflected in the newly published EBMT/ESID guidelines, which have positioned gene therapy such as Strimvelis as first-line therapy for patients without a matched related donor [EBMT/ESID Guidelines, 2017]. These guidelines have been recommended by an independent scientific and clinical committee that included key experts in England, such as Dr Andrew Gennery and Prof Bobby Gaspar. The guidelines represent a paradigm shift in the

management of ADA-SCID that, according to our external expert clinical advice, is expected to be followed in England.

We think it is important to avoid deviating from the parameters of published data, which have been properly scrutinized and deemed relevant for the current decision problem. In our discussions with the NICE project team, we were assured that any speculation about the current or future efficacy of HSCT should be supported by data and fully applicable to current English practice. If any of the estimates of improved efficacy provided are based on data applicable to both England and ADA-SCID, GSK would greatly appreciate the opportunity to review and provide a full assessment of these data in advance of the ERG reporting and first Appraisal Committee meeting.

Before providing sensitivity analyses that we believe are entirely out of line with current English practice and available information in the literature, we would appreciate the opportunity to discuss the basis for this request further with NICE.

C1. Why was Strimvelis not included in the EMBASE search strategy for clinical data in Appendix 1, section 17.2.4, page 263?

The search term “gene therapy” was expected to capture all Strimvelis articles. In addition, because GSK is the manufacturer of Strimvelis, we were confident that we were aware of all Strimvelis publications.

C2. Why was the EMTREE term adenosine deaminase deficiency/ not included in the clinical data EMBASE search strategy (Appendix 1, section 17.2.4, page 263) and the economic data EMBASE search strategy (Appendix 3, section 17.3.4, page 269)?

We believed the keyword searches for adenosine deaminase deficiency would be sufficient to capture all relevant results.

C3. Is there a specific reason why truncation has not been used in any of the EMBASE search strategies in Appendices 1, 3, and 5?

Our assumption was that truncation was unlikely to yield additional relevant articles and potentially would have resulted in a large number of irrelevant articles. As a result, we believed truncation was not necessary.

C4. **Priority question**: NICE considers it essential that evidence on which the Evaluation Committee's decisions are based is publicly available. NICE have noted that some of the confidentiality marking is not in line with the instructions sent with the invitation to submit. Specifically, NICE believes that the following data that has been redacted or marked as commercial in confidence is publically available:

i) Individual patient numbers, individual demographics, and data on each specific patient (page 57, 60, 65, 69, 70, 71, 74, 75, 76, 77, 78, 79, 80, 81, 85, 86, 94, 96, 102, 103, 112, 281, 285):
Within the original submission, this data was marked as 'commercial in confidence' (CiC). Following GSK's concern over sharing potentially patient identifiable information with the committee, NICE agreed that this data could be redacted from the submission. The ERG have highlighted that much of the data is publically available, for example in the European public assessment report and the paper by Cicalese (2016). NICE therefore considers that this redacted information must be shared with committee, and further that all data that is publically available cannot be considered confidential. Please reconsider the marking of any of the remaining data that is not yet publically available, given that the rationale for its marking was that it could be used to identify patients.

ii) The acquisition cost of Strimvelis (page 16, 172, 200, 201, 233, 236, 238):
The submission marks this data as CiC. However the European acquisition cost used in this submission is publically available from numerous sources, and therefore cannot be considered confidential.

iii) Other data, for which the rationale given for confidentiality is that it could be used to back-calculate the acquisition cost:
Given that the acquisition cost of Strimvelis is publically available and cannot be marked as confidential, please remove the confidentiality marking of all data for which the only rationale given for confidential status is that it can be used to back-calculate the acquisition cost of Strimvelis.

A significant portion of text marked as CiC is proposed on the basis of an anonymisation approach, which puts protection of patient privacy at the forefront. The proposed sections for redaction from public presentation are in line with

redacted documents agreed with and provided to the EMA for public posting under Policy 70 ‘European Medicines Agency policy on the publication of clinical data for medicinal products for human use’.

EMA Guidance [EMA/90915/2016] notes the need to redact quasi identifiers is dependent upon the number of quasi identifiers per trial participant; frequency of trial participants with the same category/value for identifier; and size of the population. A higher risk category would be assigned if a study enrolled a small number of subjects [Hrynaszkiewicz, 2010], treatment was provided at one site, or if the total disease population is extremely small (diseases with a prevalence of less than 1 in 50,000 are considered to be ‘ultra-orphan’ diseases [Schuller, 2015, National Institute for Clinical Excellence 2004]). All of these criteria apply to the Strimvelis studies.

The small trial population, treating patients with an ultra-rare disease, presents a significantly higher risk of re-identification compared with very large studies in common disease areas due to the low number of trial participants (many of whom are the only participants from their country), low frequency/rare events observed in the trial, and the unusual nature of the treatments involved. The heightened concern about the potential impact of identification must also be considered for trials in very rare diseases involving vulnerable subjects, including, but not limited to, infants and young children.

Given the small number of participants in the program (N=18) and the limited disease population (less than 50 children per year in the United States and European Union combined), in order to be transparent to regulators and NICE to enable the most complete and robust assessment of the safety and efficacy of Strimvelis, the clinical reports and summaries included in submissions contain considerable amounts of individual patient level data. There is a considerable risk that these data could be used for patient identification if publicly posted without substantial redaction, especially if combined with other information already in the public domain. These risks are considerably higher for data presented in the submission from the pilot studies (AD1117054 [n=1], AD1117056 [n=2]) and the CUP (AD1117064 [n=3]), which present extensive patient-level data, compared to the pivotal study and long-term follow-up (AD1115611; n=12 and n=18 for LTFU), which mostly presents aggregate data. Significantly more redaction is therefore considered appropriate where data are presented from these studies in isolation; this primarily concerns Tables C18, C19, and C20.

GSK carefully considered the impact of the anonymisation methodology described here on data utility but considered that the protection of personal data is of paramount importance in these cases. Gene therapy, while potentially life-saving, is effectively an irreversible treatment. Patients treated as very young

children, who may have been too young to be part of the decision making process to participate in clinical trials, most likely will remain under study for a very long time. Aggregate summaries of data for the pivotal study and associated long-term follow-up and clinical summaries have been retained. Such summaries provide the greater utility of knowledge in support of scientific conclusions reached in the Strimvelis submission. Further rationale for specific proposed redactions is provided in the table below.

Full narratives	Full narratives included within the documents include extensive details for an individual participant including demographic details, medical history diagnoses and previous treatments, concomitant medication, and details of event plus associated treatments. These narratives are often presented as verbatim text, include multiple quasi identifiers and contain a high degree of detail that may be recognisable to a potential adversary. In light of these factors, such narratives have been redacted in full in all cases.
Mini-narratives and textual references	For textual references about one subject containing multiple quasi identifiers, the entire bullet / sentence / paragraph will be redacted in full as above given the high/very high risk identified. In accordance with EMA Guidance [EMA/90915/2016] data that may give away geographic location (e.g. site number, site address, investigator name) linked to a specific patient, especially in the context of studies with three or fewer participants, have also been redacted. A similar approach has been taken with publication details when linked to a specific participant.
Population details	Textual descriptions from which a subject identifier may be inferred for participants in the pilot studies and CUP were judged to present a high-risk of re-identification through association with other known data; therefore, they were redacted in order to limit linkability. Similarly, duration of treatment and trial initiation / end dates have been redacted for subjects in pilot studies and CUP. These data were retained for AD1115611.
Aggregate tables	For pilot studies and CUP, data were almost exclusively presented at the individual subject level; therefore, full redaction was employed as per mini-narratives and textual references above. Where aggregations were present, the limited number of participants was considered to present a high risk of re-identification and so full redaction was felt to be required in order to prevent re-identification. Aggregate tables which did not contain any quasi identifiers were retained in full. For AD1115611, aggregate presentations of data were retained. Only subject identifiers were redacted for textual references of aggregate data.

GSK agrees that the acquisition cost of Strimvelis can be made publicly available. However, other costs related to hospitalisation and procedures at OSR should remain confidential as this information was provided to GSK in confidence and have requested they not be made public.

References

EMA/90915/2016: External guidance on the implementation of the European Medicines Agency policy on the publication of clinical data for medicinal products for human use

Hrynaszkiewicz I., Norton ML, Vickers AJ, Altman DG. Preparing raw clinical data for publication: guidance for journal editors, authors, and peer reviewers. *BMJ*. 2010;340: c181.

Schuller Y, Hollak CEM, Biegstraaten M. The quality of economic evaluations of ultra-orphan drugs in Europe – a systematic review. *Orphanet J Rare Dis*. 2015; 10: 92.

Appendix: Additional scenario analyses exploring all issues raised in the clarification questions from NICE together

Following a teleconference with the NICE technical team and the Evidence Review Group, it was noted there would be an interest in testing how eventual individual changes responding to the issues brought up at the clarification stage would impact the results when taken together. We have therefore decided to run a scenario analysis and to explore that scenario further with the respective sensitivity analyses. It should be noted we do not necessarily agree with all of the assumptions tested and that the inputs used in this analysis were taken from the most conservative spectrum of the possible range. This scenario analysis should therefore not be perceived as a new base case.

As it can be seen from the results presented below the impact on the ICERs is very limited and it is not expected the conclusion about the cost-effectiveness of Strimvelis would change. The differences observed in the ICERs versus MUD are entirely negligible (£36,427/QALY versus the previous £36,360/QALY) and with no impact whatsoever on the conclusion derived from results presented in the base case. In the comparison with transplant from a haploidentical donor, although the absolute ICERs do change meaningfully (£22,755/QALY versus £14,645/QALY previously), they remain comfortably under the threshold applied in the HST Evaluation Programme. Therefore, the model results and the perceived cost effectiveness of Strimvelis are shown to be robust and insensitive to any variation in these inputs. The same applies to all sensitivity analyses performed for this scenario.

Table 12. Updates to inputs tested in response to NICE clarification

Model input	Value in scenario analysis	Comments
Weekly cost of PEG-ADA	£9,000 (1 vial) (previous value £13,500)	This was estimated on the basis of patient's body weight, dose per kg/per week and the number of vials needed to deliver the dose ①. It should be noted that this is the lowest possible cost and a conservative assumption given that, as per advice received, there will be patients that will require 2 vials per week
Cost of administration of IVIG	£216 (£108 x 2 hours) (previous value £306)	This was re-estimated based on the hospital nurse time (PSSRU 2016) and the estimated time needed to deliver IVIG ②
Cost of administration of PEG-ADA	£54 (£108 x 0.5 hour) (previous value £306)	PEG-ADA is given as a jab, and it was assumed that 30 min of nurse time would be required. We used the same cost (from PSSRU) for Band 6 nurse and the updated cost of admin would be £108x0.5 = £54
New inputs (cost not included previously)		
Cost of air travel to clinic in Italy, a round trip for a child and parents	£600	Assumed £200 per person (£200 x 3 for family) for a round trip from London to Milan.
Cost of travel to and from airport in the UK	£472	UK ambulance cost (one way) is based on UK NHS Reference cost 2016, Section Ambulance, code ASS02 "See and treat and convey", the national average £236 → £472 for two trips. In this scenario analysis the cost of ambulance travel is conservatively applied to all patients despite the fact only one patient in the Strimvelis trials needed ambulance transportation.
Cost of travel from and to airport in Italy	£340	Italian ambulance cost (one way - Malpensa airport to OSR), €170 Euro were quoted in communication with OSR; for the model we rounded it to €200 →x 2 journeys → €400 = £340 (converted using 0.85 exchange rate, the same rate applied to other Euro values). In this scenario analysis the cost of ambulance travel is conservatively applied to all patients despite the fact only one patient in the Strimvelis trials needed ambulance transportation.

Notes:

① The cost of vial of PEG-ADA is £9000 (advice from clinical expert after contact with the Hospital Pharmacy); the number of units in a vial is 375 (see Adagen[1]); patient weight (using the 25th percentile in growth charts) in the first three years is 8.6, 10.9 and 13 kg at year 1, 2 and 3 respectively; the estimated weekly dose at the per kg dosage is 258, 326 and 389 within year 1, 2 and 3 respectively, which requires 1 vial a week at the cost of £9,000. .

② From PSSRU 2016 (Chapter 14, Hospital based nurses.) We applied the cost of nurse patient contact and used Band 6 (nurse specialist), the hourly cost was £108, and it was assumed that 0.5 will be required for preparation, 0.5 hour for the infusion procedure, and 1 hour for monitoring.

For the new cost elements, for simplicity of calculations we have added these costs to the cost of initial hospitalization for Strimvelis (£92,217, (although half of the travel costs occur after procedure)) and presented these costs as cost of transportation in the tables in this analysis.

[1] Adagen, product monograph: adagen.com/pdf/ Adagen_Monograph_Final.pdf

Table 13. List of tables included in this update

Table requested by NICE	Included in update
D14	Included
D15	Not affected by update
D16	Not affected by update
D18	Not affected by update
D19,	Not affected by update
D20	Not affected by update
D21	Not affected by update
D22	Included
D23	Included
D29	Included

Table 14. (D6) Costs of Strimvelis by stage of treatment (scenario analysis and base case)

Stage	Average Duration (Range)	Value in scenario analysis	Value in base case
Cost of transportation	Includes estimated round-trip flight to Italy for child and parents, and the cost of transportation to and from airport (see Table 12 for detail); this is a combined cost that occurs before and after the procedure.	£1,412	Not included in the base case
Confirmation of Eligibility for Strimvelis Treatment	24 days, performed in England	[redacted]	[redacted]
Baseline patient preparation (CVC placement, obtain bone marrow back-up)	31 days (31-45 days), including 3 day inpatient stay	[redacted]	[redacted]
Treatment	50 days in isolation room (may be longer if complications occur)		
Outpatient follow-up in Milan	60 days (60-90 days)		
Outpatient follow-up in England	4 months	[redacted]	[redacted]
	Continued for lifetime as per routine care for all patients with ADA-SCID	[redacted]	

Table 15. (D 8) Costs per treatment/patient associated with the technology in the cost-effectiveness model (scenario analysis and base case)

Items	Value in scenario analysis	Source	Value in base case
Initial PEG-ADA, before procedure	£81,486	Calculated from the model, based on estimated duration of PEG-ADA, cost per week, and cost of administration	£124,254
Price of the technology per treatment/patient	£505,000	The cost of Strimvelis in Italy is €594,000 and currency conversion for the analysis is based on the average exchange rate 1€ = £0.85 on 08 May 2017 (source www.xe.com). Please note that the San Raffaele Hospital is to be paid €594,000 in euros for Strimvelis. Conversation with NHS England confirmed that they have contracts in place for another therapy to be paid in local currency so did not see this as a concern.	£505,000
Confirmation of Eligibility for Strimvelis Treatment	[redacted]	Note: cost of confirmation of eligibility for Strimvelis is a part of the initial hospitalization (administration) cost	[redacted]
Administration cost	[redacted]	The cost of the hospital stay in Italy and any patient follow-up required during the time in Italy is [redacted][2]. Currency conversion is based on the average exchange rate 1€ = £0.85 on 08 May 2017 (source www.xe.com)	[redacted]
Transportation costs	£1,412	See Table 12 for detail	N/A
Follow-up costs	[redacted]	[redacted]	[redacted]
Total cost per treatment/patient	[redacted]		[redacted]

[2] Note that the UK cost calculated from this figure is [redacted] and included the cost of confirmation of eligibility for Strimvelis; the cost of confirmation presented in the row above is part of the cost of hospitalisation

Table 16. (D 9) Costs per treatment/patient associated with the comparator technology HSCT from a MUD in the cost-effectiveness model (scenario analysis and base case)

Items	Value in scenario analysis	Source	Value in base case
Initial PEG-ADA before procedure and screening	£172,026	Calculated from the model, based on estimated duration of PEG-ADA, cost per week, and cost of administration	£262,314
Initial hospitalization	£95,516	'Bone Marrow Transplant, Allogeneic Graft (cord blood), 18 years and under' Currency Code SA22B. [National Schedule of Reference Costs - Year 2015 - 16 NHS trusts and NHS foundation trusts]	£95,516
Follow-up costs	£59,541 per living patient	[This figure is based on total follow-up estimates of €62,096 [van Agthoven, 2002], adjusted for inflation (Netherlands inflation index for category Health Expenditures [060000]), and converted to pounds (exchange rate 1€ = £0.85 on 08 May 2017 (source www.xe.com)).	£59,541 per living patient
Total cost per treatment/patient	**£327,083**		**£417,371**

Table 17. (D 10) Costs per treatment/patient associated with the comparator technology HSCT from a haploidentical donor in the cost-effectiveness model (scenario analysis and base case)

Items	Value in scenario analysis	Source	Value in base case
Initial PEG-ADA before procedure and screening	£172,026	Calculated from the model, based on estimated duration of PEG-ADA, cost per week, and cost of administration	£262,314
Initial hospitalisation	£108,760	'Bone Marrow Transplant, Allogeneic Graft (Haplo-Identical), 18 years and under' Currency Code SA23B [National Schedule of Reference Costs - Year 2015 - 16 NHS trusts and NHS foundation trusts]	£108,760
Follow-up costs	£59,541 per living patient	Assumed to be the same cost as follow-up for HSCT from a MUD.	£59,541
Total cost per treatment/patient	**£340,327**		**£430,615**

Table 18. (D14) Summary results (scenario analysis)

Technologies	Total cost (£)	Total LYs gained	Total QALYs gained	Incremental costs (£)	Incremental LYG	Incremental QALY	ICER incremental (£/QALY)
Strimvelis	£939,245	46.1	41.4				
MUD	£444,078	31.0	27.8	£495,167	15.1	13.6	£36,427
Haplo	£674,064	33.2	29.7	£265,182	12.9	11.7	£22,755

Table 19. (D14) Summary results (base case)

Technologies	Total cost (£)	Total LYs gained	Total QALYs gained	Incremental costs (£)	Incremental LYG	Incremental QALY	ICER incremental (£/QALY)
Strimvelis	£1,059,425	46.1	41.4				
MUD	£565,170	31.0	27.8	£494,255	15.1	13.6	£36,360
Haplo	£888,757	33.2	29.7	£170,668	12.9	11.7	£14,645

Table 20. (D 22) Summary of costs by category of cost per patient – Strimvelis versus HSCT from a MUD (scenario analysis)

Category	Costs for Strimvelis therapy	Costs for HSCT from a MUD therapy	Difference: Strimvelis - HSCT from a MUD
Screening pre-procedure	£0	£45,127	-£45,127
Cost of transportation	£1,412	£0	£1,412
Confirmation of eligibility for Strimvelis treatment	[redacted]	£0	[redacted]
PEG-ADA pre-procedure	£81,486	£172,026	-£90,540
Product	£505,000	£0	£505,000
Severe infection cost	£13,103	£8,735	£4,368
Rescue transplant cost	£16,119	£6,090	£10,030
Rescue PEG-ADA cost	£142,345	£53,775	£88,570
Hospitalisation cost	[redacted]	£95,516	[redacted]
Follow-up cost, includes VCN in Strimvelis	[redacted]	£43,027	[redacted]
GvHD	£0	£7.834	-£7,834
IVIG cost	£18,927	£11,949	£6,979
Total	**£939,245**	**£444,078**	**£495,167**

Table 21 (D22) Summary of costs by category of cost per patient – Strimvelis versus HSCT from a MUD – base case

Category	Costs for Strimvelis therapy	Costs for HSCT from a MUD therapy	Difference: Strimvelis - HSCT from a MUD
Screening pre-procedure	£0	£45,127	-£45,127
Confirmation of eligibility for Strimvelis treatment	[redacted]	£0	[redacted]
PEG-ADA pre-procedure	£124,254	£262,314	-£138,060
Product	£505,000	£0	£505,000
Severe infection cost	£13,103	£8,735	£4,368
Rescue transplant cost	£16,119	£6,090	£10,030
Rescue PEG-ADA cost	£217,055	£81,999	£135,051
Hospitalisation cost	[redacted]	£95,516	[redacted]
Follow-up cost, includes VCN in Strimvelis	[redacted]	£43,027	[redacted]
GvHD	£0	£7.834	-£7,834
IVIG cost	£23,041	£14,529	£8,512
Total	**£1,059,425**	**£565,170**	**£494,255**

Table 22. (D 23) Summary of costs by category of cost per patient – Strimvelis versus HSCT from a haploidentical donor (scenario analysis)

Category	Costs for Strimvelis therapy	Costs for HSCT from a haploidentical donor therapy	Difference: Strimvelis - HSCT from a haploidentical donor
Screening pre-procedure	£0	£45,127	-£45,127
Cost of transportation	£1,412	£0	£1,412
Confirmation of eligibility for Strimvelis treatment	[redacted]	£0	[redacted]
PEG-ADA pre-procedure	£81,486	£172,026	-£90,540
Product	£505,000	£0	£505,000
Severe infection cost	£13,103	£9,359	£3,744
Rescue transplant cost	£16,119	£26,098	-£9,979
Rescue PEG-ADA cost	£142,345	£230,464	-£88,118
Hospitalisation cost	[redacted]	£108,760	[redacted]
Follow-up cost	[redacted]	£58,259	[redacted]
GvHD	£0	£8,354	-£8,354
IVIG cost	£18,927	£15,617	£3,310
Total	**£939,245**	**£674,064**	**£265,182**

Table 23. (D 23) Summary of costs by category of cost per patient – Strimvelis versus HSCT from a haploidentical donor (base case)

Category	Costs for Strimvelis therapy	Costs for HSCT from a haploidentical donor therapy	Difference: Strimvelis - HSCT from a haploidentical donor
Screening pre-procedure	£0	£45,127	-£45,127
Confirmation of eligibility for Strimvelis treatment	[redacted]	£0	[redacted]
PEG-ADA pre-procedure	£124,254	£262,314	-£138,060
Product	£505,000	£0	£505,000
Severe infection cost	£13,103	£9,359	£3,744
Rescue transplant cost	£16,119	£26,098	-£9,979
Rescue PEG-ADA cost	£217,055	£351,423	-£134,367
Hospitalisation cost	[redacted]	£108,760	[redacted]
Follow-up cost	[redacted]	£58,259	[redacted]
GvHD	£0	£8,354	-£8,354
IVIG cost	£23,041	£19,063	£3,978
Total	£1,059,425	£888,757	£170,668

Table 24. (D 24) Strimvelis vs HSCT from a MUD, incremental cost effectiveness ratio (Base-case: £36,427 per QALY gained) – (scenario analysis)

Categories and inputs scenario analysis base case ICER £36,427	base-case	lower	upper	ICER at lower value	ICER at upper value	ICER spread
Variation in discount rates and time horizon						
Discount costs	1.5%	0%	3.5%	£36,679	£36,110	£569
Discount outcomes	1.5%	0%	3.5%	£21,311	£62,433	£41,122
Discount costs and outcomes	1.5%, 1.5%	0%, 0%	3.5%, 3.5%	£21,458	£61,891	£40,433
Time horizon 50 years	lifetime	50 years	lifetime	£46,921	£36,427	£10,494
Time horizon 20 years	lifetime	20 years	lifetime	£94,669	£36,427	£58,242
Variations in survival						
HSCT from a MUD - survival 1st 6 months	67%	67%	83.75%	£36,427	£72,997	£36,570
Clinical probabilities						
Rates of severe Infections, Years 1-3 Strimvelis	26%	26%	42.9%	£36,427	£36,868	£441
Rates of severe Infections, Years 1-3 MUD	26%	26%	42.9%	£36,427	£36,133	£294
IVIG - at Year 8 in Strimvelis	0%	0%	20%	£36,427	£38,437	£2,010
IVIG - at Year 8 in MUD	0%	0%	20%	£36,427	£36,222	£205

Categories and inputs scenario analysis base case ICER £36,427	base-case	lower	upper	ICER at lower value	ICER at upper value	ICER spread
Severe acute GvHD of all patients, HSCT from a MUD	10.7%	5%	16%	£36,469	£36,388	£81
Severe chronic GvHD of all patients, HSCT from a MUD	3.6%	0%	7.1%	£36,519	£36,335	£184
Proportion of rescue transplants that are from a MUD	0%	0%	50%	£36,427	£36,601	£174
Proportion who receive a rescue transplant, Strimvelis	17.6%	8.30%	22.70%	£29,736	£40,053	£10,317
Proportion who receive a rescue transplant, HSCT from a MUD	6.70%	5.00%	8.30%	£37,625	£35,253	£2,372
Timing and duration						
Weeks on PEG-ADA before Strimvelis (+/- 2)	9	7	11	£35,192	£37,655	£2,463
Weeks on PEG-ADA before MUD (+/- 2)	19	17	21	£37,655	£35,192	£2,463
Weeks on PEG-ADA before MUD	19	9	24	£42,500	£33,327	£9,173
Timing of rescue transplant	Year 3	Year 3	Year 4	£36,427	£40,132	£3,705
Timing of rescue transplant	Year 3	Year 3	Year 5	£36,427	£43,730	£7,303
Timing of rescue transplant	Year 3	Year 2	Year 3	£32,729	£36,427	£3,698

Categories and inputs scenario analysis base case ICER £36,427	base-case	lower	upper	ICER at lower value	ICER at upper value	ICER spread
Variations in costs						
Cost of PEG-ADA, weekly (+/-50% of base case)	£9,000	£4,500	£13,500	£36,499	£36,355	£144
Cost of PEG-ADA, weekly (+/- 25% of base case)	£9,000	£6,750	£11,250	£36,463	£36,391	£72
Cost of PEG-ADA, weekly (10% of base-case)	£9,000	£900	£9,000	£36,556	£36,427	£129
Cost of administration of PEG-ADA (-50%/+100%)	£54	£27	£108	£36,427	£36,426	£1
Price of IVIG per gram (+/- 25%)	£40.1	£30.1	£50.1	£36,366	£36,488	£144
Cost of administration of IVIG (-50%/+100%)	£216	£108	£432	£36,291	£36,698	£407
Cost of screening (+/- 25%)	£45,127	£33,845	£56,409	£37,257	£35,597	£1,660
Cost of severe infection, all arms (+/- 25%)	£12,143	£9,107	£15,179	£36,359	£36,495	£136
Cost confirmation of eligibility for Strimvelis treatment and initial hospitalization, Strimvelis (+/- 25%)	[redacted]	[redacted]	[redacted]	£34,731	£38,123	£3,392
Cost initial hospitalization, MUD (+/- 25%)	£95,516	£71,637	£119,395	£37,999	£34,855	£3,144
Cost of follow-up, Strimvelis (+/- 25%)	[redacted]	[redacted]	[redacted]	£35,471	£37,383	£1,912

Categories and inputs scenario analysis base case ICER £36,427	base-case	lower	upper	ICER at lower value	ICER at upper value	ICER spread
Cost of follow-up, MUD (+/- 25%)	£59,541	£44,656	£74,426	£37,034	£35,820	£1,214
Cost of rescue transplant, Strimvelis (+/- 25%)	£95,516	£71,637	£119,395	£36,130	£36,723	£593
Cost of rescue transplant, MUD (+/- 25%)	£95,516	£71,637	£119,395	£36,539	£36,315	£224
Cost of GVHD - all arms (+/- 25%)	£29,420	£22,065	£36,775	£36,571	£36,283	£288
Drugs dosage						
Duration of PEG-ADA use in bridge to rescue transplant	1.75 years	1.5 years	2 years	£35,476	£37,378	£1,902
Cost of IVIG based on average dose years 0-8	weight	weight	average	£36,427	£36,505	£78
Utilities						
Health utility in the period before HSCT or Strimvelis	0.98	0.49	1	£36,177	£36,438	£261
QALY loss due to an aGvHD, MUD (+/- 25%)	0.41	0.3	0.5	£36,446	£36,407	£39
QALY loss due to a cGvHD, MUD (+/- 25%)	1.44	1.1	1.8	£36,450	£36,404	£46
Utilities by age band	General population.	x 0.95	x 1.05	£38,349	£34,689	£3,660
Utilities by age band @0.90 general population	General population.	x 0.90	General population.	£40,484	£36,427	£4,057

Categories and inputs **scenario analysis base case ICER £36,427**	**base-case**	**lower**	**upper**	**ICER at lower value**	**ICER at upper value**	**ICER spread**
Utilities by age band @0.85 general population	General population.	x 0.85	General population.	£42,872	£36,427	£9,132
Utilities by age band @0.80 general population	General population.	x 0.80	General population.	£45,559	£36,427	£9,132
Weight for IVIG disutility	1.00	0.75	1.00	£37,227	£36,427	£800
Utility decrement 6 months (Strimvelis and MUD)	0.57	none	1.00	£36,095	£36,681	£586
Carer's QALY loss due to premature death of child	none	none	accounted for	£36,427	£31,532	£4,895

Table 25. (D 24) Strimvelis vs HSCT from a MUD, incremental cost effectiveness ratio (Base-case: £36,360 per QALY gained) – (base case)

Categories and inputs Base case ICER £36,360	base-case	lower	upper	ICER at lower value	ICER at upper value	ICER spread
Variation in discount rates and time horizon						
Discount costs	1.5%	0%	3.5%	£36,689	£35,945	£744
Discount outcomes	1.5%	0%	3.5%	£21,271	£62,318	£41,047
Discount costs and outcomes	1.5%, 1.5%	0%, 0%	3.5%, 3.5%	£21,464	£61,607	£40,143
Time horizon 50 years	lifetime	50 years	lifetime	£46,835	£36,360	£10,475
Time horizon 20 years	lifetime	20 years	lifetime	£94,494	£36,360	£58,134
Variations in survival						
HSCT from a MUD - survival 1st 6 months	67%	67%	83.75%	£36,360	£72,766	£36,406
Clinical probabilities						
Rates of severe Infections, Years 1-3 Strimvelis	26%	26%	42.9%	£36,360	£36,800	£440
Rates of severe Infections, Years 1-3 MUD	26%	26%	42.9%	£36,360	£36.066	£36,324
IVIG - at Year 8 in Strimvelis	0%	0%	20%	£36,360	£38,536	£2,176
IVIG - at Year 8 in MUD	0%	0%	20%	£36,360	£36,127	£233

Categories and inputs **Base case ICER £36,360**	**base-case**	**lower**	**upper**	**ICER at lower value**	**ICER at upper value**	**ICER spread**
Severe acute GvHD of all patients, HSCT from a MUD	10.7%	5%	16%	£36,402	£36,321	£81
Severe chronic GvHD of all patients, HSCT from a MUD	3.6%	0%	7.1%	£36,452	£36,268	£184
Proportion of rescue transplants that are from a MUD	0%	0%	50%	£36,360	£36,534	£174
Proportion who receive a rescue transplant, Strimvelis	17.6%	8.30%	22.70%	£26,741	£41,573	£14,832
Proportion who receive a rescue transplant, HSCT from a MUD	6.70%	5.00%	8.30%	£38,081	£34,674	£3,407
Timing and duration						
Weeks on PEG-ADA before Strimvelis (+/- 2)	9	7	11	£34,424	£38,285	£3,861
Weeks on PEG-ADA before MUD (+/- 2)	19	17	21	£38,285	£34,424	£3,861
Weeks on PEG-ADA before MUD	19	9	24	£45,881	£31,499	£14,382
Timing of rescue transplant	Year 3	Year 3	Year 4	£36,360	£41,971	£5,611
Timing of rescue transplant	Year 3	Year 3	Year 5	£36,360	£47,456	£11,096
Timing of rescue transplant	Year 3	Year 2	Year 3	£30,699	£36,360	£5,661

Categories and inputs Base case ICER £36,360	base-case	lower	upper	ICER at lower value	ICER at upper value	ICER spread
Variations in costs						
Cost of PEG-ADA, weekly (50% of base-case)	£13,500	£6,750	£13,500	£36,468	£36,360	£108
Cost of PEG-ADA, weekly (25% of base-case)	£13,500	£3,375	£13,500	£36,522	£36,360	£162
Cost of PEG-ADA, weekly (10% of base-case)	£13,500	£1,350	£13,500	£36,554	£36,360	£194
Cost of PEG-ADA, weekly (+/- 25%)	£13,500	£10,125	£16,875	£36,414	£36,306	£108
Cost of administration of PEG-ADA (+/- 25%)	£306	£230	£383	£36,361	£36,359	£2
Price of IVIG per gram (+/- 25%)	£40.1	£30.1	£50.1	£36,299	£36,420	£121
Cost of administration of IVIG (+/- 25%)	£306	£230	£383	£36,264	£36,456	£192
Cost of screening (+/- 25%)	£45,127	£33,845	£56,409	£37,190	£35,530	£1,660
Cost of severe infection, all arms (+/- 25%)	£12,143	£9,107	£15,179	£36,279	£36,440	£161
Cost confirmation of eligibility for Strimvelis treatment and initial hospitalization, Strimvelis (+/- 25%)	[redacted]	[redacted]	[redacted]	£34,664	£38,056	£3,392
Cost initial hospitalization, MUD (+/- 25%)	£95,516	£71,637	£119,395	£37,932	£34,788	£3,144

Categories and inputs **Base case ICER £36,360**	**base-case**	**lower**	**upper**	**ICER at lower value**	**ICER at upper value**	**ICER spread**
Cost of follow-up, Strimvelis (+/- 25%)	[redacted]	[redacted]	[redacted]	£35,404	£37,316	£1,912
Cost of follow-up, MUD (+/- 25%)	£59,541	£44,656	£74,426	£36,967	£35,753	£1,214
Cost of rescue transplant, Strimvelis (+/- 25%)	£95,516	£71,637	£119,395	£36,063	£36,656	£593
Cost of rescue transplant, MUD (+/- 25%)	£95,516	£71,637	£119,395	£36,472	£36,248	£224
Cost of GVHD - all arms (+/- 25%)	£29,420	£22,065	£36,775	£36,504	£36,216	£288
Drugs dosage						
Duration of PEG-ADA use in bridge to rescue transplant	1.75 years	1.5 years	2 years	£34,910	£37,810	£2,900
Cost of IVIG based on average dose years 0-8	weight	weight	average	£36,360	£36,439	£79
Utilities						
Health utility in the period before HSCT or Strimvelis	0.98	0.49	1	£36,110	£36,371	£261
QALY loss due to an aGvHD, MUD (+/- 25%)	0.41	0.3	0.5	£36,379	£36,340	£39
QALY loss due to a cGvHD, MUD (+/- 25%)	1.44	1.1	1.8	£36,383	£36,337	£46

Categories and inputs **Base case ICER £36,360**	**base-case**	**lower**	**upper**	**ICER at lower value**	**ICER at upper value**	**ICER spread**
Utilities by age band	General population.	x 0.95	x 1.05	£38,278	£34,625	£3,653
Utilities by age band @0.90 general population	General population.	x 0.90	General population.	£40,410	£36,360	£4,050
Utilities by age band @0.85 general population	General population.	x 0.85	General population.	£42,793	£36,360	£6,433
Utilities by age band @0.80 general population	General population.	x 0.80	General population.	£45,475	£36,360	£9,115
Weight for IVIG disutility	1.00	0.75	1.00	£37,158	£36,360	£798
Utility decrement 6 months (Strimvelis and MUD)	0.57	none	1.00	£36,029	£36,614	£585
Carer's QALY loss due to premature death of child	none	none	accounted for	£36,360	£33,201	£3,159

Table 26. (D-25) Strimvelis vs HSCT from a haploidentical donor, incremental cost effectiveness ratio (Base-case: £22,755 per QALY gained) – (scenario analysis)

ICER = £22,755	base-case	lower	upper	ICER at lower value	ICER at upper value	ICER spread
Variation in discount rates and time horizon						
Discount costs	1.5%	0%	3.5%	£22,568	£22,992	£424
Discount outcomes	1.5%	0%	3.5%	£13,312	£39,011	£25,699
Discount costs and outcomes	1.5%, 1.5%	0%, 0%	3.5%, 3.5%	£13,202	£39,417	£26,215
Time horizon 50 years	lifetime	50 years	lifetime	£29,309	£22,755	£6,554
Time horizon 20 years	lifetime	20 years	lifetime	£59,117	£22,755	£36,362
Variations in survival						
HSCT from a Haplo - survival 1st 6 months	71.4%	71.4%	80%	£22,755	£31,659	£8,904
Clinical probabilities						
Rates of severe Infections, Years 1-3 Strimvelis	26%	26%	42.9%	£22,755	£23,269	£514
Rates of severe Infections, Years 1-3 Haplo	26%	26%	42.9%	£22,755	£22,387	£368
IVIG - at Year 8 in Strimvelis	0%	0%	20%	£22,755	£23,269	£514
IVIG - at Year 8 in Haplo	0%	0%	20%	£22,755	£21,529	£1,226

ICER = £22,755	base-case	lower	upper	ICER at lower value	ICER at upper value	ICER spread
Severe acute GvHD of all patients, HSCT from a haploidentical donor	11.1%	5.6%	17%	£22,787	£22,691	£96
Severe chronic GvHD of all patients, HSCT from a haploidentical donor	0.0%	0%	3.6%	£22,755	£22,683	£72
Proportion of rescue transplants that are from a MUD	0%	0%	50%	£22,755	£22,552	£203
Proportion who receive a rescue transplant, Strimvelis	17.6%	8.30%	22.70%	£14,980	£26,971	£11,991
Proportion who receive a rescue transplant, HSCT from a haploidentical donor	28.6%	21.40%	35.70%	£28,755	£16,809	£11,946
Rates of severe Infections, Years 1-3 Strimvelis	26%	26%	42.9%	£22,755	£23,269	£514
Rates of severe Infections, Years 1-3 HSCT from a haploidentical donor	26%	26%	42.9%	£22,755	£22,387	£368
IVIG - at Year 8 in Strimvelis	0.0%	0.0%	20.0%	£22,755	£25,099	£2,344
IVIG - at Year 8 in HSCT from a haploidentical donor	0.0%	0.0%	20.0%	£22,755	£21,529	£1,226
Timing and duration						
Weeks on PEG-ADA before Strimvelis (+/- 2)	9	7	11	£21,270	£24,230	£2,960
Weeks on PEG-ADA before Haplo (+/- 2)	19	17	21	£24,230	£21,270	£2,960

ICER = £22,755	base-case	lower	upper	ICER at lower value	ICER at upper value	ICER spread
Weeks on PEG-ADA before Haplo	19	9	24	£30,039	£19,024	£11,015
Timing of rescue transplant	Year 3	Year 3	Year 4	£22,755	£18,759	£3,996
Timing of rescue transplant	Year 3	Year 3	Year 5	£22,755	£14,721	£8,034
Timing of rescue transplant	Year 3	Year 2	Year 3	£26,540	£22,755	£3,785
Variations in costs						
Cost of PEG-ADA, weekly (50% of base-case)	£9000	£4500	£9000	£30,374	£22,755	£7,619
Cost of PEG-ADA, weekly (+/-25% of base-case)	£9000	£6,750	£11,250	£26,564	£18,945	£7,619
Cost of PEG-ADA, weekly (10% of base-case)	£9000	£900	£9000	£36,470	£22,755	£13,715
Cost of administration of PEG-ADA (- 50%/ x 2)	£54	£27	£108	£22,800	£22,663	£73
Price of IVIG per gram (+/- 25%)	£40.1	£30.1	£50.1	£22,718	£22,791	£7,619
Cost of administration of IVIG (- 50%/ x 2)	£216	£108	£432	£22,686	£22,892	£206
Cost of screening (+/- 25%)	£45,127	£33,845	£56,409	£23,723	£21,787	£1,936
Cost of severe infection, all arms (+/- 25%)	£12,143	£9,107	£15,179	£22,674	£22,835	£161

ICER = £22,755	base-case	lower	upper	ICER at lower value	ICER at upper value	ICER spread
Cost confirmation of eligibility for Strimvelis treatment and initial hospitalization, Strimvelis (+/- 25%)	[redacted]	[redacted]	[redacted]	£20,776	£24,733	£3,957
Cost initial hospitalization, Haplo (+/- 25%)	£108,760	£81,570	£135,950	£25,088	£20,422	£4,666
Cost of follow-up, Strimvelis (+/- 25%)	[redacted]	[redacted]	[redacted]	£21,640	£23,870	£2,230
Cost of follow-up, Haplo (+/- 25%)	£59,541	£44,656	£74,426	£23,657	£21,853	£1,804
Cost of rescue transplant, Strimvelis (+/- 25%)	£95,516	£71,637	£119,395	£22,409	£23,100	£691
Cost of rescue transplant, HSCT from a haploidentical donor (+/- 25%)	£95,516	£71,637	£119,395	£23,315	£22,195	£1,120
Cost of GVHD, all interventions (+/- 25%)	£29,420	£22,065	£36,775	£22,934	£22,575	£359
Drugs dosage						
Duration of PEG-ADA use in bridge to rescue transplant (no change in time to rescue transplant)	1.75 years	1.5 years	2 years	£23,858	£21,651	£2,207
Cost of IVIG based on average dose years 0-8	weight	weight	average	£22,755	£22,771	£16
Utilities						
Health utility in the period before HSCT or Strimvelis	0.98	0.49	1.0	£22,573	£22,763	£190

ICER = £22,755	**base-case**	**lower**	**upper**	**ICER at lower value**	**ICER at upper value**	**ICER spread**
One-off QALY loss due to a utility decrement from acute GvHD (+/- 25%)	0.41	0.31	0.51	£22,771	£22,739	£32
One-off QALY loss due to a utility decrement from chronic GvHD (+/- 25%)	1.44	1.08	1.80	£22,755	£22,755	£0
Utilities by age band	General population.	x 0.95	x 1.05	£23,965	£21,661	£2,304
Utilities by age band @0.90 general population	General population.	x 0.90	General population.	£25,311	£22,755	£2,556
Utilities by age band @0.85 general population	General population.	x 0.85	General population.	£26,818	£22,755	£4,063
Utilities by age band @0.80 general population	General population.	x 0.80	General population.	£28,515	£22,755	£5,760
Utility weight for IVIG	1.00	0.75	1.00	£23,098	£22,755	£343
Utility decrement 6 months (Strimvelis and MUD)	0.57	none	1.00	£22,654	£22,831	£177
Carer's QALY loss due to premature death of child	none	none	accounted for	£22,755	£19,698	£3,057

Table 27. (D-25) Strimvelis vs HSCT from a haploidentical donor, incremental cost effectiveness ratio (Base-case: £14,645 per QALY gained) – (base case)

Base case ICER £14,645	base-case	lower	upper	ICER at lower value	ICER at upper value	ICER spread
Variation in discount rates and time horizon						
Discount costs	1.5%	0%	3.5%	£14,373	£14,989	£616
Discount outcomes	1.5%	0%	3.5%	£8,567	£25,107	£16,540
Discount costs and outcomes	1.5%, 1.5%	0%, 0%	3.5%, 3.5%	£8,408	£25,697	£17,289
Time horizon 50 years	lifetime	50 years	lifetime	£18,863	£14,645	£4,218
Time horizon 20 years	lifetime	20 years	lifetime	£38,047	£14,645	£23,402
Variations in survival						
HSCT from a Haplo - survival 1st 6 months	71.4%	71.4%	80%	£14,645	£19,987	£5,342
Clinical probabilities						
Rates of severe Infections, Years 1-3 Strimvelis	26%	26%	42.9%	£14,645	£15,159	£514
Rates of severe Infections, Years 1-3 Haplo	26%	26%	42.9%	£14,645	£14,277	£368
IVIG - at Year 8 in Strimvelis	0%	0%	20%	£14,645	£17,183	£2,538
IVIG - at Year 8 in Haplo	0%	0%	20%	£14,645	£13,316	£1,329

Base case ICER £14,645	base-case	lower	upper	ICER at lower value	ICER at upper value	ICER spread
Severe acute GvHD of all patients, HSCT from a haploidentical donor	11.1%	5.6%	17%	£14,665	£16,624	£1,959
Severe chronic GvHD of all patients, HSCT from a haploidentical donor	0.0%	0%	3.6%	£14,645	£14,599	£46
Proportion of rescue transplants that are from a MUD	0%	0%	50%	£14,645	£14,442	£203
Proportion who receive a rescue transplant, Strimvelis	17.6%	8.30%	22.70%	£3,473	£20,703	£17,230
Proportion who receive a rescue transplant, HSCT from a haploidentical donor	28.6%	21.40%	35.70%	£23,261	£6,106	£17,155
Rates of severe Infections, Years 1-3 Strimvelis	26%	26%	42.9%	£14,645	£15,159	£514
Rates of severe Infections, Years 1-3 HSCT from a haploidentical donor	26%	26%	42.9%	£14,645	£14,277	£368
IVIG - at Year 8 in Strimvelis	0.0%	0.0%	20.0%	£14,645	£17,183	£2,538
IVIG - at Year 8 in HSCT from a haploidentical donor	0.0%	0.0%	20.0%	£14,645	£13,316	£1,329
Timing and duration						
Weeks on PEG-ADA before Strimvelis (+/- 2)	9	7	11	£12,315	£16,959	£4,644
Weeks on PEG-ADA before Haplo (+/- 2)	19	17	21	£16,959	£12,315	£4,644

Base case ICER £14,645	base-case	lower	upper	ICER at lower value	ICER at upper value	ICER spread
Weeks on PEG-ADA before Haplo	19	9	24	£26,071	£8,792	£17,279
Timing of rescue transplant	Year 3	Year 3	Year 4	£14,645	£8,414	£6,231
Timing of rescue transplant	Year 3	Year 3	Year 5	£14,645	£2,147	£12,498
Timing of rescue transplant	Year 3	Year 2	Year 3	£20,822	£14,645	£6,177
Variations in costs						
Cost of PEG-ADA, weekly (50% of base-case)	£13,500	£6,750	£13,500	£26,074	£14,645	£11,429
Cost of PEG-ADA, weekly (25% of base-case)	£13,500	£3,375	£13,500	£31,788	£14,645	£17,143
Cost of PEG-ADA, weekly (10% of base-case)	£13,500	£1,350	£13,500	£35,217	£14,645	£20,572
Cost of PEG-ADA, weekly (+/- 25%)	£13,500	£10,125	£16,875	£20,359	£8,930	£11,429
Cost of administration of PEG-ADA (+/- 25%)	£306	£230	£383	£14,774	£14,515	£259
Price of IVIG per gram (+/- 25%)	£40.1	£30.1	£50.1	£14,608	£14,681	£73
Cost of administration of IVIG (+/- 25%)	£306	£230	£383	£14,596	£14,693	£97
Cost of screening (+/- 25%)	£45,127	£33,845	£56,409	£15,613	£13,677	£1,936

Base case ICER £14,645	base-case	lower	upper	ICER at lower value	ICER at upper value	ICER spread
Cost of severe infection, all arms (+/- 25%)	£12,143	£9,107	£15,179	£14,564	£14,725	£161
Cost confirmation of eligibility for Strimvelis treatment and initial hospitalization, Strimvelis (+/- 25%)	[redacted]	[redacted]	[redacted]	£12,666	£16,623	£3,957
Cost initial hospitalization, Haplo (+/- 25%)	£108,760	£81,570	£135,950	£16,978	£12,312	£4,666
Cost of follow-up, Strimvelis (+/- 25%)	[redacted]	[redacted]	[redacted]	£13,530	£15,760	£2,230
Cost of follow-up, Haplo (+/- 25%)	£59,541	£44,656	£74,426	£15,547	£13,743	£1,804
Cost of rescue transplant, Strimvelis (+/- 25%)	£95,516	£71,637	£119,395	£14,299	£14,990	£691
Cost of rescue transplant, HSCT from a haploidentical donor (+/- 25%)	£95,516	£71,637	£119,395	£15,205	£14,085	£1,120
Cost of GVHD, all interventions (+/- 25%)	£29,420	£22,065	£36,775	£14,824	£14,465	£359
Drugs dosage						
Duration of PEG-ADA use in bridge to rescue transplant (no change in time to rescue transplant)	1.75 years	1.5 years	2 years	£16,327	£12,962	£3,365
Cost of IVIG based on average dose years 0-8	weight	weight	average	£14,645	£14,662	£17

Base case ICER £14,645	base-case	lower	upper	ICER at lower value	ICER at upper value	ICER spread
Utilities						
Health utility in the period before HSCT or Strimvelis	0.98	0.49	1.0	£14,527	£14,650	£123
One-off QALY loss due to a utility decrement from acute GvHD (+/- 25%)	0.41	0.31	0.51	£14,665	£14,634	£31
One-off QALY loss due to a utility decrement from chronic GvHD (+/- 25%)	1.44	1.08	1.80	£14,645	£14,645	£0
Utilities by age band	General population.	x 0.95	x 1.05	£15,424	£13,941	£1,483
Utilities by age band @0.90 general population	General population.	x 0.90	General population.	£16,290	£14,645	£1,645
Utilities by age band @0.85 general population	General population.	x 0.85	General population.	£17,260	£14,645	£2,615
Utilities by age band @0.80 general population	General population.	x 0.80	General population.	£18,356	£14,645	£3,711
Utility weight for IVIG	1.00	0.75	1.00	£14,865	£14,645	£220
Utility decrement 6 months (Strimvelis and MUD)	0.57	none	1.00	£14,580	£14,694	£114
Carer's QALY loss due to premature death of child[a]	none	none	accounted for	£14,645	£13,373	£1,272

Figure 3 Tornado diagram analysis Strimvelis vs HSCT from a MUD (scenario analysis)

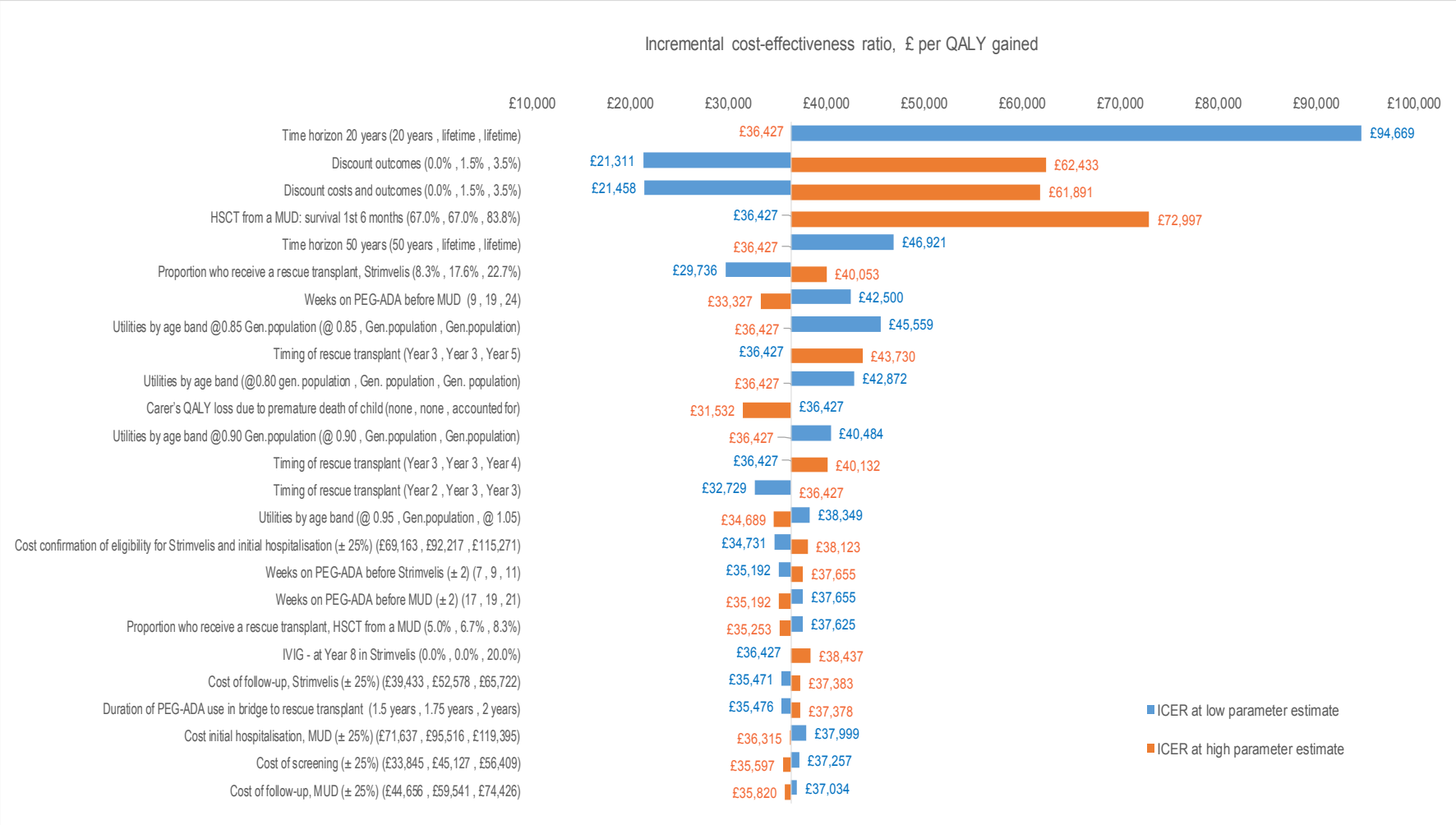


Figure 4 Tornado diagram analysis Strimvelis vs HSCT from a MUD (base case)

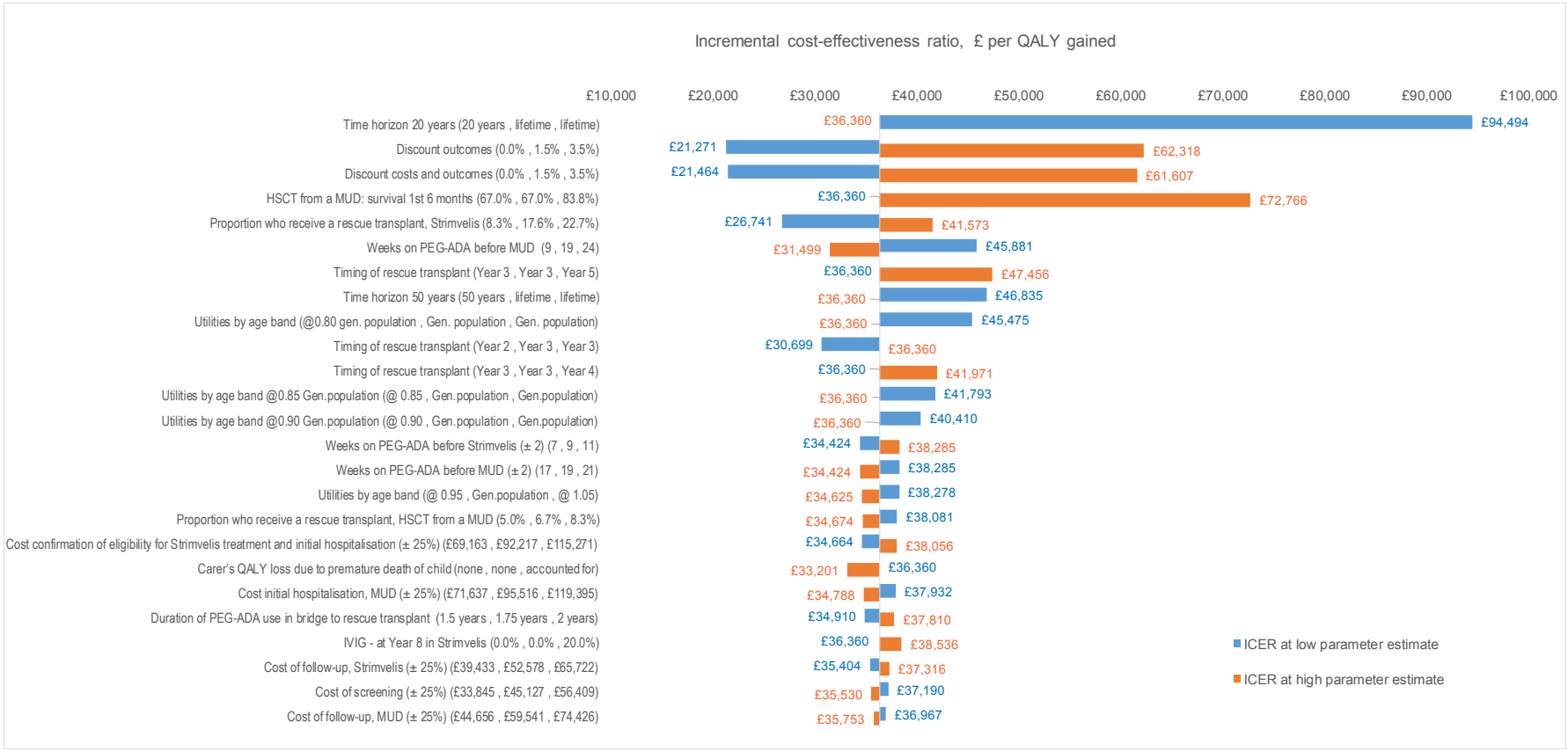


Table 28. (D 29) Percentage of total costs by cost category (scenario analysis)

Cost category	Costs for Strimvelis therapy	HSCT from a MUD	HSCT from a haploidentical donor
Screening pre-procedure	0.0%	10.2%	6.7%
Confirmation of eligibility for Strimvelis treatment	[redacted]	0.0%	0.0%
PEG-ADA pre-procedure	8.7%	38.7%	25.5%
Product	53.8%	0.0%	0.0%
Severe infection cost	1.4%	2.0%	1.4%
Rescue transplant cost	1.7%	1.4%	3.9%
Rescue PEG-ADA cost	15.2%	12.1%	34.2%
Hospitalisation cost[3]	[redacted]	21.5%	16.1%
Follow-up cost	[redacted]	9.7%	8.6%
GvHD	0.0%	1.8%	1.2%
IVIG cost	2.0%	2.7%	2.3%
Total	**100%**	**100%**	**100%**

[3] Note that the cost of travel has been added to the cost of initial hospitalisation for Strimvelis

Table 29. (D 29) Percentage of total costs by cost category (base case)

Cost category	Costs for Strimvelis therapy	HSCT from a MUD	HSCT from a haploidentical donor
Screening pre-procedure	0.0%	8.0%	5.1%
Confirmation of eligibility for Strimvelis treatment	[redacted]	0.0%	0.0%
PEG-ADA pre-procedure	11.7%	46.4%	29.5%
Product	47.7%	0.0%	0.0%
Severe infection cost	1.2%	1.5%	1.1%
Rescue transplant cost	1.5%	1.1%	2.9%
Rescue PEG-ADA cost	20.5%	14.5%	39.5%
Hospitalisation cost	[redacted]	16.9%	12.2%
Follow-up cost	[redacted]	7.6%	6.6%
GvHD	0.0%	1.4%	0.9%
IVIG cost	2.2%	2.6%	2.1%
Total	**100%**	**100%**	**100%**

We re-ran a threshold analysis to determine the range of values for these important parameters that will produce ICERs above £140,000/QALY gained (for Strimvelis vs HSCT from a MUD) or above £120,000/QALY gained (for Strimvelis vs HSCT from a haploidentical donor).

Table 30. Threshold analysis – Strimvelis vs HSCT from a MUD (scenario analysis) and (base case)

	Value in scenario analysis	Value in base case
Post-procedure survival (Strimvelis vs HSCT from a MUD)		
The model produces ICERs >£140,000/QALY gained if:		
the survival for HSCT from a MUD is	>92%	>92%
or, the survival in Strimvelis is	<74%	<74%
Price of Strimvelis (Strimvelis vs HSCT from a MUD)		
The model produces ICERs >£140,000/QALY gained if:		
the price of the Strimvelis procedure is	>£1,912,918	>£1,913,831
Long-term post-procedure utility values		
For Strimvelis vs HSCT from a MUD, model ICERs >£140,000/QALY gained are produced if, and only if:		
the utility weight is	<0.26	<0.26
Utilities in these ranges are not expected to be realistic.		

Table 31. Threshold analysis – Strimvelis vs HSCT from a haploidentical donor (scenario analysis) and (base case)

	Value in scenario analysis	Value in base case
Post-procedure survival (Strimvelis vs HSCT from a haploidentical donor)		
The model produces ICERs >£120,000/QALY gained if:		
the survival for HSCT from a haploidentical donor is	>95%	>97%
or, the survival in Strimvelis is	<76%	<73%
Price of Strimvelis (Strimvelis vs HSCT from a haploidentical donor)		
The model produces ICERs >£120,000/QALY gained if:		
the price of the Strimvelis procedure is	> £1,638,290	>£1,732,803
Long-term post-procedure utility values		
For Strimvelis vs HSCT from a haploidentical donor, model ICERs >£120,000/QALY gained are produced if, and only if:		
the utility weight is	<0.20	<0.13
Utilities in these ranges are not expected to be realistic.		

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Strimvelis for treating severe combined immunodeficiency caused by adenosine deaminase deficiency

Thank you for agreeing to give us your views on the condition, the technology and the way it should be used in the NHS.

Patients, carers and patient organisations can provide a unique perspective on the condition and the technology, which is not typically available from the published literature.

To help you give your views, we have provided a template. The questions are there as prompts to guide you. You do not have to answer every question. Where appropriate, please provide case studies of individual patients, their families or carers. Please do not exceed 30 pages.

About you

Your name: Dr Susan Walsh

Name of your organisation: Primary Immunodeficiency UK (PID UK)

Brief de*scrip*tion of the organisation:
(*For example: who funds the organisation? How many members does the organisation have? What proportion of the total English patient population does this represent?)*

PID UK supports individuals and families affected by a primary immunodeficiency in the UK. Our aims are to be the first port of call for those in the UK seeking information on all aspects of having a PID; to promote awareness and understanding of PID; to provide direct support to individuals and families affected by PID; act as an advocate and campaigner for the needs and rights of people affected by PID. We have over a thousand members representing approximately one fifth of the population affected by PID (approx 4,800 patients are registered on the UK PIN registry). PID UK is funded by a mixture of income from donations, fundraising activity, legacies, grants from foundations and sponsorship from pharma. No funding has been received from GSK.

Are you (tick all that apply):

- a patient with the condition for which NICE is considering this technology?
- a carer of a patient with the condition for which NICE is considering this technology?
- √ an employee of a patient organisation that represents patients with the condition for which NICE is considering the technology? If so, give your position in the organisation where appropriate (e.g. policy officer, trustee, member, etc). Director

- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

NONE
http://www.piduk.org/aboutus/sponsorsandfunders

How does the condition impact on patients, their families or carers?

1(i). Please describe whether patients experience difficulties or delays in receiving:
- a diagnosis
- appropriate treatment
- helpful information about the condition

and the impact these difficulties have on patients and their families or carers.

a diagnosis

Babies with SCID may seem well at birth and first signs usually occur within the first three – six months. The baby is likely to suffer infections more frequently than other infants, and ordinary problems, such as coughs and colds, will seem more severe and last longer than would be expected, requiring repeated and prolonged courses of treatment.

Unless here is a family history of ADA-SCID, parents often have a long diagnostic odyssey due to it being a very rare disorder and it not being recognised by healthcare professionals. Families may seek help from their family doctor (GP) or local A&E because of repeated infections, poor weight gain or feeding problems, and the baby may be referred to a local paediatrician. However, the first indication that something is wrong can be a serious infection that causes rapid deterioration in the baby's condition, requiring urgent admission to hospital, and sometimes to an intensive care unit. As a result of routine investigations, SCID may be suspected, usually because of a low lymphocyte count in the blood. As soon as the possibility of SCID is suspected, the infant will be referred to a specialist immunology centre, and further investigations are then necessary to confirm the diagnosis, and subsequently to determine the type of SCID. Infants with typical early onset ADA-SCID have poor growth and frequent, severe and unusual infections, such as pneumonia with an organism called *Pneumocystis jirovecii* (a yeast-like fungus) that does not usually cause illness in healthy individuals. Breathing difficulties can also occur in infants with ADA-SCID without any detectable infection. Central nervous system: development may be slower than in healthy children and there may be behavioural and psychological problems, such ashyperactivity and poor social behaviour. Deafness may also be a problem and there may also be problems with other body systems, including the kidneys, liver and lungs.

A typical story of the diagnostic odyssey of a child affected by SCID

[redacted] our second son, was born on [redacted]. He was a huge baby weighing 10lbs 8oz. He was very strong, alert and engaging. He fed well, gained weight and thrived. At 5 months of age, at the beginning of February, things took a dramatic turn for the worse. I can only describe what happened over the course of the next 2 and a half months as utterly nightmarish. He developed a cough and cold that he just could not get over. This developed into a chest

infection. Despite going to our GP and having antibiotics prescribed he did not get better. He began to develop breathing difficulties. This was very frightening and often he would become worse at night. During the whole of February and March and half way through April we were back and forth from the GP, to the out of hours "Grab a Doc" service and multiple visits to Accident and Emergency. In total we visited A&E 6 times during those 2 months, we visited the "Grab a doc" out of hours service twice and our GP 3 times and also saw our health visitor. He was hospitalised on 4 occasions at our local hospital. Consultants were baffled, they couldn't understand why he was repeatedly ill and having lengthy stays on the ward. The first and second admission was put down to Broncilitous and the 3rd admittance was put down to Pneumonia , but on the 4th stay they really didn't know what was wrong. They thought he may have Whooping cough or Cystic Fibrosis so he was tested for these conditions but both came back negative.

During these 2 months of toing and froing and sitting for hours upon hours in A&E waiting room and in Grab a Doc centres and GP waiting rooms etc we were unbeknown to us exposing him to even more germs and viruses.
My son began to rapidly lose weight. He had been a good weight at birth and had been on the 98th centile, which is just as well, as by the time he was finally diagnosed at 7 months he was on the 25th centile and weighed less than he did when he was 4 months old. Now during these 2 months of consultants trying to reach a diagnosis he was growing weaker and I could see that he was wasting away. I had asked a consultant if he was dying and he laughed off my concern and said "Children lose weight when they are ill". I began to be afraid of the hospital discharging him home because he would become unwell within a few days of being home and I found the worry unbearable. I felt as though he was being pumped with IV antibiotics, he would perk up and then we would be discharged and then a few days later the nightmare would continue. He would struggle to breath and we would be back at A&E again. Even on our 4th admission the plan had been to get my son well and send him back home while we wait for an outpatient appointment for the allergy clinic. They had also referred him as an outpatient to Kings Respiratory and GOSH Immunology, although the Immunology was being pursued as a side line. There was no sense of emergency and I was worried that he didn't have time to wait. I took it upon myself to contact Kings Respiratory and GOSH and asked if they had received the referral letters. I found out after calling them that neither had received the referral letters . So I faxed the letters over myself and rang to confirm receipt. Once GOSH had the letter they acted on it and asked for his bloods to be taken and couriered to them. The next day we were transferred to GOSH where we received the most shocking and devastating news, My son was diagnosed with a SCID. I felt my world crash around me!'

'We nearly lost him twice' – [redacted], mother to her son [redacted] diagnosed with ADA-SCID at 10 weeks old.

Implementation of a national newborn screening programme for SCID (under consideration) would mean that this costly diagnostic odyssey is avoided and appropriate infection preventative treatments e.g. prophylactic antibiotics, antifungals etc can be given with the option of curative therapy at a later date.

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- appropriate treatment

Once diagnosed a referral to a specialist centre (GOSH and Newcastle) is made and appropriate treatments are given. This is the time that parents feel that they are in the best hands with experts that understand the condition and know what to do. This can be a relief to parents but comes with the bewilderment and panic of the seriousness of the condition [see ii below}.

The immediate priority is to provide an environment that protects the child from infection. Possible treatments that can correct the defect such as GT and HSCT [if a suitable match is available] are then discussed with the family. The first stages of treatment and precautions are the same as in all forms of SCID. In ADA-SCID it is possible to replace the missing enzyme using PEG-ADA. It is given as a weekly injection into a muscle, for instance, the thigh muscle. PEG-ADA treatment corrects the ADA and adenosine levels in the blood. Treatment usually leads to gradual improvement and partial correction of immune function. It is used until a more definitive therapy is available.

[redacted] *'He was given synthetically produced ADA-SCID every week, which kept him alive while doctors searched for a bone marrow donor.' Our lives were turned upside down. No one could come round and see us if they had colds and coughs. Basically our family was on lockdown for a whole year.'*

- helpful information about the condition

Both GOSH and Newcastle have information on the condition, HSCT, and gene therapy available for affected families. This is currently being updated in collaboration with PID UK. Booklets available are SCID [available at http://www.piduk.org/static/media/up/SCID.pdf] and ADA-SCID [in production].

(ii) Please describe how patients and their families or carers have to adapt their lives as a result of the condition, and the impact the condition has on the following aspects:

- physical health
- emotional wellbeing
- everyday life (including if applicable: ability to work, schooling, relationships, social functioning)

other impacts not listed above (any impact the condition has had on carers and family members, specifically the ability to work and requirements to update the family home)

Prolonged hospitalisation, separation from extended family, blood tests and uncomfortable procedures will contribute to a great deal of stress and anxiety and even guilt for parents of a child with ADA- SCID. It may be possible for the affected child to go home for a period of time before he or she goes ahead with corrective treatment. Most parents are delighted to get home, but it can be a worrying time. Anxiety about catching or passing on an infection can make life very stressful. The hospital team, nurses and support groups provide guidance

on protecting a child from infection, keeping the house clean and coping with diet and any medication.
The impact is on the whole family including unaffected siblings who may experience anxiety and stress and feelings of jealousy and exclusion as the affected child gets more attention.

One parent giving up work to become a fulltime carer is not uncommon. Loss of income in conjunction with paying for travel for hospital visits and or time off work puts a financial strain on the family. The psychological impact on the family of a diagnosis is profound and can often put a strain on a marriage.

'Our lives were turned upside down. No one could come round and see us if they had colds and coughs. Basically our family was on lockdown for a whole year.'

'This all put a huge strain and worry on the whole family. The uncertainty of it all was very stressful. Once [redacted] *received a diagnosis even though it was terrible we knew that at least he would now receive the care and treatment he desperately needed and the diagnosis also confirmed to us that we were not going crazy, he really did have something wrong with him. I had no idea how serious it was! It was so shocking I had a panic attack and had to leave the ward to get some air.'*

What do patients, their families or carers consider to be the advantages and disadvantages of the technology for the condition?

2. Advantages

(i) Please list the specific aspect(s) of the condition that you expect the technology to help with. For each aspect you list please describe, if possible, what difference you expect the technology to make for patients, their families or carers.

Technology will result in a child developing a functional immune system – less worry about getting infections, ability to have a normal childhood, less concern about being made to feel different, less dependence on medication, able to have vaccinations.

Families – a cure for their child, less stress and concern about their child's future, less worry about infections, removal of feelings of isolation about having a child with a rare condition, not having to explain constantly about their child's condition and need for time off work and hospital appointments, potential to re-enter job market as caring needs are less, improving financial stability of family, reestablishment of normal family life.

(ii) Please list any short-term and long-term benefits that patients, their families or carers expect to gain from using the technology. These might include the effect of the technology on:
- the course and outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (lifestyle, work, social functioning etc.)
- other quality of life issues not listed above
- other people (for example friends and employers)
- other issues not listed above

A cure through the technology offers a improvement of quality of life for the child and their families. See above.

3. Disadvantages

Please list any problems with or concerns you have about the technology. Disadvantages might include:
- aspects of the condition that the technology cannot help with or might make worse
- difficulties in taking or using the technology
- side effects (please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- impact on others (for example family, friends, employers)
- financial impact on the patient or their family (for example cost of travel needed to access the technology, or the cost of paying a carer)

It is our understanding that gene therapy will not reverse any neurological problems associated with ADA-SCID in children who may already have damage due to late diagnosis and not being put on PEG-ADA replacement therapy. Deafness will still persist after gene therapy. We understand that HSCT will also not impact on these complications.

Families travelling to receive STRIMVELIS may have to set up supportive care for other members of the family. This may include care for siblings, care for elderly parents etc and may be have to be covered by a paid carer. Parents will have to take time off work to access treatment for their child and this will have a big financial impact. Employers might not be understanding of the need for time and there may be anxiety of how having time off may influence promotion opportunities for the parent employee.

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4. Are there differences in opinion between patients about the usefulness or otherwise of this technology? If so, please describe them.

5. Are there any groups of patients who might benefit **more** from the technology than others? Are there any groups of patients who might benefit **less** from the technology than others?

Children with ADA-SCID who are unable to find a suitable matched donor for HSCT or for whom a HSCT is deemed too risky will benefit more from this technology.

6. Comparing the technology with alternative available treatments or technologies
NICE is interested in your views on how the technology compares with existing treatments for this condition in the UK.

(i) Please list current standard practice (alternatives if any) used in the UK.

Management of condition - ADA-PEG enzyme replacement therapy – twice weekly into thigh. Antibiotics, antiviral and antifungal medicines to protect against serious infection.

Curative therapies - Allogeneic HSCT
And
Gene therapy clinical trials using lentiviral ADA vector – GOSH.

(ii) If you think that the new technology has any **advantages** for patients over other current standard practice, please describe them. Advantages might include:
- improvement of the condition overall
- improvement in certain aspects of the condition
- ease of use (for example tablets rather than injection)
- where the technology has to be used (for example at home rather than in hospital)
- side effects (please describe nature and number of problems, frequency, duration, severity etc)

Management of ADA-SCID is not enough to ensure good outcomes for children with ADA-SCID affected. Curative therapies either by GT or by HSCT offer a definitive treatment of ADA-SCID.

Gene therapy is a relatively straightforward procedure compared to HSCT and does not require chemotherapy. Those treated with GT spend less time in hospital and as it uses the child's own stem cells there is less risk of GvHD.

(iii) If you think that the new technology has any **disadvantages** for patients compared with current standard practice, please describe them. Disadvantages might include:

- worsening of the condition overall
- worsening of specific aspects of the condition
- difficulty in use (for example injection rather than tablets)
- where the technology has to be used (for example in hospital rather than at home)
- side effects (for example nature or number of problems, how often, for how long, how severe).

We are unaware of any health disadvantages to affected patients and families. The only disadvantage is having to have STRIMVELIS treatment in Milan – see section below.

7. Research evidence on patient, family or carer views of the technology

(i) If you are familiar with the evidence base for the technology, please comment on whether patients' experience of using the technology as part of their care reflects that observed under clinical trial conditions. Were there any unexpected outcomes for patients?

(ii) Are there any adverse effects that were not apparent in the clinical trials but have come to light since the treatment has become available?

PID UK is not aware of any.

(iii) Are you aware of any research carried out on patient, family or carer views of the condition or existing treatments that is relevant to an evaluation of this technology? If yes, please provide references to the relevant studies.

No.

8. Availability of this technology to patients

(i) What key differences, if any, would it make to patients, their families or carers if this technology was made available?

Chance of a cure for their child with a life threatening condition, having a child with a functional immune system removing the stress and anxiety of living in constant fear of infection, less dependence on prophylactic medication, having a child who can feel different and enable them to have a normal and healthy school life and to grow up contributing to society.

(ii) What implications would it have for patients, their families or carers if the technology was **not** made available?

STRIMVELIS gene therapy is an important part of the armoury for the curative treatment of children affected by ADA-SCID when a suitable matched donor is not available for HSCT. Because the technology uses autologous blood stem cells there is a reduced risk of graft versus host disease. These children would be left without the life-line of this treatment option and the chance of a cure and therefore the potential of leading a normal productive life.

(iii) Are there groups of patients that have difficulties using the technology?

No, not to our knowledge.

(iv) Are there any situations where patients may choose not to use this technology?

It is our understanding that STRIMVELIS treatment involves travel to Milan. This would represent a huge upheaval for a family and may have cost implications in terms of family income and having on hand support from family and friends. Cultural differences such as language, approach to healthcare, different foods, dealing with a new healthcare team may be too daunting for some families to handle. For some families this may not present a challenge and they may decide this route to a cure is in the best interest of the child.

For others having gene therapy through clinical trials at GOSH may be a more attractive option as nearer home and more culturally aligned to their needs in an environment where they have already built up a trusting relationship with health professionals. Supportive networks are closer, there may be more potential for one parent still to work and 'normal life' may be easier to maintain.

The important thing is patient choice based on good information and having as many available options as possible.

9. Please provide any information you may have on the number of patients in England with the condition. How many of them would be expected to receive treatment with the technology?

The UK PIN REGISTRY has 28 reported cases of ADA-SCID in England although this is known to be an underestimate due to underreporting.

Based on current knowledge of incidence 6-10 children will present with ADA-SCID per annum, of these most will be eligible for this technology.

Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this evaluation:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which strimvelis is/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

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

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Other Issues

Please consider here any other issues you would like the Evaluation Committee to consider when evaluating this technology.

Survey for families affected by ADA-SCID

NICE is currently undertaking an assessment of a commercial gene therapy medicine for the treatment of ADA-SCID to help understand the value of this treatment option to those affected and their families.

The name of the medicine under assessment is Strimvelis, produced by the company GlaxoSmithKline. At present no-one in the UK has had treatment with Strimvelis but several families have been treated by gene therapy and by a stem cell transplant (a haematopoietic stem cell transplant or BMT).

On the 28th September this year PID UK has been asked to give the patient/carer perspective on the impact of the condition ADA-SCID on families and the impact of having gene therapy for ADA-SCID compared to other treatment options such as stem cell transplant. By completing this survey and sharing your experiences you will help us to give an informed opinion. Please return the survey to Susan at PID UK – [redacted]

Thank you.

Completing the questionnaire

Please fill in sections 1, 2, 3 and 4 and additionally the sections relevant to the treatments your child has received e.g. section 5 and 6 if your child has had a stem cell transplant or sections 7 and 8 if your child has had gene therapy.

Section 1. About you

Please tick all that apply

I am a parent of a child affected by ADA-SCID ☐

My child has had a stem cell transplant to treat their ADA-SCID ☐

My child has had gene therapy to treat their ADA-SCID ☐

My child receives ADA replacement therapy ☐

Section 2. Concerning your child's ADA-SCID did you experience any difficulties or delays in receiving:

A) A diagnosis? Yes/No
B) Appropriate treatment? Yes/No
C) Helpful information about the condition? Yes/No

D) Please describe how these difficulties impacted on your child and family.

Section 3. Assessing the impact of the condition of ADA-SCID on your child.

Please score the effect of the condition on the following aspects using a score of 1 to 10 where 1 would indicate no effect to 10 indicating a severe effect.

A) Their physical health ☐

B) Their emotional well-being ☐

C) Their everyday day life – going to nursery, school, making friends ☐

E) Please describe the problems your child may have had in relation to the above and any other impacts ADA-SCID had on your child.

Section 4. Assessing the impact of the condition of ADA-SCID on parents and family

Please score the effect of the condition on the following aspects using a score of 1 to 10 where 1 would indicate no effect to 10 indicating a severe effect.

A) On your physical health ☐

B) On your emotional well-being ☐

C) On your everyday day life – ability to work, relationships, social interactions ☐

D) Please describe the problems your family may have had in relation to the above and any other impacts ADA-SCID had on your family.

F) Have you had to make any adjustments in your family life/home environment due to your child's condition?

Yes/No

If YES please describe:

Section 5.

This section is for parents of children who received stem cell transplant to treat their ADA-SCID.

A) How long after diagnosis did the stem cell transplant take place?

B) How long did it take to find a suitable donor?

C) Please grade how having a stem cell transplant has impacted on the health and well-being of your child using a score of 1 to 10 where 1 would indicate no effect and 10 would indicate a highly beneficial effect.

1. Improvement of your child's condition overall ☐
2. Physical symptoms ☐
3. Child's emotional well-being and quality of life ☐
4. Any pain or discomfort experienced before treatment ☐
5. Need for other medications ☐
6. Level of disability e.g. hearing problems, behavioral problems ☐
7. Quality of life (school, social interactions etc) ☐

Please give examples of how a stem cell transplant has made a difference to your child.

D) Please grade the overall impact of how having stem cell therapy for your child has impacted on you and the family unit using a score of 1 to 10 where 1 would indicate no effect and 10 would indicate a highly beneficial effect. ☐

Please give examples of how life has changed since stem cell therapy.

C) What key difference does having had stem cell therapy made to your child, you and your family?

D) What implications would it have had for your child and your family if stem cell therapy had not been made available?

E) Did the graft fail or was it rejected? Yes/No

F) Overall how would you grade any disadvantages of having stem cell therapy for ADA-SCID for your child using a score of 1 to 10 where 1 would indicate no disadvantage and 10 would indicate a serious disadvantage.

☐

G) Please describe any disadvantages you may have experienced for your child or your family. These might include aspects of the condition that stem cell therapy couldn't help with or made worse, for example these may include

- difficulties in having stem cell therapy
- any side effects e.g. graft versus host disease
- financial impact on the you or your family (for example cost of travel needed to have the stem cell therapy, loss of earnings, accommodation costs, cost of paying a carer etc)
- were there any unexpected outcomes?

H) What type of donor was used for the stem cell transplant?

Family sibling donor Yes/No If yes please answer questions H1a, b and c

Non-family donor Yes/No If yes please answer questions H2a

H1) Stem cell therapy using a family sibling donor

a) Please grade the overall impact on the health and well-being of your child that donated their stem cells using a score of 1 to 10 where 1 would indicate no effect and 10 would indicate a highly positive effect.

☐

b) Please describe what impact donating stem cells had on the sibling donor e.g. any pain or discomfort before, during or after the procedure, any feelings of anxiety, effects on their emotional well being and quality of life.

c) If the graft failed or was rejected what impact did this have on your affected child, the donor child and your family?

H2) Stem cell therapy using a non-family donor

a) If the graft failed or was rejected graft fail what impact did this have on your affected child and your family?

Section 6

Convenience and advantages of having stem cell transplant as a treatment option

A). In your opinion what are the advantages of having a stem cell transplant for ADA-SCID over other treatment options such as gene therapy or ADA replacement therapy?

Please describe the reasons for your answer above.

Section 7.

This section is for parents of children who have received gene therapy to treat their child's ADA-SCID.

A) How long after diagnosis did the gene therapy take place?

B) Please grade how having gene therapy has impacted on the health and well-being of your child using a score of 1 to 10 where 1 would indicate no effect and 10 would indicate a highly beneficial effect.

1. Improvement of your child's condition overall ☐
2. Physical symptoms ☐
3. Child's emotional well-being and quality of life ☐
4. Any pain or discomfort experienced before treatment ☐

5. Need for other medications
6. Level of disability e.g. hearing problems, behavioural problems
7. Quality of life (school, social interactions etc)

Please give examples of how gene therapy treatment has made a difference to your child.

B) Please grade the overall impact of how having gene therapy for your child has impacted on you and the family unit using a score of 1 to 10 where 1 would indicate no effect and 10 would indicate a highly beneficial effect.

Please give examples of how life has changed since gene therapy treatment.

C) What key difference does having had gene therapy made to your child, you and your family?

D) What implications would it have had for your child and your family if gene therapy had not been made available?

E) Overall how would you grade any disadvantages of having gene therapy for ADA-SCID for your child using a score of 1 to 10 where 1 would indicate no disadvantage and 10 would indicate a serious disadvantage

F) Please describe any disadvantages you may have experienced for your child or your family. These might include aspects of the condition that gene therapy couldn't help with or made worse, for example these may include

- difficulties in having gene therapy
- any side effects
- financial impact on the you or your family (for example cost of travel needed to have gene therapy, loss of earnings, accommodation costs, cost of paying a carer etc)
- were there any unexpected outcomes?

Section 8

Convenience and advantages of having gene therapy as a treatment option

A). In your opinion what are the advantages of having ADA-SCID gene therapy over other treatment options such as stem cell transplant or ADA replacement therapy?

B). If gene therapy treatment for ADA-SCID was not available in the UK. Would you travel abroad to access treatment? Yes/no

Please describe the reasons for your answer above and indicate any challenges you would face.

Thank you. We sincerely value your input and the time taken in completing the survey.

With kind regards,

[redacted]

[redacted]

National Institute for Health and Care Excellence

Highly Specialised Technologies Evaluation (HST)

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ID926 strimvelis PID UK Survey ADA 06092017

Section 1: about you

RESPONDEE	ABOUT YOU	HAS CHILD HAD GT?	HAD HSCT?	CHILD RECEIVES ADA REPLACEMENT THERAPY
Respondee 1	Parent, Father	YES	NO	yes
Respondee 2	Parent, Father (USA)	YES	NO	No
Respondee 3	Parent, Mother, UK	YES	NO	NO

Section 2: Concerning your child's ADA-SCID did you experience any difficulties or delays in receiving

RESPONDEE	DIAGNOSIS	APPROPRIATE TREATMENT	HELPFUL INFO	FREE TEXT
1	yes	yes	yes	Our daughter was born in Poland whilst I was working as an ex pat the hospital and doctors had no experience of testing or looking for SCID. Whilst in hospital in Poland she contracted bacterial pneumonia, rotavirus and sepsis as she was not properly isolated from other sick children. In end we virtually self-diagnosed through google reference her symptoms and then shared our findings with the Polish Doctors who confirmed our daughter has SCID but they misdiagnosed it as a non ADA form of SCID. Luckily we managed to get my daughter medically evacuated by jet to GOSH where they immediately diagnosed [redacted] correctly.
2	No	No	No	No text supplied
3	yes	yes	no	[redacted] wasn't diagnosed until she was 2 years old and by then she had suffere a lot through infections/pneumonia and other complications. This has had an impact on her future health and traeting her by the usual means of BMT was not possible intially and was still not the preferred option later on

Section 3: impact of ADA-SCID on your child's

Comment 1: Score out of 10

	PHYSICAL HEALTH	EMOTIONAL WELL-BEING	EVERYDAY DAY LIFE	FREE TEXT	FREE TEXT - OTHER IMPACTS
1	10	10	10	[redacted] remained in isolation away from mainstream nursery until she was almost 4 years old, we also had to keep her sister out of school for fear of bringing home illnesses whist [redacted] was recovering at home after her treatment for 1 year	[redacted] suffers from permanent hearing loss in high range frequencies which has affected her speech. She struggles to put on weight and is exceptionally small for her age. [redacted] was very late in speaking and had trouble eating any solid food due to the lack of muscle development in her face. She will need to take penicillin for the rest of her life.
2	1	1	8	Our daughter was diagnosed within 10 days of birth so we were able to find treatment and get her on preventative medication by the time she was 1 month old. Although she has been unable to be out in public with other children and has yet to meet most of her family, she is healthy and happy.	

3	10	10	8	[redacted] struggled at school due to time off for weekly infections and other appointments.She ended up repeating her last year of primary school to catch up. Due to her ADA not being picked up early enough she has been left with life-long lung issues and serious kidney problems, as well as the issue SCIDs bring. Emotionally, especially as getting older she struggled with what had to happen to her.	

Section 4: Impact on parents

	PHYSICAL HEALTH	EMOTIONAL WELL-BEING	EVERYDAY DAY LIFE	FREE TEXT	AJUSTMENTS TO HOME
1	10	10	10	My wife almost has a total breakdown due to the strain and worry. I almost lost my job due to the time needed to support my wife and to be present in hospital with [redacted]. We had to leave our other daughter in Poland with her grandmother for 6 months so we were split up as a family. We had to rent a new house on 3 floors so we could create a sterilization zone for when [redacted] was recovering at home. We had no social interaction for almost 2 years and had to avoid any crowds , public transport or groups of children and anyone unwell – family members included	yes
2	3	7	9	We were both lucky enough to have the option of working from home, as well as having parents who have all retired and could act as nannies in our home. Without this, I don't know how we could have coped without depleting all of our savings and incurring severe emotional distress. Dealing with a child is stressful without any additional concerns, and it has been a trying experience to keep everyone calm and at peace.While most of our friends and associates have been supportive and understanding, separating oneself from society for 6 months is a taxing mental and physical experience. We would happily have lived in a bubble for this time without talking to anyone at all if it meant that our daughter could live a happy and healthy life, but the experience has taken a toll on our levels of stress.	yes As mentioned above, we have largely isolated ourselves from outside contact except when necessary, and one of us has always been at home with the baby. On it's own this isn't that different than many parents' experience but we have also had to avoid anyone with illnesses, eschew visitors, wash our hands with alcohol constantly, and worry in the extreme at every cough or sneeze.

3	10	10	10	Myself and [redacted]'s dad separated shortly after her diagnosis. I suffered from anxiety and always had a constant sense of a huge weight on my shoulders.	Yes. When [redacted] was isolated and at her sickest we had to isolate her from friends/family i.e.no-one allowed to come visit us at all, no children around her. Clean house always.

Section 7: Impact of gene therapy

Comment 1: Score out of 10

NO.	HOW LONG AFTER DIAGNOSIS DID GT TAKE PLACE?	IMPROVEMENT OF CHILD'S CONDITION OVERALL	PHYSICAL SYMPTOMS	CHILD'S EMOTIONAL WELL-BEING	ANY PAIN OR DISCOMFORT EXPERIENCED BEFORE TREATMENT	NEED FOR OTHER MEDS	LEVEL OF DISABILITY E.G. HEARING PROBLEMS, BEHAVIOURAL PROBLEMS	QUALITY OF LIFE (SCHOOL, SOCIAL INTERACTIONS ETC)	OVERALL IMPACT OF GT ON YOUR CHILD AND THE FAMILY UNIT
1	9 months	10	9	10	10	10	8	8	10
2	5 months (at 6 months old)	10	10	10	7	5	9	9	10

3	approx 1 year after initial diagnosis and then attempted again 10 years later.	10	10	10	10	8	8	10	10

1:

how gene therapy treatment has made a difference?

" Our daughter is alive and now attends a nursery school without us having to take any special precautions"

how life has changed

"Now we have both our daughter alive and our lives back on track we now operate as a normal family unit. "

Key difference GT has made

as last answer

2:

how gene therapy treatment has made a difference?

The moment she came home from isolation in the hospital was equivalent in excitement and relief to the moment she came home from the hospital after birth.

how life has changed

We have spent every day since we learned of her condition in a constant state of fear. We aren't free of that worry yet and likely never will be but each day gets a little easier.

Key difference GT has made

Normalcy. Our child will live, and will live like a normal child.

3:

how gene therapy treatment has made a difference?

[redacted] no longer has to get weekly injections or 3 weekly transfusions. This has helped a lot with her school life and emotionally

how life has changed

We now plan for the future and can arrange things like holidays etc. We no longer worry about her catching illneses she may not have coped with before. She has no limits on her whatsever.

Key difference GT has made

We can imagine a future with [redacted] in it. I cannot put into words how the thought of losing her affected us, it has given us and her own lives back.

Section 8: Advantage of gene therapy

	ADVANTAGES OF GT OVER OTHER TREATMENT OPTIONS SUCH AS STEM CELL TRANSPLANT OR ADA REPLACEMENT THERAPY	IF GENE THERAPY TREATMENT FOR ADA-SCID WAS NOT AVAILABLE IN THE UK. WOULD YOU TRAVEL ABROAD TO ACCESS TREATMENT?	FREE TEXT - REASONS
1	It is a great option where you have no donor or a poor donor match. The chemotherapy is very mild The overall treatment for the child is very non-intrusive and pain free If it fails you can still pursue a bone marrow donor option whereas if you have a bone marrow donor first and it fails you cannot have gene therapy	yes	Our daughter was dying we would have sold out house and everything we own to give her a fighting chance of life. We told ourselves that even if [redacted] died by following the course of gene therapy the doctors could learn more so that one day other children could be treated and live .
2	We were informed that all other treatments would require a longer wait before our daughter's immune system would begin to recover. With this disorder, every additional day is another chance for a severe infection.	yes	I would travel to any country required to get this treatment.
3	ADA replacement therapy may only work for so long if your child has a good response to it. Gene therapy is a far less invasive an long treatment option with less risks than BMT.	YES	If there is a chance to do a treatment for your child that is less demanding on them, guaranteed to not make them sick or put pressure on other parts of them already weak and stressed bodies, you'd travel the world to make them better.

Appendix D – NHS organisation statement template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Strimvelis for treating severe combined immunodeficiency caused by adenosine deaminase deficiency

Thank you for agreeing to give us your views on the technology and the way it should be used in the NHS.

Commissioners provide a unique perspective on the technology, which is not typically available from the published literature. NICE believes it is important to involve NHS organisations that are responsible for commissioning and delivering care in the NHS in the process of making decisions about how technologies should be used in the NHS.

To help you give your views, we have provided a template. The questions are there as prompts to guide you. You do not have to answer every question. Short, focused answers, giving a commissioners perspective on the issues you think the committee needs to consider, are what we need.

About you

Your name: Edmund Jessop

Name of your organisation NHS England

Please indicate your position in the organisation:

- commissioning services specific to the condition for which NICE is considering this technology

Links with, or funding from the tobacco industry - please declare any direct or indirec links to, and receipt of funding from the tobacco industry:

None

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there a specialised or highly specialised service provision? Is there significant geographical variation in current practice? Are there differences in opinion between professionals as to what current

practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

ADA SCID is currently treated by the NHS under a Highly Specialised Services specification at either Newcastle Children's hospital or Great Ormond Street hospital (GOSH). Standard treatment is haemopoietic stem cell transplant (HSCT). Where no suitable donor is available patients are treated under the gene therapy programme at GOSH. Patients are usually treated with pegylated ADA while awaiting definitive treatment.

Under the national service there are no geographical variations in practice and there are no substantive differences between the teams at Newcastle and GOSH about what current practice should be.

Following a request for further clarification from NICE surrounding patients treated under the gene therapy programme at GOSH, NHSE state:

State of play of the lentiviral programme is as follows:
Initial lenti trial was completed and recruited 20 patients (10 on trial and 10 off trial. Success was very high and during this, the programme was licensed to Orchard therapeutics with a view to make it a licensed product. As a part of the road to license, a second study using the same vector but with a cryopreserved formulation (so as to allow access to patients in different locations) is in the process of being initiated (est. to open Oct 2017). In the meantime, 2 patients have been treated off trial with the cryo formulation out of clinical need. A third is awaiting treatment. The cryo study remains sponsored by GOSH but is funded by Orchard, hence the OTL 101 designation.

To what extent and in which population(s) is the technology being used in your local health economy?

- is there variation in how it is being used in your local health economy?
- is it always used within its licensed indications? If not, under what circumstances does this occur?
- what is the impact of the current use of the technology on resources?
- what is the outcome of any evaluations or audits of the use of the technology?
- what is your opinion on the appropriate use of the technology?

This technology (Strimvelis) is not in current use in the NHS.

Potential impact on the NHS if NICE recommends the technology

What impact would the guidance have on the delivery of care for patients with this condition?

Dependent on the NICE evaluation Strimvelis appears to offer an alternative treatment option but with no impact on the delivery of care for patients with ADA SCID since there is no unmet need in England.

Appendix D – NHS organisation statement template

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Would there be any requirements for additional resources (for example, staff, support services, facilities or equipment) to enable this technology to be used?

The key additional resource would be the cost of treatment in Milan and the cost of travel for patient and parent(s) to Milan. Arrangements for follow up, after care and management of complications if any would also need to be explicit.

Can you estimate the likely budget impact? If this is not possible, please comment on what factors should be considered (for example, costs, and epidemiological and clinical assumptions).

At present about two patients per annum present with ADA SCID and no suitable HSCT donor. These patients are treated under the GOSH gene therapy programme at the same marginal rate as we pay (reimburse) for HSCT.

It is however important to note that the GOSH gene therapy product is currently being commercialised. At commercial launch, the publicly declared price is likely to be considerably greater than the amount currently paid per patient by NHS England.

Would implementing this technology have resource implications for other services (for example, the trade-off between using funds to buy more diabetes nurses versus more insulin pumps, or the loss of funds to other programmes)?

The trade off would be against other proposals in the contemporaneous prioritisation round.

Would there be any need for education and training of NHS staff?

The NHS already has experience in gene therapy for SCID but this particular technology is new.

Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this evaluation:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which treatment is licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

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

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Strimvelis for treating severe combined immunodeficiency caused by adenosine deaminase deficiency

None

Other Issues

Please include here any other issues you would like the Evaluation Committee to consider when evaluating this highly specialised technology?

The critical budget issue is the comparator – namely the current and future cost to NHS England of treating ADA SCID in the GOSH gene therapy programme.

There have been some initial helpful discussions between NHS England and the drug company about commissioning/contracting for the patient's stay in Milan. The arrangements would need to be very clear prior to a patient being referred.

In response for further clarification from NICE on commissioning/contracting for the patient's stay in Milan, NHSE state:

There are no major issues with Milan; the outstanding issue is around how the contract between Milan and NHS England would operate. NHS England would expect to pay for the service as a public sector commissioner and the contract would need to be managed within NHS England's usual financial processes.

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Highly Specialised Technology Evaluation

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

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed 12 pages.

About you

Your name: Prof. Alessandro Aiuti

Name of your organisation : San Raffaele Hospital, Milan, Italy

Are you (tick all that apply):

- **X** a specialist in the treatment of people with the condition for which NICE is considering this technology?
- **X** a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)?
- other? (please specify)

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What is the expected place of the technology in current practice?
The technology under evaluation (Strimvelis) is a gene therapy based medicine consisting of autologous CD34+ stem/progenitor cells engineered with a retroviral vector encoding a normal copy of the ADA gene. Strimvelis is intended to be administered on a single time and is meant to provide corrective genetic modification of patients' bone marrow stem cells. Since CD34+ stem/progenitor stem cells are able to engraft in the bone marrow and repopulate the hematopoietic system, they can act as a source of circulating or resident hematopoietic producing pharmacologically active levels of intracellular ADA enzyme, enabling to restore immune function life long. Considering that Strimvelis is based on reinfusion of autologous cells, it requires only a low intensity conditioning and there is no need of immune suppression. Thus, it is expected that it could be offered to the large majority of ADA-SCID patients for whom a matched sibling donor is not available (up to 80% of the patients).

How is the condition currently treated in the NHS?
ADA-SCID is a life-threatening disease, typically fatal within the child's first years of life if untreated. According to current practice, a patient with SCID is immediately started with anti-microbial therapy/prophylaxis and human immunoglobulin infusion. Following diagnosis of ADA-deficiency by enzymatic testing (and confirmed subsequently by genetic testing), usually enzyme replacement therapy (PEG-ADA) is started to stabilize the patient and provide metabolic detoxification. At the same time, if a healthy sibling is available in the family he/she is also immediately HLA-typed and in case of full matching, allogeneic transplantation is performed. In consanguineous families fully matched donors can be occasionally found also beyond siblings (in parents or close relatives). Allogeneic transplantation from a matched sibling donor is usually given without preconditioning, thanks to the selective advantage for the lymphoid lineage. However, there is still discussion on whether a reduced intensity conditioning would be preferable to provide also stem cell engraftment.
Since the probability of having an HLA-identical sibling available for transplantation is about 20% the remaining patients are proposed alternative curative treatments.
In Italy patients without an HLA-identical sibling donor are proposed treatment with Strimvelis according to EBMT guidelines
For patients who are not suitable to receive Strimvelis (see below) or who have failed gene therapy, a matched unrelated donor (MUD) search is started while the patient is maintained on enzyme replacement therapy. Haploidentical transplantation is considered only if no MUD is available.
In the UK, the policy is similar but, to my knowledge, patients without an HLA-identical sibling donor are usually enrolled in a clinical trial with lentiviral vector mediated gene therapy (at Great Ormond Street Hospital (GOSH), London) and in the past have been offered compassionate use /hospital exemption with experimental lentiviral gene therapy.

Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be?
The general tendency is to provide a definitive treatment of the disease by gene therapy or allogeneic transplantation. There are two main reference centers in the

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Highly Specialised Technology Evaluation

UK, Newcastle and GOSH. Since Strimvelis is currently not available in the UK, lentiviral mediated gene therapy is offered as an experimental treatment at GOSH.

What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?
In the absence of an HLA-identical sibling donor (treatment of choice), enzyme replacement therapy with bovine enzyme (PEG-ADA) is usually given to provide rapid detoxification to the patient and initial immune recovery. However, PEG-ADA is less suitable for long-term use due to incomplete immune reconstitution, evidence of declining efficacy over time, and risk of anti-ADA autoimmunity. PEG-ADA requires weekly injections and its costs over a subject life span are also considerably higher than Strimvelis. Finally, PEG-ADA provides external detoxification while Strimvelis provides stable intracellular ADA enzyme to immune cells.
Allogeneic transplantation from an unrelated donor is an established procedure that leads to a definitive cure. It can be performed in UK reference centers for primary immunodeficiencies (GOSH, Newcastle). Unlike a patients treated for Strimvelis, the family will not need to travel in Italy, but still will have to move in most cases for a few months to the reference center. Survival for ADA-SCID patients undergoing matched unrelated donor is reported to be lower (67%, Hassan et al. Blood 2012) than Strimvelis (100%). Moreover, patients undergoing transplantation are at risk of GVHD, infections due prolonged immune suppression and toxicity due to high dose chemotherapy.
Allogeneic transplantation from a mismatched related donor is performed for other types of SCID and is improving under new experimental approaches to reduce risk of rejection and GVHD. It is currently rarely performed in the UK (or Italy), also due to the previous history of higher morbidity and mortality rate in the Hassan paper.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? *Patients who experience early organ damage due to infections may have sequelae which may impact their quality of life. Patients with late onset form may develop symptoms in infancy, often milder immunodeficiency, but may develop autoimmune manifestations or other non immunological problems.*

Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology? *Gene therapy could potentially benefit all subgroups, from early onset to late onset. Differences in age at treatment could impact the ability to collect sufficient amount of autologous CD34+ cells, with older patients usually having a lower cell content in the bone marrow.*

What is the likely impact of the technology on the delivery of the specialised service? Would there be any requirements for additional staffing and infrastructure, or professional input (for example, community care, specialist nursing, other healthcare professionals)?
At present Strimvelis is not available in the UK, and patients would be required to travel to Italy to receive the product. To my knowledge there are two main centers in the UK (Dr. Gaspar, GOSH and Dr. Gennery, Newcastle) which diagnose a SCID patient and both have a strong knowledge of the disease and of the current treatment guidelines. These centers have all the expertise to refer patients, perform initial screening tests and follow the patients once they return to UK. In my opinion I do not see the need for additional resources for the current approach. The only specific

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tests that are not part of routine testing for bone marrow transplantation is the measurement of transduction after gene therapy, which is a molecular test, PCR based. Since GSK has informed us that is developing a cryopreserved formulation, the future administration of the cryopreserved product could be envisaged in the same highly qualified centers that perform allogeneic transplantation and have experience with managing the disease, as the requirement are similar.

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur? *Not applicable*

Please tell us about any relevant clinical guidelines and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.
The most relevant guidelines the from joint ESID and EBMT, Inborn error Working Party. *(https://www.ebmt.org/Contents/Research/TheWorkingParties/IEWP/Documents/ESID%20EBMT%20HSCT%20Guidelines%202017%20%281%29.pdf)*
The guideline was developed by the Inborn Error Working group to advice transplant centers in Europe on how to manage patients with inborn error disease, including primary immunodeficiencies. A general discussion on the principles of guideline revision occurred at the 2016 meeting of the Inborn Error meeting held in Leiden Nov 4-6 (chairmen Dr AR Gennery, Local chair V. Bordon). The conclusion of the discussion was that gene therapy should be proposed as a second line treatment, after excluding an HLA matched sibling donor in the family. A revised flow chart describing this concept and the proposed recommendations in case of failure or unavailability of gene therapy was drafted by a restricted group (Dr. A. Gennery, Dr. A. Lankaster (Leiden), Dr HB Gaspar, Dr. C. Booth (GOSH), Dr. A. Aiuti). The draft was circulated in February to the whole Inborn Error group and finally adopted at the meeting of EBMT meeting of Marseille (March 2017) the draft was presented, adopted by the group and published on the website.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

Strimvelis is based on the same principle of autologous transplantations and therefore there would be no special requirements in a center that routinely performs allogeneic and autologous transplantation for genetic diseases and has experience in primary immunodeficient patients. The patients undergoes typical procedures associate with transplantation such as central line placement, bone marrow aspiration, bone marrow harvest. If the treatment will be available directly in the UK with the cryopreserved formulation, an adequate collection of bone marrow CD34+ cells will be important to be achieved to guarantee a good dose at infusion of

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Strimvelis. The only specific tests that are not part of routine testing for bone marrow transplantation is the measurement of transduction after gene therapy, which is a molecular test, PCR based.

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

Differences in age at treatment could impact the ability to collect sufficient amount of autologous CD34+ cells, with older patients usually having a lower cell content in the bone marrow. Although never observed in our clinical trial, another relevant excluding condition is represented by myelodysplasia or karyotypic alterations.
If a patient has acquired infection with HIV, HBV or HCV it is not eligible for Strimvelis treatment. An HCV patient successfully treated with new antiviral drugs may become eligible.

[redacted]

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

The circumstances in which the clinical trials were conducted reflect UK experience and were quite conservative. Patients were enrolled only if they had failed PEG-ADA (as assessed by immunological parameters) or had intolerance, allergy or had no access to PEG-ADA. Most patients included in the integrated population (n=15) were on PEG-ADA with unsuccessful response and four underwent haploidentical transplantation from a parent (without conditioning) who had failed due to lack of engraftment. Although the clinical trial was conducted in Italy, patients management during the trial and long-term follow up was similar to UK practice, including use of prophylactic drugs, IVIg, growth factor in case of prolonged neutropenia, vaccination policy.

With an experience of more than 16 years we have observed an excellent clinical outcome in the majority of patients (overall survival of 100%) treated with Strimvelis. with a positive safety profile. A total of five (out of 22 patients) required initiation of PEG-ADA or allogeneic transplantation (3 out 18 at the data data cut off of May 2014). Patients treated successfully with Strimvelis had significant reduction in severe infections, improvement in T cell counts, functional restoration of immune system. Moreover, they displayed normal growth for age and most were able to enter and maintain attendance to school or pre-school.
What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's

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quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

The safety findings observed after Strimvelis were in line with those expected in an ADA-SCID population that has undergone busulfan conditioning and is undergoing immune reconstitution. The most frequent Serious Adverse Events were infections (CVC-related infections, gastroenteritis, and pneumonia), which is expected due to the transient neutropenia after chemotherapy and temporary reduction in lymphocyte counts after PEG-ADA discontinuation. The majority of severe infections were reported during the 3-month to 3-year treatment phase, which is not unexpected as immune reconstitution occurs over time. Adverse events likely related to chemotherapy were cytopenias, mild increased liver enzymes and hypertension. On the other hand, we did not observe the usual complication of allogeneic transplantation (ie VOD, GVHD, severe mucositis requiring parenteral nutrition) which are associate to donor-recipient disparity and high dose chemotherapy. The 3 most frequently reported infection adverse events were infections (URTI, gastroenteritis, rhinitis) which are usual in childhood.
Most patients had neurologic or hearing impairment adverse events reported (before or after gene therapy) and Strimvelis does not seem to have an impact on the neurological issues, similarly to what observed for PEG-ADA and allo-transplantation. Finally, autoimmune SAEs were reported in five patients, which all resolved. The most relevant one were Guillain-Barré syndrome in one patient; 2 autoimmune thrombocytopenia events in a single patient; autoimmune aplastic anaemia, aplastic anaemia, and autoimmune hepatitis in another patient. These and the other autoimmune AE observed may be related to the fact that immune dysregulation may occur while immune function is progressively restored.

[redacted]

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

[redacted]

As of August 9th 2017, the survival is 100%. In total, 5 patients have required >3 months of ERT and/or HSCT. There have been no incidences of leukaemia or myelodysplasia reported following gene therapy with Strimvelis.

[redacted]

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Since the data cut off of May 2014, two additional patients have discontinued IVIg use, resulting in a total of 14 out of 18 patients of the integrated dataset who discontinued IVIg throughout the programme with positive antibody response to vaccination.
In the two patients treated under the named patient program in whom gene therapy was successful, IVIg have been discontinued with positive antibody response in one patient and are being discontinued in the other patient.

[redacted]

Implementation issues

Following a positive recommendation, NICE will recommend that NHS England provide funding for the technology within a specified period of time.

If the technology is unlikely to be available in sufficient quantity or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within the specified period of time, NICE may advise NHS England to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

At present Strimvelis is not available in the UK, and patients would be required to travel to Italy to receive the product. To my knowledge there are two main centers in the UK (Dr. Gaspar, GOSH and Dr. Gennery, Newcastle) which diagnose a SCID patient and both have a strong knowledge of the disease and of the current treatment guidelines. These centers have all the expertise to refer patients, perform initial screening tests and follow the patients once they return to UK. In my opinion I do not see the need for additional resources for the current approach. The only specific tests that are not part of routine testing for bone marrow transplantation is the measurement of transduction after gene therapy, which is a molecular test, PCR based. Since GSK has informed us that is developing a cryopreserved formulation, the future administration of the cryopreserved product could be envisaged in the same highly qualified centers that perform allogeneic transplantation and have experience with managing the disease, as the requirement are similar.

Equality and Diversity

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this evaluation:

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- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment is/are/will be licensed;
- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

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

Considering that Strimvelis is not currently available in the UK, to guarantee its availability to all people, patients and their family (especially families with lower income or with numerous number of people), should be helped in the travel, logistics and overall care to guarantee their well being.

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

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed 12 pages.

About you

Your name: Dr Claire Booth

Name of your organisation UCL GOS Institute of Child Health/Great Ormond Street Hospital

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? YES
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? YES
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)? YES
- other? (please specify)

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What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

What is the likely impact of the technology on the delivery of the specialised service? Would there be any requirements for additional staffing and infrastructure, or professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

- Currently patients with a diagnosis of ADA-SCID commence on PEG-ADA (enzyme replacement therapy) to allow detoxification and stabilisation of clinical status. Active infections will be treated appropriately and patients receive supportive therapy including with prophylactic anti-microbial agents and immunoglobulin replacement therapy. These are continued until, and for some time after, haematopoietic stem cell transplant (HSCT).

- If an HLA-identical family donor is available current practice is to proceed with unconditioned infusion of HSCs.

- If an HLA-identical family donor is not available the patient is eligible to participate in a clinical trial of lentiviral mediated gene therapy available at GOSH. This involves cytoreductive preparative chemotherapy (low dose busulfan).

- If a patient has no HLA-matched family donor and is not eligible for a clinical trial of gene therapy they may proceed to a matched unrelated donor HSCT or mismatched HSCT which carried increased risks of mortality and involves chemotherapy conditioning.

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- The condition is managed in one of two centres commissioned to provide HSCT for primary immune deficiencies (GOSH and Great North Children's Hospital Newcastle) and there is no geographical variation in management. Both centres are guided by the EBMT (European Society for Blood and Marrow Transplantation) guidelines for treating ADA-SCID which is based on published outcome data and extensive clinical experience in numerous European centres.

- Long term ERT with PEG-ADA is not considered a feasible treatment option.

- As mentioned above, Phase I/II clinical trials of lentiviral mediated autologous CD34+ stem cell gene therapy are underway in the UK, based at GOSH. 49 patients have been treated between the parallel sites of GOSH and UCLA with 100% survival. The vector used in this trial is a lentiviral vector which differs in several ways to the gammaretroviral vector used in Strimvelis. Most open gene therapy clinical trials for several primary immune deficiencies (PID) employ self-inactivating lentiviral vectors, as evidence suggests these vectors have an improved safety profile in terms of insertional mutagenesis (oncogenesis related to integration of a vector close to or affecting expression of oncogenes).

- In terms of delivery of specialised services, my understanding is that patients receiving Strimvelis are required to undergo treatment in Milan and will stay in Milan for a period of months until haematopoietic recovery following conditioning. This would be a significant disadvantage in terms of cost of delivery of treatment and disruption to the families, compared to the current treatment algorithm.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the

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trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

- As mentioned above, my understanding is that currently patients receiving Strimvelis are required to undergo treatment in Milan and will stay in Milan for a period of months until haematopoietic recovery following conditioning, which has practical implications for patients and families. I would expect that follow up of patients post treatment is similar to that for patients post-HSCT.

- Given the nature of this advanced therapy regular monitoring will be required as there is a potential risk of cancer related to the gene therapy procedure. Gammaretroviral vectors have been associated with the development of leukaemia and myelodysplasia in a number of previous clinical trials. However, over 40 patients with ADA-SCID have been treated in the past with gammaretroviral vectors with no reports of leukaemia of vector related toxicity to date. Patients treated with this vector have documented integrations in genetic loci associated with oncogenesis in previous trials and are therefore monitored.

- The clinical trial conditions reflect clinical practice. It was well conducted with appropriate endpoints and outcome measures.

- The results of 18 patients treated with Strimvelis (12 in a pivotal trial, 6 as pilot patients or compassionate use) show 100% overall survival with reduced frequency of infections. 92% of the 12 pivotal trial patients demonstrated intervention free survival (82% when 17 patients evaluated) meaning they did not require HSCT or to restart PEG-ADA. T cell numbers and function improved following treatment as did NK cell numbers although they remained generally below the normal range. TRECs levels also improved. 58% of treated patients were able to stop immunoglobulin therapy. Evidence of autoimmunity was seen in 67% of patients. (Data available through EMA website).

- The results suggest that some patients will require lifelong immunoglobulin replacement therapy, which can impact on quality of life and has cost implications. Some patients required a further procedure (HSCT) or to re-start ERT this also has cost implications and significant effect on patient and family quality of life.

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Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

Implementation issues

Following a positive recommendation, NICE will recommend that NHS England provide funding for the technology within a specified period of time.

If the technology is unlikely to be available in sufficient quantity or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within the specified period of time, NICE may advise NHS England to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

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How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

- If patients are required to travel to Milan for treatment then this has little implications for service provision in the UK

- If the treatment becomes available in the UK patients could be treated at the two commissioned centres in the UK where HSCT for PID is undertaken with little impact on delivery of care or resource use. Patients should still be treated and followed up in specialised centres with expertise in the disease.

Equality and Diversity

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this evaluation:

- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment is/are/will be licensed;
- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

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

N/A

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

Thank you for agreeing to give us your views on the technology and the way it should be used in the NHS.

Patients, carers and patient organisations can provide a unique perspective on the technology, which is not typically available from the published literature.

To help you give your views, we have provided a template. The questions are there as prompts to guide you. You do not have to answer every question. Please do not exceed 12 pages.

About you

Your name: [redacted]

Name of your organisation:

Brief description of the organisation:
(*For example: who funds the organisation? How many members does the organisation have? What proportion of the total English patient population does this represent?)*

Are you (tick all that apply):

- a patient with the condition for which NICE is considering this technology?
- ✓ a carer of a patient with the condition for which NICE is considering this technology?
- an employee of a patient organisation that represents patients with the condition for which NICE is considering the technology? If so, give your position in the organisation where appropriate (e.g. policy officer, trustee, member, etc)
- other? (please specify)

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How does the condition impact on patients, their families or carers?

Please describe whether patients experience difficulties or delays in receiving:
- a diagnosis
- appropriate treatment
- helpful information about the condition

and the impact these difficulties have on patients and their families or carers.

If you have GP's who aren't knowledgable about the symptoms of SCIDS or not picking up the regular trips for antibiotics, concerns etc, this can result in every visit and symptom being treated but the child not being referred for further investigation which could lead to a quicker diagnosis.

This can also lead to difficulties in appropriate treatment due to damage already being done due to the effects of SCIDS.

There is helpful information out there, what I would add is that offering counselling during and after diagnosis would be beneficial. You have a child which you know is ill but at the time of diagnosis, you don't really understand the severity due to the shock and disbelief, having someone to talk to would help a lot.

My daughter was 2 before she was diagnosed with SCIDS. This was after numerous visits to GP's, having kidney failure, bouts of pneumonia, numerous chest infections. All we wanted was someone to take heed and the frustration of constantly repeating yourself to different doctors and GP's when you know something is wrong with your child is almost as much stress as when you finally know what is wrong. Probably more so. I was once even called an overprotective mother. Due to all of this, [redacted] was never going to be able to be treated the conventional way by BMT.

Please describe how patients and their families or carers have to adapt their lives as a result of the condition, and the impact the condition has on the following aspects:
- physical health
- emotional wellbeing
- everyday life (including if applicable: ability to work, schooling, relationships, social functioning)
- other impacts not listed above

Everything is affected with a diagnosis of SCIDS. Your world is literally turned upside down and is not normal for a long long time. The impact of stress on the family and individuals is immense.
My daughters emotional health became obviously affected as she got older and more aware of her condition and many hospital visits and treatments. She was kept away from other children until the age of 4, when she did start nursery, the teachers had to help her adapt to wanting to play with the children rather than the adult teachers, adults were all she was used to at this stage. Schooling gets affected due to time off for appointments, My daughter has ended up repeating her last year at Primary school due to time off for treatment. Although it means it has helped her to catch up, being a year older than her peers at this age and them knowing she was 'kept back' had a negative effect on her for a while.

Personally, my relationship with my daughter's father starting breaking down even before diagnosis due to the strain of having a sick child and knowing something was wrong and having to watch her suffer terribly with severe illnesses before we even knew she had SCIDS. After diagnosis, you then had the strain of having to think about what lay ahead in terms of treatment, life changes, myself giving up my job, it was all too much.
Relations with family and friends suffer also. You are either in a hospital environment or your home is a sterile environment and you need to keep your child away from people. Friends drift away and don't return and family take offence at you trying to keep your child 'safe' and don't understand why they can't be allowed to visit.
With your own physical health, the stress of being outwardly strong for your child and to be able to put on a front can have a huge effect on your own personal health and well being. Anxiety is a huge emotion to have to deal with.

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What do patients, their families or carers consider to be the advantages and disadvantages of the technology for the condition?

Advantages

Please list the specific aspect(s) of the condition that you expect the technology to help with. For each aspect you list please describe, if possible, what difference you expect the technology to make for patients, their families or carers.

The overall immune system. This technology is a safer, less risky, less harsh. Again, the difference to patients and their families is greater than I could put to words.

Please list any short-term and/or long-term benefits that patients, their families or carers expect to gain from using the technology. These might include the effect of the technology on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (lifestyle, work, social functioning etc.)
- other quality of life issues not listed above
- other people (for example friends, employers)
- other issues not listed above.

The benefits are life changing. Children will be able to mix with other children, be in crowded areas, go to nursery/school, see family and friends, the whole quality of life is changed. I know from personal experience everything from emotional wellbeing, physical appearance, quality of life, I could go on but I don't actually think I can put into words how life changing the benefits can be.

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Disadvantages

Please list any problems with or concerns you have about the technology.
Disadvantages might include:

- aspects of the condition that the technology cannot help with or might make worse.
- difficulties in taking or using the technology
- side effects (please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- impact on others (for example family, friends, employers)
- financial impact on the patient and/or their family (for example cost of travel needed to access the technology, or the cost of paying a carer).

I can't think of any disadvantages or concerns. There is the aspect of financial and impact on family, work but you would get this with any other treatment.

Are there differences in opinion between patients about the usefulness or otherwise of this technology? If so, please describe them.

I would not say so.

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Are there any groups of patients who might benefit more from the technology than others? Are there any groups of patients who might benefit less from the technology than others?

My daughter has kidney issues which made treating her with a BMT too risky. This gave her another option where she would not have had any and I know personally she is not the only patient like this. There are children who do not have a good match for a BMT or have other health issues which make other treatments seriously risky. There are children who are seriously unwell and literally cannot survive being made sicker.

I suppose children who have a good match for BMT IE siblings have another option but I would not say they would benefit less.

Comparing the technology with alternative available treatments or technologies

NICE is interested in your views on how the technology compares with existing treatments for this condition in the UK.

Please list any current standard practice (alternatives if any) used in the UK.

I do not know of any other than the treatment she received herself.

If you think that the new technology has any **advantages** for patients over other current standard practice, please describe them. Advantages might include:

- improvement in the condition overall
- improvement in certain aspects of the condition
- ease of use (for example tablets rather than injection)
- where the technology has to be used (for example at home rather than in hospital)
- side effects (please describe nature and number of problems, frequency, duration, severity etc.)

Side effects,I would say, is the most advantage to this technology. My daughter was not sick at all, there was no need for blood products, extra nursing, intervention with feeding, the only way you could tell she had had the treatment was that she had lost her hair.
The side effects were minimal, she lost weight but I would say this was more due to the dislike of hospital food and being in a hospital room than due to side effects of the treatment. After her treatment, the difference in her after a few weeks at home was incredible. For the first time in years she put on weight and is now at the size of clothes she should be wearing rather than wearing3 year sizes below. There was no need for weekly injections after the treatment, the most she has had are blood tests and these are now only 6 monthly. There was an increase slightly in medicines for a while after treatment but even these are now at a minimal.

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If you think that the new technology has any **disadvantages** for patients compared with current standard practice, please describe them. Disadvantages might include:

- worsening of the condition overall
- worsening of specific aspects of the condition
- difficulty in use (for example injection rather than tablets)
- where the technology has to be used (for example in hospital rather than at home)
- side effects (for example nature or number of problems, how often, for how long, how severe).

I honestly cannot list any.

Research evidence on patient or carer views of the technology

If you are familiar with the evidence base for the technology, please comment on whether patients' experience of using the technology as part of their routine care reflects that observed under clinical trial conditions.

Are there any adverse effects that were not apparent in the clinical trials but have come to light since the treatment has become available?

No, not that I am aware of so far.

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Are you aware of any research carried out on patient, family or carer views of the condition or existing treatments that is relevant to an evaluation of this technology? If yes, please provide references to the relevant studies.

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Availability of this technology to patients in the NHS

What key differences, if any, would it make to patients, their families and/or carers if this technology was made available?

What implications would it have for patients, their families and/or carers if the technology was **not** made available?

Are there groups of patients that have difficulties using the technology?

Equality and Diversity

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this evaluation:

- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;

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- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

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

Other Issues

Please include here any other issues you would like the Evaluation Committee to consider when evaluating this technology.

CONFIDENTIAL UNTIL PUBLISHED
Evidence Review Group's Report
Strimvelis for treating severe combined immunodeficiency caused by adenosine deaminase deficiency

Produced by CRD and CHE Technology Assessment Group, University of York, Heslington, York YO10 5DD

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Declared competing interests of the authors

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Susan Griffin and Edward Cox undertook the critique of the cost-effectiveness submission and conducted the economic analyses, with Susan Griffin taking overall responsibility for the cost effectiveness sections. Nick Meader and Emily South undertook the critique of the clinical effectiveness submission, with Nick Meader taking overall responsibility for the clinical effectiveness sections of the report. Melissa Harden critiqued the literature searches in the submission. Nerys Woolacott provided advice and commented on drafts of the report.

Note on the text

All commercial-in-confidence (CIC) data have been highlighted in blue and underlined, all academic-in-confidence (AIC) data are highlighted in yellow and underlined

Copyright statement

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List of abbreviations

ADA	Adenosine deaminase
ADA-SCID	Adenosine deaminase deficiency severe combined immune deficiency
AE	Adverse event
aGvHD	Acute graft versus host disease
cGvHD	Chronic graft versus host disease
CNS	Central nervous system
CS	Company submission
CUP	Compassionate use programme
CVC	Central venous catheter
dATP	Deoxyadenosine triphosphate
dAXP	Deoxyadenosine nucleotides
EMBT	European Society for Blood and Marrow Transplantation
EQ-5D	EuroQol 5-dimension questionnaire
ERG	Evidence Review Group
ERT	Enzyme replacement therapy
ESID	European Society for Immunodeficiences
GCP	Good Clinical Practice
G-CSF	Granulocyte-colony stimulating factor
GSK	GlaxoSmithKline
GT	Gene therapy
GvHD	Graft versus host disease
HLA	Human leukocyte antigen
HRQoL	Health related quality of life
HSCT	Hematopoietic stem cell transplant
HST	Highly specialised technology
ICER	Incremental cost-effectiveness ratio
IQ	Intelligence quotient
IVIG	Intravenous immunoglobulin
LTFU	Long term follow up
LY	Life years
LYG	Life years gained
MeSH	Medical Subject Heading
MFD	Matched family donor
MRD	Matched related donor
MSD	Matched sibling donor

MUD	Matched unrelated donor
NHS	National Health Service
NK	Natural killer
NICE	National Institute for Health and Care Excellence
OS	Overall survival
OSR	Ospedale San Raffaele
PEG-ADA	Adenosine deaminase conjugated with polyethylene glycol
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
RBCs	Red blood cells
SCID	Severe combined immunodeficiency
SR-TIGET	San Raffaele Telethon Institute for Gene Therapy
TREC	T cell receptor excision circles
UCB	Umbilical cord blood
VCN	Vector copy number

1 Summary

1.1 Critique of the decision problem in the company's submission

The company's decision problem reflects the population specified in the NICE scope: people with ADA-SCID for whom no suitable HLA-matched related stem cell donor is available. The clinical evidence presented also reflects this population but the ERG identified some minor differences with the characteristics of the population that would be eligible for Strimvelis in England.

Based on the clinical pathway presented in the company submission (CS), the ERG would expect patients in England eligible for Strimvelis to be younger on average and have had a different treatment history, including much shorter average duration of PEG-ADA treatment. Additionally, information on race and country of origin of the patients in the clinical studies suggests they are unlikely to reflect the ethnicity of patients in England. Lastly, no patients had a confirmed active viral infection at screening. Given the potential for viral infection in ADA-SCID patients, and advice from the clinical advisor to the ERG that the presence of viral infection may be prognostic, it is unclear the extent to which the data can be generalised to patients presenting with viral infection. Despite these minor differences, the ERG acknowledges that due to the rarity of ADA-SCID and the small patient numbers, the population presented is appropriate for the decision problem in question.

The intervention in the submission is Strimvelis (retroviral-transduced autologous CD34+ cells), which matches the intervention described in the final NICE scope.

The company identifies the comparator as bone marrow transplant, specifically HSCT from an HLA-MUD or an HLA-haploidentical donor. This matches the NICE scope although the clinical advisor to the ERG advised that patients can be treated with HSCT using donated umbilical cord blood rather than bone marrow. The ERG notes that the study used as a historical comparator includes some cord blood transplants.

The decision problem in the CS includes all the outcomes described in the NICE scope, including overall survival, intervention-free survival, immune function, non-immunological aspects, need and duration of inpatient treatment and health-related quality of life for patients and carers. The outcomes are all addressed in the clinical evidence presented except for carer quality of life.

1.2 Summary of clinical effectiveness evidence submitted by the company

The company submission was focused on the Strimvelis Intergrated Population, although data on further patients receiving Strimvelis in the Named Patient Programme were also provided in

Appendix 6. Data on HSCT from a MUD (n=15) and HSCT from a haploidentical donor (n=7) were based primarily on a multi-centre study of reported outcomes in usual practice. In addition, data from smaller case reports and case series were also narratively synthesised.

Strimvelis

Evidence presented in the company submission for Strimvelis was based on the Strimvelis Integrated Population of 18 patients recruited from four studies (AD1117054 Pilot 1, AD1117056 Pilot 2, AD1115611 Pivotal, AD1117064 CUP) and AD1115611 LTFU a feeder study for longer term follow up data from these patients. Data were pooled and discussed as an integrated population. That is, the four studies were treated as if they were one study in contrast to a meta-analysis where data is analysed separately and weighted by study. A further [redacted] patients received Strimvelis in the Named Patient Programme but these were not included in the evidence synthesis.

Overall survival was 100% in the 18 patients that comprised the Strimvelis Integrated Population and the [redacted] patients from the Named Patient Programme. Follow up time in the Strimvelis Integrated Population ranged from 2.3 to 13.4 years (median =6.95 years); it was not reported for the Named Patient Programme.

Data on intervention free survival with Strimvelis was available for [redacted] patients: There was insufficient data on PEG-ADA use for Patient[redacted] to evaluate intervention-free survival for these patients. Of the evaluable patients [redacted] experienced intervention-free survival (i.e. did not require either ≥ 3 months of PEG-ADA treatment or HSCT): 14/17 (82.3%) in the Strimvelis Integrated Population, and [redacted] in the Named Patient Programme.

[redacted]

HSCT from a MUD or haploidentical donor

The key historical comparator data for HSCT is provided by Hassan et al which are the largest data source on outcomes for patients with ADA-SCID receiving HSCT currently available in the literature. Overall survival was 67% (10/15 patients) for those receiving HSCT from a MUD between 1995 and 2009. For HSCT from a haploidentical donor, overall survival was 71% (5/7 patients). This was based

only on data from 2000-2009 as this was considered a more applicable comparison with Strimvelis due to substantial improvements in effectiveness over time.

Intervention free survival data are very limited for HSCT from a MUD or haploidentical donor and it is not clear if the data reported on those receiving additional treatment is comparable with data on Strimvelis patients. Hassan et al reported one patient receiving a rescue transplant after HSCT from a MUD but no further information is provided about additional treatment. Following HSCT from a haploidentical donor (2000-2009 subgroup), 2/7 did not engraft, resulting in one patient receiving gene therapy and the other patient starting PEG-ADA followed by two rescue transplants before death.

Adverse events
Adverse events were largely similar for Strimvelis, HSCT from a MUD and HSCT from a haploidentical donor. Almost all (17/18) of the Strimvelis Integrated Population experienced a neurological, CNS or hearing event during treatment or follow up. Cognitive disorders were the most common event (n=5). Deafness was also a common problem with two patients reporting deafness and a further two patients reporting bilateral deafness. Three patients reported psychomotor hyperactivity. High incidence of non-immunological problems was also found for ADA-SCID patients following HSCT including behavioural problems and IQ scores substantially below general population means. The CS concluded that neither gene therapy nor HSCT appear to be effective in reducing non-immunological problems. The major difference between Strimvelis and HSCT in terms of adverse events was that some patients experienced Graft versus Host Disease (GvHD) after HSCT, whereas no patients experienced this adverse event following Strimvelis.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The clinical effectiveness evidence was based on a systematic review of Strimvelis, HSCT from a MUD and HSCT from a haploidentical donor. Although some limitations were identified with the search strategy the ERG did not identify any relevant studies that had been missed.

All data for the four studies and long term follow up feeder study that comprised the Strimvelis Integrated Population were pooled and treated as if comprising a single study. Although there were differences in methods between studies (particularly between the pilot studies and the pivotal study in terms of GCP) the ERG considered there was sufficient similarity between studies that this approach was unlikely to lead to substantial bias. However, the ERG did not consider it appropriate that data from the Named Patient Population were excluded from the narrative synthesis of clinical

effectiveness evidence. This is particularly important given the small sample size of the Strimvelis Integrated Population (n=18) and therefore the need to consider all available data when evaluating the effectiveness of this treatment.

Some concerns were noted regarding the representativeness of the Strimvelis Integrated Population to UK ADA-SCID patients. Firstly, there was lack of clarity regarding numbers screened or excluded for Pilot study 1, Pilot study 2, the Compassionate Use Programme and the [redacted]. Therefore, it is unclear if patients at greater risk were excluded from these studies or other selection biases occurred. Secondly, our clinical advisor noted that presence of viral infections at screening may be an important prognostic factor for treatment outcomes. In response to a request for clarification the company confirmed no patients had viral infections at screening. Therefore, this potentially raises issues regarding the generalisability of these patients to the UK and it is unclear the extent to which these findings are applicable to those with viral infections at baseline. Thirdly, it is likely that duration of PEG-ADA use was longer than would be expected in UK practice however since there is no evidence that this is an important prognostic factor it may not have impacted on outcomes. Whilst noting these concerns, the ERG concluded that as a whole data on Strimvelis is likely to be generalizable to the UK.

Although overall survival was 100% across all [redacted] patients that have received Strimvelis there are substantial limitations to these data. Firstly, this evidence is based on small open label single arm trials that are inherently at a high risk of bias and lack precision. A small number of deaths or treatment failures can lead to substantial changes in survival estimates making such estimates highly uncertain. Secondly, historical data on overall survival following HSCT from a MUD and HSCT from a haploidentical donor likely reflect an underestimate of the current effectiveness of these treatments. For example, there have been substantial improvements in matching of donors and provision of supportive care. Thirdly, the overall survival outcome overestimates the effectiveness of the intervention since those who experienced a Strimvelis treatment failure but did not die due to receiving an alternative treatment (such as PEG-ADA or HSCT) are still counted as a treatment success. Intervention-free survival was lower for Strimvelis ([redacted] and in the view of the ERG provides a better assessment of clinical effectiveness.

Although the CS demonstrated that some patients experienced GvHD following HSCT but not following Strimvelis there were limitations in estimating the rates of this adverse event. Estimates are based on very small case reports (ranging from n=1 to n=7) and by variations in definitions and reporting of these events. In addition, there were important limitations in how estimates of GvHD

were calculated in the company submission with data in case reports from different centres and different time periods pooled as if from a single study rather than using meta-analytic methods.

Although no events have occurred in Strimvelis-treated or other ADA-SCID patients, a potential risk of gene therapy identified in other SCID patients is the risk of leukaemia. Given the small sample size of patients who have received Strimvelis this cannot yet be ruled out as an important potential risk.

1.4 Summary of cost effectiveness submitted evidence by the company

The company submission included a review of published health-related quality of life data and a de novo economic evaluation. The economic evaluation compared Strimvelis to either HSCT from a MUD or HSCT from a haploidentical donor in a hypothetical cohort of patients aged one year old. The model consisted of a decision tree to establish the proportion of patients surviving initial transplant procedure and the proportion requiring rescue transplant in the first three years, combined with a Markov modelling approach to extrapolate costs and quality adjusted survival over a lifetime time horizon. The model assumed patients would be maintained on ERT with PEG-ADA while awaiting initial or rescue transplant procedures, and incorporated post-procedure IVIG use and risk of severe infection. Rescue transplant was assumed to occur two years after the initial procedure and to consist of HSCT from a MSD, with no risks of death or failure to engraft. It was assumed that the decision to utilise Strimvelis would be made before any search for a MUD was undertaken, and that HSCT from a haploidentical donor would only be used after a search for a MUD.

Patients who survived transplant procedures were assumed to return to the mortality and morbidity risk of the general population, and a discount rate of 1.5% was applied to costs and health outcomes to reflect this assumption of cure. The model characterised three main treatment benefits for Strimvelis: (i) reduced duration of ERT with PEG-ADA before the initial transplant procedure; (ii) reduced procedural mortality; and (iii) avoidance of GvHD. The model also assumed differences in the rates of rescue transplant between treatment arms.

The primary clinical effectiveness parameters in the model were informed by the Strimvelis Integrated Population long-term follow up study (n=17) and a retrospective, international survey of HSCT. The company model assumed overall survival of 100% with Strimvelis, 66.67% for HSCT from a MUD (based on 15 transplants performed between1995-2009) and 71.4% for HSCT from a haploidentical donor (based on seven transplants performed between 2000 and 2009). The rate of rescue transplant following failure to engraft was assumed to be 17.6% following Strimvelis, 6.7% following HSCT from a MUD and 28.6% following HSCT from a haploidentical donor. Rate of GvHD was informed

by the literature and assumed to occur in approximately of one third of patients undergoing HSCT, while Strimvelis was assumed to carry no risk of GvHD.

Health related quality of life was assumed equal to that of the general population, with decrements applied for six months in patients recovering from transplant procedures and to patients experiencing GvHD events.

The cost of Strimvelis was composed of two elements: (i) the cost of the retroviral mediated transduced cell product (£505,000); and (ii) related hospital procedures, including screening, blood tests, bone marrow sample, chemotherapy, infusion of Strimvelis, inpatient recovery and outpatient follow-up ([redacted]). These costs were informed by the clinical schedule and estimates provided by the HSR-TIGET and OSR hospital in Milan and converted to GBP using an exchange rate of €1=£0.85. The costs of HSCT from a MUD or haploidentical donor were based on NHS reference costs. Costs of screening for a MUD, long-term follow-up after any transplant procedure, cost of GvHD and cost of severe infection were informed by the literature and inflated to 2016 prices. The costs of PEG-ADA were informed by clinical expert opinion.

The company base case found Strimvelis to be more costly (cost difference £494,255 and £170,668) and more effective (QALY difference 13.6 and 11.7) compared to HSCT from a MUD and haploidentical donor, respectively. The deterministic ICERs were £36,360 for Strimvelis compared to HSCT from a MUD and £14,645 for Strimvelis compared to HSCT from a haploidentical donor. The ICERs remained lower than £100,000 per QALY gained across a range of one and two-way sensitivity analysis and scenario analyses.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The ERG considered the company's economic submission to meet the requirements of the NICE reference case. The ERG was concerned that the model failed to characterise alternative points in the treatment pathway at which a decision to use Strimvelis may be taken. The company model applies only to younger patients in whom the decision is taken immediately following diagnosis and before any search for a MUD is undertaken.

The ERG thought it was unrealistic to assume that patients with ADA-SCID who survive an initial transplant procedure with either Strimvelis or HSCT are returned to the same level of health and life expectancy as the general population. The ERG felt that this would overestimate quality adjusted survival and underestimate health care costs due to the cognitive and neurological deficits of ADA-SCID and potential long-term adverse events associated with pre-transplant conditioning regimens.

Of similar concern was the assumption of 100% survival and 100% successful engraftment with rescue transplant, which overestimates quality-adjusted survival and underestimates the health care costs in patients that fail to engraft following the initial procedure. These factors cause the company model to overestimate the benefit of reductions in procedural mortality.

The ERG identified a number of costs associated with Strimvelis that were omitted from the company base case, including NHS supported travel costs to and from Milan, the cost of screening incurred for patients deemed unable to produce sufficient CD34+ cells to proceed to treatment with Strimvelis, additional hospitalisation costs for patients whose length of stay after Strimvelis exceeds 55 days and administration of back up bone marrow. The cost per HSCT from a MUD and per GvHD event in the company base case appear to have been overestimated.

The ERG consider that the available evidence does not support the assumption that Strimvelis will reduce the use of PEG-ADA prior to transplant. The ERG also consider that for some patients the decision to utilise Strimvelis will be taken only after a search for a MUD has been completed, and for these patients search costs will not be avoided.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

The company submission included a systematic review which reflected the NICE scope and decision problem. Although there were some limitations to the search strategy, the ERG considered it unlikely that important studies had been missed when the addition of the Named Patient Programme data for all [redacted] patients were considered.

The ERG company economic submission met the requirements of the NICE reference case and utilised appropriate available evidence. The company submission included a range of sensitivity and scenario analyses to address uncertainties, and addressed additional uncertainties in response to ERG requests and clarifications.

1.7 Weaknesses and areas of uncertainty

The ERG identified several limitations to the clinical effectiveness evidence. Firstly, the data is based on small open label single arm trials that are inherently at a high risk of bias and lack precision. Therefore all survival estimates are highly uncertain and future data could substantially change conclusions. Secondly, historical data on overall survival following HSCT from a MUD and HSCT from a haploidentical donor likely reflect an underestimate of the current effectiveness of these

treatments. For example, there have been substantial improvements in matching of donors, reduced conditioning, and better provision of supportive care. Thirdly, the overall survival outcome overestimates the effectiveness of the intervention since those who experienced a Strimvelis treatment failure but did not die due to receiving an alternative treatment (such as PEG-ADA or HSCT) are still counted as a treatment success. Intervention-free survival was lower for Strimvelis ([redacted] and in the view of the ERG provides a better assessment of clinical effectiveness.

The ERG identified a number of relevant costs and outcomes that were omitted from the company model, and that caused the benefits of reductions in procedural mortality to be overestimated. The simplified pathway in the company model does not characterise all the relevant routes by which patients may arrive to treatment with Strimvelis. Given the small sample sizes used to inform the key model parameters, each additional patient treated can have a large influence on estimates of overall survival, rates of successful engraftment and rates of rescue transplant.

While acknowledging that the company submission incorporates the best available evidence for survival in patients with ADA-SCID treated with HSCT from a MUD or haploidentical donor, the ERG understands that techniques for HSCT and overall survival continue to improve over time. In contrast, the use of overall survival rather than intervention-free survival to characterise the efficacy of Strimvelis at 100% means that survival for patients treated with Strimvelis is likely to reduce over time. The respective 33 and 29 percentage point reductions in procedural mortality with Strimvelis compared to HSCT from a MUD or from a haploidentical donor applied in the company submission may therefore represent the upper limit of additional benefit from Strimvelis.

1.8 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG made a number of changes to the company model that utilised a number of scenario analyses provided by the company:

- Disutility weight applied to patients receiving IVIG;
- Duration of chronic GvHD in line with timing of rescue transplant;
- Revised PEG-ADA dose determined by patient weight;
- Revised administration costs for PEG-ADA and IVIG;
- Inclusion of travel costs to and from Milan;

combined with further changes:

- Incorporate NPP to inform efficacy of Strimvelis

- Minor parameter corrections to company model;
- Assume equal duration of PEG-ADA pre-procedure across treatment arms;
- Assume rescue transplant has same cost and health outcomes as initial transplant from a MUD;
- Include ongoing healthcare costs and health related quality of life decrement for bilateral hearing impairment;
- Lower unit costs for HSCT from a MUD and per GvHD event;
- Incorporation of baseline screening costs incurred by patients deemed ineligible to proceed to Strimvelis.

The ERG use the revised base case to explore the sensitivity of the model to survival rates following Strimvelis and HSCT, the cost of Strimvelis, whether MUD search costs are avoided in patients treated with Strimvelis, and the rate of rescue transplant.

The ERG preferred base case predicts lower QALYs for all comparators compared to the company base case. This is attributable to the increased mortality and morbidity associated with rescue transplants and the application of HRQoL decrements for IVIG use and bilateral hearing impairment. The ERG's preferred base case predicts higher costs for Strimvelis, lower costs for HSCT from a MUD, and higher costs for HSCT from a haploidentical donor compared to the company base case. This is attributable to higher rates of rescue transplant for patients treated with Strimvelis and HSCT from a haploidentical donor, combined with the increased health care costs per rescue transplant to reflect risks of severe infection and GvHD, and the lower unit cost for HSCT from a MUD.

The ERG's base case ICERs are £86,815 for Strimvelis compared to HSCT from a MUD and £16,704 for Strimvelis compared to a haploidentical donor. These are higher than those estimated by the company, but remain below £100,000 per QALY. The ICER for Strimvelis compared to HSCT from a haploidentical donor is robust to a range of sensitivity analysis. However, the ICER for Strimvelis compared to HSCT from a MUD is very sensitive to the assumed difference in procedural mortality between the two procedures. If survival following HSCT from a MUD exceeds 75%, the ICER for Strimvelis compared to a MUD would no longer fall beneath the adjusted cost-effectiveness threshold determined by the extent of the undiscounted QALY gain with Strimvelis. Strimvelis must reduce procedural mortality by at least 30 percentage points compared to HSCT from a MUD in order for the ICER to remain below £100,000 per QALY gained. If survival with Strimvelis falls below 100%, the ICER for Strimvelis compared to HSCT from a MUD is also sensitive to variation in the additional cost of Strimvelis.

If search costs for a MUD are not avoided prior to treatment with Strimvelis the ICER increases to £91,644 compared to HSCT from a MUD and to £20,786 for HSCT from a haploidentical donor. The results were sensitive to alternative assumptions regarding the rate of rescue transplant. It is anticipated that the ICER for Strimvelis compared to HSCT may increase in patients that have a worse prognosis, in older patients and in those with active viral infection. Older patients are likely to incur greater drug acquisition costs for PEG-ADA and IVIG as dose is determined by patient weight. Older patients and or those with active viral infection are expected to experience worse procedural outcomes, which may diminish the potential reduction in procedural mortality and also the QALY gains from deaths avoided.

2 Background

2.1 Critique of company's description of underlying health problem.

2.1.1 Overview of the condition

The company submission (CS) provides a brief summary of disease morbidity, mainly focusing on the morbidity associated with current treatment options for adenosine deaminase-severe combined immunodeficiency (ADA-SCID).

The CS states that ADA-SCID is a fatal autosomal recessive monogenic inherited immune disorder. People with ADA-SCID have profound lymphopenia, impaired differentiation and function of T cells, B cells and natural killer cells, recurrent infections and failure to thrive. Unlike other forms of SCID, non-immunological abnormalities can also occur due to the systemic metabolic defect. Symptoms of ADA-SCID are developmental delay, chronic diarrhoea, failure to thrive and recurrent infections.[1]Patients can be hospitalised and kept in isolation due to frequent infections. ADA-SCID is usually diagnosed within the first year of life and without treatment patients are unlikely to survive beyond one to two years.[2] The CS claims that ADA-SCID is perceived in the clinical community as more difficult to treat than other types of SCID,[3] although the ERG notes that the cited paper says there is "no objective data to support this notion".[3]

This section of the CS provides details of the morbidity associated with current treatment options, particularly haematopoietic stem cell transplant (HSCT). HSCT involves the transplantation of haemopoietic progenitor cells from bone marrow or blood, which are able to differentiate into other cell types, including cells of the immune system.[4] For patients that receive HSCT from a human leukocyte antigen (HLA) matched related donor (MRD), the CS cites survival rates of 86% for matched sibling donors (MSD) and 83% for matched family donors (MFD).[3] According to the CS, only 20-25% of patients have an MRD available.[1, 5] The other main types of HSCT available for ADA-SCID are HSCT from a matched unrelated donor (MUD) or haploidentical donor. Based on external expert clinical advice, the CS states that HSCT from a MUD is preferred in the UK, with HSCT from a haploidentical donor not performed in an ADA-SCID patient in England in the last 15 years. The clinical advisor to the ERG confirmed that, based on European guidance, HSCT from a haploidentical donor is not carried out for ADA-SCID.

Survival rates provided in the CS for HSCT from a MUD are 67% in procedures since 1995.[3] For HSCT from a haploidentical donor the survival rate is 43% but this rises to 71% if just the more recent procedures performed in this cohort (from 2000-2009) are considered.[3] The ERG agrees that

these estimates reflect the best available published data on ADA-SCID patients. However, these data are based on small sample sizes (for HSCT from a MUD: n=15, HSCT from a haploidentical donor: n=30 and HSCT from a haploidentical donor 2000-2009: n=7) and therefore are inherently uncertain. In addition, the clinical advisor to the ERG advised that outcomes have continued to improve markedly in HSCT from MUD and haploidentical donors since 2009. Unfortunately the ERG has not been able to find any published data on more recent cohorts of ADA-SCID patients, although data on HSCT in other cohorts shows improvement over time.[6 4] The clinical advisor to the ERG estimated that, using new techniques, for HSCT from a haploidentical donor survival is now over 90% in other conditions. The clinical advisor also suggested that with current methods and techniques results achieved with MRDs are not necessarily better than those with MUD or haploidentical donors. However, these techniques are very recent and not yet reflected in published data. In addition, these improvements are not based exclusively on ADA-SCID patients. Therefore, there are important limitations in estimating overall survival after HSCT from a MUD or haploidentical donor based on published data and questions regarding the extent to which they reflect the effectiveness of currently provided treatment.

A complication associated with HSCT is graft versus host disease (GvHD), which the CS highlights can lead to significant morbidity and mortality.[3] The CS also mentions that, for ADA-SCID patients that survive bone marrow transplant, central nervous system (CNS) abnormalities represent a remaining unmet need for treatment.[7, 8]

The CS also addresses morbidity associated with supportive enzyme replacement therapy (ERT) with PEG-ADA. The CS cites a study by Chan et al that found with long-term PEG-ADA treatment lymphocyte counts, thymic function and mitogenic proliferative responses all started declining.[9] This was thought to be due to incomplete metabolic reconstitution in the thymus leading to gradual loss of immune function.

The CS identifies an unmet need for treatment options that provide long-term corrective therapy for those patients without an available MRD, with improved survival rates and without the complication of GvHD.

2.1.2 Incidence of ADA-SCID

There is a lack of data on ADA-SCID incidence in the UK, but the CS estimates an incidence of three to four patients with ADA-SCID per year in the UK, with three or fewer patients in England. As approximately 20% of these patients would have an MRD available,[1, 5] the CS claims that no more

than two patients per year in England would be eligible for Strimvelis. The CS notes that uptake of Strimvelis is not expected to be 100% due to the practicalities of treatment in Milan. The clinical advisor to the ERG confirmed that families may be reluctant to choose treatment in Milan if other options (e.g. a trial in the UK) are available.

There is difficulty estimating incidence of ADA-SCID in the UK based on the very limited data available. Additionally, given that ADA-SCID is concentrated within certain communities, it is not clear that the estimate used in the company submission takes into account demographic differences between the nations of the UK to calculate the England estimate. Results from newborn screening for SCID in the US have shown an incidence of SCID that was higher than previously reported[10, 11] so it is also possible that a screening programme for SCID in the UK would have an impact on the number of infants diagnosed with ADA-SCID. However, the ERG agrees incidence is likely to be very low and received a similar estimate from a clinical advisor based on their experience at one of the two treatment centres for ADA-SCID in the UK.

2.1.3 Life expectancy

The CS claims that with no treatment children with ADA-SCID rarely survive beyond two years,[2] but that there is currently no data available on life expectancy after HSCT. The clinical advisor to the ERG confirmed that there is very limited evidence on life expectancy, with a maximum of about 25-30 years of follow-up data on ADA-SCID patients after HSCT. The ERG notes that although the first bone marrow transplant for SCID took place in 1968, techniques to deplete T cells, making bone marrow transplantation possible in all forms of SCID, were only developed in the 1980s.[12] The clinical advisor predicted a normal life expectancy after a good quality transplant, although he noted that due to the metabolic nature of ADA-SCID there are heart and neurological impacts and a long term risk of cancer.

2.1.4 Quality of life

The CS describes how ADA-SCID impacts on the quality of life for both patients and carers. It highlights that without any treatment quality of life for patients and family members would decline as infections increased and patients would be expected to die at a young age.

[redacted]

[redacted]

The CS also suggests that choosing treatment with HSCT could have quality of life impacts for carers. The ERG identified two reviews of the literature on quality of life in children who survived HSCT (not specifically for SCID), which found a short-term decline in health-related quality of life following conditioning for HSCT and transplant.[13, 14]

The CS identifies one study of patients with SCID after HSCT (median 11 years post-transplant) which found a significantly lower quality of life in those with ADA-SCID than the UK normal on all components except emotional.[15] Patients with ADA-SCID were more at risk of poor quality of life than those with other types of SCID, which the CS suggests may be due to the impact of the non-immunological manifestations of ADA-SCID. The ERG notes that this study was in patients who had undergone treatment with HSCT and therefore indicates an ongoing impact on quality of life after curative treatment, rather than representing the impact on patients awaiting treatment.

The company expects quality of life for patients treated with Strimvelis, their carers and families to improve, with shorter waits for treatment than for HSCT from a MUD and reduced mortality risk. Overall, given the limited research and data available due to the rarity of ADA-SCID, the CS provides an appropriate and relevant summary of the disease area.

2.2 Critique of company's overview of current service provision

2.2.1 Current clinical pathway

The CS provides a summary of the current clinical pathway of care for ADA-SCID patients in England. Patients are usually diagnosed at one of the specialist SCID centres (Great Ormond Street Hospital or Great North Children's Hospital, Newcastle). The majority are diagnosed in the first year of life according to the CS,[2] although some have a delayed or late onset.[16] After diagnosis, the immediate clinical priorities are to reduce infection risk, conduct tests and assessments and provide supportive care. Patients are also screened for an MRD. The clinical advisor to the ERG specified that screening starts for an MRD while tests are ongoing to diagnose ADA-SCID. The clinical advisor also advised that patients are put on PEG-ADA as soon as they are diagnosed to help build immunity, to clear infections and reduce toxicities, improving the likelihood of treatment success.

The CS gives a figure of 20-25% of patients who have an MRD available,[1] although the ERG is not aware that there is currently any good quality epidemiological data available to inform this estimate. If patients do not have an MRD available, HSCT from a MUD is the current standard of care. The

clinical advisor to the ERG clarified that this could be from either umbilical cord blood (UCB) or a bone marrow donor, with the search for a cord blood match beginning at the same time as diagnostic tests and MRD screening. Clinicians decide whether to use cord blood or an adult donor, mainly based on availability and the level of infection. The CS explains that PEG-ADA is used as a supportive treatment, while the search for a MUD is ongoing. The CS specifies an average waiting time for a MUD of 19 weeks.[17] However the ERG notes that a presentation on the UK Stem Cell Strategic Forum Recommendations gives average times to transplant as 50 days for bone marrow and 13.5 days for cord blood.[18] Although this is not based on ADA-SCID patients specifically, it suggests some uncertainty over waiting times. HSCT from a haploidentical donor is currently not performed in ADA-SCID patients in England and long-term PEG-ADA is also not considered. The clinical advisor to the ERG confirmed that this is the basic pathway, and also advised that if a good match from an unrelated donor is not available then gene therapy may be considered. Kohn & Gaspar's overview of the management of ADA-SCID,[19] though not exclusively UK based, also confirms that HSCT from an MRD is the current standard of care where possible, with ERT, HSCT from a MUD or haploidentical donor, or gene therapy as options for those without an MRD.

2.2.2 Issues relating to clinical practice

The CS highlights some of the clinical issues relating to the current treatment options. While HSCT from an MRD usually doesn't need preconditioning, other types of HSCT may require chemotherapeutic preconditioning. They also have increased risk of mortality and morbidity from inadequate immune reconstitution and GvHD. While the CS claims that there is significantly decreased survival from MUD or haploidentical donors compared with MRD, the clinical advisor to the ERG advised that using current methods survival from HSCT from a MUD or haploidentical donor would be expected to be much higher than the most recent published data, which is based on transplants only up to 2009. The CS also mentions that MUD donor availability can depend on ethnicity, with non-White patients facing a longer wait.[20-22]

In terms of ERT with PEG-ADA, the CS mentions that it is a non-curative and expensive treatment that requires weekly or bi-weekly injections and regular monitoring. Long-term efficacy can be limited due to incomplete immune reconstitution and the development of antibodies.[23-25] Although it is available through expanded access and compassionate use programmes, it is not approved in the EU and is used to stabilise patients before HSCT or gene therapy rather than as a long term treatment (although the ERG notes that this may depend on the waiting time until curative treatment). The clinical advisor to the ERG confirmed that although patients are put on PEG-ADA initially, it is used as a bridge to curative treatment in the UK.

Overall, the CS provides an accurate and appropriate overview of the current treatment pathway for ADA-SCID and some of the associated issues.

2.2.3 Description of technology under assessment

Strimvelis is a gene therapy treatment in which autologous bone marrow-derived cells are transduced to express adenosine deaminase (ADA). After infusion, CD34+ cells engraft in the bone marrow, where they repopulate the haematopoietic system with a proportion of cells that express pharmacologically active levels of the ADA enzyme. If engraftment is successful, the effects of a single dose are expected to be life-long. Strimvelis was given EU marketing authorisation on 26 May 2016. It is given as an intravenous infusion, which must be administered in a specialist transplant centre by a physician with previous experience in the treatment and management of ADA-SCID and the use of autologous CD34+ ex vivo gene therapy products. It is currently only available at the Hospital San Raffaele Telethon Institute for Gene Therapy (HSR-TIGET) in Milan, Italy. For successful manufacture of Strimvelis, the patient needs to be able to donate adequate CD34+ cells and a CD34+ stem cell back up is also required. This is harvested at least 3 weeks before treatment with Strimvelis and is required as a rescue treatment if there is failure during product manufacture or transplant or prolonged bone marrow aplasia after treatment.

Similarities and differences between Strimvelis and HSCT from a MUD or haploidentical donor

Gene therapy with Strimvelis is a type of autologous transplant, which includes any treatment where stem cells are collected from the patient themselves and then re-infused. [4] HSCT from a MUD or haploidentical donor is allogeneic, which means the stem cells are from a donor.[4]

The CS states that low dose busulfan conditioning is used for Strimvelis. While the clinical advisor to the ERG explained that there is no consensus on conditioning regimes, he advised that more conditioning is required for HSCT from an unmatched donor than for gene therapy. According to the CS, Strimvelis does not carry the risk of graft versus host disease that has a significant effect on morbidity and mortality in allogeneic HSCT. Strimvelis also differs in that it does not require the search for a donor before treatment. In terms of similarities, the clinical advisor to the ERG advised that both gene therapy and HSCT require the insertion of a central venous catheter (CVC), with the same risk of infection in both cases. The clinical advisor also does not expect much difference in the frequency of follow up between the two procedures, although there may be small differences in the testing required. According to the CS the hospital stay required after treatment would also be very similar.

2.2.4 New pathway of care

The CS describes the new pathway of care incorporating Strimvelis that would exist following national commissioning by NHS England. According to the CS, patients without an MRD should be offered Strimvelis. Screening would be conducted at specialist centres in England once established that an MRD is not available. HSR-TIGET would liaise with the clinical team in England to confirm that treatment with Strimvelis is appropriate for the patient. Before the Strimvelis treatment, patients would be seen at HSR-TIGET for just over a month for necessary procedures, including obtaining a bone marrow backup. Hospitalisation during Strimvelis treatment is for approximately 50 days before being seen as an outpatient for 2-3 months. After this the patient would return to the UK and follow-up care will be given by the referring physician, with specific guidance and recommendations from HSR-TIGET.

Although this pathway reflects the EMBT/ESID guidance,[26] the ERG questions whether all patients without an MRD would choose to receive Strimvelis as their first choice treatment. Based on expert clinical advice, the ERG understands that the need to travel to Milan may act as a barrier to some families and a decision may be taken to initially explore HSCT from a MUD as a treatment option. Therefore in practice, the ERG considers that Strimvelis may be a first line treatment for some patients in England but also a second line treatment for others either after the search for a MUD is unsuccessful or following a failed HSCT from a MUD.

3 Critique of company's definition of decision problem

3.1 Population

In the statement of the decision problem, the company identifies the population as people with ADA-SCID for whom no suitable HLA-matched related stem cell donor is available. This reflects the population specified in the NICE scope and the population in the clinical evidence presented. However, the ERG notes some minor differences between the population in the clinical evidence and the characteristics of the patient population that would be eligible for Strimvelis in England.

Firstly 16 of the 18 patients in the integrated population (the combined population of patients that received Strimvelis in the four trials and one LTFU study presented in the clinical evidence) had previously received either HSCT from a haploidentical donor and/or PEG-ADA treatment for over six months (median 12 months; range: one to 71 months). Neither long-term PEG-ADA nor HSCT from a haploidentical donor are currently used as treatments for ADA-SCID patients in the UK. According to the clinical pathway presented in the CS, most patients eligible for Strimvelis in England would be

referred for treatment soon after diagnosis of ADA-SCID and therefore will have had a much shorter duration of PEG-ADA than the average in the clinical evidence. However, the clinical advisor to the ERG advised that PEG-ADA use is not prognostic for HSCT outcomes so it is possible that it would not have an effect on the efficacy of Strimvelis. Additionally, due to uncertainties around the clinical pathway discussed in section 2.2.4, the ERG believes some patients in England may have prior treatment before referral for Strimvelis.

The median age of the integrated population was 1.37 years and seven of 18 patients were over two years old. The CS states that the majority of ADA-SCID patients are diagnosed in the first year of life[2] and the time to Strimvelis treatment provided in the company's model is nine weeks. Based on the clinical pathway presented, the ERG would therefore expect eligible patients in England to be younger on average than the patients in the clinical studies. The clinical advisor to the ERG advised that younger patients tend to respond better to HSCT, as they are less likely to have an active infection, which is prognostic for HSCT outcomes.[27, 28] The ERG therefore acknowledges that younger age may also have a positive effect on treatment outcomes with Strimvelis, if less infections are present in the population. However, as above, the ERG believes there may be uncertainties around the clinical pathway presented so it is not possible to draw firm conclusions on how the average age of the eligible population would differ.

According to the CS and the clinical advisor to the ERG, ADA-SCID is concentrated in several ethnic minority groups within the UK, including those of Somalian ethnicity.[29] None of the patients included in the CS came from the UK and information on their race and country of origin suggests they are unlikely to reflect the population in England in this respect. However the clinical advisor to the ERG confirmed that he would not expect differences in the efficacy of treatment due to patient ethnicity.

Additionally, the ERG requested further clarification regarding the proportion of patients with viral infection at baseline. The company responded that there was no data on this but that no patients had a confirmed active viral infection at screening. Given the potential for viral infection in ADA-SCID patients, and advice from the clinical advisor that the presence of viral infection may be prognostic,[27, 28] it is unclear the extent to which the data on the integrated population can be generalised to ADA-SCID patients presenting with viral infections.

Overall, while the population presented in the clinical evidence matches the NICE scope, the ERG considers there to be small differences compared with the population that would be eligible for Strimvelis treatment in England. However the ERG acknowledges that, due to the rarity of ADA-

SCID and the small patient numbers, the population presented is appropriate for the decision problem in question.

3.2 Intervention

The intervention in the CS is Strimvelis (retroviral-transduced autologous CD34+ cells), which matches the intervention described in the final NICE scope. Strimvelis is a gene therapy treatment in which autologous bone marrow-derived cells are transduced to express ADA and is intended to be administered once per lifetime as an intravenous infusion. However the ERG notes that one patient in the clinical evidence presented in the CS received a second dose of Strimvelis after an unsuccessful response to the first treatment.

3.3 Comparators

The comparator in the decision problem described in the CS is bone marrow transplant, specifically HSCT from an HLA-MUD or an HLA-haploidentical donor, which matches the NICE scope. However the clinical advisor to the ERG advised that UK patients will often be treated with HSCT using donated UCB rather than bone marrow. The decision to use cord blood often depends on how much infection the patient has. The ERG notes that the Hassan et al. study[3] (used as a comparator in the CS) includes a small number of transplants which used UCB (n=9). Hassan et al. do not report which transplants UCB was used in, so it is not possible to ascertain whether cord blood was used in the MUD or haploidentical HSCT procedures that the comparison is based on.

Long term enzyme replacement therapy (ERT) can act as an efficacious alternative to transplantation.[30] However, it is not licensed for such use in the UK, and in line with the NICE scope, this comparator was omitted from the cost-effectiveness analysis. Alternative treatment options for ADA-SCID are continuing to develop. An ongoing Phase III clinical trial is exploring a recombinant preparation of ADA ERT, which has the potential to reduce manufacturing costs compared to bovine derived PEG-ADA (NCT01420627 expected to report March 2019). There is an ongoing trial in the UK for an alternative gene therapy delivered via a lentiviral vector (NCT01380990). While this is not yet available as a comparator, patients in the UK may enter into the trial and it has the potential to be a relevant comparator in the future. These initial trials of lentiviral vector gene therapy have used concomitant ERT until 1 month after transplant, and so immediate survival may be confounded by use of PEG-ADA. However, initial reports are promising, showing 100% overall survival in 32 patients treated with lentiviral vector mediated gene therapy.[19]

3.4 Outcomes

The decision problem set out in the CS includes all the outcomes described in the final scope: overall survival; intervention-free survival; immune function (rate of severe infections, lymphocyte counts, thymopoiesis, use of IVIG, vaccination response); non-immunological aspects; need and duration of in-patient treatment; and health-related quality of life for patients and carers. All of these outcomes are included as part of the clinical evidence presented, except for carer quality of life which is not addressed. The ERG considers outcomes to be appropriately measured. However, quality of life was measured only as part of the long-term follow up (LTFU) study and some of the measures used were non-standardised assessments, which were not pre-specified and for which no baseline assessments were collected.

3.5 Other relevant factors

The CS includes a section on equity considerations. It identifies no ways in which the evaluation could impact adversely on people protected by equality legislation. It does highlight that MUD donor availability can vary by ethnicity, with finding a donor more difficult for non-White patients[20, 21] and suggests that using gene therapy treatments such as Strimvelis will avoid the longer wait for these patients. The CS also mentions that no sub-analysis by race was carried out due to the small number of patients.

4 Clinical Effectiveness

This section contains a critique of the methods of the review of clinical effectiveness data, followed by a description and critique of the trials included in the review, including a summary of their quality and results and the results of any synthesis of studies.

4.1 Critique of the methods of review(s)

4.1.1 Searches

The company submission (CS) contained the search strategies used to identify relevant clinical data on the treatment of ADA-SCID with HSCT or gene therapy. The search strategies were briefly described in the main body of the submission in Section 9.1.1 (published studies) and Section 9.1.1 (unpublished studies). Full details were provided in Appendix 1, Section 17.1.

The electronic database EMBASE was searched on 20th May 2016 via the Elsevier host. The search combined terms for ADA-SCID with terms for the following treatments: gene therapy, stem cell transplantation, or bone marrow transplantation. The EMBASE search was limited by date from 2000 onwards, and restricted to English language studies.

The company supplemented the search of EMBASE with unpublished data of completed and ongoing GSK studies of Strimvelis. In addition, unpublished studies on any treatments for ADA-SCID were sought from searches of ClinicalTrials.gov, the Cochrane Central Register of Controlled Trials (CENTRAL), the UK Clinical Trials Gateway, the EU Clinical Trials Register and the World Health Organisation International Clinical Trials Registry Platform. The trial register searches were carried out on 20th May 2016.

The reporting of the searches was clear with sufficient detail to allow the searches to be reproduced. The databases searched, the service providers used, the date of the searches, limits, and complete strategies were all clearly reported. However, some limitations are noted below which may have reduced the comprehensiveness of the searches.

The CS noted that EMBASE hosted by Elsevier includes the PubMed database. However, the information provided by Elsevier on their website (https://www.elsevier.com/solutions/embase-biomedical-research/learn-and-support) indicates that records from MEDLINE are added to EMBASE. PubMed includes extra records that are not included in MEDLINE. Therefore a search of PubMed in addition to EMBASE would have been a better option to identify relevant records from PubMed that are not contained in MEDLINE.

The sources used to search for unpublished data were comprehensive, including data from the company on Strimvelis and a wider search of several national and international trial registers to capture ongoing studies of any treatments for ADA-SCID.

The EMBASE search strategy could not be fully appraised by the ERG due to a lack of access to the Elsevier hosted version of EMBASE. However, it was possible to note some general limitations of the EMBASE search strategy presented in the CS. Firstly, truncation was not used throughout the strategy. For example, the strategy contained text word searches for bone marrow transplantation, which may miss studies that used the terms bone marrow transplant or bone marrow transplants. It is good practice when producing search strategies for systematic reviews to make use of truncation to ensure that the search strategy is sensitive enough to capture all relevant studies. Although the use of truncation will increase the numbers of records identified it is essential to ensure the comprehensiveness of the search. Secondly, the term gene therapy was included in the search strategy, but the term Strimvelis was missing. Although the company clarified that that they were aware of all Strimvelis publications, it is usual to include all possible alternative terms and synonyms for the interventions under consideration within the search strategy for a systematic review. Finally, the main subject heading (EMTREE term) for the population, adenosine deaminase deficiency/, was not included in the EMBASE strategy which may have further limited the comprehensiveness of the search.

For the search of CENTRAL, the company did not include the Medical Subject Heading (MeSH) Severe Combined Immunodeficiency/ or Adenosine Deaminase/. Unlike the other trial registers searched, CENTRAL has an advanced search interface which allows MeSH searching as well as searching in the title and abstracts of records. Inclusion of these MeSH terms would have improved the comprehensiveness of the search strategy to ensure that all potentially relevant studies about ADA-SCID were retrieved from CENTRAL.

Although the company were aware of all publications about Strimvelis, studies of other comparator treatments for ADA-SCID may not have been identified by the searches presented in the CS, due to the limitations described above.

4.1.2 Inclusion criteria

In the systematic review in the CS, the following inclusion criteria were stated for both published and unpublished studies (see Table 1).

Table 1 Inclusion criteria for systematic review included in CS

Inclusion criteria	Description
Population	Patients with ADA-SCID
Interventions	HSCT from an HLA-matched unrelated donor or HLA haploidentical donor, gene therapy
Outcomes	overall survival, intervention-free survival, rate of severe infections, in-patient hospital stay, lymphocyte counts, AEs, quality of life, and neurological/neurodevelopment events (including deafness).
Study design	No restrictions applied
Other restrictions	English language only

The inclusion criteria are largely appropriate and reflect the decision problem. However the submission lacks transparency and consistency in its treatment of gene therapy in the systematic review. It is unclear whether the systematic review included all studies of gene therapy in ADA-SCID populations as is implied by the inclusion criteria. The main clinical effectiveness section (section 9) discusses only gene therapy data on Strimvelis, which appropriately reflects the decision problem but is a narrower focus than suggested by the inclusion criteria. However Appendix 17.7.2 includes adverse events in other gene therapy trials, which suggests these trials were included in the systematic review.

4.1.3 Critique of data extraction

Limited information is provided on the study selection and data extraction processes used in the systematic review. For example, it was not reported whether study selection or data extraction was completed by one reviewer or whether appropriate methods for minimizing error and bias were used (e.g. a second reviewer either checking the first reviewer's responses, or conducting the same process independently and in duplicate). Therefore, potential errors in study selection and data extraction cannot be ruled out.

4.1.4 Quality assessment

The critical appraisal questions were based on an adaptation of the CASP tool for cohort studies. The criteria were appropriate and included items on recruitment, measurement of exposure, measurement of outcome, identification and adjustment for important confounding factors, completeness of follow up and precision of results.

There were limitations in the reporting of the quality assessment. Firstly, quality assessments were only reported for studies on the effectiveness of Strimvelis and not for all studies included in the systematic review. Secondly, it was not reported whether quality assessment was completed by one reviewer or whether appropriate methods for minimizing error and bias were used (e.g. a second reviewer either checking the first reviewer's responses or conducting the same process independently and in duplicate). Therefore, potential errors in quality assessment cannot be ruled out.

4.1.5 Evidence synthesis

The company did not undertake a meta-analysis of all included studies due to substantial heterogeneity between included studies (e.g. patient characteristics, inclusion criteria, treatment duration and follow up time). The ERG agrees that narrative syntheses were appropriate given the nature of these data.

However, data from 4 studies (AD1117054 Pilot 1, AD1117056 Pilot 2, AD1115611 Pivotal, AD1117064 CUP) and the feeder study which included longer term follow up data from patients in these studies (AD1115611 LTFU) in the Strimvelis clinical programme were pooled and discussed as an integrated population which is equivalent to conducting an unweighted meta-analysis. Although there are some differences in methods between studies (particularly between the pilot studies and the pivotal study in terms of GCP) the ERG considered there was sufficient similarity in populations and study conduct for this approach to be appropriate.

Data from the Named Patient Programme (patients [redacted]) were not included in the pooling of the Strimvelis Integrated Population nor were they included in the narrative syntheses. However some data from this population is provided in Appendix 6. Although GSK does not sponsor the programme and has limited ongoing access to the data, it would appear these data meet the inclusion criteria of the systematic review and should have been included in the narrative syntheses.

There was a lack of transparency regarding how the survival data from HSCT was narratively synthesised. The narrative synthesis on survival focused on studies of HSCT with five or more patients, but it is unclear whether the decision to use a threshold of five patients was made *a priori* or

driven by the data, and no justification is provided for this judgement. However, data from all included studies were provided in Table C22 of the CS.

4.1.6 Summary statement

The reporting of the searches was clear with sufficient detail to allow the searches to be reproduced. However, limitations in the search strategy reduced comprehensiveness of the searches. Therefore some studies of comparator treatments for ADA-SCID may not have been identified by the searches presented in the CS. Appropriate criteria were used to critically appraise Strimvelis treatment however no critical appraisal was conducted on studies of comparator treatments.

Narrative synthesis was an appropriate method of synthesis for the nature of the evidence included in the CS. Although limited data were available from the Named Patient Programme the ERG did not judge it appropriate to exclude these data from the narrative syntheses. Since the Strimvelis Integrated Population comprised only 18 patients, the ERG considered it important to take into account data on the further [redacted] patients of the Named Patient Programme when drawing conclusions about the effectiveness of Strimvelis.

4.2 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

4.2.1 Studies on the clinical efficacy and safety of Strimvelis

Table 2 provides a summary of the Strimvelis Integrated Population and the Named Patient Programme.

The company narrative synthesis includes only data from the Strimvelis Integrated Population. This is the combined total of 18 patients treated in four trials: AD1117054 (Pilot study 1 (N=1)); AD1117056 (Pilot study 2 (N=2)); AD1115611 (Pivotal study (N=12)); and AD1117064 (Compassionate Use Programme (N=3). In addition, patients from these four studies who completed three years of follow up (N=17) were enrolled in a long term follow up study (AD1115611 LTFU); these data were also included in the Integrated population. However long term follow up study data from only 14 patients were available as one patient withdrew (to receive HSCT from a sibling matched donor) and follow up data at year 4 were not available for two patients in the compassionate use programme.

Table 2 Summary of the Strimvelis Integrated Population and the Named Patient Programme (adapted from Tables C5-C9 and Appendix 6).

Study Population	Study Design	Intervention and Comparator (where applicable)	Survival	Immune function	Health related quality of life
Strimvelis Integrated Treatment Population	Combined population of 4 open label, single arm trials and a long term follow up study (includes data from AD1117054, AD1117056, ,AD1117064 , AD1115611, AD115611 LTFU) with historical comparator	Strimvelis (n=18) versus HSCT for haploidentical donor (n=7) versus HSCT for a MUD (n=15)	Survival at longest follow up period Intervention-free survival at longest follow up period	Key secondary outcomes: Severe infection rate, Lymphocyte subset counts, T cell receptor excisions circle analysis, T cell proliferative capacity Post-hoc analyses: Transduced cell engraftment in CD15+ and CD34+ cells, antibody response to vaccination, duration of IVIG administration	Lansky performance index Paediatric Quality of Life Inventory
Named Patient Programme 200893	Investigator sponsored study initiated in 2014 after the enrolment in AD1117064 compassionate use programme had ended	Strimvelis ([redacted])	Survival at longest follow up period Intervention-free survival at longest follow up period	Not reported	Not reported

Outcome data from a long term follow up of ADA-SCID patients receiving HSCT from a matched unrelated donor or HSCT from a haploidentical donor [3] were included as historical comparators to studies AD1115611 and AD1115611 LTFU. Overall survival was the primary outcome in the pivotal (AD1115611) and long term follow up studies (AD1115611 LTFU). Key secondary outcomes

focused on factors related to immune reconstitution such as rate of severe infections, T-cell counts and modification of systemic metabolic defects. Physical growth was also listed as a key secondary outcome in the long term follow up study. Primary and secondary outcomes were not available for Pilot study 1 (AD1117054), and while outcomes were predefined for Pilot study 2 (AD1117056), no distinction was made between primary and secondary. For the Compassionate Use Programme (AD1117064), the primary outcome was the safety of Strimvelis.

Data from [redacted] patients in the Named Patient Programme (recruited from 2014 after the data cut from AD1115611 LTFU) were not included in the company submission evidence synthesis. The reasons given for this were, firstly that the company did not have direct access to the data in the same way as for the other studies of Strimvelis as the study was not sponsored by GSK. Secondly, formal data analysis is planned after 3 years of follow up has been completed. However, some data from the Named Patient Programme was provided in Appendix 6 and the company also provided additional patient characteristics in response to a request for clarification made by the ERG (where applicable these data will be discussed below).

Although there are limitations in terms of reporting study design, methods and results for the Named Patient Programme, the ERG judged it important to consider all available data on patients receiving Strimvelis. This is particularly important given the small sample size (N=18) of the Strimvelis Integrated Population included in the narrative synthesis of the company submission. Including the Named Patient Programme increases the total Strimvelis-treated population to [redacted].

4.2.2 Inclusion Criteria for Strimvelis Integrated Population and the Named Patient Programme

The main inclusion criteria across studies in the Strimvelis Integrated Population were:

- ADA-SCID patients
- No available HLA-identical sibling donor
- ≥ 6 months of PEG-ADA treatment with demonstrated inefficacy or intolerance; or where PEG-ADA treatment was not a long term option

The inclusion criteria appear appropriate and reflect the NICE scope. The criterion of ≥ 6 months of PEG-ADA treatment with demonstrated inefficacy or intolerance is likely to differ from current UK practice. However, this may not be important as there is no evidence that duration of PEG-ADA use is prognostic for treatment outcomes.

No inclusion criteria were reported for the Named Patient Programme.

4.2.3 Patient Characteristics

Strimvelis Integrated Population

Summary characteristics for the 18 patients included in the Strimvelis Integrated Population are provided in Table C21 of the company submission. Four patients had received a prior HSCT from a haploidentical donor. Only three patients did not receive any prior PEG-ADA treatment, the other 15 patients received PEG-ADA for a mean of 20.4 months (range 1 to 71 months).

The median age was 1.37 years (mean= 2.09 years, range 0.5 to 6.1 years); 40% were female; 55.6% were White, 27.8% White/Arabic, 11.1% African heritage, and 5.6% Asian. 44.4% travelled from a European country to receive treatment, 27.8% from the Middle East, 16.7% from South America, 11.1% from North America.

The ADA-SCID treatment population in the UK is very small and epidemiological data for this population is limited. Therefore it is difficult to draw firm conclusions on the representativeness of the data to the UK. Although no patients from the UK have yet received Strimvelis, in consultation with a clinical advisor (Dr Andrew Gennery, who treats ADA-SCID patients at one of the two specialist centres in UK), the ERG judged that there did not appear to be substantial concerns regarding the representativeness of the Strimvelis Integrated Population to ADA-SCID patients in England.

In terms of important prognostic indicators, the clinical advisor suggested viral infection at baseline would be an important factor to consider when evaluating the generalisablity of this population. He suggested that viral infection is likely to be high in ADA-SCID patients (except for very young patients). We requested clarification from the company on presence of viral infection at baseline. The company response stated that no patients were identified with viral infections at screening. Therefore, this potentially raises issues regarding the generalisability of these patients to the UK and it is unclear the extent to which these findings are applicable to those with viral infections at baseline.

A further ERG request for clarification was on number of patients screened for eligibility and the number of patients excluded. The company responded that 12 patients were screened for the Pivotal Study and no patients were excluded. However, no information was available on numbers screened or excluded for Pilot Study 1, Pilot Study 2 and the Compassionate Use Programme (comprising a third of the Strimvelis Integrated Population). Therefore, there is uncertainty regarding recruitment of these 6 patients and whether patients at greater risk were excluded from these studies.

The historical comparator population[3] of patients receiving HSCT from a MUD had a similar but slightly lower median age of 0.58 years (range was narrower than for Strimvelis: 0.08 to 2 years). The

median age for patients receiving HSCT from a haploidentical donor was lower (0.42 years, range 0.17-1.33 years) but these data were not available for the subgroup (receiving treatment from 2000-2009) used for historical comparison in the company submission.

Prior PEG-ADA treatment was much lower in the historical comparator population (22% compared with 83% for the Strimvelis Integrated Population)[3]but was not broken down by type of transplant so this is the average for all included transplants, not just MUD and haploidentical.

Named Patient Programme

The ERG requested comparable patient characteristics for those included in the Named Patient Population (see Table 3).

[redacted]

Table 3 Patient characteristics included studies of the evaluation of clinical efficacy and safety (provided by company in response to ERG request A3 for clarification)

Subject	Sex	Race	Country of origin at diagnosis	Prior SCT or PEG-ADA treatment	Age at gene therapy, years	GSK2696273 treatment date	GSK2696273 dose, CD34+ cells x 106/kg	VCN of product

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

4.2.4 Quality assessment of studies of Strimvelis Patients

The ERG's critical appraisal of data from the Strimvelis Integrated Population is given in Table 4.

Table 4 ERG's critical appraisal of data from the Strimvelis Integrated Population

Study question	Response	How is the question addressed in the study?
Was the cohort recruited in an acceptable way?	Not clear	There were limitations in reporting of recruitment methods particularly for Pilot Study 1, Pilot Study 2, and the Compassionate Use Programme. Particularly in terms of numbers screened and excluded.
Was the exposure accurately measured to minimise bias?	Yes	No evidence of bias was identified regarding measurement of exposure
Was the outcome accurately measured to minimise bias?	Not clear	Only results for the pivotal study are reported as being collected according to GCP.
Have the authors identified all important confounding factors?	No	Although some discussion of confounding was included it was judged that the impact of potential confounding was not sufficiently considered in the description of the results in the company submission.
Have the authors taken account of the confounding factors in the design and/or analysis?	N/A	As indicated in the company submission it was not possible to adjust for confounding in the analyses.
Was the follow up of patients complete?	Yes	All patients are described and withdrawals from the study are accounted for.
How precise (for example, in terms of confidence interval and p values) are the results?	N/A	As reported in the company submission all comparisons are descriptive.

Critical appraisals were conducted separately for studies AD1115611: Pivotal, AD1115611 LTFU, AD1117056: Pilot 2, AD1117054: Pilot 1, AD1117064 CUP (see tables C11-C15 in the company submission) which comprised the Strimvelis Integrated Population. No critical appraisal was conducted for the study of the Named Patient Programme. All included studies were open label, single armed trials, with small sample sizes ranging from 1-14 patients providing data on a total of [redacted] patients receiving Strimvelis. Small single arm trials compared to historical comparators are often at

strong risk of bias and lack precision in estimation of effects. However, given the low incidence of ADA-SCID the study design used to evaluate clinical effectiveness was considered appropriate.

The ERG conducted their own critical appraisal for each study using the same questions provided in the company submission. Given the similarity of methods and critical appraisal ratings across studies these will be discussed as a whole for the Strimvelis Integrated Population. There was insufficient information reported to conduct critical appraisal for data from the Named Patient Programme.

The ERG critical appraisal largely agreed with that conducted by the company (see Table 4). The main difference in judgement was whether all important confounding had been identified. The ERG considered that the potential impact of confounding between Strimvelis and the historical comparator was substantial and judged that this was not sufficiently communicated in the company submission.

4.2.5 Summary of data on overall survival and intervention-free survival

The data on overall survival and intervention-free survival are summarised in Table 5.

Table 5 Survival outcomes and reported additional treatment for Strimvelis patients

Patient number	Clinical study	Repeat dose or second bone marrow harvest	Overall survival	Intervention-free survival	Additional treatment required	Length of follow up, years
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Overall survival

Strimvelis

Overall survival was 100% in the [redacted] patients that comprised the Strimvelis Integrated Population and the Named Patient Programme (see Table 5). Follow up time in the Strimvelis Integrated Population ranged from 2.3 to 13.4 years (median =6.95 years); it was not reported for the Named Patient Programme.

A limitation of the overall survival data is that it overestimates the benefits of Strimvelis as those who survived but required alternative treatments (such as HSCT or long-term PEG-ADA treatment) due to the lack of efficacy of Strimvelis are counted as treatment successes. As noted by the European Medicines Agency,[31] intervention-free survival (see below) is more likely to provide a better reflection of the effectiveness of Strimvelis.

HSCT from a MUD or a haploidentical donor

The key historical comparator data for HSCT is provided by Hassan et al[3] which is the largest data source on outcomes for patients with ADA-SCID receiving HSCT currently available in the literature. Overall survival was 67% (10/15 patients) for those receiving HSCT from a MUD between 1995 and 2009. For HSCT from a haploidentical donor, overall survival was 71% (5/7 patients). This was based only on data from 2000-2009 as this was considered a more applicable comparison with Strimvelis due to substantial improvements in effectiveness overtime.

Although the ERG acknowledges these are the best available published estimates for HSCT in ADA-SCID patients, there are substantial limitations of these data as a historical control for Strimvelis. As noted by our clinical advisor, overall survival has increased substantially over time following HSCT after data was collected in this historical comparison. This reflects several innovations such as genomic tissue typing which improves matching of unrelated donors, more frequent use of reduced-intensity conditioning to reduce mortality, improved surveillance and treatment of infections, and advances in supportive care. [6]

For HSCT from a haploidentical donor overall survival improved from 43% for patients receiving for all treatment periods to 71% for patients receiving treatment between 2000 and 2009.[3] A similar subgroup analyses by year for HSCT from a MUD was not available from that dataset which particularly limits the comparison between this treatment and Strimvelis. Therefore the data used in the company submission suggests HSCT from a haploidentical donor is more effective than HSCT from a MUD for overall survival. This lacks face validity since currently HSCT from a haploidentical donor is considered a second line option in UK practice after HSCT from a MUD.

Although data for improvements in HSCT from a MUD are not currently available specifically for ADA-SCID patients, a study[6]assessing outcomes in children with non-malignant diseases observed an increase in 5 year overall survival from 72% (in 1992-2002) to 93% (in 2003-2013).

The CS also provided a narrative synthesis of case reports and case-series of overall survival in patients receiving HSCT from a MUD or a haploidentical donor. Their narrative synthesis reported ranges of overall survival for studies with a minimum of 5 patients (and Table C22 summarises all included studies). Reported ranges in the narrative synthesis of 60-71% for HSCT from a MUD and 23-68% for HSCT from a haploidentical donor potentially overestimate the precision of overall survival for these treatments. Small changes in the threshold of minimum included patients impacts substantially on the range of overall survival estimates. For example, for HSCT from a MUD if the threshold changes to four or more patients the range for overall survival is 60-100%. Similarly for

HSCT from a haploidentical donor, reducing the threshold to at least 4 patients (range: 0-68%) or at least 3 patients (range 0-100%) changes the range substantially. When considering all studies included in CS Table C22 overall survival estimates ranged from 0-100% for both HSCT from a MUD and HSCT from a haploidentical donor. Therefore, the ERG judged the data reported as a whole in Table C22 provided a better reflection of the uncertainty regarding overall survival from HSCT from a MUD or haploidentical donor than the reported ranges provided in the text of the narrative synthesis.

Intervention free survival

Strimvelis

Data on intervention free survival with Strimvelis was available for [redacted] patients: There was insufficient data on PEG-ADA use for Patient[redacted] to evaluate intervention-free survival for these patients. Of the evaluable patients [redacted] experienced intervention-free survival (i.e. did not require either ≥ 3 months of PEG-ADA treatment or HSCT): 14/17 (82.3%) in the Strimvelis Integrated Population, and [redacted] in the Named Patient Programme.

[redacted]

Of the [redacted] patients requiring additional interventions, two received a sibling donor transplant (Patient[redacted] and Patient [redacted]) [redacted] One patient (Patient[redacted]) received a second dose of Strimvelis and 8.7 years of PEG-ADA treatment at the time of last follow-up. [redacted]

In response to an ERG request for clarification, the company stated that [redacted] Strimvelis patients (four from the Strimvelis Integrated Population [redacted]) received back up bone marrow cells. The company reported that one patient received a contaminated product, three patients received back up bone marrow cells due to events after Strimvelis. However, in an additional request for clarification the company stated that two patients had a contaminated drug product so the data provided appeared inconsistent.

[redacted]

HSCT from a MUD or a haploidentical donor

Intervention free survival data is very limited for HSCT from a MUD or haploidentical donor and it is not clear if the data reported on those receiving additional treatment is comparable with data on Strimvelis patients. Hassan et al[3]reported one patient receiving a rescue transplant after HSCT from a MUD but no further information is provided about additional treatment. Following HSCT from a haploidentical donor (2000-2009 subgroup), 2/7 did not engraft, resulting in one patient receiving gene therapy and the other patient starting PEG-ADA followed by two rescue transplants before death.

4.2.6 Immune function

Key secondary endpoint data relating to immune reconstitution are summarised in Table 6 below. Comparisons between Strimvelis, HSCT from a MUD and HSCT from a haploidentical donor were limited by a lack of comparable data. The proportion of Strimvelis patients experiencing a severe infection (requiring hospitalisation or prolonging hospitalisation after first 3-months of treatment) reduced from 14/17 (pre-gene therapy) to 10/17 (post-gene therapy) as did the severe infection rate. Although infection rates were described for HSCT from a MUD or haploidentical donor, differences in reporting prevented the ability to draw comparisons across treatments.

Rates of metabolic detoxification (based on dAXP and dATP levels) were high for Strimvelis, HSCT from a MUD, and HSCT from a haploidentical donor. The European Medicines Agency assessment[31] also reported responder rates for lymphocyte ADA activity in Strimvelis patients. Data were more variable with 56% responding at year 2 of follow up which dropped to 20% at year 4 and reached 75-100% at all other follow up periods. However, a comparison of dAXP levels at year 4 suggested ADA enzyme activity was sufficient for metabolic detoxification. Comparable data on lymphocyte ADA activity were not available for patients after HSCT from a MUD or haploidentical donor.

For Strimvelis patients CD3+ T cell counts increased substantially at 1 year from baseline and these improvements were maintained up to 8 year follow up. However, data on CD19+ B cells and CD16+ CD56+ NK cells were more variable. CD19+ cell counts remained below baseline levels throughout the duration of follow up. Geometric means for CD16+ CD56+ cell counts remained below baseline levels up to year 5 but then increased above baseline levels in years 6-8 (median levels were more variable but consistently above baseline between years 5-8). Differences in reporting made comparisons with HSCT challenging, however there was evidence that a high proportion of HSCT patients were able to return to normal counts for CD3+ (71% for HSCT from a MUD and 63% from a haploidentical donor) and CD4+ (86% for HSCT from a MUD and 100% from a haploidentical donor) cells. The presence of T cell receptor excision circles (TREC) is considered a marker of thymic activity. TREC in peripheral blood lymphocytes increased from baseline at Years 1-3 post treatment in Strimvelis patients, but declined from years 5-8 (although remaining above baseline levels). Comparable data for either HSCT comparator was not identified and therefore meaningful comparisons with Strimvelis were not possible.

The company submission reported nine Strimvelis patients discontinuing IVIG, however, in response to a request for clarification by the ERG, the company reported 11 patients had currently discontinued IVIG: in total, 11/17 (65%) Strimvelis patients discontinued IVIG during the follow up period (8 before 3 years follow up and 3 after 3 years follow up).

Most of the 11 Strimvelis patients that discontinued IVIG exhibited antibodies to a number of infectious antigens (e.g.10 patients had detectable antibodies to pertussis, 11 for tetanus toxoid, and 8 for hepatitis B). Although data is limited, vaccination response appears comparable for patients receiving HSCT from a MUD. [32-36]Comparable data were not identified for patients receiving HSCT from a haploidentical donor.

Of the six patients who did not discontinue IVIG, three patients experienced an unsuccessful response to Strimvelis treatment. No data were available for the Named Patient Programme.

A slightly higher discontinuation rate was found for HSCT from a MUD with 5/7 (71%) patients discontinuing over time.[3] All patients with data available (7/7, 100%) who received HSCT from a haploidentical donor discontinued IVIG treatment.[3]

Table 6 Summary of key secondary endpoints

Outcomes	Strimvelis Integrated Population	Strimvelis Named Patient Programme	HSCT from a MUD	HSCT from a haploidentical donor
Severe infection	Patients with an event: pre-GT 14/17 (82%) post-GT 10/17 (59%) Total events post-GT: 15 Severe Infection Rate: pre-GT 1.17 4 months to 3 year 0.26 8 years 0.17	Not reported	No comparable data reported	No comparable data reported
Metabolic detoxification	dAXP responders (<100 nmol/mL): 100% Lymphocyte ADA activity responders: ≥ 210 nmol/h/mg): 56% at year 2 20% at year 4 75-100% all other follow up periods	Not reported	Hassan 2012[3]: median dATP =56.5µM (range 0-227 µM) (n=6)	Hassan 2012[3]: two patients who received HSCT from a haploidentical donor both showed evidence of metabolic detoxification (dATP values of 5 µM and 37 µM).
Lymphocyte counts	CD3+ improved from year 1and maintained till year 8 CD19+ cell counts below baseline levels throughout follow up CD16+ CD56+ cell counts variable – geometric means below baseline until year 5 and above baseline years 6-8	Not reported	CD3+ 71% reached normal levels (Hassan 2012[3]) CD4+ 86% reached normal levels (Hassan 2012[3])	CD3+ 63% reached normal levels (Hassan 2012[3]) CD4+100% reached normal levels (Hassan 2012[3])
Thymopoiesis	TREC in peripheral blood lymphocytes increased from baseline at Years 1-3 post treatment, but declined from years 5-8 (although remaining above baseline levels)	Not reported	Not reported	Not reported

Discontinued IVIG	Total: 11/17 (65%) < 3 years: n=8 > 3 years: n=3	Not reported	5/7 (71%) (Hassan 2012[3])	7/7 (100%) (Hassan 2012[3])
Vaccination response	109 patients had detectable antibodies to pertussis, 9 11 for tetanus toxoid, and 7 8 for hepatitis B	Not reported	appears comparable to Strimvelis patients (Bhattacharya, 2005[32]; Grunebaum, 2006[33]; Honig, 2007[34]; Patel, 2009[35]; Baffelli, 2015[36]).	No comparable data available

4.2.7 Non-immunological events

Almost all (17/18) of the Strimvelis Integrated Population experienced a neurological, CNS or hearing event during treatment or follow up. Cognitive disorders were the most common event (n=5). Deafness was also a common problem with two patients reporting deafness and a further two patients reporting bilateral deafness. Three patients reported psychomotor hyperactivity.

High incidence of non-immunological problems was also found for ADA-SCID patients following HSCT.[7] The CS concluded that neither gene therapy nor HSCT appear to be effective in reducing non-immunological problems.

4.2.8 Patient and Carer Health Related Quality of Life results

Strimvelis

Lansky performance index data were available at year 4 (n=8), year 5 (n=9), year 6 (n=6), year 7 (n=6), year 9 (n=1) and year 13 (n=1) for the Strimvelis Integrated Population. All were rated as 'fully active, normal' at these follow up periods with the exception of one patient who had minor restrictions on strenuous physical activity at year 7. Although this patient did not experience neurological deficits, they had a foot deformity and muscle atrophy. Patient [redacted] completed the Paediatric Quality of Life Inventory at year 13 with a total score expected in an average healthy adolescent of that age. This quality of life data is potentially inconsistent with other data showing that 17/18 patients experienced a neurological, CNS or hearing impairment.

Additional data (although not pre-specified) showed that most (12/14) patients reported on-time vaccinations, attendance at school or preschool as appropriate for their age. However, most patients reported not participating in sports. The CS stated that this was mainly due to the wishes of parents however the ERG noted this may potentially be reflective of impairment of health.

The ERG requested if the company had collected data on families and carers of Strimvelis patients. The company responded that the Telethon Foundation (the charity responsible for care services in the Milan treatment centre providing Strimvelis treatment) had begun an anonymous formal assessment in July 2017. The company provided an example quote of a parent reporting that their stay in Milan was "…just like home". In addition, further quotes of positive feedback from patients on the experiences of families were provided:

"The biggest help was to find a babysitter for my daughter. It was a wonderful evening and we were really happy to go out together"; "We are so grateful for all that you did for us. We really felt welcomed by friends. We would never have imagined to receive all this. Now we only hope that all will be good for our son"; "Me and my family did not thank you enough for all the things you brought to us, it was too much and it helped us a lot, so thank you so much for everything."

HSCT from a MUD or haploidentical donor

Data on quality of life for patients receiving HSCT from a MUD or haploidentical donor were limited. A study of quality of life in SCID patients treated with HSCT in Newcastle included 12 patients with ADA-SCID.[15] Patients with ADA-SCID had significantly lower quality of life (except for the emotional domain) compared with published UK norms. However, as this was a poster presentation very limited data was provided including no information about the type of HSCT performed.

ADA-SCID patients treated with HSCT were associated with IQ levels more than two standard deviations below the general population mean (100) and had greater risk of behavioural problems as indicated by the Strengths and Difficulties Questionnaire. [37] However, since there is no comparable IQ data for Strimvelis patients and behavioural problems are measured differently, comparisons between treatments are not possible.

4.2.9 Summary of Critique

Summary of Survival data

Data on the effectiveness of Strimvelis are based on a total of [redacted] patients collected in a series of open label single arm trials. Of these, 18 comprised the Strimvelis Integrated Population which was the focus of the CS narrative synthesis (data for the [redacted] patients in the Named Patient Programme are summarized in Appendix 6 of the CS). Overall survival was 100% across the [redacted] patients (follow up time ranged from 2.3 to 13.4 years in the Strimvelis Integrated Population). Intervention free survival was [redacted] for all patients but rates differed substantially between the Strimvelis Integrated Population (82.3%) and the Named Patient Programme ([redacted]). Small open label single arm trials are

inherently at a high risk of bias and lack precision. A small number of deaths or treatment failures can lead to substantial changes in survival estimates making such estimates highly uncertain.

Historical controls for HSCT from a MUD and from a haploidentical donor were provided by Hassan et al (2012).[3] Overall survival was 67% (10/15 patients) for those receiving HSCT from a MUD between 1995 and 2009. For HSCT from a haploidentical donor, overall survival was 71% (5/7 patients) based on transplants from 2000-2009. The main limitation of these historical controls is that overall survival from HSCT has improved substantially over time. Therefore, these published estimates of overall survival (particularly for HSCT from a MUD which includes data from 1995) from HSCT are likely to be an underestimate compared with current provision and therefore potentially overestimate the comparative benefits of Strimvelis. In addition, other case reports or case series were narratively reviewed, overall survival estimates in these studies range from 0-100% for both treatments. As with Strimvelis, overall survival estimates for HSCT from a MUD and HSCT from a haploidentical donor are very uncertain and based on small sample sizes.

Summary of other outcomes

Although there was some variability across outcomes and over time, generally there was positive data supporting the benefits of Strimvelis for improving immune function (e.g. 100% responders based on dAXP levels, reduction in severe infections over time, high discontinuation rates of IVIG). Although there were challenges in comparing data on immune function after HSCT from MUD or haploidentical donors with Strimvelis all three treatments appeared to improve immune function and there was no strong evidence of differences in effectiveness between them.

None of the treatments included in the narrative synthesis found evidence of effectiveness in reducing non-immunological symptoms of ADA-SCID including CNS, neurological and hearing deficits.

Generalisabilty

The ADA-SCID treatment population in the UK is very small and epidemiological data for this population is also limited. Therefore it is difficult to draw firm conclusions on the representativeness of the data to the UK.

Although no patients from the UK have yet received Strimvelis, in consultation with a clinical advisor Dr Andrew Gennery (who treats ADA-SCID patients at one of the two specialist centres in the UK), the ERG judged that there did not appear to be substantial concerns regarding the representativeness of the Strimvelis Integrated Population to ADA-SCID patients in England. However, there still remain substantial uncertainties. Data were not available on numbers screened or excluded for six patients in

the Strimvelis Integrated Population in addition to the [redacted] patients in the Named Patient Programme which in total reflects almost half of all patients treated with Strimvelis. It is therefore unclear if patients at greater risk were excluded from these studies.

Similarly, there were no concerns that the patients included in Hassan et al[3] differed from current patients receiving HSCT in the UK. Similar limitations regarding reporting of viral infections and numbers of patients screened for inclusions were found for this study. However, the nature of the study (a survey of treatment outcomes in usual practice) suggests a lower potential for selection bias.

4.3 Adverse events

Strimvelis

All patients in the Strimvelis Integrated Population reported an adverse event (see table C27 in the company submission for further details). In addition, all patients experienced an infection or infestation. The most common infection adverse events were upper respiratory tract infections, gastroenteritis, and rhinitis. Fifteen patients experienced serious adverse events, these were most frequently due to infections (e.g. device-related infections, gastroenteritis, and pneumonia). For further discussion of serious infections see section 4.2.6 above.

As discussed above (see section 4.2.7) 17/18 of the Strimvelis Integrated Population experienced neurological, CNS or hearing impairment which is potentially inconsistent with the quality of life ratings which suggested patients returned to normal health.

Twelve patients experienced 27 adverse events potentially related to auto-immunity. Antinuclear antibody positive was the most frequent event. Four patients experienced six serious auto-immunity adverse events (anti-neutrophil antibody-induced neutropenia, autoimmune thrombocytopenia [2 events], autoimmune aplastic anaemia, autoimmune hepatitis, and Guillain-Barre syndrome). Of these, two required reintroduction of PEG-ADA to restore immune function.

Other Gene Therapy

The CS included information on the adverse events associated with other gene therapies. Cases have been reported of SCID patients developing leukaemia after gene therapy.[38, 39] Although no cases of leukaemia have been reported yet in ADA-SCID patients receiving gene therapy further long term follow up is needed to confirm the risk in this population. There is also a theoretical risk of gene

silencing leading to a loss of therapeutic benefit although this requires further study to confirm the risk in ADA-SCID patients.

HSCT from a MUD or haploidentical donor

Table C28 in the company submission summarises adverse events for HSCT from MUD and haploidentical donors. A key adverse event focused on in the company systematic review was graft versus host disease (GvHD).

Eight case reports/case series contributed to the estimation of GvHD rates following HSCT from a MUD in the company submission providing data on 28 patients, although data from Booth[7]was not used as numbers of events were not reported (Table C28). Nine patients experienced GvHD (Grade I, n=1; Grade II, n=2; Grade III, n=4 and Grade not reported, n=2). One patient was reported to have experienced chronic GvHD (grading not reported) and seven patients acute GvHD, and chronicity not reported for one patient.

The company submission used an unweighted pooling of these events across studies to estimate rates of GvHD. They reported a summary total of 32.1% (9/28) of patients experiencing GvHD across studies. In addition, they estimated number of acute (3/28) and chronic GvHD (1/28) Grade III or IV events.

Five case reports/case series contributed to the estimation of GvHD rates following HSCT from a haploidentical donor in the company submission providing data on nine patients. As above, data from Booth [7] was not used as number of events were not reported. Similarly, an unweighted pooling of events across studies was conducted with 3/9 patients in these studies experiencing GvHD. One patient experienced Grade III GvHD and since it was not reported whether this was acute or chronic the company submission conservatively assumed acute GvHD.

There are a number of limitations to the GvHD data which makes these estimates very uncertain. As the company submission notes, definitions for categorising GvHD differ widely in the literature which makes comparisons across studies challenging. For example, definitions and reporting of acute and chronic GvHD differ across studies and also some studies did not report the grade. Despite acknowledging these substantial differences the company decided to conduct an unweighted pooling of these data across studies (i.e. number of events was added up across studies as if the data constituted a single study). This was not considered appropriate as this ignores important between-study differences such as varied definitions of GvHD, differences in usual care over time and across centres. In addition, the summaries did not include an estimation of the precision associated with the

estimated rates which is important because these estimated rates are likely to be highly imprecise and this is not clear in the submission.

A further important limitation was that rates of Grade III or IV acute and chronic GvHD events following HSCT from a MUD reported in the company submission lacked justification. While it is clear that three acute Grade III events were reported across studies, there is no justification provided why the fourth patient (for whom it was not reported whether the event was acute or chronic) was assumed to experience chronic Grade III GvHD.

Summary
Infections were common after Strimvelis, however, severe infection rates reduced over time, potentially due to improvement in immune function. There is no evidence that rates of infection after treatment differ between Strimvelis, HSCT from a MUD, and HSCT from a haploidentical donor, but variability in reporting makes comparisons difficult.

A major difference between Strimvelis and HSCT was that some patients experienced GvHD events after HSCT, whereas no GvHD events were reported for Strimvelis-treated patients. However, there were important limitations in how estimates of GvHD were calculated in the company submission and some rates lacked justification.

A potential risk of gene therapy identified in other SCID patients was the risk of leukaemia but no events have occurred in ADA-SCID patients. However, given the small sample size of patients who have received Strimvelis, this cannot yet be ruled out as an important potential risk.

4.4 Critique of the indirect comparison and/or multiple treatment comparison

Not applicable

4.5 Additional work on clinical effectiveness undertaken by the ERG

Not applicable

4.6 Conclusions of the clinical effectiveness section

The clinical effectiveness section in the company submission was based on a systematic review of Strimvelis, HSCT from a MUD and HSCT from a haploidentical donor. The ERG considered the submitted evidence largely reflected the decision problem provided in the final scope.

For Strimvelis, the narrative synthesis included data only from the Strimvelis Integrated Population although limited data from the Named Patient Programme was provided in Appendix 6. Although

there were some limitations in the comprehensiveness of the search for HSCT clinical effectiveness data, the ERG judged it was unlikely important studies had been missed.

Overall survival rate was substantially higher for Strimvelis patients (100%) than historical comparator data for HSCT from a MUD (67%) and HSCT from a haploidentical donor (71%). However, there are important limitations to these data:

- Firstly, this is based on a very small sample of patients: [redacted] patients receiving Strimvelis, 15 patients receiving HSCT from a MUD and seven patients receiving HSCT from a haploidentical donor. Therefore there is substantial uncertainty regarding the precision of these estimates of overall survival. A small number of deaths during further follow up would substantially impact on conclusions of the efficacy of Strimvelis.
- Secondly, the overall survival outcome overestimates the benefits of Strimvelis as patients who survived but required an alternative treatment (such as long-term PEG-ADA or an HSCT) due to lack of efficacy are still counted as a treatment success. Intervention-free survival was lower for Strimvelis ([redacted] and there was no comparable data for this outcome in HSCT from a MUD or a haploidentical donor. In agreement with the European Medicines Agency, the ERG considered intervention-free survival to be a more relevant outcome for evaluating the clinical effectiveness of Strimvelis.
- Thirdly, empirical data and clinical expert opinion suggest overall survival from HSCT has improved substantially over time. Therefore, the historical comparator probably provides an underestimate of the likely survival rate in HSCT from a MUD or from a haploidentical donor and therefore likely overestimates the comparative benefits of Strimvelis.

On key secondary endpoints, there was positive evidence for improved immune function in Strimvelis, HSCT from a MUD and HSCT from a haploidentical donor. There was no evidence of substantial differences on immune function between these treatments. Similarly, there was no evidence of substantial differences in non-immunological outcomes (such as neurological and developmental effects of ADA-SCID). None of the included treatments showed strong improvements from baseline.

Comparisons of adverse events between Strimvelis, HSCT from a MUD and HSCT from a haploidentical donor were limited due to variable reporting across studies. However, the most frequent adverse events were similar such as infections. Key differences were in terms of the presence

of GvHD events which were experienced by some patients receiving HSCT but not by those receiving Strimvelis.

On the other hand, adverse events reported in gene therapy trials in other conditions have identified important potential risks. For example, leukaemia has been reported in some patients included in gene therapy trials. Although similar data have not yet emerged in ADA-SCID patients continued follow up is needed before this can be ruled out as a potential risk of Strimvelis treatment given the small sample size of included studies (a total of [redacted] patients). If such adverse events were identified in future studies this would substantially change the risk-benefit profile of the treatment. Theoretically, there is also a potential risk of gene silencing that could lead to a loss of therapeutic benefit over time.

5 Cost Effectiveness

This section focuses on the economic evidence submitted by the company and the additional information provided in response to the ERG's points for clarification. The submission was subject to a critical review on the basis of the company's report and by direct examination of the electronic version of the economic model. The critical appraisal was conducted with the aid of a checklist to assess the quality of the economic evaluation[40] and a narrative review to highlight key assumptions and areas of uncertainty. Section 6 presents additional analyses and scenarios independently undertaken by the ERG to further explore these uncertainties.

The company's economic submission included:

- A description of a systematic review conducted to identify published HRQoL data (CS, Section 10.1.5) with further details presented in separate appendices (CS, Appendices 3, 5).
- A report on the de novo economic evaluation conducted by the company. The report included a description of the patient population, the model structure and assumptions used in the economic model (CS, Section 12.1); the clinical, quality-of-life and resource use parameters used in the economic model (CS, Section 12.2); the measurement and valuation of health effects and quality-of-life data used in the cost-effectiveness analysis (CS, Section 10.1.9); the cost and healthcare resource use identification, measurement, and valuation (CS, Section 12.3); the approach to sensitivity analysis (CS, Section 12.4); the cost-effectiveness results for the base-case and sensitivity analyses (CS, Section 12.5); an overview of any subgroup analyses (CS, Section 12.6); the methods of validation (CS, Section 12.7); and the final interpretation and conclusion of the economic evidence (CS, Section 12.8).
- An electronic copy of the company's economic model developed in Microsoft Excel®.

In response to a number of points for clarification raised by the ERG, the company further submitted:

- A descriptive reply to the ERG's points for clarification, alongside additional data and analyses requested by the ERG.

5.1.1 Searches

The CS contained the search strategies used to identify relevant economic studies concerning ADA-SCID. The search strategies were briefly described in the main body of the submission in Section 11.1.1 and Section 10.1.5. Full details were provided in Appendix 3, Section 17.3.

The electronic database EMBASE was searched on 28th February 2017 via the Elsevier host. The search combined terms for ADA-SCID with terms for cost-effectiveness.

The sources searched to find economic evidence are limited. The NHS Economic Evaluation Database, EconLit and PubMed are all relevant databases that could have yielded further economic studies. In addition, no searches for unpublished economic studies were carried out. Sources such as Research Papers in Economics (RePEc) and abstracts from relevant conferences may have been worth searching to capture any unpublished economic literature.

The EMBASE search strategy could not be fully appraised by the ERG as we do not have a subscription to the Elsevier version of EMBASE. However, it was possible to note some general limitations of the EMBASE search strategy presented in the CS.

The subject heading (EMTREE term) adenosine deaminase deficiency/ was not included in the EMBASE strategy which may have limited the comprehensiveness of the search. In addition, the terms used for the cost-effectiveness section of the strategy are very limited. No subject headings (EMTREE terms) have been included, a very narrow range of text word searches are included and truncation has not been used. The search could have been improved by utilising an economic study design search filter or a recognised search strategy for the retrieval of economic studies such as those listed on the ISSG Search Filters Resource website. This would have ensured a more comprehensive search strategy for economic studies of ADA-SCID and minimised the risk of missing studies.

5.2 ERG's summary and critique of company's submitted economic evaluation

Table 7: ERG's summary and critique of company's submitted economic evaluation

	Approach	Source / Justification	Location in CS
Model	A short term decision tree is used to establish the proportion of patients who achieve each outcome from initial procedure (HSCT or Strimvelis); Markov health states calculate quality adjusted survival and costs in those who have successful treatment procedures. At the outset, patients are assigned to HSCT treatment or to Strimvelis treatment and all patients begin receiving PEG-ADA treatment (19 weeks vs 9 weeks respectively). The pathway probabilities dictate the initial transplant outcomes (see states and events). Surviving patients are assumed to have mortality and health-related quality of life in line with the general population. Those who fail initial treatment are assigned further rescue treatments, delays and costs. 100 year (lifetime) time horizon is used.	The structure reflects the UK's treatment pathway for ADA-SCID for patients without a MRD. The structure was formed on the basis of expert clinical and health economic advice sought by the company.	Section 12.1.3; p136-1377 Section 12.1.4; p138-140
States and events	The model includes four main outcomes: (i) Success, long term survival; (ii) unsuccessful engraftment, PEG-ADA, awaiting rescue HSCT; (iii) death; (iv) long term survival after rescue HSCT. Patients with unsuccessful engraftment (ii) are assumed to undertake a rescue MSD HSCT two years after initial procedure.	The modelling approach was reported to be validated by expert advice.	Section 12.1.3; p136-1377 Section 12.1.4; p138-140
Comparators	For patients without a MRD, current treatment options for ADA-SCID include: • HSCT from a matched unrelated donor (MUD) • HSCT from a haploidentical donor • Long term enzyme replacement therapy Long-term ERT is not seen as a preferred treatment option in England	Aligned with NICE's final scope: "*Bone marrow transplant (including HSCT from an HLA - matched unrelated donor or HSCT from an HLA - haploidentical donor)"*	Section 12.1.2; p136
Natural History	It was assumed that all patients survive the wait to the initial procedure. QALYs gained in the wait period are added as a lump sum those calculated in the Markov process for extrapolation. The survival outcomes from initial procedures are applied to the simulated cohort at the end of the initial wait period.	The estimates of survival, modelling approach and associated cure assumptions were reported to be validated by expert clinical advisors.	Section 12.2.1; p149-150

	Three years after a successful treatment Strimvelis and HSCT patients were assumed to be cured with general population mortality risks from lifetables. Thus the treatment benefits of Strimvelis and HSCT are assumed to be life-long.		
Treatment effectiveness	Strimvelis and HSCT survival outcomes were derived from the long-term integrated population study (n=18) and a historic cohort [Hassan et al (2012)] respectively. Patients in the integrated population of the Strimvelis clinical programme (median follow-up of 6.9 years) had a 100% survival rate and an 82.4% intervention-free survival rate. Three patients suffered failed engraftment. Two patients received a HSCT from a HLA-matched sibling donor a third patient continues to receive PEG-ADA following unsuccessful gene therapy. The NPP also recorded 100% survival. Patients analysed in Hassan et al (2012) (median follow-up 6.5 years) reported an overall survival from patients who received a MUD and haploidentical HSCT of 67% (10/15) and 43% (13/30) respectively. However, the 71% (5/7) OS after HSCT from a haploidentical donor recorded in Hassan (2012) for the 2000-2009 cohort (N=7) was deemed a better reflection of survival than the 43% recorded for the entire Hassan cohort by the manufacturer and NICE at a HST scoping meeting. From those patients that survived initial therapy, three Strimvelis patients (3/17) two haploidentical patients (2/7) and one MUD patient (1/15) required rescue therapies after unsuccessful engraftment. [redacted] Approach to modelling OS as described in natural history. GvHD treatment benefit described in adverse events.	The chief driver of QALY gain with Strimvelis is higher rates of survival. Alternative treatment benefits include circumventing the need for a stem cell donor search, no risk of immune rejection (GvHD) and a reduced wait time to procedure. The company acknowledged the limited data available concerning ADA-SCID patients' long-term outcomes and provides an additional two-way sensitivity analysis to explore the uncertainty around the mean life expectancy and utility scores of ADA-SCID patients.	Section 12.2.1; p149-151
Adverse events	GvHD rates (acute and chronic) were sourced from the ADA-SCID literature and case reports which were included in the model as a treatment-related AE after MUD or haploidentical HSCT. The expected duration of aGvHD or cGvHD was sought by clinical advisors. The disutility of incurring GvHD was taken from the published literature. The product of the duration of GvHD and its disutility provided a one-off QALY burden applied to the model. The cost of GvHD was taken from the literature also. The Strimvelis Integrated population was the primary source of adverse event (AE) data. Infections were the most common SAEs and were included as a cost in the model. The cost of infection was taken from the literature. Rates of severe infection were 26% for the first 3 years, 7% for years 4-8 per person per year as observed in the Strimvelis integrated population. It was assumed this rate of severe infections was equal to that experienced by patients having a HSCT from a MUD or haploidentical donor. It was assumed patients do not experience a HRQoL decrement when incurs a serve infection.	GvHD rates and the utilities used in the model were based on values sourced from the literature. The duration of GvHD was informed by expert clinical advice. The safety findings of Strimvelis are in line with those expected in an ADA-SCID population that has undergone conditioning and is undergoing immune	Section 12.2.4; p155

	AEs related to conditioning regimens or specific to gene therapy were not included in the cost-effectiveness model.	reconstitution. AEs related to conditioning regimens were not included in the model due to data limitations.	
Mortality	Mortality stemmed from only two sources in the model: first, as a direct result of an initial HSCT; second, from general all-cause mortality. The rates of mortality for each procedure used in the model are as follows: Strimvelis: 0% HSCT - MUD: 33.3% Haploidentical donor: 28.6% MSD: 0% Only procedural mortality was captured in first three years. It was assumed patients incurred no mortality risk between diagnosis and initial procedure or while awaiting rescue transplant.	General population all-cause mortality rates for England and Wales were taken from national life tables and applied 3 years after a successful procedure. Expert clinical advice deemed this assumption reasonable.	Section 12.1.5; p140-141 Section 12.2.1; p149-151
Health-related quality of life	No disutility was applied to patients prior to initial procedure (i.e. Strimvelis or HSCT). Post-procedural morbidity was assumed to result in a utility decrement for six months for both initial and rescue procedures. One time QALY losses were applied for instances of GvHD. GvHD QALY losses were calculated as the product of the utility decrement of a GvHD event and the expected duration of an episode. Treatment with IVIG, occurrence of severe infection, AEs related to conditioning regimens and the systematic sequelae of ADA-SCID were assumed not to impact on HRQL. For patients six months beyond initial or rescue procedure the model applies general population EQ-5D scores by age band. Bereaved parent QALY loss associated with child's death was explored in a scenario analysis.	For simplicity no disutility was applied to patients prior to initial procedure (i.e. Strimvelis or HSCT). External acute myeloid leukaemia literature was used to estimate the utility of patients during the first six months after receiving initial or subsequent therapies (i.e. Strimvelis, an initial HSCT or a rescue HSCT).	Section 12.2.6; 163-164 Section 12.4.2; p179

		External literature was used to inform the relevant utility decrement of a GvHD event and the expected average duration of a GvHD episode was sourced through clinical advice. Uncertainties in GvHD related values were explored through scenario analysis. Uncertainties in health related quality of life values were explored through scenario analysis, including a lower HRQL for those receiving IVIG.	
Resource utilisation and costs	Resource use and costs included: Strimvelis' drug acquisition cost (unit price), administration and follow-up; management of adverse events; HSCT costs (initial procedure and follow-up) and subsequent treatment costs. The costs of conditioning therapies and adverse events not related to GvHD or severe infection were excluded from the model. Costs for GvHD events were applied across all patients in year 1 whilst severe infection costs were applied over 1-7 years post-procedure. Rescue therapy costs were applied as a lump sum to patients in the year 3. PEG-ADA costs were incorporated over the period preceding the initial procedure and during the wait to rescue procedure for those that failed engraftment. Strimvelis follow-up costs were assumed to be equal to those applied to HSCT, although an adjustment was made for VCN tests and the first two months of follow-up being conducted in Italy. The costs of follow-up extend for two years post-HSCT procedures and three years for gene therapy on account of VCN tests.	Unit costs were based on the literature, NHS Reference costs, the British National Formulary (BNF) / Medicine Complete and expert opinion. Where appropriate, unit costs were inflated to 2015/2016 prices and converted to British pounds using the exchange rate €1=£0.85. The price of the technology is set in euros and is to be paid to the San Raffaele Hospital. Administration costs for Strimvelis were based on a length of stay assumption	Section 12.2.6; p156-168 Section 12.3.6; p169-175

		informed by assumed administration periods for baseline patient preparation (31 days), treatment (50 days) and outpatient follow-up (60 days). Cost per severe infection was informed from the literature using a figure representing the proportion of hospital costs attributable to severe infections. The IVIG dosage was calculated using an exponential curve across the 25th percentile of the average weight of boys and girls in the UK. Resource use and costs associated with PEG-ADA drug acquisition was based on a dosage and unit cost acquired from expert advice. Initially the model applied the following annual cost for PEG-ADA: Annual PEG-ADA doses *(Average price of PEG-ADA per week + Infusion cost for PEG-ADA) However, in response to a request made by the ERG, the company estimated the dosage and costs of PEG-ADA based	

		on weight, as was undertaken for IVIG dosing. Administration costs of PEG-ADA and IVIG were assumed to follow NHS reference costs for "Consultant Led. Paediatric Clinical Immunology and Allergy Service". In response to clarification from the ERG, the company provided alternative administration costs calculated as the product of the PSSRU defined unit cost for nurse's time and the expected administration times for each drug. Costs associated with the HSCT procedure were assumed to follow NHS references costs for 'Bone Marrow Transplant, Allogeneic Graft (Haplo-Identical), 18 years and under' and 'Bone Marrow Transplant, Allogeneic Graft (cord blood), 18 years and under' for haploidentical and MUD transplants respectively. The procedural cost of a rescue transplant was assumed to equal the cost of a MUD transplant. Long term follow duration and costs was taken from the literature.	

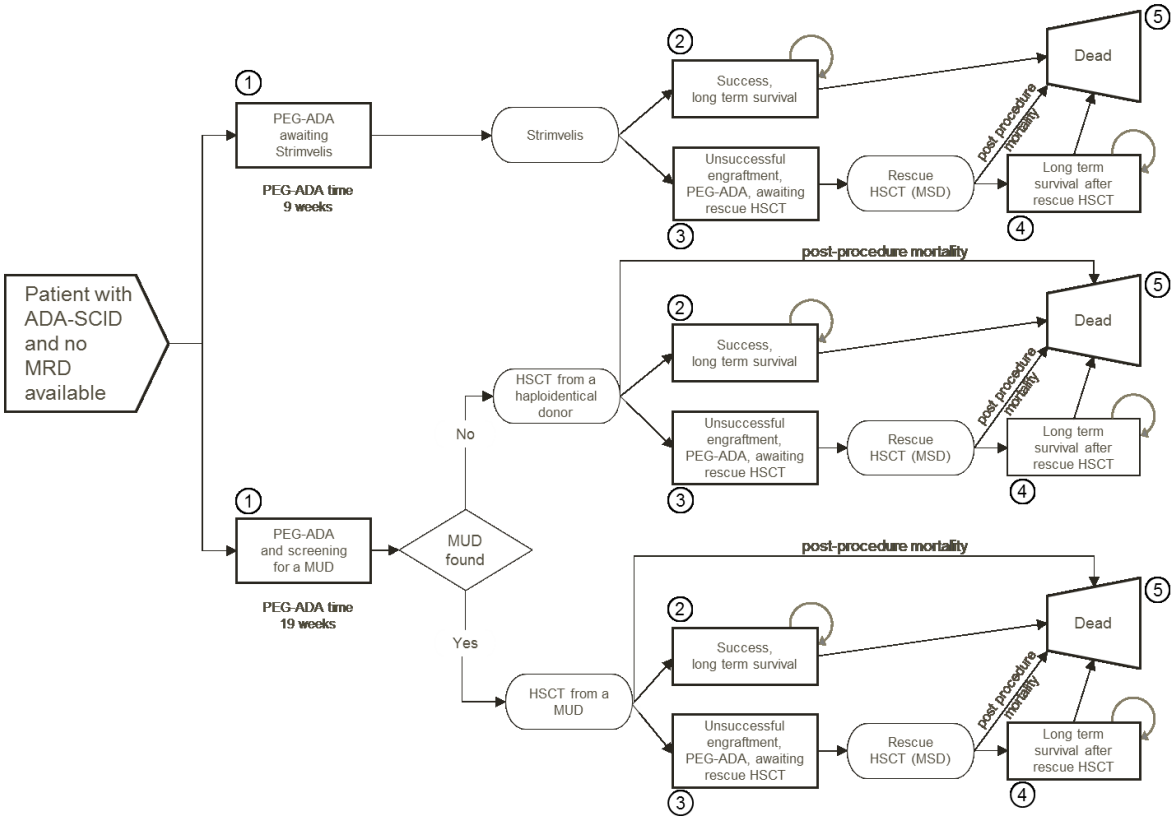
Discount rates	1.5% for utilities and costs (base case). 3.5% discount rates were presented as a scenario.	NICE Methods Guide	Section 12.1.7; p146-147
Population and Subgroups	No formal subgroups were presented due to the small numbers of patients in each treatment group.	The final scope did not specify specific populations and subgroups.	Section 12.6.1; p219
Sensitivity analysis	Deterministic sensitivity analysis and threshold analyses were performed on a series of model parameters. Probabilistic sensitivity analysis and scenario analyses were also performed. Tornado diagrams were produced on request.	NICE reference case	Section 12.5.11; p197-208 Section 12.5.12; p209-210 Section 12.5.13; p210-211 Section 12.5.14; p211-216
Key: HSCT: Haematopoietic stem cell transplant; OS: Overall survival; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; IVIG: Intravenous immunoglobulin; PEG-ADA: Adenosine deaminase conjugated with polyethylene glycol; VCN: Vector copy number; GVHD: Graft versus host disease; ERG: Evidence Review Group; QALY: Quality adjusted life year; CVC: Central venous catheter; AE: Adverse event; SAE: Serious adverse event; MUD: Matched unrelated donor; ADA-SCID: Adenosine deaminase deficiency severe combined immune deficiency: HLA; Human leukocyte antigen; ERT: Enzyme replacement therapy; EQ-5D; EuroQol 5-dimension questionnaire			

5.2.1 Model structure

In the absence of previously published cost-effectiveness analyses for Strimvelis or any other ADA-SCID treatment (CS, Section 11), the company undertook a *de novo* economic evaluation. The submission is based on a decision tree model, with long-term survival extrapolated using a Markov modelling approach. The decision tree characterises the first three year period and is used to establish the proportion of patients successfully treated with each initial procedure (HSCT or Strimvelis) and the proportion that require rescue transplant following failed engraftment. A Markov model approach is used to calculate quality adjusted survival and costs in patients who survive to the end of three years. Figure 1 reports the model structure used by the company. The post-procedural model structure comprises four main outcomes:

(i) *Success, long term survival*
(ii) *Unsuccessful engraftment, PEG-ADA, awaiting rescue transplant*
(iii) *Death*
(iv) *Long term survival after rescue HSCT*

Figure 1: Schematic of company model structure



CS, Figure 5 - p137

At entry to the model patients are assigned to either Strimvelis or HSCT and assumed to start enzyme replacement therapy (ERT) with PEG-ADA immediately to 'bridge' them to the transplant procedure. All patients assigned to Strimvelis go on to receive gene therapy, and hence the model does not incorporate a pathway for patients unable to donate adequate CD34+ cells. While the schematic of the model structure implies that patients allocated to HSCT are split between transplants from a MUD or a haploidentical donor, the model does not estimate the proportion of patients for whom no suitable MUD is available; hence the model compares Strimvelis with either HSCT from a MUD or HSCT from a haploidentical donor.

The model assumes the time between diagnosis and procedure differs between HSCT (19 weeks) and Strimvelis (9 weeks). The time between diagnosis and HSCT procedure characterises the process of searching for and obtaining stem cells from an appropriate donor. In patients who are allocated to receive HSCT from a haploidentical donor it is assumed that a search for a MUD is undertaken. The time between diagnosis and Strimvelis procedure characterises the process of determining eligibility for Strimvelis, arranging travel to Milan, and baseline patient preparation, and assumes no donor screening is undertaken. All patients are assumed to survive the initial wait to procedure.

After the initial procedure, patients are divided into one of three outcomes: (i) *Success, long term survival*; (ii) *Unsuccessful engraftment, PEG-ADA, awaiting rescue transplant*; (iii) *Death*. The decision tree incorporates only procedural based mortality, and patients who die as a result of their procedure are assumed to do so at the point of the procedure. Patients that survive the initial procedure with successful engraftment survive until entry to the Markov process after year 3. Patients that survive the initial procedure, but have unsuccessful engraftment, commence ERT with PEG-ADA and wait for a rescue HSCT ("*Unsuccessful engraftment, PEG-ADA, awaiting rescue transplant*"). All patients waiting for a rescue transplant are assumed to survive two years before receiving the transplant from a MSD. The company recognise that not all rescue treatments may take the form of transplant from a MSD and so include a sensitivity analysis in which the rescue transplant is from a MUD. Following rescue transplant patients are divided between two health outcomes (iii) *Death* and (iv) *Long-term survival after rescue HSCT*.

In the model, all patients who survive either an initial or rescue procedure begin IVIG treatment, the rate of which gradually reduces to zero at 8 years after the procedure. Patients who survive an initial procedure are also at risk of severe infection until 8 years have passed. It is assumed that the rate of severe infections and IVIG usage post-procedure is the same for Strimvelis and HSCT. A proportion of patients who survive an initial HSCT from a MUD or haploidentical donor are assumed to

experience GvHD, which may be acute or chronic. The onset of GvHD was associated with a one-off cost, and a QALY loss dependent on the severity of a GvHD event. Neither risk of GvHD nor severe infection was incorporated for rescue procedures. Surviving patients from the decision tree in (i) *"Success, long term survival"* and (iv) "*Long term survival after rescue HSCT*" enter a Markov process to model subsequent long-term health outcomes and costs from three years following the initial procedure, and are assumed to follow the survival rates and health related quality of life of the general population.

In summary, the decision model allocates procedural outcomes within the first three years plus 9 weeks for Strimvelis, and three years plus 19 weeks for HSCT; thereafter extrapolation occurs over a lifetime horizon with a cycle length of one year.

The ERG is not aware of any existing economic models for this condition and considers that the use of a decision tree with a Markov approach to extrapolating long term survival is appropriate for comparing the costs and health outcomes of alternative treatments for ADA-SCID. However, while the company model structure was stated to be "verified" by an expert modeller, the company provides no details concerning how the initial structure was informed. The simple pathway characterised in the company model provides an incomplete description of the routes by which patients may arrive to treatment. The alternative routes to treatment may imply additional pathways and/or additional treatment strategies. Furthermore, the company model may oversimplify the procession of events after the initial procedure. Both of these factors may obscure potentially important differences in cost and outcome between alternative treatment strategies and are discussed in more detail below.

The model assumes that all patients allocated to Strimvelis proceed to receive gene therapy. However, in practice the recommended minimum dose of Strimvelis is between 2 and 20 million purified CD34+ cells/kg, and patients must be assessed by bone marrow biopsy to determine their ability to donate sufficient CD34+ cells before any treatment can commence. The company report that one patient from the Strimvelis integrated population was unable to deliver the minimum purified CD34+ cells/kg (company response to clarification A6), and suggest that in practice the initial screening process would identify this patient as unsuitable to continue to treatment with Strimvelis. On this basis, if Strimvelis were approved it may be expected that a proportion of patients would incur the cost of an initial baseline assessment for gene therapy but would not subsequently receive treatment with Strimvelis. These costs are not accounted for within the model.

The model assumes that a decision to use gene therapy will be made before any search for a MUD is undertaken. While this reflects some recent clinical guidelines,[26] it does not necessarily reflect clinical practice (see Section 2.2.4). Some patients and their families may first wish to explore the potential for a MUD and reconsider gene therapy if no appropriate donor is found. For those patients the screening and wait time for Strimvelis would be in addition to, and not instead of, the screening and wait time for HSCT. For patients that undertake a search for a MUD and do find an appropriate donor, gene therapy might be considered as a second line treatment following failure to engraft. A proportion of patients who received Strimvelis in the integrated population did so after an unsuccessful HSCT from a MUD. In these patients the screening and wait time for Strimvelis would be in addition to the screen and wait time for HSCT, and the cost of both procedures would be incurred.

The probability of identifying an appropriate MUD, and the potential wait time for an HSCT, may differ according to patient characteristics such as ethnicity and the patient's HLA type. The ability to wait may depend on patient characteristics such as the presence of an active viral infection, which may indicate greater urgency in finding a donor. The clinical advisor to the ERG described that in UK practice, concurrent with tests undertaken to confirm a diagnosis for ADA-SCID, tissue samples are taken from the patient's parents and immediate family for typing and a search of the Anthony Nolan registry would be initiated. The results of the tissue sample tests would be expected within approximately one week, and information regarding the existence of a cord blood match would be expected within approximately two weeks. The ERG found evidence to suggest that the wait time for HSCT from a MUD using cord blood is approximately 2 weeks, and is shorter than the wait time for transplant using adult bone marrow.[18] Hence shortly after it is established that patients do not have a suitable MRD, information regarding the potential wait time and cord blood match should be available. The clinical advisor to the ERG described that the search process for a MUD would be paused if at this point the patient decides to undergo gene therapy.

The ERG therefore note that the expected wait time, and the potential difference in wait time between gene therapy, HSCT from a MUD and HSCT from a haploidentical donor may be predictable by, and differ according to, known patient characteristics. If a reduction in wait time is an important factor in either the choice of treatment or in establishing the value for money of Strimvelis, then these factors could have been reflected in the model structure, for example by including branches with different expected wait times (e.g.to indicate the existence of a cord blood match in the bone marrow registry), or with the use of subgroups (e.g. to indicate longer expected wait times in certain ethnic groups).

In the process of preparing for treatment with Strimvelis, patients are required to donate and have stored a 'back up' bone marrow transplant that could be used in the event of failure. Similar 'back up' transplants may be used in HSCT. The model does not incorporate the usage of such back up, which may be associated with additional resource use and impact on health related quality of life.

The decision to include only procedural based mortality in the first three years of the model may be inadequate to describe the possible sequence of events for sicker patients, including those with active viral infections and who require urgent treatment. These patients may have worse prognosis regardless of treatment received, and may experience mortality during the wait for the initial or rescue procedure. Omission of non-procedural mortality may therefore overestimate quality adjusted survival, and correspondingly overestimate the benefits of avoiding deaths attributed to transplant procedures. Similarly, the characterisation of procedural based mortality as immediate does not reflect the experience of patients who die months after a procedure having undergone substantial further treatment for infection and multiple rescue attempts. The assumption of immediate mortality may underestimate both the health care resource use and the quality adjusted survival of patients who die as a consequence of their HSCT or gene therapy procedure. The potential overestimation of quality adjusted survival in patients that survive transplant procedures combined with the underestimation of quality adjusted survival in those that suffer post-procedural mortality will overestimate the benefits of treatments that reduce procedural mortality.

The ERG believes that following an unsuccessful transplant not all patients would find a MSD to provide a rescue transplant. In practice many rescue transplants come from a MUD (and potentially even haploidentical donor), and this may be especially likely in patients for whom the decision was made to use gene therapy before a search for a MUD was complete. The ERG therefore considers that the type of rescue therapy could differ between patients initially allocated to gene therapy and those initially allocated to HSCT, as the former would be more likely than the latter to identify a suitable MUD for rescue transplant, having not already exhausted that option. Another concern is that some patients may fail to identify any appropriate donor, and these patients in the UK could continue to receive PEG-ADA for an extended period. Compared to the model structure in which transplant from a MSD is the mode of rescue, in practice use of haploidentical donors may be greater, and for some patients duration of PEG-ADA may be longer than is characterised in the model. The implication is that QALYs may be overestimated and health care resource use underestimated for patients requiring rescue transplants.

5.2.2 The company's economic evaluation compared with the NICE reference case checklist

Table 8: Comparison of the company economic evaluation against the NICE reference case checklist

Attribute	Reference Case	Included in CS	Comment on whether *de novo* evaluation meets requirements of NICE reference case
Comparator(s)	The NICE scope defined comparators as follows: Bone marrow transplant including HSCT from an: - HLA matched unrelated donor - HLA haploidentical donor	Yes	Yes
Type of economic evaluation	Cost-effectiveness analysis	Yes	Yes
Perspective - costs	NHS and PSS	Yes	Yes
Perspective – benefits	All health effects on individuals	Yes	
Time horizon	Sufficient to reflect any differences in costs or outcomes between the technologies being compared.	Yes	The economic model had a life-time horizon of 100 years. No patients were expected to be alive beyond this period.
Synthesis of evidence on outcomes	Systematic review	Yes	
Outcome measure	QALYs	Yes	
Health states for QALY measurement	Described using a standardised and validated instrument	Partial	All utility values were derived from the external literature, with duration of utility decrements informed by expert opinion. Utilities for the states defined by long term survival were derived from the general population EQ-5D scores. Health states for the 6 months post-procedure and for GvHD were described using vignettes in the corresponding source studies.
Benefit valuation	Time Trade Off or Standard Gamble	Partial	Utility values for long-term survival and for GvHD were based on time trade off. Utility values for post-procedural morbidity were based on visual analogue scale.
Source of preference data	Representative sample of the public	Partial	Utility values for long-term survival and GvHD were based on a sample of the public. Utility values for post-procedural morbidity were based on physician preferences.
Discount rate	3.5% on costs and health benefits	No	Costs and benefits have been discounted at 1.5% per annum in the base case analysis. A 3.5% discount rate is explored in scenario analyses.
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes	
Sensitivity analysis	Probabilistic sensitivity analysis	Yes	Yes

NHS: National Health Service; NICE: National Institute for Health and Care Excellence; PSS; Personal Social Services; IVIG: Intravenous immunoglobulin; HSCT: Haematopoietic stem cell transplant; ADA-SCID: Adenosine deaminase deficiency severe combined immune deficiency: HLA; Human leukocyte antigen; EQ-5D; EuroQol 5-dimension questionnaire QALY: Quality adjusted life year; GVHD: Graft versus host disease

5.2.3 Population

The primary sources of data used to inform the cost-effectiveness model was the Strimvelis Integrated Population long-term follow-up study and selected patients from a retrospective international study.[3] As previously stated in Section 3.1, the populations in these studies can be considered to match the NICE scope, but some differences may exist between patients in the Strimvelis Integrated Population and those eligible to receive Strimvelis treatment in England. Further differences exist between the modelled patient population in the company's cost-effectiveness analysis and the patients observed in the primary data sources.

The model population is a cohort aged 1, with 50% male and 50% female patients. No further information is provided as to the assumed population characteristics, for example whether they may have received prior therapy. The Strimvelis Integrated Population are older (mean 2.1 years at gene therapy), more frequently male (61%) and a proportion had already undertaken a HSCT prior to gene therapy (22.2%) or received PEG-ADA (83% PEG-ADA of any duration; 67% PEG-ADA of duration >3 months). The ERG considers the modelled patient cohort broadly reflects the licenced indication for treatment of patients with ADA-SCID for whom no suitable human leukocyte antigen (HLA) - matched related stem cell donor is available.

In line with the final scope issued by NICE, no subgroup populations were considered. The company justified this on the basis of small numbers of patients in each treatment group. While the ERG considers this a reasonable argument, it is noted that certain patient characteristics may alter expected outcomes. Age at transplant and presence of an active viral infection, pre-existing respiratory impairment and septicemia are associated with lower expected survival following HSCT. [3, 27, 28] The clinical advisor to the ERG noted that age may be a proxy for the presence of an active viral infection, [27] and that while the published survival data for HSCT certainly include patients who received transplant with active infection, it was unclear whether any patients in the Strimvelis integrated population received gene therapy in the presence of active viral infection. In response to clarification, the company stated that no patients had active viral infection at screening for inclusion in the Strimvelis integrated population (company response to clarification A1). Age is a factor that may determine suitability and success of gene therapy; in response to clarification, the company noted that cellularity typically decreases with age, and patients with lower cellularity may be unable to deliver the minimum amount of cells required for treatment with Strimvelis (company response to clarification A6). Finally, a key component of the model is the reduction in usage of PEG-ADA to bridge to transplant. As doses of PEG-ADA and IVIG are determined by patient weight, older patients would be expected to incur greater costs while being maintained on ERT, and to incur greater

costs for IVIG post-procedure. Overall, the ERG considers that mortality and health care costs would be expected to increase with patient age, and that the results of the company model are not generalisable to older patient populations.

Given the importance of a number of the uncertainties in the treatment pathway and patient population, additional analyses which consider the potential impact of these uncertainties on the cost-effectiveness results were undertaken by the ERG and are presented in Section 6.

5.2.4 Interventions and comparators

The intervention assessed is the retroviral-transduced cell product Strimvelis. While the transduced cell product is separate from the transplant procedure that utilises the product, in practice the short shelf life means that Strimvelis can only be transplanted in SR-TIGET, Milan. Patients cannot be treated with Strimvelis without also travelling to, and additionally pay for the transplant procedure, in the specialist centre in Milan.

The comparators included in the economic evaluation are HSCT from a MUD and HSCT from a haploidentical donor, as specified in the NICE scope. While HSCT from a haploidentical donor was incorporated into the company's economic analysis, the company considers MUD transplants to be the only relevant comparator on the basis of expert clinical advice.

"*We have assumed that Strimvelis will be replacing 1 HSCT from a MUD based on clinical expert explanation that HSCT from a haploidentical donor has not been performed in England in the last 15 years."* CS, p225

Long term enzyme replacement therapy (ERT) can act as an efficacious alternative to transplantation.[30] However, the company report that long-term ERT is not seen as a preferred treatment option in England, which may be due to the inconvenience of the weekly or bi-weekly treatment schedule, significant long-term cost, limited availability, and uncertainty regarding the development of antibodies that could reduce efficacy with prolonged use. In line with the NICE scope, this comparator was omitted from the cost-effectiveness analysis. The ERG's clinical expert agreed with the conclusions drawn by the company.

The ERG note that the rarity of observed haploidentical transplants may be attributable in part to the small number of ADA-SCID patients over time and the preference in clinical practice to consider first transplant from a MUD or entry into available trials of gene therapy. Recent developments in the techniques for HSCT with a haploidentical donor are associated with improving rates of survival,[4, 6]

and it offers the advantage of being available to nearly all patients with ADA-SCID without the need to undergo a lengthy search procedure. The ERG therefore considers haploidentical donor bone marrow transplants as a relevant comparator, although recognises that based on current clinical guidelines it may be considered as second-line alternative to transplant from a MUD. The ERG notes that the company submission does not characterise the costs and health outcomes of avoiding search costs and wait times through first-line use of haploidentical donors.

The comparison of Strimvelis with HSCT from a MUD is appropriate if the availability of a MUD is known before choosing between gene therapy and HSCT. This is inconsistent with company's assumption that this information is not available at the point of the treatment decision. To inform decisions made without knowledge of the availability of MUD the relevant comparator may be a weighted combination of MUD for the proportion of patients that find a suitable donor, with haploidentical donor restricted to those who fail to find an appropriate MUD.

5.2.5 Perspective, time horizon and discounting

The perspective of the company's analysis was the NHS and Personal Social Services (NHS & PSS). The time horizon used in the model was assessed over a life-time (100 years). This was justified on the basis that expert clinical advice sought by the company suggests a successful engraftment from Strimvelis or HSCT related procedures offer a cure from ADA-SCID, and that patients surviving after three years would revert to the mortality of the general population.

A discount rate of 1.5% per annum was applied to both costs and outcomes in the company's base case. The NICE Methods Guide states that a discount rate of 1.5% for costs and benefits may be considered in cases when the treatment restores individuals who would otherwise die or have a very severely impaired life to full or near full health, and when this is sustained over a very long period (normally at least 30 years).[41] The company justified the use of a 1.5% discount rate on the basis that patients treated with Strimvelis are expected to have a long and sustained benefit, regaining normal life expectancy.

The ERG considers that the time horizon used in the model adequately encapsulates all the benefits and costs related to Strimvelis and HSCT. However, the ERG note that the different wait time before the initial procedures in the decision tree means that the model time horizon is 10 weeks shorter for Strimvelis compared to HSCT. In response to clarification the company asserted that the 10 weeks difference would be realised at the end of a patient's life, and that with discounting the impact on the model results would be negligible (company response to clarification B15). The ERG agrees that this

10 week differential is unlikely to be influential on the results if realised at the end of the time horizon. The ERG considers the 1.5% discount rate applied to the model may be reasonable according to NICE guidance, but is concerned that many patients with ADA-SCID will not return to general population life expectancy and morbidity after successful transplant.

5.2.6 Treatment effectiveness and extrapolation

The company's base case model assumes that gene therapy with Strimvelis will alter the outcomes of patients who would otherwise have received HSCT from a MUD or haploidentical donor in four ways:

- Wait time to procedure and duration of ERT
- Survival
- Rate of rescue therapy
- Rates of GvHD

5.2.6.1 Wait time to procedure and duration of ERT

The wait time between diagnosis and procedure determines the duration of ERT with PEG-ADA, which is assumed to be used in all patients to stabilise them and 'bridge' to procedure. The wait times for HSCT were taken from Gaspar et al (2013), which reported an average wait time of 129 days.[17] The company rounded this figure to 19 weeks. Based on the clinical schedule defined by San Raffaele Telethon Institute for Gene Therapy, the company assume a 9 week wait time between diagnosis and treatment with Strimvelis. This 9 week wait time differs from the length of the 'pre-treatment phase' observed for patients recruited to the Strimvelis pivotal study (average 5.7 months, equivalent to 25 weeks).

As part of the clarifications stage the ERG requested the company justify the discrepancy between recorded and modelled time to treatment. The company response noted concerns about the age of the data '*The pivotal study treated its first patient in October 2002 and its last patient in June 2008*', and that '*Time to treatment will be shorter now post-authorisation as the need for ethical approval and other such delays will be eliminated*'. The company also note that, '*If Strimvelis receives positive approval from NICE, then NHS England will be obliged to provide funding so that there will be no need for further approvals in order to refer a patient to Milan for treatment with Strimvelis*' (company response to clarification B8).

The ERG notes that the data from the Strimvelis pivotal study is contemporary with that used to inform the wait time to HSCT. Furthermore, the ERG understands that for most clinical studies

ethical approval would be required prior to recruitment, and would not introduce delay between recruitment of a patient to a study and receipt of study treatment. It is unclear what role funding barriers may have played in the length of the pre-treatment phase in the pivotal study, which included no patients from the UK. The ERG notes that the company's preference for using the clinical schedule of the San Raffaele Telethon Institute for Gene Therapy (SR-TIGET) to determine the wait time to Strimvelis in preference to observed wait times could be considered inconsistent with the preference to use observed wait times for HSCT and not the UK Stem Cell Forums recommendations of 6-8 weeks wait to HSCT (company response to clarification B1). The ERG does not consider that the assumed treatment benefit of reducing PEG-ADA usage was adequately justified by the company on the basis that no evidence was provided to demonstrate that Strimvelis will be delivered within the quoted 9 week schedule. The ERG assesses the potential impact of a treatment independent time to procedure on cost-effectiveness in Section 6.

The company model assumes all patients receive PEG-ADA for the duration of the wait to the initial procedure, and throughout the wait between an unsuccessful engraftment and a rescue transplant. The company note that PEG-ADA '*is usually stopped 20 days before infusion of Strimvelis*' and that they have overlooked this in the model for the sake of simplicity (company response to clarification B1). The ERG is also aware that PEG-ADA may be stopped to allow cellular immunity to wane in preparation to receive HSCT, in order to reduce the risk of graft rejection.[19] The company submission highlights the limited availability of PEG-ADA and the reluctance to supply it as a long-term treatment option. The ERG notes that many patients with ADA-SCID did not receive ERT prior to HSCT, including 83/106 (78%) of those reported in Hassan 2012.[3] In contrast the majority of patients in the Strimvelis Integrated Population did receive ERT prior to gene therapy (15/18; 83%). As UK centres contributed 44 patients to the Hassan study, even with the extreme assumption that all of the 23 patients that did receive ERT were from the UK, this would give a maximum rate of PEG-ADA use of 23/44 (52%) prior to HSCT. The ERG note that there is little data on the use of PEG-ADA as secondary therapy following a failed HSCT, with Gaspar 2009 reporting use in fewer than 10% of patients.[30] Thus there is uncertainty not only regarding the duration of PEG-ADA use, but also the rate of PEG-ADA use. Clinical advice to the ERG indicated that most patients in the UK would be expected to receive PEG-ADA while awaiting transplant. The ERG therefore accepts the simplifying assumption that patients will receive PEG-ADA for the duration of the wait until transplant, but cautions that this likely overestimates any savings from reducing the duration of time between diagnosis and transplant procedure.

5.2.6.2 Survival

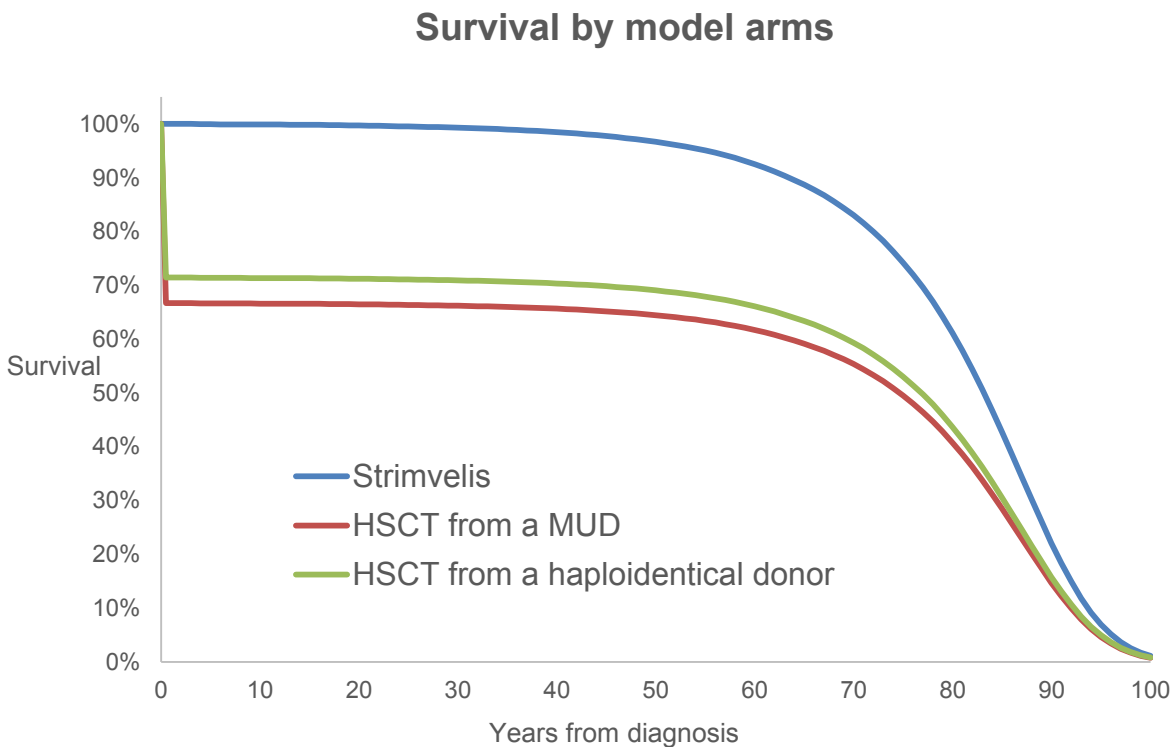
The primary clinical effectiveness parameters used in the model are the survival probabilities for each initial procedure. The source used to inform survival probabilities for Strimvelis is the long-term follow-up study of the Strimvelis Integrated Population. The source used to inform survival after HSCT is a retrospective survey of 16 international transplant centres, which included 44/106 (44%) HSCTs provided in the UK.[3] Overall survival after Strimvelis is reported to be 100%; however this includes three patients with unsuccessful response to Strimvelis and who required further intervention. Intervention-free survival, defined in the Strimvelis clinical programme as survival without post-gene therapy PEG-ADA use for a continuous period of ≥3 months, SCT, or death, was 82.4%. Survival probabilities for transplants performed between 2000-2009 was used for haploidentical donors (5/7 patients, 71%) while survival for MUD patients was informed from by the entire duration of the study (10/15 patients, 66.6%) (see Section 4.2.5).

Given the small sample sizes the ERG consider it important to utilise all available data on patients receiving Strimvelis, including data from the Named Patient Programme ([redacted]) to inform model parameters. All patients from the Named Patient Programme remain alive, and [redacted] are considered to be intervention-free. This leaves overall survival unchanged at 100%, and [redacted].

The ERG has concerns that data selected by the company to inform survival following HSCT suggests that survival after transplant from a MUD is lower than that from a haploidentical donor, which lacks face validity. A further concern is whether the historical data provided in Hassan appropriately characterises current survival rates following HSCT. As noted in Section 4.2.5, survival rates with HSCT are widely considered to be improving over time, with the UK Stem Cell report showing sustained year on year improvements in one year survival following unrelated donor stem cell transplantation from 2003 to 2012.[4] A recent study from a transplant centre in Sweden showed that five year survival following transplant from a MUD for children with non-malignant diseases improved from 72% in the period 1992-2002 to 93% in the period 2003-2013 (p=0.02), with a corresponding drop in transplant related mortality.[6] The ERG believes that overall survival following HSCT may now be higher than that reported in Hassan. In contrast, survival with Strimvelis can only reduce from 100%, and this is not implausible given the severe nature of ADA-SCID as a condition and the less than 100% response rate to gene therapy. The ERG is therefore concerned that the absolute difference in overall survival between Strimvelis and HSCT may be overestimated in the company model.

Mortality stemmed from only two sources in the company base case: first, as a direct result of an initial HSCT; second, from general all-cause mortality. The company assume after a successful treatment using Strimvelis or HSCT patients are cured from ADA-SCID and experience the same mortality risk as the general population. Figure 2 displays the survival outcomes by treatment arm within the model.

Figure 2: Modelled survival outcomes by treatment arm



Company model, "*Inputs Survival*"

The company justify the ways in which mortality is incorporated into the model on the basis that:

- Procedural survival is informed using the most recent evidence
- Kaplan-Meier overall survival curves for patients who received HSCT from a MUD or haploidentical donor, do not show deaths after approximately 1 year

The ERG are concerned that the underlying message from the model is that all ADA-SCID patients without a matched related donor can be cured and return to general population mortality and morbidity if they survive the initial procedure, regardless of engraftment success, patient characteristics or prior health state. Expert clinical advice confirmed the assumption that patients surviving beyond three years since the time of initial procedures could return to the mortality risk for

the general population. However, it was noted that HSCT has only been provided to patients with ADA-SCID within the last 25 years, and so data on life expectancy is not available.

It is observed that a proportion of patients require immune support with IVIG and experience severe infections for up to 8 years following transplant, which is suggestive of less than full health. Furthermore, the systemic sequelae of ADA-SCID remain even after successful transplant, and patients continue to be underweight. In general being underweight may compromise health, and is associated with increased all-cause mortality. The Royal College of Paediatrics and Child Health BMI centile charts indicate that children on the 25th percentile have a BMI of approximately 15, increasing slowly over time to a BMI of approximately 20 at age 19. BMI of less than 20 is associated with increased hazard ratio for all-cause mortality in adults compared to those with a BMI between 22.5 and 24.9. [42] Individuals who have ADA-SCID are more likely to experience hearing loss, respiratory complications and neurologic abnormalities compared to the general population.[1, 8, 34, 43, 44] Fourteen (78%) patients in the Strimvelis Integrated Population had ongoing neurological impairments at baseline and 10 of these experienced further events after gene therapy (56%). [45] These factors all indicate that ADA-SCID patients with successful engraftment may not be entirely comparable with the general population after a period of three years. While many long-term adverse events and the systemic sequelae of ADA-SCID consequences are assumed not to differ between gene therapy with Strimvelis and HSCT from a MUD or haploidentical donor, omitting these from the model risks overestimating the QALY gain from any deaths avoided and underestimates the health care resource use of survivors. This would be expected to overestimate the cost-effectiveness of treatment strategies that reduce initial procedural mortality.

5.2.6.3 Rescue transplant

The same sources used to inform the rates of overall survival are used to inform the rates of rescue therapy for each comparator. Following unsuccessful engraftment, two patients from the Strimvelis integrated population (patients 8, 17) started continuous PEG-ADA post-gene therapy before receiving a HSCT from a HLA-matched sibling donor whilst a third patient (patient 2) continues to receive PEG-ADA. On the basis of expert clinical advice, the company assumed the latter patient would eventually receive a rescue transplant in UK practice.

Table 9 displays the treatment specific pathway probabilities for each of the three procedural outcomes used in the model along with the patient numbers used to inform them.

Table 9: Summary of primary efficacy data reported by the company

	Success, long term survival	Unsuccessful engraftment, PEG-ADA, awaiting rescue transplant	Death	Source
Strimvelis	14/17 (82.4%)	3/17 (17.6%)	0/17 (0%)	Strimvelis long-term integrated population study
MUD	9/15 (60.0%)	1/15 (6.7%)	5/15 (33.3%)	Hassen et al (2012)
Haploidentical	3/7 (42.9%)	2/7 (28.6%)	2/7 (28.6%)	Hassan et al (2002) [using 2000-2009 cohort]

The ERG notes that [redacted] patients in the Named Patient Programme required rescue therapy, and inclusion of these data would give a rescue transplant rate of [redacted] and a corresponding successful engraftment rate of [redacted].

The ERG has concerns regarding the calculation of rescue therapy rates conducted by the company as they are not conditional on survival following the initial procedure. Further to this, the use of overall survival rather than transplant related mortality means that deaths from all causes, including rescue treatment attempts, are applied at the point of the initial procedure in the model. Consequently, the outcomes in the company model structure are not mutually exclusive. In the sensitivity analysis that explores rescue using transplant from a MUD with 66.67% survival, the failure to use transplant related mortality and conditional probabilities of rescue transplant is particularly problematic, as it may double count fatal events.

For the outcomes in the decision tree to be mutually exclusive the rescue therapy rates ought to be calculated from the number of patients who survived initial procedure rather than from the initial sample size. Since Strimvelis is recorded as having a 0% mortality rate, the rates of rescue therapy for Strimvelis are by default based only on survivors. Transplant related mortality, defined as death within 100 days of transplant, was reported in Hassan et al to be 4/15 (27%) from a MUD. For haploidentical donors transplant related mortality was only reported for the full cohort at 10/30 (33%) and was not available for the subset of transplants conducted between 2000-2009. The conditional rate of rescue therapy following HSCT from a MUD is 1/10 (10%) based on overall survival and 1/11 (9%) based on transplant related mortality. The conditional rate of rescue therapy following transplant from a haploidentical donor is 2/5 (40%) based on overall survival. These rates are

somewhat higher than those applied in the company model (6.7% for MUD and 28.6% for haploidentical). However, the sample size in Hassan is very small and there may be other relevant evidence as to the rate of rescue transplant following HSCT.[27] The ERG note that while the limited evidence suggests that the rate of rescue transplant may be higher following HSCT from a haploidentical donor compared to a MUD, it is highly uncertain as to whether there is any difference in the rate of rescue therapy between Strimvelis and HSCT. The potential impact of a treatment independent rate of rescue therapy on cost-effectiveness is explored in Section 6.2.

5.2.6.4 Rates of GVHD

A further treatment benefit incorporated into the model was the avoidance of GvHD in patients treated with Strimvelis. This treatment benefit is clinically justified on the basis that Strimvelis is made from a patient's own cells and as such incurs no risk of rejection due to HLA mismatching or minor antigen incompatibility. This conclusion is in line with what was observed in the clinical programme.

The company calculated rates of any GvHD, chronic GVHD and acute GVHD by summing the number of events reported across the literature. A summary of the sources referenced in the company submission and the company's calculated rates of GvHD are shown in Table 10. The ERG express concerns regarding the derivation of the rates of GvHD applied in the economic model (see Section 4.3). It is unclear from the company submission which GvHD events may have resulted in death and whether these events were then used to calculate GvHD rates. Including GvHD events resulting in death would double count the negative consequences of GvHD given that the company apply HSCT procedural mortality that incorporates mortality from GvHD and assumes death is immediate. Although the ERG has concerns regarding the approach to calculation for the rates of GvHD applied in the company model, the rates themselves appear reasonable in comparison to broader studies assessing GvHD following HSCT for SCID.[27]

Table 10: Rates of GvHD used in the company submission

Donor	GvHD grade		N	Rates	Source
MUD	Grade I/II		5	17.9%	Baffelli, 2015; Serana, 2010; Dvorak, 2014; Gennery, 2001
	Grade III/IV	Acute	3	10.7%	Dvorak, 2014; Grunebaum, 2006
		Chronic	1	3.6%	
	Total GvHDs		9	32.1%	
	Total patients		28		

Haploidentical	Grade I/II		2	22.2%	Honig, 2007; Borghans, 2006
	Grade III/IV	Acute	1*	11.1%	Honig, 2007
		Chronic	0	0%	
	Total GvHDs		3	33.3%	
	Total patients		9		

5.2.6.5 Costs and outcomes not included in the model

The model does not include costs or health outcomes related to the use of conditioning regimens prior to HSCT or gene therapy. Conditioning regimens used before Strimvelis and HSCT are a source of adverse events. Clinical advice to the ERG suggested that busulfan would be the most common conditioning agent in the UK, and that regimens have become less toxic over time. Low-dose busulfan is used as a pre-treatment for Strimvelis, and this may be lower intensity on average compared to the conditioning regimen used for HSCT. Therefore, the company assert that the omission of conditioning regimens from the economic analysis can be regarded as conservative and would underestimate the benefits of gene therapy compared to HSCT. Clinical advice to the ERG supports this assumption.

Following the initial procedure, the company assume that the rates of IVIG use and severe infections are the same across treatment arms. This was considered to be a reasonable assumption by the clinical experts and ERG. While IVIG use is included after both the initial procedure and any rescue procedure, severe infections are incorporated only following the initial procedure. Adverse events not related to GvHD or severe infections were omitted from the analysis. The model does not characterise any particular adverse events that may be connected to use of gene therapy such as leukemic events, and assumes that retroviral insertion site testing and replication competent retrovirus testing will not be undertaken. The company state that no leukemic adverse events have been observed in the Strimvelis clinical programme, and assume that adverse events so far observed are attributable to the conditioning regimen used and other factors common to both HSCT and gene therapy transplant procedures, such as the placement of a central venous catheter. The ERG note that the assumption of no risk of adverse event associated with gene therapy is based on a small population thus far treated with Strimvelis, and that these adverse events have been observed with retroviral vector gene therapy for other SCIDs (see Section 4.6).

The form of rescue therapy was assumed to be the same regardless of initial transplant procedure. In the base case rescue transplant was assumed to come from a MSD donor, with 100% survival, 100% successful engraftment and no risk of GvHD or severe infection. The ERG note that transplant from MSD donor is associated with less than 100% survival, less than 100% success and carries a risk of GvHD.[27] A scenario analysis considered the use rescue transplant from a MUD, using the same survival rate as initial transplant from a MUD (66.67%), but again without further consideration of GvHD or risk of severe infection. As the company use the data from overall survival to model deaths from the initial procedure, any deaths following rescue transplants received have already been incorporated in the initial post-procedural survival rate. Consequently, scenarios that add further mortality at the point of rescue transplant risk double counting mortality events in patients assigned to HSCT. Double counting is so far not possible for Strimvelis as no deaths are attributed to the initial procedure. The ERG thinks that it is reasonable to assume that there will be similar mortality rates from a given rescue transplant procedure among patients who have failed to engraft following gene therapy as for those who fail to engraft following HSCT. The ERG believes that the current scenario that explores mortality associated with rescue transplant is favourable to Strimvelis by overestimating mortality in patients assigned to HSCT. Further to this the ERG believes that the form of, and pathway, to rescue transplant could differ between patients who fail gene therapy without ever having completed a search for a MUD and those who fail initial HSCT after having completed such a search.

The ERG noted several other relevant treatment related events not considered by the company that could have been included in the model structure, including the proportion of patients who could produce sufficient CD34+ cells to be eligible for Strimvelis, the proportion of ADA-SCID patients expected to find no appropriate MUD, and the use of 'back up' bone marrow transplantation. In response to clarification the company reported that one patient from the Strimvelis integrated population was unable to produce sufficient CD34+, which would provide a rate of 1/18 (6%) patients with ADA-SCID who may be considered unsuitable to progress to treatment following a bone marrow biopsy (company response to clarification A6). In response to clarification the company provided further information on the use of 'back up' bone marrow transplantation. The company note that, '*In the integrated population, 1 subject (6%) received back up bone marrow cells because the subject was unable to receive the scheduled infusion of Strimvelis at the first attempt due to contamination, and 3 subjects (17%) received stored back up of unmanipulated bone marrow cells due to events after Strimvelis.* [redacted] *There is no further information on the use of back up bone marrow in the available NPP data (company response to*

clarification A7).' The observed use of 'back up' bone marrow transplant is therefore 4/18 (22%) in the Strimvelis Integrated Population, which [redacted] if the Named Patient Programme is included. The company submission does not contain any evidence to determine whether the rate of 'back up' bone marrow transplant differs between Strimvelis and HSCT.

5.2.7 Health related quality of life

The LTFU study AD1115611 collected general HRQL evidence from participants using both the Lansky performance status index (collected for all LTFU patients) and the Paediatric Quality of Life Inventory (PedsQL) (not collected for subjects younger than 5 years old). The company submission also contained three search strategies used to identify: 1) HRQL studies concerning ADA-SCID; 2) health-related utility values after HSCT, and; 3) health-related utility values in GvHD. The search strategies were briefly described in the main body of the submission in Section 10.1.5. Full details were provided in Appendix 3, Section 17.3 and Appendix 5, Sections 17.5.1 and 17.5.2.

1) Health-related quality of life studies concerning ADA-SCID

The results of the search for economic evidence were used to identify HRQL studies. The electronic database EMBASE was searched on 28th February 2017 via the Elsevier host. The search combined terms for ADA-SCID with terms for cost-effectiveness. This search did not contain any terms for quality of life or measurement tools for quality of life so may not have identified all relevant studies on HRQL in ADA-SCID. Reliable search filters to restrict retrieval to utility values are available and the ERG considers that a search using terms for ADA-SCID combined with a utility values search filter would have been a more appropriate.

In addition to this search, the company note on page 123 of the submission that they also searched the results from the clinical data literature search in an attempt to identify HRQL data. However this clinical data search was restricted to studies in patients with ADA-SCID treated with gene therapy, stem cell transplants or bone marrow transplants.

2) Health-related quality of life values after HSCT

The electronic database EMBASE was searched on 10th March 2017 via the Elsevier host. The search combined terms for quality of life with terms for HSCT. Retrieval was restricted to studies from 2007 onwards. The search contained both textword searches and subject heading searches of the main terms

relating to quality of life. However more reliable search filters to identify utility values are available and it would have been more appropriate to utilise a tried and tested filter within the strategy. In addition a lack of truncation within the strategy presented may have restricted retrieval of relevant studies.

3) Health-related quality of life values in GvHD

The electronic database EMBASE was searched on 6th March 2017 via the Elsevier host. The search combined terms for quality of life with terms for GvHD. Retrieval was restricted to studies from 2007 onwards. The search contained both textword searches and subject heading searches of the main terms relating to quality of life. However more reliable search filters to identify utility values are available and it would have been more appropriate to utilise a tried and tested filter within the strategy. The subject heading Graft versus host reaction/ is missing from the strategy. In addition a lack of truncation within the strategy presented may have restricted retrieval of relevant studies.

The systematic searches identified no relevant utility related articles for the ADA-SCID patient population. Instead, the company identified one article directly reporting preference-based utilities in GvHD for patients with relapsing/refractory Hodgkin lymphoma (R/R HL) and R/R systemic anaplastic large-cell lymphoma (Swinburn, 2015) and two HSCT articles deemed to have potential utility information assessing patients with chronic lymphocytic leukaemia (Kharan-Dabaja, 2012) and chronic myelogenous leukaemia patients (Rochau, 2015). Results reported in the clinical and economic systematic literature reviews did not contain any relevant HRQL data. Each systematic literature review reported only one final relevant study. This was partly due to the exclusion criteria only permitting articles reporting preference-based utilities directly. The subsequent health-related quality of life review was conducted with three reports, none of which were those deemed relevant in the systematic literature reviews for preference based utilities.

In the absence of relevant preference-specific utilities for ADA-SCID patients in the Strimvelis Integrated Population, the utility values applied in the model were derived from a combination of alternative patient populations and studies sourced in the systematic literature review and expert clinical opinion. Table 11 provides a summary of the utility values used within the model, including the source and justification.

Table 11: Utilities applied in the cost-effectiveness model

	Value	Reference in submission	Justification
Health utility in the period before HSCT or Strimvelis	0.98		Assumed equal to the general population utility at age 1. We do not consider the potential disutility patients incur whilst waiting for Strimvelis or HSCT (e.g. due to being in isolation and receiving PEG-ADA). Given that patients receiving Strimvelis are likely to wait less than patients receiving HSCT, this is a conservative assumption.
Utility decrement during the first 6 months after Strimvelis, HSCT from a MUD or haploidentical donor, or rescue transplant	0.57	Sung, 2003	In the absence of information on utilities after treatment for ADA-SCID, utility values after BMT in leukaemia were considered the best available information
Utility values for surviving patients with ADA-SCID	Age-specific utility	Jones-Hughes, 2016 Ara, 2010	No specific values on utilities of patients with ADA-SCID were identified. Age-specific normal values were used, and the possibility of lowering utilities was explored in the sensitivity analysis
One-off QALY loss due to a utility decrement from acute GvHD	0.41	Swinburn, 2015	The utility value for patients with acute GvHD and complete remission from relapsed/refractory Hodgkin lymphoma or systemic anaplastic large cell lymphoma was used to calculate a utility decrement and then adjusted based on the expected average duration of an episode of acute GvHD (8 months) based on expert clinical advice.
One-off QALY loss due to a utility decrement from chronic GvHD	1.44	Swinburn, 2015	Utility value for patients with chronic GvHD and complete remission from relapsed/refractory Hodgkin lymphoma or systemic anaplastic large cell lymphoma was used to calculate a utility decrement and then adjusted based on the expected duration of an episode of chronic GvHD (3 years) based on expert clinical advice.

CS, Table C29 – p127-128

The HRQL of patients in the model is comprised of three separate stages:

- pre-treatment;
- 0-6 months after transplant; and
- 6 months post-procedure for the remaining life time horizon.

The health utility applied in the period before HSCT or Strimvelis did not consider decrements in patients' utility. The health related quality of life estimate applied in the first 6 months post-procedure was based on a study by Sung (2003) which surveyed 12 physicians with experience of bone marrow transplant using visual analogue scale to determine a HRQL 'disutility' of 0.57 for transplant in patients with acute myeloid leukaemia. The utility values applied from 6 months after transplant for the remainder of the time horizon were age-specific normal population values taken from the Jones-Hughes analysis of the Health Survey for England (2012). Patients with failed engraftment are assigned two 6 month periods with a utility of 0.57. The first period coincides with the 6 months following the initial failed procedure and the second occurs after rescue therapy. The remaining time between initial and rescue procedure follows the age-specific normal population values.

Utility values are not differentiated by treatment in the model with the exception of GvHD events, which apply to HSCT procedures only. GvHD of grade III or IV is associated with a one-off QALY decrement applied as a lump-sum. The average QALY losses for acute and chronic GvHD were calculated as the product of their assumed duration and associated disutility. The expected duration of a GvHD event was informed by expert clinical advice whilst the utility value was taken from an international valuation survey that used time trade off to determine public preferences for health states relating to relapsing/refractory Hodgkin lymphoma.[46] Acute GvHD was assumed to last for eight months, and during those eight months patients were assumed to have a utility score of 0.39. Chronic GvHD was assumed to last for three years, during which patients experience a utility of 0.52.

The model assumes no disutility in relation to severe infections, IVIG administration or central venous catheter placement. The company had identified a cost-effectiveness study that estimated a mean health utility of 0.66 associated with use of IVIG in patients with chronic lymphocytic leukaemia. However this was not incorporated due to the age of the study and the fact that health utility value was based on a small sample of physicians (company submission p130).[47] The company did provide a one-way sensitivity analysis in which a disutility weight of 0.75 was applied to patients receiving IVIG. Adverse events related to conditioning regimens were not included in the cost-

effectiveness analysis. The economic evaluation incorporated the HRQL of parents as an additional scenario, and conducted a range of further one-way sensitivity analyses for HRQL values.

The ERG considers that prior to transplantation the HRQL of patients awaiting treatment may be lower than that of the general population. Establishing HRQL values for very young patients is challenging, and the rarity of ADA-SCID compounds this. As the period before transplantation constitutes a very small proportion of the modelled time horizon, the ERG expects that the results are unlikely to be sensitive to the simplifying assumption that health related quality of life in this initial period is equal to that of the general population.

The ERG noted that the assumed duration of three years for chronic GvHD means that the impact extends beyond the assumed timing of the rescue transplant. In response to clarification the company confirmed that rescue transplant would not normally be provided to patients with ongoing chronic GvHD (company response to clarification B22). The company provided an additional sensitivity analysis to show the impact on the ICER of either delaying rescue transplant to year 4 or year 5, or reducing the duration of chronic GvHD to two years. The company also note in their response that as Strimvelis carries no risk of GvHD that the timing of rescue transplant could potentially be earlier following failed engraftment with gene therapy compared to failed engraftment of HSCT.

The ERG consider that the company's justification for omitting the health related quality of life impact of IVIG is inconsistent with their acceptance of physician survey as a source of the health-related quality of life value for HSCT. Both values were obtained using a similar methodology and sample, and the ERG therefore considers that a health related quality of life value for IVIG use could have been incorporated in the base case analysis. The ERG note that where the company submission applies absolute health utility values taken from source studies in different disease areas it would have been preferable to calculate the decrement from the reference population in the respective studies. This would suggest utility weights of 0.43 (0.39/0.91) for acute GvHD, 0.57 (0.52/0.91) for chronic GvHD[46] and 0.76 (0.66/0.87) for IVIG.[47]

The ERG considers that the searches to identify utility values may not have picked up the full range of potentially relevant studies. A pragmatic search by the ERG identified two recent reviews of health related quality of life in children who undergo HSCT.[13, 14] One study from these reviews directly assessed the impact of severe chronic GvHD using a generic multidimensional self-reported instrument, the SCHQ-CF87, in a cohort of 52 children at least three years beyond HSCT.[48] In this

study seven patients continued to experience GvHD related symptoms three to nine years following transplant.

The ERG identified one longitudinal study of quality of life in paediatric recipients of allogenic stem cell or bone marrow transplant that applied the HUI Mark 2/3 to estimate health related quality of life at 35 and 7 days prior to, and 10, 28, 100, 180 and 360 days after bone marrow transplantation.[49, 50] This study provides a preference based measure of health-related quality of life derived from children aged three years and older. The study did not report the mean HUI global utility score for each time point, although it is noted that 10 days after transplant is the nadir for observed quality of life. The reported difference in HUI global utility score from 35 days prior to bone marrow transplant to 360 days after bone marrow transplant was -0.13 (standard error 0.16; $p \leq 0.01$) as rated by children aged at least 10 (n=21), and -0.08 (not significant) as rated by parents (n=26) or physicians (n=27).

While these reviews did not identify alternative values that could directly replace those applied in the company model, they do offer support for the company assumption that quality of life decrement from receipt of HSCT lasts for about 6 months.[14] However, evidence cited in the company submission contradicts the assumption that quality of life for patients with ADA-SCID returns to population norms thereafter[15, 37]. Patients with ADA-SCID have been reported to have a high incidence of bilateral sensorineural deafness (58%).[43] A pragmatic search by the ERG identified a study that used the HUI Mark 3 to estimate a mean health-related quality of life decrement for bilateral permanent hearing impairment of -0.294 ($p<0.01$) compared to children with normal hearing. Children with SCID exhibit worse emotional and behavioural outcomes compared to population norms as measured by the strengths and difficulties questionnaire (SDQ), and ADA-SCID is predictive of a worse SDQ score compared to other SCIDs.[37] The SDQ score has been linked directly to a preference based measure of health-related quality of life [51].

5.2.8 Resources and costs

The company submission provided details of the resource use and costs associated with each relevant strategy of care. The company highlight the three elements of cost associated with sending a patient to Milan for gene therapy:

1. The cost of Strimvelis itself;
2. Related hospital procedures, including screening, baseline tests, bone marrow sample, chemotherapy, infusion of Strimvelis, recovery in isolation room and outpatient follow-up; and

3. Patient support, such as accommodation, food, and transport services as well as travel to/from Milan.

The costs and resource use for HSCT include: (1) the cost of searching for and obtaining stem cells; (2) related hospital procedures; and (3) costs related to GvHD. Additional elements of resource use common across all strategies of care include drug acquisition and administration costs for PEG-ADA and IVIG, follow-up costs for patients who have successful engraftment, and costs related to severe infection.

To identify cost and resource use data to inform the assessment of cost-effectiveness, the company performed a pragmatic review of the literature for ADA-SCID patients. The CS did not contain any searches for resource data on ADA-SCID. The company stated that this was due to a scarcity of published data on ADA-SCID. However, it would have been useful if the search strategies to demonstrate that published data was not available were included in the company submission. The costs reported in the CS are denoted in pound sterling by applying an exchange rate of €1= £0.85).

5.2.8.1 Treatment and administration costs

The price of the Strimvelis technology, which constitutes the transduced stem cells for transplant, is set in euros (€594,000) and is to be paid to the Ospedale San Raffaele (OSR) Hospital, Milan. The company are reported to be in discussion with NHS England to determine a fixed price in local currency for Strimvelis, and funding arrangements are anticipated to align with the EU directive route which is currently paying for proton beam therapy outside of the UK.

Administration costs for Strimvelis, i.e. the transplant procedure and related hospitalisation, were based on a length of stay schedule informed by the expected administration periods for baseline patient preparation (31 days), treatment (50 days) and outpatient follow-up (60 days). This schedule was revealed during the clarification stage to be defined by the San Raffaele Telethon Institute for Gene Therapy (SR-TIGET) and OSR (company response to clarification B5). The administration costs of Strimvelis are shown in Table 12. The company assume that the [redacted] per patient screening cost, which comprises an outpatient visit for informed consent and clinical tests along with a hospital diagnostic bone marrow aspirate to determine ability to produce sufficient CD34+ cells, would be incurred in England prior to travel to Italy. The initial hospitalisation cost of [redacted] (baseline + treatment + follow-up, month 1 and 2 from discharge) requires a fixed payment to OSR for those patients who go on to receive Strimvelis.

Table 12: Schedule of Payments by Ospendale San Raffael

ADA SCID – Patient's Procedural Phases and Reimbursement	
SCREENING	[redacted]
BASELINE	[redacted]
TREATMENT	[redacted]
FOLLOW-UP, month 1 and 2 from discharge	[redacted]
Total	[redacted]

Response to ERG clarifications, Table 8 p36

The ERG requested clarification as to whether the technology cost (€594,000) and cost of initial hospitalisation ([redacted]) would apply to all patients, or whether different charges may apply in a range circumstances applicable to the patient population under consideration. Table 13 presents the response from the company.

Table 13: Costs of patients with unplanned complications

Circumstance	Company Response/Costs
Extended hospitalisation resulting from severe infection.	Estimated technology cost of €594,000 (£505,000) and the initial hospitalisation cost of [redacted] would apply in this case. Additional days in the hospital beyond the assumed clinical schedule (i.e., > 55/days standard stay) would be charged at [redacted] per day for Italian statutory patients. If the patient does not come with an approved S2 form, then they would be charged for each procedure conducted during that period.
Patients for whom the product contains less than 2 million CD34+ cells/kg Cases of product failure e.g. contamination	If Strimvelis was not administered the Strimvelis product cost of €594,000 (£505,000) and the initial hospitalisation cost of [redacted] would not apply. The patient may receive its own back-up as rescue therapy as he/she has already received chemotherapy. In this scenario, i) If the patient is supported through an S2 Form (i.e. the patient would be treated as an Italian statutory patient), the administration of the back-up will fall under the autologous transplantation and the tariff/DRG for the autologous transplantation will be charged to the NHS (i.e., [redacted]; DRG 481, Oct 2016). ii) If the patient does not come with an approved S2 form, the administration of the back-up would fall under the autologous transplantation, but in this case, any clinical service paid in advance and not provided will be reimbursed after the patient is discharged.
Cases of transplant failure, or prolonged bone marrow aplasia after treatment with Strimvelis which require the use of the rescue product	Estimated technology cost of €594,000 (£505,000) and the initial hospitalisation cost of [redacted] would apply in this case. In the case of treatment failure, if the back-up bone marrow is used to facilitate hematopoietic recovery, then this cost is covered by the initial hospitalisation cost up to 55/days standard stay. Additional days in the hospital beyond the assumed clinical schedule (i.e., > 55/days standard stay) would be charged at [redacted] per day for Italian statutory patients. If

	the patient does not come with an approved S2 form, then they would be charged for each procedure conducted during that period.

A cost of public transport and support necessary for a patient and their parent(s)/carer(s) to relocate to Milan was estimated by the company in their original submission but not applied in the model (company submission Section 12.3.9). In clarification, the company acknowledge that the NHS may support travel arrangements (company response to clarification B9). Clinical advice to the ERG indicated that some patients require transfers by ambulance depending on their clinical condition. At clarification the ERG requested the method of transport by which patients arrived for treatment with Strimvelis and the estimated cost of ambulance transfers within the UK and Italy, and by air between UK and Italy. It was reported that 1 patient required ambulance transportation, and none air ambulance (company response to clarification B10). The company provided updated travel costs and additional scenario analyses in response to the ERG's request. The updated travel costs consisted of: air travel at £200 per round trip per person, assuming each patient travels with two additional persons; ambulance transfer from and to the airport within the UK at £472 per patient (based on NHS reference cost code ASS02); and ambulance transfer from and to airport within Italy at £340 per patient (based on communication with OSR). This provided a total travel cost of £1,412 per patient treated with Strimvelis if it is assumed that all patients are funded for within country travel to and from the airport using ambulance (and do not use self-funded public transport). The company estimated that the cost of air ambulance with respiratory assistance would be in the range €11,000 to €17,500 (£9,350 to £14,875 @0.85£/1€) per one way trip. However, they comment that the likelihood of air ambulance being needed is small if it is assumed that patients are always stabilised before they travel (company response to clarification B10).

The cost of obtaining stem cells for HSCT was included in a £45,127 cost of screening for a MUD. The source of this cost was omitted from the original company submission and provided in a separate response to clarification which cited van Agthoven (2002), who reported the screening cost for a MUD transplant of €47,063 (company response to clarification B2).[52] The estimate was based on costs observed in the Netherlands in 1999, which the company inflated to a 2016 value using a health inflation adjustment of 12.8% reported by Statistics Netherland and converted to British pounds using an exchange rate of €1= £0.85. The company consider these costs "*reasonably transferable to the English reality*". A summary of the costs related to screening for a donor are presented in Table 14.

Table 14: Cost components for donor screening from Van Agthoven

Cost Component	Cost (€)
Family HLA typing	6,842
Requesting blood samples	5,506
Sample typing	12,232
Requesting donor graft	15,971
Europdonor intermediation	1,920
CD34 selection/T cell depletion	4,592
Total costs (excluding personnel costs)	47,063

Response to ERG clarifications, Table 3 p20

The 'Family HLA typing' component assumes four non-sibling family members are typed for every patient, and for 15% of patients on average an additional six cousins are typed. The total cost estimated for family HLA typing includes the costs of typing undertaken for the 55% of MUD patients assumed not to undergo transplantation. The 'Requesting blood samples' component includes an average of four fulfilled blood samples requests on potential donors with a weighted average cost of €620 per sample. The 'Sample typing' component includes HLA retyping for the four blood samples, and includes the costs of retyping for patients who do not undergo transplantation. The 'Requesting donor graft' comprises a weighted average cost of stem cells, which are reported to be generally sourced from bone marrow.[52]

The administration of stem cells for HSCT was based on NHS reference costs. The unit cost applied for a HSCT from a MUD was £95,516, which is the national average unit cost for 'Bone Marrow Transplant, Allogeneic Graft (Cord Blood), 18 years and under' Currency Code SA22B. The corresponding cost used for HSCT from a haploidentical donor is £108,760, which is the national average unit cost for 'Bone Marrow Transplant, Allogeneic Graft (Haplo-Identical), 18 years and under' Currency Code SA23B.[53]

The ERG identified two potentially relevant uncertainties regarding the reported costs for Strimvelis. The first is the funding arrangement for Strimvelis, as VAT may be payable dependent on whether a patient arrives in Milan via the S2 or EU directive route. The NICE methods guide (2013) states that value added tax (VAT) should be excluded from all economic evaluations as the NHS does not pay VAT for drugs purchased locally.[41] Whether a fixed price in euros agreed between the company and NHS England will include any taxes remains unknown to the ERG. The second uncertainty is the exchange rate at the time of purchase. The ERG has concerns that this uncertainty is not addressed in the CS but deserves consideration. The ERG has conducted further analyses to explore the impacts of these uncertainties in Section 6.

The ERG is concerned that by applying only the standard hospitalisation charge to all patients in the Strimvelis arm the company model significantly underestimates the potential costs to the NHS of treatment with Strimvelis. For patients that remain in hospital in Milan for longer than the standard stay of 55 days additional hospital costs would be incurred at a rate of [redacted] per day, and the cost of any additional procedures. The median and mean length of hospitalisation in the Strimvelis Integrated Population was 45 days and 53 days. One patient stayed hospitalised for a maximum of 110 days, which would increase the hospitalisation charge by [redacted] (company submission p234). If it is conservatively assumed that only 6% (1/18) patients have hospital stay exceeding 55 days and that they receive no further procedures during this time, the hospitalisation charge is underestimated by a minimum of [redacted] per patient treated with Strimvelis. Where back-up marrow is administered outside of the 55 day standard hospitalisation the charge would be [redacted]. These costs are not accounted for in the company model. In response to clarification the company state that 1 subject received back up marrow cells due to product contamination and 3 subjects (17%) received stored back up due to events after Strimvelis from the Strimvelis Integrated Population, [redacted] (company response to clarifications A7). Assuming that 3/18 subjects from the Strimvelis Integrated Population (17%) receive back up outside the 55 day window would produce an additional cost of [redacted] per patient treated with Strimvelis, while assuming that all [redacted] subjects who received back up bone marrow did so outside of the 55 day window would produce an additional cost of [redacted] per patient treated with Strimvelis. The company submission does not contain any evidence to determine whether excess hospitalisation costs and back up bone marrow transplantation may similarly occur for patients undergoing HSCT.

The ERG considers that had the patient who required ambulance transport for treatment with Strimvelis been travelling from the UK, an air ambulance may have been required, and so travel costs may have been underestimated. Including air ambulance travel could increase average travel costs for Strimvelis by approximately 1/18*£12,113=£673 using the mid-range of the company air ambulance costs and assuming a one way trip. However, the ERG note that the additional scenario analysis provided by the company incorporated travel costs assumes within country ambulance transfer for all patients, which the company consider to overestimate the rate of ambulance transfer. The ERG considers that the underestimation of air ambulance use may be balanced by the overestimation of

ambulance transfer within country, and that this scenario analysis may be reasonably representative of the expected travel costs to be reimbursed by the NHS.

To determine whether the per patient cost of screening for Strimvelis is applicable to UK practice the ERG identified that the cost of a diagnostic bone marrow extraction based on NHS reference costs is £493.90 (ref Total HRG's code SA33Z).[53] Depending on the nature of the outpatient visit and additional tests required for determining eligibility for Strimvelis, the [redacted] based on estimates from OSR may be reasonably representative of costs to the NHS. To address concerns as to whether costs taken from van Agthoven were representative to current UK practice the ERG requested further information from the Anthony Nolan register, who provided an average price of £18,300 for stem cells from bone marrow or PBSC, £28,200 for stem cells from cord blood, and £650 per blood sample for confirmatory typing (Louise Nazir, personal communication). These prices appear broadly comparable with the corresponding unit costs from van Agthoven.

The NHS main schedule of reference costs includes two estimates for the cost of bone marrow transplant, allogeneic graft, that differ based on whether the stem cells are from cord blood (£95,517 code SA22B as applied in company base case) or from volunteer unrelated donor (£79,199 code SA21B).[53] The company submission does not contain any information regarding the proportion of transplants that are from cord blood compared to adult bone marrow. In Hassan 2012 the majority of stem cells were sourced from bone marrow (88/106, 83%) and the same is noted in van Agthoven 2002.[3, 52] Therefore the ERG considers that the cost of HSCT from a MUD may be overestimated in the company model.

5.2.8.2 Drug acquisition costs

The company's original model assumed administration costs of PEG-ADA and IVIG in line with NHS reference costs for "Consultant Led. Paediatric Clinical Immunology and Allergy Service", £306. In response to clarification the company provided an alternative estimate of administration costs of £54 for PEG-ADA based on 30 minutes of Grade 6 hospital nurse time, and £216 for IVIG based on two hours of nurse time (company response to clarification B6).

After consultation with a clinical expert, the company base case assumed a cost of £9,000 per vial of PEG-ADA, and that on average patients would require 1.5 vials per week, giving a cost per dose of PEG-ADA of £13,500. In response to a request from the ERG, the company provided an alternative estimate for the weekly cost of PEG-ADA as a function of body weight, assuming the average patient was on the 25th percentile for weight. Table 15 displays the weekly cost of PEG-ADA based on

weight using an estimated dosage consistent with the maximum dose recommended by the manufacturer of PEG-ADA (30 units per kg).

Table 15: Weekly cost of PEG-ADA based on weight

Age	Weight * (25th percentile)	Units per patient per week **	Vials per patient per week ***	Vials rounded	Weekly cost of PEG-ADA
1 year	8.6 kg	258	0.69	1.0	£9,000
2 years	10.9 kg	326	0.87	1.0	£9,000
3 years	13.0 kg	389	1.04	1.0	£9,000

Response to ERG clarifications, Table 8 p36

The duration of PEG-ADA in the model is dependent on the initial treatment procedure (i.e. Strimvelis or HSCT from a MUD or haploidentical donor) and the rates of rescue therapies required post-procedure (see Section 5.2.1). The model assumes patients undergoing Strimvelis require only 9 weeks of PEG-ADA to bridge to treatment and that 17.6% of Strimvelis patients will require 21 months of PEG-ADA to bridge to rescue therapy after failed engraftment. HSCT procedures are assumed to require 19 weeks of PEG-ADA prior to initial procedure and that 6.7% and 28.6% of MUD and haploidentical patients respectively require 21 months of PEG-ADA to bridge to rescue therapy after failed engraftment.

The annual costs of IVIG were estimated based on the cost per gram of IVIG sourced from a medical data base (medicines complete). IVIG dosing was calculated using the 25th percentile of weight by age in the United Kingdom with an exponential curve fitted to the data. The duration of IVIG in the model was calculated based on rates observed in the Strimvelis integrated population. At the time of data cut (08-May-2014) information regarding IVIG use existed at 0, 3 and 8 years since receipt of Strimvelis. It was assumed the rates of IVIG usage diminished at a constant rate between observations, and that no patients would continue use beyond 8 years. This was justified by the assumption that the patient administered with IVIG for at least 8 years in the Strimvelis integrated population would have received a rescue transplant in the UK. The rates of IVIG drug use were assumed to be equal between patients treated with Strimvelis and those treated with HSCT. This assumption is consistent with expert clinical advice received by the ERG. Table 16 displays the rates of IVIG usage applied to each comparator in the model.

Table 16: Proportion of patients on IVIG by year in company model

Year 1	100.0%
Year 2	79.4%
Year 3	58.8%
Year 4	47.0%
Year 5	35.3%
Year 6	23.5%
Year 7	11.8%
Year 8	0%
Year 9	0%
Year 10	0%

Company model, "*parameters*"

The ERG note that the weight based costs applied in the company model would be higher for patients who are older, such as those included in the NPP.

5.2.8.3 Follow up costs

The company assume equivalence in long-term follow-up requirements for Strimvelis, MUD and haploidentical HSCTs (including use as rescue therapies), with the exception of vector copy number (VCN) testing which is required only for gene therapy. However, the company base the follow up costs for Strimvelis directly on the figures provided in the UK Stem Cell Oversight committee report, and calculate follow up costs for HSCT directly from van Agthoven 2002.[4, 52] In response to clarification the company explained that the estimates from the UK Stem Cell Oversight report (which themselves are extrapolated from van Agthoven) were considered to include other types of transplant, but van Agthoven refers specifically to transplants from a MUD (company response to clarification B13, p34). The average post-transplant care costs in the UK Stem Cell Oversight report are reported as: [redacted] (0-6 months); [redacted] (6-12 months) and [redacted] (12 to 24 months). The company model appears to incorporate a minor typographical error in which the first 6 month period is costed at [redacted] rather than [redacted]. The company assume that the first two months of follow up for Strimvelis is provided in Italy and are incorporated in the [redacted] initial hospitalisation cost for Strimvelis, and so adjust the first six month cost from [redacted] to [redacted], reducing the total follow-up cost to from [redacted] to [redacted] per living patient after Strimvelis.

In contrast, the total follow up cost per living patient after HSCT is assumed to be £59,541 using van Agthoven directly. Gene therapy follow-up included an additional 6 VCN tests (two per year for three years). Each test was costed at £1,199 which amounted to a total cost of £7,194. The company

model appears to include a minor typographical error in which the cost per VCN test applied is £1,207 rather than £1,199. No reference is given in the submission or response to clarifications regarding the source of the unit cost or recommended VCN test schedule.

Table 17 provides a summary of the average costs associated with Strimvelis and HSCT in the company's economic model.

Table 17: Company base case cost per treatment per patient.

Items	Strimvelis	HSCT from a MUD	HSCT from a haploidentical donor
Confirmation of Eligibility for Strimvelis Treatment	[redacted]	-	-
Cost of Strimvelis	£505,000	-	-
Cost of screening, including stem cells	-	£45,127	£45,127
Initial PEG-ADA before procedure and screening	£124,254 (10 weeks)	£262,314 (19 weeks)	£262,314 (19 weeks)
Hospitalisation for transplantation	[redacted]	£95,516	£108,760
Follow-up costs	[redacted] per living patient*	£59,541 per living patient	£59,541 per living patient
Total cost per treatment/patient	[redacted]	**£462,498**	**£475,742**

*Assumes first 2 months' follow up incorporated in cost of hospitalisation for transplantation and includes VCN testing

In response to clarifications the company provided updated costs that determined dose of PEG-ADA based on patient weight, an updated administration cost for PEG-ADA and for IVIG, and updated travel costs for patients travelling to Milan for treatment. The rationale for the changes to unit costs is summarised in the company response to clarifications Table 12, p60. The updated costs for PEG-ADA reduce the 'Initial PEG-ADA before procedure and screening' from £124,254 to £81,486 for Strimvelis, and from £262,314 to £172,026 for HSCT. With the addition of travel costs for Strimvelis, this gives an alternative lower total cost per treatment per patient of [redacted] (including VCN testing) for Strimvelis, £417,371 for HSCT from a MUD and £430,615 for HSCT from a haploidentical donor (company response to clarification Tables 15, 16 and 17).

5.2.8.4 Adverse event costs

Adverse events deemed relevant to the economic evaluation were severe infections after any transplant procedure and GvHD after HSCT from a MUD or a haploidentical donor. The incidence of severe infections was drawn from the Strimvelis Integrated Population. It was assumed that the rates of severe infection observed after receipt of Strimvelis were also applicable to patients who received HSCT from a MUD or haploidentical donor. The rates of severe infections were 26% between years 1 and 3 and 7% between years 4 and 8 post-procedure. The company based the cost per severe infection on a US study that estimated that infection increased allogeneic transplantation costs by $15,300, and that the median inpatient cost was $105,300.[54] The company assume that severe infection costs can be estimated as 15% of hospitalisation costs and apply a cost per severe infection of £12,143.

The same unit cost was applied to all GvHD events, with the rates determined in a literature review (company submission, Table C28). For HSCT from a MUD the rate of GvHD of any grade was 32.1% (9/28) while for HSCT from a haploidentical donor the rate was 33.3% (3/9). The unit cost was based on a single UK study which reported hospital readmission costs associated with GvHD.[55] The company took the mean cost of readmission for patients without GvHD (£13,405) and the cost of readmission with severe (Grade III/IV) GvHD (£40,012) and inflated the difference from £26,607 to £29,420 to represent 2016 prices. The cost for GvHD events was applied across all patients in year 1 of the model. The company assumes no risk of severe infection of GvHD after rescue transplant.

Table 18 presents the average undiscounted costs of managing each of the adverse events deemed relevant to the decision problem.

Table 18: Summary of total adverse event costs

Treatment	Average cost of severe infection	Average cost of GvHD	Total
Strimvelis	£13,719	£0	£13,719
MUD	£9,146	£7,880	£17,026
Haploidentical	£9,799	£8,406	£18,205

The ERG consider it inappropriate to apply a cost of severe (Grade III/IV) GvHD to GvHD events of all grades as this will overestimate the adverse event costs associated with HSCT. The study by Dignan 2013 provides a mean readmission cost separately for Grade I/II and Grade III/IV GvHD

events, and also reports an estimate for any GvHD event, which gives a lower cost per GvHD event of £15,455 (£28,860 - £13,405), which would be £17,089 inflated to 2016 prices.

The company note that retroviral insertion site testing is expected to cost €7,299 per test (£6,204 @ 1€ = £0.85), and replication competent retrovirus testing would be expected to cost €1,420 per test (£1,207 @ 1€ = £0.85). However, these costs are not included in the company base case as they would only be incurred in the event of a leukemic adverse event, which has not yet been observed in the Strimvelis clinical programme (company response to clarification B11, p32).

The ERG is concerned that the model underestimates the ongoing healthcare costs of patients with successful engraftment. The ongoing systemic sequelae of ADA-SCID and any long-term adverse events from conditioning regimens may imply higher healthcare costs compared to the general population. A pragmatic search by the ERG found a UK study that estimated the increase in mean annual NHS (£83) and PSS (£1368.20) healthcare costs of £1,451 associated with bilateral permanent childhood hearing impairment.[56]

5.2.9 Cost effectiveness results

5.2.9.1 Base case results

The company base case cost-effectiveness results are presented in Table 19. The base case results used a discount rate of 1.5% for costs and QALYs and a life time horizon (CS, Section 5.2.5). The company found Strimvelis to be more costly (cost difference of £494,255 and £170,668) but also more effective (gains of 13.6 and 11.7 QALYs) compared with HSCT from a MUD and haploidentical donor respectively. The estimated deterministic ICER for Strimvelis is £36,360 per QALY gained compared to HSCT from a MUD, and £14,645 per QALY gained compared to HSCT from a haploidentical donor.

Table 19: Company base case results

Technologies	Costs (£)	LYs gained	QALYs gained	Incremental			
				Costs (£)	LYs gained	QALYs gained	ICER (£/QALY)
Strimvelis	£1,059,425	46.1	41.4				
MUD	£565,170	31.0	27.8	£494,255	15.1	13.6	£36,360
Haplo	£888,757	33.2	29.7	£170,668	12.9	11.7	£14,645

CS, Table D14 – p185

Table 20 provides the disaggregation of accrued QALYs and life years, which shows that the majority of QALYs are accrued within the *Post-procedure, successful engraftment* state. The *Rescue transplant and post-transplant* state was the secondary source of QALYs accrued in the model.

Table 20: Summary of discounted QALY gain by health state

Strimvelis		
Outcome	LY	QALY
Pre-procedure (PEG-ADA)	0.2	0.2
Post-procedure, successful engraftment	37.8	34.0
Failure to engraft, PEG-ADA	0.3	0.3
Rescue transplant and post-transplant	7.8	6.9
Total	46.1	41.4
HSCT from a MUD		
Outcome	LY	QALY
Pre-procedure (PEG-ADA)	0.4	0.4
Post-procedure, successful engraftment	27.6	24.7
Failure to engraft, PEG-ADA	0.1	0.1
Rescue transplant and post-transplant	2.9	2.6
Total	31.0	27.8
HSCT from a haploidentical donor		
Outcome	LY	QALY
Pre-procedure (PEG-ADA)	0.4	0.4
Post-procedure, successful engraftment	19.7	17.7
Failure to engraft, PEG-ADA	0.6	0.4
Rescue transplant and post-transplant	12.6	11.2
Total	33.2	29.7

CS, Table D17 – p190

The HST interim methods process guide indicates that the magnitude of therapeutic improvement, as revealed by the QALY gain, determines the acceptability of a technology as an effective use of NHS resources. The methods guide indicates that an increased weight can be applied to QALYs gained where there is compelling evidence that the improvement in health exceeds 10 QALYs. The ERG and company were informed by NICE that the magnitude of the QALY gain should be based on undiscounted QALYs. In response to clarification the company report that the undiscounted QALY gain for Strimvelis compared to HSCT from a MUD is 23.2 QALYs, which would imply a weight of

2.3, or alternatively an increase in the cost-effectiveness threshold from £100,000 to £230,000 per QALY gained (company response to clarifications B19, p43). The undiscounted QALY gain for Strimvelis compared to HSCT from a haploidentical donor is 19.9, which would imply a weight of 2 to be applied to QALY gains or an increase in the cost-effectiveness threshold from £100,000 to £200,000 per QALY gained (Company submission Section 12.5.7, Table D 21).

The costs by category and their contribution to the total cost for each comparator are shown in Table 21. The cost of Strimvelis is the major cost component of total Strimvelis costs, followed by rescue PEG-ADA costs. In contrast PEG-ADA pre-procedure is the major component of total cost for HSCT from a MUD, followed by hospitalisation costs. For HSCT from a haploidentical donor the major component of total cost is rescue PEG-ADA costs followed by PEG-ADA pre-procedure costs (Company submission Section 12.5.16).

Table 21: Total costs by cost category

Cost category	Costs for Strimvelis therapy (% of total)	HSCT from a MUD (% of total)	HSCT from a haploidentical donor (% of total)
Screening pre-procedure	£0 (0.0%)	£45,127 (8.0%)	£45,127 (5.1%)
Confirmation of eligibility for Strimvelis treatment	[redacted]	£0 (0.0%)	£0 (0.0%)
PEG-ADA pre-procedure	£124,254 (11.7%)	£262,314 (46.4%)	£232,314 (29.5%)
Product	£505,000 (47.7%)	£0 (0.0%)	£0 (0.0%)
Severe infection cost	£13,103 (1.2%)	£8,735 (1.5%)	£9,359 (1.1%)
Rescue transplant cost	£16,119 (1.5%)	£6,090 (1.1%)	£26,098 (2.9%)
Rescue PEG-ADA cost	£217,055 (20.5%)	£81,999 (14.5%)	£351,423 (39.5%)
Hospitalisation cost	[redacted]	£95,516 (16.9%)	£108,760 (12.2%)
Follow-up cost (includes VCN in Strimvelis)	[redacted]	£43,027 (7.6%)	£58,259 (6.6%)
GvHD	£0 (0.0%)	£7,834 (1.4%)	£8,354 (0.9%)
IVIG cost	£23,041 (2.2%)	£14,529 (2.6%)	£19,063 (2.1%)
Total	**£1,059,425 (100%)**	**£565,170 (100%)**	**£888,757 (100%)**

Abbreviations: HSCT= HSCT=haematopoietic stem cell transplantation; GvHD=graft-versus-host disease; IVIG=intravenous immunoglobulin; MUD=matched unrelated donor; PEG-ADA=polyethylene glycol-modified bovine adenosine deaminase.

The company report that the product cost for Strimvelis is responsible for most of the increased cost compared to HSCT from a MUD, and is only somewhat offset by lower pre-procedure PEG-ADA and avoidance of MUD screening (Company submission Section 12.5.8). The product cost is compensated somewhat by a reduction in rescue transplant and rescue PEG-ADA costs when Strimvelis is compared to HSCT from a haploidentical donor, but not from a MUD.

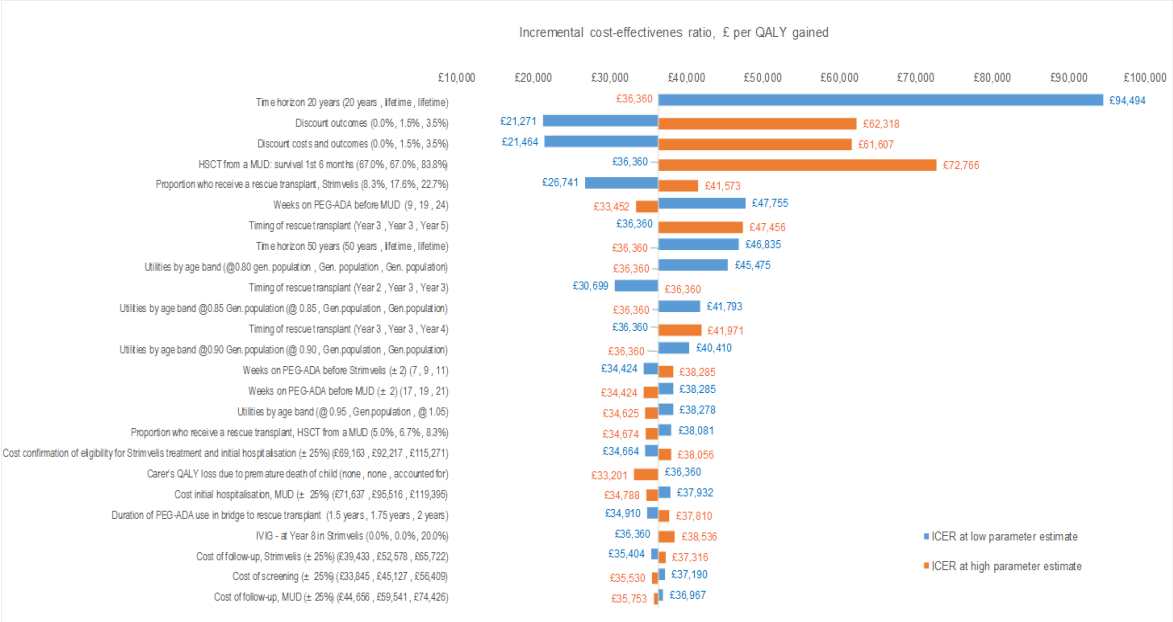
5.2.9.2 Deterministic sensitivity analysis

The company presented a series of one-way deterministic sensitivity analyses to assess the impact of varying key model input parameters on the ICER. Model parameters varied included the discount rate and time horizon, survival rates, clinical probabilities, timing and duration, costs, drug dosages, and utilities. The interval range applied for the parameters varied, though the majority of variables were adjusted by +/- 25%. A summary of the variables and ranges used in the company's one-way and two-way sensitivity analyses were provided in Tables D12 and D13 of the CS.

The results from all 1-way deterministic univariate sensitivity analyses are presented in Table D24 and Table D25 of the CS, with the results applying alternative discount rates presented in Appendix 8. In response to clarification the company provided tornado diagrams, shown in Figure 3 and Figure 4, summarising the 25 most influential parameters on the company ICER for Strimvelis compared to HSCT from a MUD and haploidentical donor respectively. The five most influential parameters for the comparison of Strimvelis against HSCT from a MUD were the time horizon (20 years compared to lifetime), the discount rate (0% or 3.5% compared to 1.5%), overall survival following HSCT from a MUD (83.75% compared to 66.7%), the proportion requiring rescue transplant following Strimvelis (8.3% or 22.7% compared to 17.6%) and the weeks on PEG-ADA before MUD (9 or 24 compared to 19). The five most influential parameters for the comparison of Strimvelis against HSCT from a haploidentical donor were the time horizon (20 years compared to lifetime), cost of PEG-ADA (10% of base case), the discount rate (0% or 3.5% compared to 1.5%), weeks on PEG-ADA before Haplo (9 or 24 compared to 19) and the proportion who require a rescue transplant following Strimvelis (0 compared to 17.6%).

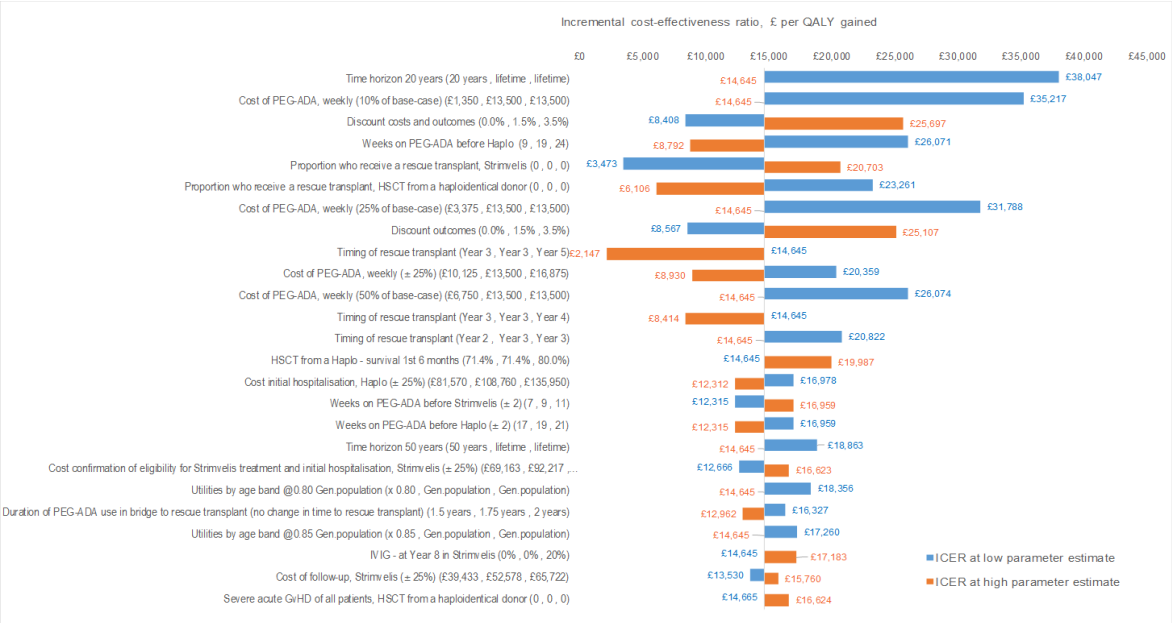
Table 22 displays the two-way sensitivity analysis conducted by the company to explore the joint uncertainties in long-term utility scores and mean life-expectancy for survivors (MLS). Overall the ICERs did not exceed £100,000 in response to the company sensitivity analyses.

Figure 3: Company tornado diagram Strimvelis vs HSCT from a MUD (base case: £36,360 per QALY)



Response to ERG clarifications, Figure 1 p48

Figure 4: Company tornado diagram Strimvelis vs HSCT from a haploidentical donor (base case: £14,645 per QALY)



Response to ERG clarifications, Figure 2 p49

Table 22: Two-way scenario analysis

	MLS*1 (79.9 yrs)	MLS*0.9 (71.9 yrs)	MLS*0.8 (63.9 yrs)
Strimvelis vs HSCT from a MUD			
Utility Score by Age * 1	£36,360	£38,375	£40,987
Utility Score by Age * 0.9	£40,410	£42,650	£45,554
Utility Score by Age * 0.8	£45,475	£47,997	£51,266
Strimvelis vs HSCT from a Haploidentical donor			
Utility Score by Age * 1	£14,645	£15,456	£16,508
Utility Score by Age * 0.9	£16,290	£17,194	£18,366
Utility Score by Age * 0.8	£18,352	£19,371	£20,694

CS, Table D26 p209; MLS = mean life expectancy of survivors

In response to clarification the company provided an additional scenario analysis that incorporated the updated cost of PEG-ADA, the updated administration costs for PEG-ADA and IVIG, and travel costs (company response to clarification Appendix, p59). This reduced the total costs for all comparators and had minimal impact on the estimated ICERs.

In response to a request from the ERG the company provided additional sensitivity analyses to explore the impact of lower rates of overall survival with Strimvelis. The ICER for Strimvelis compared to MUD increased to £41,387 using overall survival of 95% for Strimvelis, and increased to £48,601 using overall survival of 90%. The corresponding ICER for Strimvelis compared to haploidenitcal donor increased to £16,027 when survival after Strimvelis is 95% and £18,166 when survival after Strimvelis is 90% (company response to clarification B17, p40-41). The company declined to provide a sensitivity analysis that explored survival rates of 90% following HSCT from a MUD (company response to clarification B24, p50-51).

The company performed a range of threshold analyses in their original submission and in response to clarification, which are summarised in Table 23.

Table 23: Company threshold analysis

Variable	ICER compared to	Threshold		
		>£100,000/QALY	>£120,000/QALY	>£140,000/QALY

Post-procedure survival in Strimvelis and HSCT procedures	MUD	Survival after MUD >88% or survival after Strim <77%	-	Survival after MUD >92% or survival after Strim <74%
	Haplo	-	Survival after Haplo >97% or survival after Strim <73%	-
The acquisition cost of the Strimvelis procedure (baseline £505,000)	MUD	£1,370,092	-	£1,913,831
	Haplo	-	£1,732,803	-
The long-term post-procedure utility values for Strimvelis and HSCT procedures	MUD	<0.37	-	<0.26
	Haplo	-	<0.13	-

5.2.9.3 Probabilistic sensitivity analysis

The company performed a probabilistic sensitivity analysis (PSA) where parameters were sampled probabilistically from distributions based on 2,000 simulations. No justification was provided for the assigned distributions to the input parameters, although the ERG felt that those chosen were reasonable. The ERG identified a methodological error in the estimation of the probabilistic ICER in which the company provided the arithmetic mean of PSA ICERs as opposed to ICERs derived from the ratio of the mean costs and mean QALY. In response to clarification the company calculated the correct probabilistic ICERs at £36,161 ICER for Strimvelis compared with HSCT from a MUD and £14,964 when compared against HSCT from a haploidentical donor. As the decision model is linear, the probabilistic ICER is almost identical to the deterministic ICER. The company report that the ICER for exceeded £100,000 in 2% of the PSA simulations when compared to HSCT from a MUD and in 3% of the PSA simulations when compared to HSCT from a haploidentical donor (CS Section 12.5.14). The probability of Strimvelis being cost-effective at a threshold of £100,000 per QALY gained was reported to be 97% when compared to HSCT from a MUD and 99% when compared to HSCT from a haploidentical donor. The ERG considers that the slight discrepancy in the proportion of ICERs reported to exceed £100,000 per QALY is due to stochastic variation between PSA runs.

5.2.9.4 Additional sensitivity analysis undertaken by the ERG

Using the company base case results the ERG conduct a simple sensitivity analysis to inform the reduction in procedural mortality required for the ICER with Strimvelis to remain below £100,000 per QALY gained. In the company base case model each death avoided from the initial transplant procedure is associated with an additional 41 QALYs (41.4 QALYs per surviving patient using a

discount rate of 1.5%). Thus the company model estimates that for every percentage point reduction in procedural mortality there is an improvement of 0.41 QALYs. As Strimvelis is estimated to cost an additional £494,255 compared to HSCT from a MUD, the percentage point reduction in procedural mortality required to produce an ICER below £100,000 per QALY is (£494,255/£100,000)/0.41 = 12. Compared to HSCT from a haploidentical donor Strimvelis is expected to increase costs by £170,668, and so the percentage point reduction in procedural mortality must be at least (£170,668/£100,000)/0.41 = 4.

5.2.10 Model validation and face validity check

5.2.10.1 Internal consistency

The company did not provide any details on quality checks performed on the health economic model to validate its functionality. The ERG conducted a range of checks for the key calculations in the model and to examine whether varying input parameter values would generate intuitive results. A comprehensive check of all cells in the model was not performed. Overall, the company model appeared accurate, although errors existed in the estimation of probabilistic ICERs.

5.2.10.2 External consistency

The company did not conduct data validation of the economic model against existing literature on the basis that the model itself uses the most recent long term evidence on the natural history of ADA-SCID. The company states the economic model, its assumptions and results were validated by a UK clinical expert. The ERG recognises the challenges in externally validating the model results given the ultra-rare nature of the disease and the dearth of studies analysing long-term patient outcomes specific to ADA-SCID.

5.3 Conclusions of the cost effectiveness section

The ERG considered the company's economic submission to meet the requirements of the NICE reference case. The ERG considers that the company base case model applies only to younger patients in whom the decision to use Strimvelis is made immediately following diagnosis with ADA-SCID. The ERG identified a number of issues with the company model which indicate that it may underestimate the ICERs for Strimvelis compared to HSCT. The main concerns relate to four key areas:

1. *Underestimation of treatment costs with Strimvelis*
   The ERG noted that not all patients screened would be deemed eligible for treatment with Strimvelis, and the model does not incorporate the cost of initial baseline assessments in

patients unable to produce sufficient CD34+ cells. The company base case applies the standard hospitalisation charge to all patients treated with Strimvelis, and does not incorporate the additional costs incurred by the proportion of patients that exceed the standard 55 day length of stay. The model also fails to include any costs incurred for transplantation of back up bone marrow due to failure of the product or in order to facilitate recovery. However, the ERG acknowledge that excess hospital costs and use of back up bone marrow following HSCT are also excluded from the model. The company base case omits travel costs that would be reimbursed by the NHS, although these were included in a separate scenario analysis.

2. *Overestimation of costs associated with HSCT*
   The company base case assumes that the wait time before transplant is 10 weeks longer with HSCT compared to Strimvelis and that all patients are maintained on ERT using PEG-ADA during this period. The ERG consider that the available evidence does not support the assumption of greater use of PEG-ADA prior to HSCT compared to Strimvelis in terms of differential wait times and note that in practice not all patients have received ERT prior to HSCT. The company applied the higher cost of bone marrow transplant using stem cells from cord blood to all HSCT from a MUD, despite the majority of these being sourced from bone marrow, which is associated with a lower hospitalisation cost. The company also applied the cost of severe (Grade III/IV) GvHD events to GvHD events of any grade.

3. *Position of Strimvelis in the treatment pathway*
   The ERG note that some patients may utilise Strimvelis after having completed a search for a MUD. These may include patients unwilling to travel to Milan unless no appropriate MUD is found or until failure of a first-line MUD. For these patients the decision to use Strimvelis will not avoid the search costs for a MUD, but the company model structure assumes this search is avoided for all patients.

4. *Overestimation of health gains with Strimvelis*
   The company base case characterises a 33 percentage point reduction in procedural mortality with Strimvelis compared to HSCT from a MUD, and a 29 percentage point reduction compared to HSCT from a haploidentical donor. The ERG acknowledges that this is based on the best available evidence but considers that it is highly uncertain and may be an

overestimate based on improvements in survival rates following HSCT over time and the potential for overall survival following Strimvelis to fall below 100%.

The company base case assumes that patients who survive an initial transplant procedure are returned to general population longevity, and general population morbidity after three years. The ERG considers this to be unsupported by the available evidence, which indicates that following successful engraftment patients with ADA-SCID remain underweight, continue to experience cognitive and neurodevelopmental deficits and have a lower health-related quality of life compared to the general population. Following unsuccessful engraftment the ERG considers that the company base case fails to appropriately characterise the morbidity and additional health care costs associated with rescue transplant procedures.

Additional analyses based on scenarios undertaken by the company and independent analyses undertaken by the ERG are presented in Section 6 to address these uncertainties and provide an alternative set of cost-effectiveness results.

6 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

6.1 Overview

This section focuses on the additional analyses used to explore the key areas of uncertainty and concern highlighted in Section 5. The additional work undertaken by the ERG includes changes to the economic model to develop an ERG base case analysis, and a range of sensitivity and threshold analyses undertaken to explore the impact of key uncertainties.

The main changes made by the ERG to the economic model include:

1. Utilising a number of scenario analyses undertaken by the company:
    - Disuility weight of 0.75 applied for patients treated with IVIG
    - Duration of GvHD 2 years consistent with timing of rescue transplant
    - Revised PEG-ADA dose determined by patient weight
    - Revised administration costs for PEG-ADA and IVIG
    - Inclusion of travel costs
2. Incorporating the NPP to inform procedural outcomes
3. Minor corrections to the company model
4. Assuming equal wait times and pre-procedure PEG-ADA use across treatment arms
5. Assuming rescue therapy has same cost and health outcomes as initial MUD
6. Including ongoing healthcare costs and morbidity associated systemic sequelae of ADA-SCID
7. Adjusting unit costs for:
    - HSCT from a MUD to reflect proportion sourced from bone marrow
    - GvHD events to make cost per event consistent with severity
8. Incorporating cost of baseline screening for proportion of patients ineligible for Strimvelis

After demonstrating the impact of the various scenarios on the ICER, the ERG presents its preferred base-case analysis. The ERG's additional scenario analyses thereafter assess the impacts the following four uncertainties have on cost-effectiveness:

1. Survival rates for Strimvelis and HSCT
2. Cost of Strimvelis and initial hospital care in OSR
3. Strimvelis' position in the treatment pathway
4. Rescue transplant rates

6.2 ERG corrections and adjustments to the company's base case model

6.2.1 Company sensitivity analyses and alterations

The company submission recognised many of the uncertainties discussed in Section 5 and incorporated a range of scenario analyses that assessed the impact of alternative assumptions on the company's base case results.

The ERG consider that the company sensitivity analysis that incorporates a health related quality of life impact associated with IVIG use is more representative of the experience of patients with ADA-SCID. The company sensitivity analysis applies a utility weight of 0.75, which is approximately in line with the ratio of IVIG use to chronic lymphocytic leukemia without infection reported in the literature (0.66/0.87).[47]

In the company base case the duration of chronic GvHD exceeds the assumed time to rescue transplant. The ERG prefers to maintain consistency between these as rescue transplant is only performed once chronic GVHD is resolved. In response to clarification the company provided alternative results assuming rescue transplant occurred at year 4, which would maintain consistency between duration of GvHD and timing of rescue transplant. However, the company did not provide an updated economic model with this adjusted timing of rescue transplant. Instead, the ERG therefore apply the company's analysis which reduced the duration of chronic GvHD to 2 years, although noting that the impact on the ICER is much smaller than delaying rescue transplant.

In response to points for clarification, the company provided a further scenario analysis incorporating: weight based PEG-ADA dosages, cost of drug administration in line with expected administration times and the costs of travel to and from the OSR, Milan (Section 5.2.9.2 and company response to clarification Appendix p59-60). The ERG accepts this additional scenario analysis as a more appropriate account of the dosing and costs of administration and travel likely to occur in practice.

6.2.2 Incorporating the NPP

As previously discussed in Section 4.2.1, the ERG believes that it is important to use all available data on patients that have been treated with Strimvelis to inform the model parameters and considers that incorporating the NPP is consistent with the merger of studies that the company used for the Strimvelis Integrated Population. Table 24 illustrates the difference this makes to the numbers of patients informing procedural outcomes.

Table 24: Modelled procedural outcomes by patient population

	Company base case	ERG preferred
	Integrated Strimvelis population	NPP + Integrated Strimvelis population
Patients	17	[redacted]
Rescue transplants	3	[redacted]
Died	0	[redacted]
Survived	17	[redacted]
Rescue transplant	17.6%	[redacted]
Survived	100%	100.0%

6.2.3 Parameter corrections

The ERG identified and corrected minor errors in the company model for the cost applied to the first six months' follow up after Strimvelis and the cost per test for vector copy number. Table 25 provides a summary of the identified discrepancies in the company submission and the company model. The ERG's preferred base case applies the corrected values for each parameter in Table 25.

Table 25: Parameter discrepancies

	Company submission	Company model	Corrected value
Cost of follow-up (Months 0-6)	[redacted]	[redacted]	[redacted]
Cost of VCN	£1,199	£1,207	£1,199

The ERG also has concerns regarding the calculation of rescue therapy rates in the company model. As discussed in Section 5.2.6.3, the company's calculated rescue transplant rates are not conditional on survival following the initial procedure. The ERG's base case applies rescue therapy rates conditional on survival from the Strimvelis Integrated Population and the NPP. Table 26 reports the conditional and non-conditional rates of rescue therapy for each population under study.

Table 26: Conditional and non-conditional rates of rescue therapy

	Strimvelis Integrated Population			Strimvelis Integrated Population + NPP		
	Strimvelis	MUD	Haplo	Strimvelis	MUD	Haplo
Patients	17	15	7	[redacted]	15	7
Rescue transplant	3	1	2	[redacted]	1	2
Died	0	5	2	[redacted]	5	2
Survived	17	10	5	[redacted]	10	5

Non-conditional rescue transplant rates	3/17 (17.6%)	1/15 (6.7%)	2/7 (28.6%)	[redacted]	1/15 (6.7%)	2/7 (28.6%)
Conditional rescue transplant rates	3/17 (17.6%)	1/10 (10.0%)	2/5 (40%)	[redacted]	1/10 (10.0%)	2/5 (40%)

6.2.4 Equal wait times across treatments

The ERG considers that there is insufficient evidence to support a difference in wait time between Strimvelis and HSCT (see Section 5.2.6.1). The ERG preferred base case therefore assumes no difference in wait time to transplant across all comparators, which is applied by setting wait time to 0 weeks.

6.2.5 Rescue therapy

The ERG believes it is unrealistic to assume all patients following an unsuccessful engraftment would find a MSD for rescue transplantation, and unrealistic to assume that patients receiving rescue transplants will have 100% survival and 100% successful engraftment. The company had included a sensitivity analysis in which the survival rate from a rescue transplant is taken from a MUD procedure, but this did not include the risk of GvHD nor severe infections post-procedure. The ERG's preferred base case assumes that patients who receive a rescue transplant experience the health outcomes and costs associated with using a MUD. The ERG provides an alternative rescue transplant scenario which incorporates:

- The survival rate from a MUD transplant (66.6%)
- The expected cost and QALY impacts of GvHD
- The expected cost of severe infections
- Patients who fail to engraft following rescue transplant go on to receive long term PEG-ADA (≥0.3% of modelled patient cohort)

Table 27 reports the changes in costs and QALYs which result from the ERG's alternative base case for rescue therapies.

Table 27: Changes in costs and QALYs for the ERG's alternative rescue therapy scenario

	Change in costs			Change in QALYs		
	Strimvelis	MUD	Haplo	Strimvelis	MUD	Haplo
ERG alternative rescue scenario	+£186,511	+£70,460	+£301,970	-2.3	-0.9	-3.8

6.2.6 Long-term cost and health-related quality of life outcomes

As discussed in Section 5.2.7, both the company and the ERG identified evidence contradicting the assumption made in the CS that ADA-SCID patients return to the HRQoL observed in the general population 6 months post-procedure. The ERG utilise studies identified in a pragmatic review to provide an indication of the cost and HRQoL impacts of the common long-term sequelae of ADA-SCID.

As discussed in Section 5.2.7, Petrou et al estimated a mean health-related quality of life decrement for bilateral permanent hearing impairment of -0.294 ($p<0.01$) compared to children with normal hearing.[57] Schroeder et al calculated mean annual costs (relevant to the NHS & PSS) of bilateral permanent hearing impairment at £1,451.20, which is £2,095.82 inflated to 2016 prices using the PSSRU hospital and community health service index.[56]

Titman et al reported that 25% of SCID patients who survive HSCT experience higher levels of difficulties in emotional and behavioural function, as defined by a total difficulties score ≥17 on the SDQ. This was compared to 10% in the general population.[37] Using a mapping algorithm to predict preference-based utility scores based on clinical bandings of the SDQ, the ERG estimate a decrement of 0.14 for difficulties in emotional and behavioural function among SCID patients.[51]

Table 28 presents evidence sourced by the ERG relevant to the long-term expected costs and HRQoL of patients with ADA-SCID.

Table 28: Long-term ADA-SCID related cost and HRQoL values from the literature

	Decrement in HRQoL		Cost		Rates		Expected Value	
Condition	Value	Source	Value	Source	Value	Source	HRQoL	Cost
Bilateral permanent hearing impairment	-0.294	Petrou et al (2007)	£2,095.82	Schroeder et al (2006)	58.3%	Albuquerque and Gaspar (2004)	-0.172	£1221.86
Emotional and behavioural dysfunction	-0.14	Furber et al (2014)	-	-	15%	Titman et al (2008)	-0.021	-

Table 29 displays the resultant changes in costs and QALYs if these estimates are applied in the company model. Given uncertainty surrounding the application of mapping to determine the health related quality of life impact of emotional and behavioural problems, the ERG's preferred base case applies the expected costs and HRQoL impacts from bilateral permanent hearing impairments only,

while noting that these are not the only long-term sequelae of ADA-SCID that may imply ongoing costs and morbidity.

Table 29: Change in costs and QALYs from long-term ADA-SCID morbidities

	Change in costs			Change in QALYs		
Condition	Strimvelis	MUD	Haplo	Strimvelis	MUD	Haplo
Bilateral permanent hearing impairment	+£56,167	+£37,444	+£40,119	-7.8	-5.2	-5.5
Emotional and behavioural dysfunction	£0	£0	£0	-1.0	-0.6	-0.7
Total	+£56,167	+£37,444	+£40,119	-8.8	-5.8	-6.2

6.2.7 Updated unit costs

As discussed in Section 5.2.8.1, the company submission applies a unit cost derived from cord blood bone marrow transplants to all MUD transplants. However, the ERG expects that a significant proportion of MUD transplants will be undertaken using bone marrow, in line with the rate observed in Hassan 2012 (88/106, 83%) and the national schedule of reference costs (51/62, 82%).[3, 53] The NHS reference cost of bone marrow transplant, allogeneic graft, is £95,517 using stem cells from cord blood (code SA22B as applied in company base case) and £79,199 using stem cells from volunteer unrelated donor (£79,199 code SA21B). The weighted average cost used in the ERG's base case analysis is £81,973, based on the proportion of transplants sourced from bone marrow in Hassan.

As previously detailed in Section 5.2.8.4 the ERG consider it inappropriate to apply a cost of severe (Grade III/IV) GvHD to GvHD events of all grades since this will overestimate the adverse event costs associated with HSCT. The ERG believe a more appropriate unit cost per GvHD event would be calculated by the difference between the mean readmission cost of any GvHD event (£28,860) and the mean cost of readmission for patients without GvHD (£13,405). After inflating the difference of £15,455 to 2016 prices, the resultant unit cost applied in the ERG's preferred base case is £17,089.

6.2.8 Cost of ineligibility to Strimvelis

In the company's economic model, all patients assigned to Strimvelis are assumed to receive gene therapy, and hence the model does not incorporate forgone screening costs for patients unable to donate adequate CD34+ cells. Given that 1 of the 18 patients in the Strimvelis Integrated population was deemed ineligible after screening, the ERG considers it appropriate to include these costs in the Strimvelis treatment arm. The ERG's preferred base case makes a simplified adjustment in the cost of screening so that for every 18 patients tested, 17 patients advance to Strimvelis. This alteration

prompts a revised cost of [redacted] per successfully treated patient as supposed to [redacted] used in the company's original base case.

While the ERG have made adjustments to the base case company model costs for Strimvelis related screening the ERG still considers there remains a large degree of uncertainty surrounding the treatment pathway for those patients who fail screening for Strimvelis. The duration of time these patients remain on PEG-ADA is unknown and it is unclear whether inability to produce sufficient CD34+ cells will also impact on success of HSCT.

6.2.9 ERG preferred base case

Table 30 shows the effect of each individual change to the company base case ICER and how these are combined to produce the ERG's preferred base case estimates. It should be noted that the results were conducted using the company's base case discount rate (1.5%).

Table 30 - Results of the relevant scenarios and additional calculations for the ERG base cases

	Costs	QALYs	Inc. cost	Inc. QALY	ICER	Δ ICER
Company base case						
Company original base case (deterministic)						
Strimvelis	£1,059,425	41.4				-
MUD	£565,170	27.8	£494,255	13.6	£36,360	-
Haploidentical	£888,757	29.7	£170,668	11.7	£14,645	-
Company's secondary analysis (after clarifications requested to the company by NICE and the ERG)						
Weekly cost of PEG-ADA set using 1 vial @ £9,000 (from £13,500)						
Strimvelis	£948,177	41.4				
MUD	£452,943	27.8	£495,234	13.6	£36,432	+£72
Haploidentical	£688,712	29.7	£259,465	11.7	£22,264	+£7,619
PSSRU cost of administration of IVIG @ £216 (from £306)						
Strimvelis	£1,055,311	41.4				
MUD	£562,590	27.8	£492,722	13.6	£36,247	-£113
Haploidentical	£885,311	29.7	£170,001	11.7	£14,587	-£57
PSSRU cost of administration of PEG-ADA @ £54 (from £306)						
Strimvelis	£1,053,195	41.4				
MUD	£558,885	27.8	£494,310	13.6	£36,364	+£4
Haploidentical	£877,554	29.7	£175,641	11.7	£15,071	+£427
Including company's specified cost of travel to Milan						
Strimvelis	£1,060,837	41.4				

MUD	£565,170	27.8	£495,667	13.6	£36,464	+£104
Haploidentical	£888,757	29.7	£172,080	11.7	£14,766	+£121
Company's total secondary analysis						
Strimvelis	£939,245	41.4				
MUD	£444,078	27.8	£495,167	13.6	£36,427	+£67
Haploidentical	£674,064	29.7	£265,182	11.7	£22,755	+£8,110
Company's IVIG disutility scenario (utility = 0.75)						
Strimvelis	£1,059,425	40.5				
MUD	£565,170	27.2	£494,255	13.3	£37,158	+£799
Haploidentical	£888,757	29.1	£170,668	11.5	£14,865	+£221
ERG Scenario Analyses						
SA1. Named Patient Population (NPP) included to inform procedural outcomes						
Strimvelis	£1,161,783	41.3				
MUD	£565,170	27.8	£596,613	13.6	£42,950	+£7,590
Haploidentical	£888,757	29.7	£273,026	11.6	£23,465	+£8,820
SA2. Parameter corrections and conditional probabilities for rescue therapy						
Strimvelis	£1,059,381	41.4				
MUD	£611,649	27.8	£447,732	13.6	£32,917	-£3,443
Haploidentical	£1,048,115	29.7	£11,267	11.7	£964	-£13,680
SA3. Equalising duration of initial PEG-ADA prior to initial procedure (0 days)						
Strimvelis	£935,171	41.2				
MUD	£302,856	27.4	£632,315	13.8	£45,881	+£9,522
Haploidentical	£626,443	29.4	£308,728	11.8	£26,071	+£11,426
SA4. Rescue therapy transplants conducted from a MUD (reduced survival, GvHD and severe infection risk, PEG-ADA for failed engraftment)						
Strimvelis	£1,245,936	39.0				
MUD	£635,630	26.9	£610,306	12.1	£50,246	+£13,886
Haploidentical	£1,190,727	25.9	£55,209	13.1	£4,216	-£10,428
SA5. Utilities accommodating for permanent childhood hearing impairment						
Strimvelis	£1,059,425	33.6				
MUD	£565,170	22.6	£494,255	11.0	£44,913	+£8,553
Haploidentical	£888,757	24.2	£170,667	9.4	£18,121	+£3,476
SA6. Costs of permanent childhood hearing impairment						
Strimvelis	£1,155,592	41.4				
MUD	£602,615	27.8	£512,977	13.6	£37,737	+£1,377

Haploidentical	£928,876	29.7	£186,716	11.7	£16,022	+£1,377
SA7. Updated unit costs for HSCT (with bone marrow donation) and GvHD events (average costs applied)						
Strimvelis	£1,057,140	41.4				
MUD	£547,480	27.8	£509,659	13.6	£37,493	+£1,133
Haploidentical	£881,555	29.7	£175,584	11.7	£15,067	+£422
SA8. Cost of ineligibility for Strimvelis						
Strimvelis	[redacted]	41.4				
MUD	£565,170	27.8	[redacted]	13.6	[redacted]	[redacted]
Haploidentical	£888,757	29.7	[redacted]	11.7	[redacted]	[redacted]
ERG preferred base case						
Strimvelis	£1,236,768	30.1				
MUD	£425,656	20.7	£811,195	9.3	£86,815	+£50,455
Haploidentical	£1,052,166	19.0	£184,686	11.1	£16,704	+£2,060

The ERG preferred base case predicts lower QALYs for all comparators compared to the company base case. This is attributable to the increased mortality and morbidity associated with rescue transplants and the application of HRQoL decrements for IVIG use and bilateral hearing impairment. The ERG's preferred base case predicts higher costs for Strimvelis, lower costs for HSCT from a MUD and higher costs for HSCT from a haploidentical donor compared to the company base case. This is attributable to the higher rates of rescue transplant for Strimvelis and HSCT from a haploidentical donor combined with the increased health care costs per rescue transplant to reflect risks of severe infection and GvHD. As shown in Table 30, the ERG's base case ICERs are higher than the company base case, rising to £86,815 for Strimvelis compared to HSCT from a MUD and to £16,704 for Strimvelis compared to a haploidentical donor. The ERG's preferred ICER remains below the £100,000 lower tier threshold for both comparators.

Recent consultation published by NICE on arrangements for funding in highly specialised technology programmes states that the threshold used for decision making is now conditional on the size of the QALY gain the treatment offers. Table 31 reports the adjusted cost-effectiveness thresholds for both the company's and ERG's base cases.

Table 31: Relevant decision making threshold for the company and ERG base cases

	Comparator	Strimvelis' undiscounted QALY gain	Weighting of QALY	Adjusted threshold
Company base case	MUD	23.2	2.32	£232,000
	Haploidentical	19.9	1.99	£199,000
ERG base case	MUD	15.9	1.59	£159,000
	Haploidentical	18.8	1.88	£188,000

6.3 Additional ERG analyses

6.3.1 Survival rates

As discussed in Section 5.2.6.1 the rates of survival for ADA-SCID patients is highly uncertain. Figure 5 and Figure 6 show the results of two-way sensitivity analysis comparing the rates of survival following Strimvelis to overall survival following HSCT from a MUD and from a haploidentical donor respectively.

Figure 5 indicates that the ERG base case ICER is sensitive to the survival rate following HSCT from a MUD. The comparison of the results of sensitivity analyses around survival rates against adjusted cost-effectiveness thresholds is complicated by the fact that adjusting the survival rate will alter the expected QALY gain with Strimvelis. Table 32 provides a one way sensitivity analysis for overall survival following HSCT from a MUD. This indicates that Strimvelis must reduce procedural mortality by at least 23 percentage points compared to a MUD in order for the undiscounted QALY gain to exceed 10 QALYs, and that it must reduce procedural mortality by at least 30 percentage points to result in an ICER less than £100,000.

Table 32: ICER and undiscounted QALY gain dependent on overall survival with initial MUD

Survival with MUD	ICER Strimvelis vs MUD	Undiscounted QALY gain Strimvelis compared to MUD	Adjusted threshold
0.66	£84,936	16.25	£163,000
0.67	£87,787	15.70	£157,000
0.68	£90,848	15.14	£151,000
0.69	£94,143	14.58	£146,000
0.70	£97,699	14.02	£140,000
0.71	£101,549	13.46	£135,000
0.72	£105,731	12.90	£129,000
0.73	£110,289	12.35	£124,000

0.74	£115,277	11.79	£118,000
0.75	£120,759	11.23	£112,000
0.76	£126,812	10.67	£107,000
0.77	£133,529	10.11	£101,000
0.78	£141,027	9.56	£100,000 (no adjustment)

Figure 6 displays how insensitive the ICER for Strimvelis is with respect to survival outcomes of patients undergoing transplant from haploidentical donors. Increasing the rate of survival for haploidentical transplants decreases the ICER for Strimvelis. The underlying reason for this is the high rates of rescue therapy following HSCT from a haploidentical donor. Increasing survival following HSCT increases QALYs but is associated with large increases in the costs of PEG-ADA when awaiting rescue therapy and the cost and mortality risks of the rescue transplant. Given the very small numbers that inform the rates of rescue therapy the results of Figure 6 should be taken with caution.

Figure 5: Two way sensitivity analysis for initial procedure survival rates showing ICER for Strimvelis compared to MUD

Strimvelis Survival ↓ **MUD Survival →** **ERG base case***

	1.00	0.96	0.92	0.88	0.84	0.80	0.76	0.72	0.68	0.667
1.00	Dominated	Dominated	£736,937	£330,448	£214,116	£158,982	£126,812	£105,731	£90,848	**£86,815**
0.98	Dominated	Dominated	£1,696,417	£436,228	£251,934	£177,911	£137,979	£112,996	£95,890	£91,327
0.96	Dominated	Dominated	Dominated	£652,004	£308,197	£202,869	£151,788	£121,627	£101,720	£96,507
0.94	Dominated	Dominated	Dominated	£1,335,165	£400,749	£237,285	£169,301	£132,051	£108,536	£102,513
0.92	Dominated	Dominated	Dominated	Dominated	£581,415	£287,790	£192,240	£144,889	£116,613	£109,560
0.90	Dominated	Dominated	Dominated	Dominated	£1,090,350	£369,109	£223,589	£161,092	£126,337	£117,944
0.88	Dominated	Dominated	Dominated	Dominated	£11,704,595	£521,819	£269,009	£182,180	£138,268	£128,088
0.86	Dominated	Dominated	Dominated	Dominated	Dominated	£913,490	£340,718	£210,755	£153,255	£140,607
0.84	Dominated	Dominated	Dominated	Dominated	Dominated	£4,121,762	£470,834	£251,666	£172,643	£156,450
0.82	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	£779,741	£315,100	£198,705	£177,140

Figure 6: Two way sensitivity analysis for initial procedure survival rates showing ICER for Strimvelis compared to Haplo

Strimvelis Survival ↓ **Haplo Survival ⟶** **ERG base case***

	1.00	0.96	0.92	0.88	0.84	0.80	0.76	0.72	0.714
1.00	Dominant	Dominant	Dominant	£1,413	£6,707	£10,715	£13,856	£16,383	**£16,704**
0.98	Dominant	Dominant	Dominant	-£558	£5,479	£9,942	£13,376	£16,101	£16,445
0.96	Dominant	Dominant	Dominant	-£2,964	£4,024	£9,046	£12,830	£15,784	£16,153
0.94	Dominant	Dominant	Dominant	-£5,969	£2,273	£7,996	£12,202	£15,424	£15,824
0.92	Dominant	Dominant	Dominant	-£9,827	£124	£6,747	£11,473	£15,014	£15,449
0.90	Dominant	Dominant	Dominant	-£14,960	-£2,574	£5,238	£10,615	£14,542	£15,018
0.88	£1,218,861	Dominant	Dominant	-£22,127	-£6,063	£3,378	£9,592	£13,991	£14,517
0.86	£271,284	Dominant	Dominant	-£32,835	-£10,752	£1,027	£8,349	£13,342	£13,929
0.84	£160,825	£595,462	Dominant	-£50,571	-£17,387	-£2,037	£6,810	£12,565	£13,227
0.82	£118,051	£210,925	Dominant	-£85,628	-£27,497	-£6,198	£4,852	£11,617	£12,375

6.3.2 Price of Strimvelis and cost of initial hospitalisation in OSR

The product cost of Strimvelis is uncertain due to potential fluctuations in the exchange rate and the associated hospitalisation charge is still under negotiation between NHS England and the company. The ERG also identified a number of treatment relevant costs that were omitted from the company model, including additional costs for hospital stays in Milan that exceed 55 days and the costs of back up bone marrow administration. To address uncertainties in the additional costs for patients treated with Strimvelis, the ERG conducted a threshold sensitivity analysis to indicate the increase in the incremental costs for Strimvelis that would cause the estimated ICER to exceed £100,000 per QALY or the adjusted threshold indicated by the undiscounted QALY gain. An increase of £123,203 in the incremental cost of Strimvelis compared to HSCT from a MUD would result in an ICER greater than £100,000 per QALY, and an increase of £683,842 would result in an ICER greater than £160,000 compared to HSCT from a MUD. The corresponding threshold incremental cost increases are much larger when Strimvelis is compared to HSCT using a haploidentical donor, at £920,932 to produce an ICER greater than £100,000 per QALY and £1,893,876 to produce an ICER greater than £188,000 per QALY.

Figure 7 shows a two-way sensitivity analysis and provides the ICER for Strimvelis compared to MUD for variations in alternative overall survival following Strimvelis and the product cost (i.e. £505,000) of Strimvelis. It should be noted that when the survival rate following Strimvelis is reduced below 100%, the adjusted cost-effectiveness threshold in accordance with the HST methods process guide will also fall (£133,000 for overall survival at 95% and £108,000 for overall survival at 90%).

Figure 7: Two way sensitivity analysis for overall survival and product cost of Strimvelis.

Strimvelis Survival ↓ **%Change Strimvelis product cost →** **ERG base case**

	+30%	+20%	+10%	+/-0%	-10%	-20%	-30%
1.00	£103,028	£97,624	£92,219	**£86,815**	£81,410	£76,006	£70,601
0.95	£118,718	£112,277	£105,836	£99,395	£92,954	£86,513	£80,072
0.90	£141,852	£133,883	£125,914	£117,944	£109,975	£102,006	£94,036

6.3.3 Strimvelis' position in the treatment pathway

As noted in Section 5.2.1 the ERG considers that Strimvelis could take a range of different positions in the treatment pathway, each with different implications for cost and outcomes. The company decision tree structure characterises one of the possible routes in which patients arrive to treatment directly after diagnosis. The ERG highlights two alternative pathways in which patients may arrive to treatment:

- In cases where patients, families or clinicians first wish to explore the potential for a MUD before making a decision to use gene therapy;
- In cases where patients undergo HSCT but fail to engraft and subsequently undergo Strimvelis as a rescue therapy

In both these cases the costs of searching for a MUD would not be avoided in patients who go on to use Strimvelis. The ERG base case does include an alternative model structure that fully characterises these alternative pathways. Instead the ERG provide a simplistic analysis that explores the impact of assuming donor screening is undertaken before the decision is made to use Strimvelis. This simply includes the cost of donor screening in the Strimvelis arm, and leaves all other parameters such as duration of PEG-ADA unchanged from the ERG base case. Table 33 shows that incorporating donor screening costs for both Strimvelis and HSCT increases the ICERs for Strimvelis compared to HSCT by £4,830 compared to MUD and by £4,082 compared to Haploidentical donor source.

Table 33: Strimvelis incurring the cost of screening for a MUD

	Costs	QALYs	Inc. cost	Inc. QALY	ICER	Δ ERG ICER
Strimvelis	£1,281,895	30.1				
MUD	£425,656	20.7	£856,322	9.3	£91,644	+£4,830
Haploidentical	£1,052,166	19.0	£229,913	11.1	£20,786	+£4,082

In the absence of evidence regarding the proportion of ADA-SCID patients for whom no appropriate MUD can be found, it is not possible to estimate a weighted combination of HSCT from a MUD or haploidentical donor to represent the costs and health outcomes that would be expected from HSCT prior to completion of a donor search. However, the ERG note that the ICER for Strimvelis compared to a weighted combination of HSCT from a MUD and HSCT from a haploidentical donor would be lower than that estimated for Strimvelis compared to HSCT from a MUD only.

6.3.4 Equal rates of rescue therapy

To assess the effects of removing any difference between treatments in rates of rescue therapy, the ERG presents a scenario analysis in which [redacted] of patients fail to engraft, based on the rate of rescue transplant calculated in the Strimvelis Integrated Population and NPP. This implies an increase in the rate of rescue transplant following MUD from 10%, and a reduction in the rate of rescue transplant following Haplo. Table 34 displays the resultant changes in costs and QALYs. It is clear from this

scenario that the costs are highly sensitivity to the removal of differences in the rates of rescue therapy, which is predominantly driven by the assumed PEG-ADA costs required to bridge patients to rescue therapies.

Table 34: Changes in costs and QALYs when equalising rates of rescue therapy

	Costs	QALYs	Inc. cost	Inc. QALY	ICER	Δ ERG ICER
Strimvelis	£1,635,030	30.1				
MUD	£1,120,099	19.1	£514,931	11.0	£46,849	-£39,965
Haploidentical	£1,154,080	20.7	£480,950	9.4	£51,116	+£34,412

6.4 Conclusions from ERG analyses

The changes made by the ERG produce ICERs for Strimvelis compared to HSCT that are higher than the company base case, but remain below £100,000 per QALY gained. The results of the model would suggest that Strimvelis is a cost-effective alternative for patients that have no MUD available, and in whom HSCT from a haploidentical donor is the only alternative, as the ICER for Strimvelis compared to HSCT from a haploidentical donor is unlikely to exceed £100,000 per QALY for a range of sensitivity analyses.

However, the results of the comparison between Strimvelis and HSCT from a MUD are very sensitive to the assumed reduction in procedural mortality for Strimvelis compared to HSCT from a MUD. For patients with an appropriate MUD available, improvements in techniques for HSCT that increase overall survival following MUD or the occurrence of a death in a patient treated with Strimvelis, could cause the ICER for Strimvelis compared to MUD to exceed £100,000 per QALY gained. If survival following HSCT from a MUD exceeds 75%, the ICER for Strimvelis compared to a MUD would no longer fall beneath the adjusted cost-effectiveness threshold determined by the extent of the undiscounted QALY gain with Strimvelis. If overall survival with Strimvelis falls below 100%, the results are also sensitive to the additional cost of Strimvelis treatment. The rates of rescue transplant are also very influential on the estimated ICERs. Assumptions that improve the anticipated outcomes of rescue transplant after Strimvelis, for example if rescue transplantation is earlier following Strimvelis due to the avoidance of chronic GvHD or because MUD options have not yet been exhausted, this would be expected to reduce the ICER for Strimvelis compared to HSCT from a MUD.

7 Submissions from practitioner and patient groups

One submission was received from Dr Susan Walsh representing Primary Immunodeficiency UK (PDI UK). As there were no further submissions from patient groups the ERG judged there would be no added value in summarising this document and would potentially risk losing key issues. Therefore, for further details please see the submission by Dr Susan Walsh.

One submission was also received from NHS England, as above the ERG judged there would be no added value in summarising this document. For further details please see the submission by NHS England.

A further submission was also provided by Professor Aiuti an expert in the treatment of Strimvelis.

8 Overall conclusions

The ERG acknowledge that the company base case utilises appropriate available evidence to inform rates of overall survival and successful engraftment, but is concerned that the small numbers of patients mean that the extent of the estimated treatment benefit is highly uncertain. The company model was simple and straightforward, but as a consequence may have failed to appropriately characterise the cost and health differences between alternative treatment strategies and pathways.

The ERG considered that the company base case omitted potentially important costs associated with the use of Strimvelis, including the cost of screening for patients deemed ineligible to proceed to treatment with Strimvelis, travel costs, and the full health care cost implications of patients that fail to engraft and require rescue transplant. The ERG acknowledges that the company addressed some of these concerns in sensitivity analysis. While the ERG was also concerned that the omission of excess hospitalisation costs and administration of back up bone marrow in patients treated with Strimvelis, the ERG base case also omits these costs as it is uncertain whether similar costs may be incurred by patients who undergo HSCT from a MUD or haploidentical donor.

The ERG identified a number of areas where the costs associated with HSCT from a MUD or haploidentical donor may be overestimated, including the hospitalisation cost applied for HSCT from a MUD, the cost per GvHD event and the cost of PEG-ADA in terms of both duration of ERT prior to HSCT and drug acquisition and administration costs.

The ERG was very concerned with the underlying assumption in the company base case model that all ADA-SCID patients who survive the initial procedure are cured and return to general population

mortality and morbidity regardless of engraftment success, patient characteristics and prior health state. The ERG assumed greater mortality, morbidity and health care costs for rescue transplant compared to the company base case and introduced disutility associated with IVIG use and bilateral hearing impairment, and an ongoing health care cost from bilateral hearing impairment in patients that survive transplant procedures. This reduced the QALY gained predicted by the model for a given reduction in procedural mortality.

The ERG consider that the company base case applies only to younger patients in whom the decision to use Strimvelis is made immediately after diagnosis and prior to undertaking a search for a MUD. It is likely that in older patients the costs of PEG-ADA and IVIG will be increased across all comparators, and possible that overall survival and success rates will be reduced across all comparators. If the search costs for a MUD are not avoided by the time the decision to use Strimvelis is taken, the ICER for Strimvelis compared to a MUD increases, but remains below £100,000 per QALY. If assumptions about rescue transplants are more favourable to Strimvelis, this would significantly reduce the ICER for Strimvelis compared to HSCT from a MUD.

8.1 Implications for research

Overall, the ERG believes that the difference in overall survival between Strimvelis and HSCT from a MUD could well be lower than that characterised in the model or is likely to fall with time. The ERG consider that given the rarity of ADA-SCID and the changes in clinical practices over time that obtaining contemporary evidence to inform survival rates is challenging. Given the small sample sizes used to inform the key model parameters, each additional patient treated can have a large influence on estimates of overall survival and rates of successful engraftment. An update to the analysis conducted by Hassan et al. that informed more recent rates of overall survival following HSCT from a MUD may be very valuable in determining whether Strimvelis can be considered cost-effective.

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10 Appendices

10.1 Checklist

Table 35 summarises the results of the Phillips checklist applied to the company cost effectiveness submission.

Table 35: Phillips checklist for company submission

Description of quality	Response (✓,✗ or NA)	Comments	Reference
Structure			
S1 Statement of decision problem objective			
Is there a clear statement of the decision problem?	✓	The decision problem was clearly stated in the first table of the CS using the PICOS framework.	CS, Table A1, p19-22
Is the objective of the evaluation and model specified and consistent with the stated decision problem?	✓	Given the CS is submitted under the highly specialised technologies evaluation programme it is implied that the core evidence presented by the company intends to fulfil NICE's objective of determining the clinical and cost-effectiveness of Strimvelis within its marketing authorisation for patients with ADA-SCID for whom no suitable HLA-matched related stem cell donor is available.	
Is the primary decision-maker specified?	✓	Yes, NICE.	
S2 Statement of scope/perspective			
Is the perspective of the model clearly stated?	✓	Yes, the perspective of the company's analysis was the NHS and Personal Social Services (NHS & PSS).	CS, Table D4, p146-148
Are the model inputs consistent with the stated perspective?	✓	Yes.	
Has the scope of the model been stated or justified?	✓	The scope used for the company's de novo analysis was stated in the first table of the CS.	CS, Table A1, p19-22
Are the outcomes of the model consistent with the perspective, scope and overall objective of the model?	✓	Outcomes relate to life-years, quality adjusted life years and costs. The outcomes and perspective of the model are in line with NICE guidance.	
S3 Rationale for structure			

Is the structure of the model consistent with a coherent theory of the health condition under evaluation?	×	• The structural assumption that MSDs are available for all rescue transplants is not consistent with UK clinical practice. • The underlying message from the model is that all ADA-SCID patients without a matched related donor will be cured and return to general population mortality and morbidity due to Strimvelis, regardless of engraftment success, patient characteristics or prior health state. This is inconsistent with the data provided and the theory of the health condition. • No reference to how the structure and design of the model was informed • The models design suggests Strimvelis is chosen in its own right, prior to HLA-matching and without consideration of the patients' condition or availability and match of HSCT donors. In reality it is unclear when the decision to use Strimvelis is actually made in clinical practice. A better appreciation of the context in which the decision to use gene therapy is being made is required to appreciate the extent to which matching, prior condition and patient characteristics (e.g. infections, patient age, etc.) influence decision making and/or outcomes.	CS, p137-148
Are the sources of data used to develop the structure of the model specified?	×	The model was designed in line with the NICE reference case, from the perspective of the UK NHS and PSS. No details were provided in the main submission concerning the model conceptualisation process and the role of experts in validating the final model structure.	
Are the causal relationships described by the model structure justified appropriately?	✓	The causal relationship between Strimvelis and HSCT was justified but is highly uncertain given the limited non-randomised, single-arm, open label evidence available.	
S4 Structural assumptions			
Are the structural assumptions transparent and justified?	✓	Yes.	CS, Table D2 – p140-143
Are the structural assumptions reasonable given the overall objective, perspective and scope of the model?	×	No. See S3.	CS, Table D2 – p140-143
S5 Strategies/comparators			
Is there a clear definition of the options under evaluation?	✓	Yes "*The model was used to estimate the costs and outcomes for patients treated with Strimvelis and to compare these estimates with the corresponding costs and outcomes of the current practice of HSCT from either a MUD or haploidentical donor."*	CS, p138

Have all feasible and practical options been evaluated?	✓	Yes. The only omitted treatment option for ADA-SCID patients without an MRD is long term enzyme replacement therapy.	CS, Table D2 – p140-143 & p36
Is there justification for the exclusion of feasible options?	✓	Yes. Long-term ERT is not seen as a preferred treatment option in England, as verified by expert clinical advice.	CS, Table D2 – p140-143 & p36
S6 Model type			
Is the chosen model type appropriate given the decision problem and specified causal relationship within the model?	✓	Yes.	
S7 Time horizon			
Is the time horizon of the model sufficient to reflect all important differences between options?	✓	The time horizon used in the model was 100 years, which is assumed to represent a lifetime horizon.	CS, Table D4 – p146-148
Are the time horizon of the model, the duration of treatment and the duration of treatment effect described and justified?	✓	**Time horizon:** The time horizon is in line with NICE guidance. **Duration of treatment:** The schedule of treatment used in the model is consistent with the marketing authorisation **Duration of treatment effect:** Strimvelis was assumed as having a treatment effect over a patients' lifetime from increasing the long-term survival of patients with ADA-SCID.	CS, Table D4 – p146-148
S8 Disease states/pathways			
Do the disease states or the pathways reflect the underlying biological process of the disease in question and the impact of interventions?	×	• The rescue therapy state defined by a two year delay followed by a HSCT MSD transplant is not consistent with UK clinical practice. • A high degree of uncertainty exists regarding the long-term survival of ADA-SCID patients. Assuming no mortality risk above the general population may omit for the risks of oncogenesis and metabolic conditions reported in other severe combined immune-deficiencies.	
S9 Cycle Length			
Is the cycle length defined and justified in terms of the natural history of disease?	✓	A cycle length of one year was used in the model (except for the first year, which consists of 2 cycles of 6 months). A 1-year cycle length was chosen in order to be consistent with the time frame for clinical assessment.	CS, Table D4 – p146-148 & p139

Data			
D1 Data identification			
Are the data identification methods transparent and appropriate given the objectives of the model?	✓	Yes **Need CRD's view on the SLR's**. Although no systematic search was conducted for resource use, lack of transparency over the papers deemed relevant in the HRQoL HSCT systematic literature review.	
Where choices have been made between data sources, are these justified appropriately?	✓	Due to limited sources of data this was not a significant issue. In instances when alternative sources were available (e.g. unit costs) justifications for the choice of data was lacking.	
Has particular attention been paid to identifying data for the important parameters in the model?	×	Insufficient attention was given to identifying data for the long-term survival of ADA-SCID patients, or for SCID patients, post HSCT/gene therapy. A greater emphasis on the role of oncogenesis and metabolic disturbances would have been beneficial. Given the large cost of PEG-ADA insufficient justification was given regarding its unit cost and dosages.	
Has the quality of the data been assessed appropriately?	×	**Clinical Effectiveness:** A critical appraisal of each trial was conducted by the company with the use of questions adapted from a Critical Appraisal Skills Programme (CASP) **Cost Studies:** Resource use studies were collected from a pragmatic literature search. Each source identified was not formally assessed for quality. **HRQoL Studies**: HRQoL studies were collected from a systematic literature search. Each source identified was not formally assessed for quality.	CS, p64-72
Where expert opinion has been used, are the methods described and justified?	×	Expert opinion has been sought throughout the CS, however no details were provided concerning the methods used or the specific questions asked.	
D2a Baseline data			
Is the choice of baseline data described and justified?	✓	Yes.	
Has a half-cycle correction been applied to both cost and outcome?	✓	No.	
D2b Treatment effects			

If the relative treatment effects have been derived from trial data, have they been synthesised using appropriate techniques?	×	The treatment effects were not derived from trial data.	
Have the methods and assumptions used to extrapolate short-term results to final outcomes been documented and justified?	✓	Yes. The assumption that patients return to general population mortality and HRQoL is justified on the basis that Kaplan-Meier overall survival curves for patients who received HSCT from a MUD or haploidentical donor, do not show deaths after approximately 1 year and that expert clinical advice sought by the company confirmed the assumption that patients surviving beyond three years since the time of initial procedures will return to the HRQoL and mortality risk for the general population.	CS, p143
Have assumptions regarding the continuing effect of treatment once treatment is complete been documented and justified?	✓	Strimvelis was assumed as having a treatment effect over a patients' lifetime from increasing the long-term survival of patients with ADA-SCID. The 100% survival of Strimvelis LTFU cohort, flat Kaplan-Meier curves one-year post-HSCT and expert clinical advice were given as evidence of the robust nature of survival which Strimvelis and HSCT offer.	CS, p143
Have alternative extrapolation assumptions been explored through sensitivity analysis?	✓	The company acknowledged the limited data available concerning ADA-SCID patients' long-term outcomes and as such provide an additional two-way sensitivity analysis to explore the uncertainty around the mean life expectancy and utility scores of ADA-SCID patients.	CS, Table D26 – p209
Have alternative assumptions regarding the continuing effect of treatment been explored through sensitivity analysis.	✓	See above.	CS, Table D26 – p209
D2c Costs			
Are the costs incorporated into the model justified?	✓	Yes.	
Has the source of the costs been described?	✓	Resource use and costs included: Strimvelis unit price, administration and follow-up; management of an adverse events; HSCT costs (initial procedure and follow-up) and subsequent treatment costs.	CS, Table D5 – p156-164 & Table D8 – p169-172
Have the discount rates been described and justified given the target decision maker?	✓	The company has given justification for using a discount rate of 1.5% in the UK decision making context to minimise the differential impact of discounting on costs and benefits, the NICE Methods Guide states that in such cases when treatment restores people who would otherwise die to near full health over a very long period, a lower discount rate of 1.5% may be considered. 3.5% discount rates were presented as a scenario.	CS, Table D4 – p146-148 & p198, p203
D2d Quality of life weights			

Are the utilities incorporated into the model appropriate?	✓	Yes.	
Is the source of the utility weights referenced?	✓	All sources are referred and described.	CS, Table D5 – p156-164
Are the methods of derivation for the utility weights justified	✓	Yes	CS, Table D5 – p156-164
D3 Data incorporation			
Have all data incorporated into the model been described and referenced in sufficient detail?	✓	All data are referred and described.	CS, Table D5 – p156-164
Has the use of mutually inconsistent data been justified (i.e. are assumptions and choices appropriate?)	NA		
Is the process of data incorporation transparent?	✓	Data is referenced explicitly in the company's model and incorporated with the value and within the chosen distributions mentioned in Table B13 of the CS.	CS, Table B13
If data have been incorporated as distributions, has the choice of distributions for each parameter been described and justified?	✓	The chosen distributions has been described (see above) but not justified.	CS, Table
If data have been incorporated as distributions, is it clear that second order uncertainty is reflected?	✓	Yes, parameter uncertainty has been adequately addressed by the company. However, the company have not assessed first order uncertainty (on the count of limited data).	
D4 Assessment of uncertainty			
Have the four principle types of uncertainty been addressed? If not, has the omission of particular forms of uncertainty been justified?	✓	See below.	
D4a Methodological			
Have methodological uncertainties been addressed by running alternative versions of the model with different methodological assumptions?	✓	Only the effect of alternative discount rates on the company ICER has been assessed. The impacts of alternative methodological uncertainties (e.g. dosing methods, application of a half cycle correction, etc.) were not assessed.	CS, p198, p203
D4b Structural			
Is there evidence that structural uncertainties have been addressed via sensitivity analysis?	✓	A wide range of scenarios and sensitivity analyses were conducted which provided meaningful evidence of the key drivers of cost-effectiveness and areas of uncertainty in the base case model.	CS, p197-212

D4c Heterogeneity			
Has heterogeneity been dealt with by running the model separately for different subgroups?	×	Due to the small sample size the company did not run any sub group analyses as it was deemed unlikely to provide clinically meaningful information. The final scope did not specify specific populations and subgroups.	
D4d Parameter			
Are the methods of assessment of parameter uncertainty appropriate?	✓	In line with the NICE reference case deterministic sensitivity analyses were performed on a series of model parameters. Probabilistic sensitivity analyses were also performed.	CS, p197-219
If data are incorporated as point estimates, are the ranges used for sensitivity analysis stated clearly and justified?	✓	All range data is reported and incorporated as distributions.	CS, Table D13 p180-183
Consistency			
C1 Internal consistency			
Is there any evidence that the mathematical logic of the model has been tested thoroughly before use?	×		
C2 External consistency			
Are any counterintuitive results from the model explained and justified?	NA	The probabilistic ICER is significantly higher in the CS. This was due to a technical issue resolved in clarification with the ERG.	
If the model has been calibrated against independent data, have any differences been explained and justified?	NA		
Have the results of the model been compared with those of previous models and any differences in results explained?	NA		

Addendum to ERG report
Strimvelis for treating severe combined immunodeficiency caused by adenosine deaminase deficiency

1 Additional scenarios provided by ERG in response to PMB

This addendum provides additional scenario analyses exploring the impact of alternative discount rates and the impact of the exchange rate on the results of the additional economic analysis undertaken by the ERG.

1.1 Sensitivity analysis for alternative discount rate for costs and health outcomes:

The company and ERG base cases both apply a discount rate of 1.5% to costs and health outcomes. The NICE Methods Guide states that a discount rate of 1.5% for costs and benefits may be considered in cases when the treatment restores individuals who would otherwise die or have a very severely impaired life to full or near full health, and when this is sustained over a very long period (normally at least 30 years). If this condition is not met, a discount rate of 3.5% should be applied to both costs and health outcomes.

Table 1 shows the ERG base case results using alternative discount rates for costs and QALYs. Given that the adjusted threshold is calculated using undiscounted QALY gain, changes to the discount rate have no effect on the adjusted threshold values for the comparison of Strimvelis against HSCT from a MUD (£159,000) and against HSCT from a haploidentical donor (£188,000). The ICERs for Strimvelis remain below their respective adjusted thresholds against both comparators when using a discount rate of 3.5% for costs and health outcomes. However, the ICER for Strimvelis compared to HSCT from a MUD does exceed £100,000 per QALY. Table 4 provides the full set of ERG analyses calculated using a discount rate of 3.5%.

Table 1. Results of ERG base case with alternative discount rates

ERG base case (1.5% discount rate applied to costs and health outcomes)						
	Costs	QALYs	Inc. cost	Inc. QALY	ICER	Δ ERG ICER
Strimvelis	£1,236,768	30.1				
MUD	£425,656	20.7	£811,195	9.3	£86,815	-
Haploidentical	£1,052,166	19.0	£184,686	11.1	£16,704	-
ERG base case (3.5% discount rate applied to costs and health outcomes)						
	Costs	QALYs	Inc. cost	Inc. QALY	ICER	Δ ERG ICER
Strimvelis	£1,108,181	17.6				
MUD	£367,251	12.1	£740,930	5.5	£135,028	+£48,213

Haploidentical	£869,500	11.1	£238,681	6.5	£36,837	+£20,133

1.2 Sensitivity analysis to exchange rate:

The price of Strimvelis (€594,000) and the cost of the initial hospitalisation in Milan ([redacted]) and any excess hospitalisation costs will be paid in euros for those patients that receive Strimvelis. The cost of these to the NHS are uncertain due to fluctuations in the exchange rate. Table 2 and Table 3 present sensitivity analyses for the effect of variations in the exchange rate on the cost to the NHS of Strimvelis and the associated initial hospitalisation.

Table 2. ICER for Strimvelis compared to MUD for alternative exhange rates

Strimvelis vs MUD	Exchange rate (£/1€)*	Product and hospitalisation cost in GBP	ERG ICER	Δ ICER
Company base case (May)	0.85	[redacted]	£86,815	-
30 April 2017	0.8472	[redacted]	£86,280	-£535
31 May 2017	0.8561	[redacted]	£86,946	+£131
30 June 2017	0.8773	[redacted]	£88,532	+£1,717
31 July 2017	0.8865	[redacted]	£89,221	+£2,406
31 August 2017	0.9129	[redacted]	£91,196	+£4,381

Table 3. ICER for Strimvelis compared to Haplo for alternative exchange rates

Strimvelis vs Haplo	Exchange rate (£/1€)*	Product and hospitalisation cost in Milan	ERG ICER	Δ ICER
Company base case (May)	0.85	[redacted]	£16,704	-
30 April 2017	0.8472	[redacted]	£16,252	-£452
31 May 2017	0.8561	[redacted]	£16,815	+£111
30 June 2017	0.8773	[redacted]	£18,156	+£1,452
31 July 2017	0.8865	[redacted]	£18,738	+£2,034
31 August 2017	0.9129	[redacted]	£20,407	+£3,703

*OFX, Historical Exchange Rates, sourced 7th September 2017

1.3 Results for all economic analyses undertaken for ERG base case with discount rate of 3.5%

Table 4 provides the results presented in Table 30 of the ERG's report applying a discount rate of 3.5% per annum to both costs and health outcomes.

Table 4. Results of the relevant scenarios and additional calculations for the ERG base cases

	Costs	QALYs	Inc. cost	Inc. QALY	ICER	Δ ICER
Company base case						
Company original base case (deterministic – 3.5% discount rate)						
Strimvelis	£1,049,219	24.4				
MUD	£560,604	16.4	£488,614	7.9	£61,607	-
Haploidentical	£874,538	17.6	£174,681	6.8	£25,697	-
Company's total secondary analysis (3.5% discount rate)						
Strimvelis	£931,250	24.4				
MUD	£440,385	16.4	£490,865	7.9	£61,891	+£284
Haploidentical	£663,306	17.6	£267,944	6.8	£39,417	+£13,720
Company's IVIG disutility scenario (utility*0.75 – 3.5% discount rate)						
Strimvelis	£1,049,219	23.6				
MUD	£560,604	15.9	£488,614	7.7	£63,815	+£2,208
Haploidentical	£874,538	17.0	£174,681	6.6	£26,338	+£641
ERG Scenario Analyses (3.5% discount rate)						
SA1. Named Patient Population (NPP) included to inform procedural outcomes						
Strimvelis	£1,148,387	24.4				
MUD	£560,604	16.4	£587,783	7.9	£74,274	+£12,667
Haploidentical	£874,538	17.6	£273,849	6.8	£23,465	+£14,692
SA2. Parameter corrections and conditional probabilities for rescue therapy						
Strimvelis	£1,049,176	24.4				
MUD	£605,633	16.4	£443,543	7.9	£55,869	-£5,739
Haploidentical	£1,028,923	17.5	£20,253	6.8	£2,968	-£22,730
SA3. Equalising duration of initial PEG-ADA prior to initial procedure (0 days)						
Strimvelis	£924,965	24.2				
MUD	£298,290	16.1	£626,674	8.1	£77,184	+£15,577
Haploidentical	£612,224	17.2	£312,741	7.0	£44,769	+£19,072
SA4. Rescue therapy transplants conducted from a MUD (reduced survival, GvHD and severe infection risk, PEG-ADA for failed engraftment)						
Strimvelis	£1,166,299	23.0				
MUD	£604,835	15.9	£561,465	7.1	£79,034	+£17,427

Haploidentical	£1,064,097	15.4	£102,202	7.6	£13,412	-£12,286
SA5. Utilities accommodating for permanent childhood hearing impairment						
Strimvelis	£931,250	19.9				
MUD	£440,385	13.5	£488,614	6.5	£75,714	+£14,107
Haploidentical	£663,306	14.4	£174,681	5.5	£31,672	+£5,975
SA6. Costs of permanent childhood hearing impairment						
Strimvelis	£1,081,614	24.4				
MUD	£582,201	16.4	£499,413	7.9	£62,969	+£26,609
Haploidentical	£897,678	17.6	£183,936	6.8	£27,059	+£12,414
SA7. Updated unit costs for HSCT (with bone marrow donation) and GvHD events (average costs applied)						
Strimvelis	£1,047,063	24.4				
MUD	£542,989	16.4	£504,074	7.9	£63,556	+£1,362
Haploidentical	£867,575	17.6	£179,489	6.8	£26,405	+£1,362
SA8. Cost of ineligibility for Strimvelis						
Strimvelis	[redacted]	24.4				
MUD	£560,604	16.4	[redacted]	7.9	[redacted]	[redacted]
Haploidentical	£874,538	17.6	[redacted]	6.8	[redacted]	[redacted]
ERG preferred base case (3.5% discount rate)						
Strimvelis	£1,108,181	17.6				
MUD	£367,251	12.1	£740,930	5.5	£135,028	+£73,421
Haploidentical	£869,500	11.1	£238,681	6.5	£36,837	+£11,139

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Pro-forma Response

ERG report

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

You are asked to check the ERG report from York Centre for Reviews and Dissemination to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm, Tuesday 12 September 2017** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Evaluation Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Priority Issues > issues 1-5

Issue 1 Use of data NPP in the ERG preferred base case

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Throughout the document it is noted that the data available for the NPP population should be pooled with the data from the integrated population and the ERG preferred base case adopts the numbers derived from including the patients from the NPP. As the NPP is not a GSK sponsored study, which limits access to data, it is difficult to speculate on wider applicability of these immature and incomplete data. As noted by the ERG, the NPP population may be less representative of patients in England as [redacted]. The NPP is ongoing and data are not scheduled for formal analysis until all patients have reached 3 years of follow-up. Combination of incomplete and immature NPP data, without pre-specification according to ICH E6 guidelines, into the integrated population, potentially leads to incorrect conclusions. GSK has not yet	Suggest to remove the NPP population from the base case and consider it only within sensitivity analysis. If NPP patients are to be considered in analyses then there is an argument for all other patients who have been successfully treated with Strimvelis since the Marketing Authorisation was granted should also be included. The base case should be represented by the Integrated Population only, i.e. 100% survival and 83.3% (15/18) of patients not requiring a rescue transplant.	Although we acknowledge the fact that given the low number of patients all data available should be considered, given that the NPP study is ongoing, there has not been the opportunity to explore these data in context with the data from the integrated population to confirm their comparability and appreciate any key differences in the populations and any impact this may have on outcomes. This would result in a base case represented by the Integrated Population as presented by GSK – 100% survival and 83.3% (15/18) not requiring a rescue transplant. In addition, if the patients from the NPP were to be considered; within a sensitivity analysis, so should any patients that have been treated (successfully) since the Marketing Authorisation approval.	Not a factual inaccuracy

analysed the NPP and therefore cannot place these data into context with the integrated population including understanding the patient population, similarities and differences to the integrated population and considering whether they could be impacting the outcomes. Similarly, although they may be closer to the English population expected to receive Strimvelis, an additional [redacted] patients who have been successfully treated after the Marketing Authorisation approval should be left off the base case analysis, details of which can be shared by the clinical advisor from Milan at the committee meeting.			

Issue 2 Uncertainty around inputs for Strimvelis post-procedural survival

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
In the Summary section (page 18) it is noted that '… all survival estimates are highly uncertain and future data could substantially change conclusions'. Firstly, the numbers used in overall survival data are not an estimate but rather data based on formal follow of up to 13 years. No patients have died following	The ERG concerns around the uncertainty on Strimvelis post-procedural survival should be put into the context of a sample of more than 60 patients supporting 100% survival after gene therapy in ADA-SCID. Remove words 'highly' and 'substantially'.	Although it is acknowledged that, as normal for an ultra-rare disease such as ADA-SCID, the low numbers in the Strimvelis programme may result in some uncertainty, the rate of survival in the Strimvelis when added to other gene therapy programmes should suffice to provide confidence on the	Not factual inaccuracy. The company submission uses these data to infer conclusions about the efficacy of Strimvelis to ADA-SCID patients in England therefore it is appropriate in this context to refer to the data from these studies as an estimate of

treatment with Strimvelis. In addition, no deaths have been reported in any ADA-SCID patient treated with any other gene therapy (>60 patients). Should 1 death occur, the post-procedural survival for gene therapy in ADA-SCID as a whole would still be above 98.50%.		survival data available.	overall survival.

Issue 3 Uncertainty around inputs for HSCT post-procedural survival

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
In the Summary section (page 18) it is noted that '… historical data on overall survival following HSCT from a MUD and HSCT from a haploidentical donor likely reflect an underestimate of the current effectiveness of these treatments. For example, there have been substantial improvements in matching of donors, reduced conditioning, and better provision of supportive care'. Elsewhere on page 26 it is speculated that 'using current methods survival from HSCT from a MUD or haploidentical donor would be expected to be much higher than the most recent published data, which is based on transplants only up to 2009'. However, there is no available data to confirm this. As	An evidence-based balanced view on improvements in survival after HSCT from a MUD or a Haplo over time should be provided. It should be noted that the data for each of the comparators can be seen as contemporary, and that, as suggested by clinical experts, potential improvements in survival after HSCT due to less intensive conditioning regimens may have implications in terms of engraftment and, consequently, a result in a higher rate of rescue transplant. To explore this, GSK suggests that a two-way sensitivity analysis is conducted increasing both the survival and the rate of rescue transplant after HSCT. In addition, the potential impact on the rate of rescue transplant as a result of less intensity conditioning regiments must also be considered.	Speculation on improvements in the rate of survival for HSCT from MUD and haplo donors over time should be anchored on data or include appropriate caveats. The recent publication of the EBMT guidelines in 2017, which possibly congregated the largest (including English) expertise around the management of ADA-SCID, concludes that gene therapy is clearly positioned ahead of MUD and Haplo transplants. Speculating around the magnitude of such improvements with no data to support it may jeopardise the principles of evidence-based medicine	Not a factual inaccuracy

acknowledged by the ERG for a large cohort of patients specifically with ADA-SCID, Hassan provides the most up-to-date peer reviewed data. ADA-SCID is an ultra-rare condition, and evidence on treatment improvements accumulates slowly. We have made a concerted effort to incorporate all the latest peer reviewed and clinical advice data into the economic model. Whilst it is likely that outcomes for HSCT from a MUD may have improved since the Hassan paper, there is no definitive evidence to establish the extent to which this has indeed happened. If hypothesizing that this improvement in transplant techniques has occurred, then the same should be hypothesized for Strimvelis where the clinical programme has run since 2000.. It should also be noted that based on clinical advice received, any improvements observed in post-procedural survival with HSCT should not be taken in isolation, as the changes in the process that may support these improvements, e.g. reduction of intensity of conditioning regimen, may ultimately result in a difficult to engraft and, consequently, a higher rate of rescue transplant.			

Issue 4 Uncertainty around the rate of rescue transplant for Strimvelis and MUD

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
It is unwarranted to treat uncertainty around different parameters in the ERG report differently: GSK believes the uncertainty around the rate of rescue transplant to be at par with the uncertainty around survival, so the sensitivity analyses conducted and the space dedicated to reporting them should be similar. For the rate of rescue transplant, for which uncertainty may be resulting in the marked underestimation of the cost-effectiveness of Strimvelis versus MUD (the ICER of the ERG preferred base case is almost halved when no difference is assumed on rescue transplant rates), only a simple analysis is done and no further exploration exists despite the rationale to test different assumptions and having a considerable impact on results. In the case of survival however, a number of sensitivity analyses were conducted and the ERG concerns around uncertainty around survival are mentioned throughout the report.	GSK believes the uncertainty around the rate of rescue transplant to be at par with the uncertainty around survival, so would welcome a full set of sensitivity analysis (including running the two-way sensitivity analysis on survival when no difference is assumed on rescue transplant rates between MUD and Strimvelis) to be conducted and the respective discussion to receive the warranted highlight in the report. Specifically, it is recommended that the ERG explores alternative values for rate of rescue of 11.8% and 18%.	In the economic model presented in the CS, MUD rescue rates were noted as being lower than Strimvelis. Based on clinical advice sought since the submission, there is no clinical rationale to expect a higher need for a rescue transplant after Strimvelis. These rates are based on low numbers (lower than those on which survival is based on) and one additional patient more requiring a rescue in the MUD arm would result in a rate of rescue of 18% (2/11) versus the current 10%. In addition, on the Strimvelis side, Patient [redacted] who has not received a rescue transplant was incorrectly excluded in the estimation of the rate, whilst Patient [redacted] receiving Strimvelis had a lower dose (which would not happen again today) and went on to have a rescue transplant. If the calculation is corrected to account for this (adding Patient [redacted] and excluding Patient [redacted]), the rescue transplant rate for the Strimvelis Integrated Population is reduced to approximately 11,8% closer to the rate reported for MUD. Given the considerable impact expected on	Not a factual inaccuracy.

		the ICER, we would suggest this to be revised in the base case or at least extensively tested in sensitivity analyses.	

Issue 5 Incomplete representation of the safety profile of Strimvelis and inappropriate modelling of any events in the ERG preferred base case

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
In the Summary section (page 14) it is noted that 'Almost all (17/18) of the Strimvelis Integrated Population experienced a neurological, CNS or hearing event during treatment or follow up. Cognitive disorders were the most common event (n=5). Deafness was also a common problem with two patients reporting deafness and a further two patients reporting bilateral deafness. Three patients reported psychomotor hyperactivity. High incidence of non-immunological problems was also found for ADA-SCID patients following HSCT including behavioural problems and IQ scores substantially below general population means'. It is important to note that most events were grade 1 or grade 2, none were serious, and none were considered by the investigator to be related to Strimvelis treatment.	A note should be provided to clarify the severity of these events was mostly mild to moderate (mostly Grade 1 and 2 and no Grade 4 events) and that some of the issues reported were transient. In addition to this, if the preferred ERG base case is to include an estimation of the long-term impact of these events, the extrapolation should take into consideration both the rate and severity of the events reported in the Strimvelis clinical programme.	Although we acknowledge that estimating the health-related quality of life of surviving patients is relevant for the analyses, caution should be used when extrapolating from adverse events reported whilst patients are followed up on the trial. Moreover, when extrapolating to the longer term, special care should be given to the severity, duration and nature of the events reported.	Not a factual inaccuracy.

There were also no Grade 4 events. It should also be noted that some of these events are transient in nature and therefore the actual impact on daily function cannot simply be extrapolated from other conditions as demonstrated by the fact that all children treated with Strimvelis are attending school for their appropriate age. The current base case proposed by the ERG uses figures that overestimate the rate of bilateral deafness (e.g. 58% based on numbers from a HSCT cohort versus 11.1% (2/18)observed in the Strimvelis Integrated Population) which greatly increases the ICER and, as a consequence, reduces the perceived cost effectiveness of Strimvelis. In addition, the base case modelled by the ERG assumes the cost and disutility of congenital pre-lingual bilateral deafness giving no consideration to either the fact that deafness experienced in ADA-SCID patients is normally post-lingual or to the severity of the hearing impairment observed in ADA-SCID. In addition, these costs and disutility are based on children between 7 and 9 years are applied by the ERG to the whole patient lifetime without considering potential			

adjustment of patients to their condition or the fact the costs of deafness in children in a schooling age are likely to be higher than those of deafness in adults.			

Issue 6 Representativeness of the Strimvelis Integrated Population

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
It is noted in several places (particularly in summarizing section, e.g. Summary page 12) that the population may not be representative of the English population particularly in age and in ethnicity. This is at odds with the conclusions of the ERG as stated in the critique of GSK's definition of decision problem which define any differences as 'small' and the clinical advice the ERG notes has been received (page 39). The patient population in the Strimvelis programme was diverse, with a variety of races and both genders. The trial population was composed of 67% White Caucasian/ European, 25% Arabic/North African, 8% Central/ South Asian. This population is representative of England where the prevalence of ADA-SCID is seen in the Irish, Somalian, and Indian populations. Median age at	The ERG's conclusion should be represented consistently throughout the document. "Despite these minor differences, the ERG acknowledges that due to the rarity of ADA-SCID and the small patient numbers, the population presented is appropriate for the decision problem in question." (page 12). Furthermore, "the ERG judged that there did not appear to be substantial concerns regarding the representativeness of the Strimvelis Integrated Population to ADA-SCID patients in England" (page 39). Any remarks therefore relating to this not being the case should be removed.	Based on the small numbers and available data, there is insufficient evidence to support a conclusion that, there are differences between the trialed population and the English population expected to receive Strimvelis. Furthermore, there is no evidence to support a conclusion that any such differences would impact outcomes.	Not a factual inaccuracy. Given the rarity of the disease and the very limited data available, the ERG concluded that the population used was appropriate and overall did not have large concerns regarding how representative it was. However it is still important for all potential differences to be identified and considered as part of the clinical evidence, particularly as it cannot be ruled out that these differences would impact on outcomes.

procedure was 1.37 years. This is also at odds with the conclusions of the ERG as stated in the critique of GSK's definition of decision problem which define any differences as 'small' and the clinical advice the ERG notes has been received (page 39).			

Issue 7 The suggestion of possible selection bias from the exclusion of more severe patients in the Strimvelis clinical programme

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
In the Summary section (page 15) it is noted that '… there was lack of clarity regarding numbers screened or excluded for Pilot study 1, Pilot study 2, the Compassionate Use Programme and the Named Patient Programme. Therefore, it is unclear if patients at greater risk were excluded from these studies or other selection biases occurred'. Due to the nature of the pilot studies, compassionate use and named patient programmes, formal screening logs to document the number of screened and excluded patients were not recorded. This notwithstanding, it might be reasonable to consider	The wording proposed is 'Although no clear inclusion/exclusion criteria were set for the pilot studies, the pre-treatment status at baseline in this status suggests that patients at greater risk or whom are more difficult to treat, have not been excluded'. Remove wording 'it is unclear if patients at greater risk were excluded from these studies or other selection biases occurred'. .	The suggestion that a selection bias may have existed casts unreasonable doubt over the validity of the data derived from the Strimvelis Clinical Programme. This is particularly unbalanced when the reading to be made from available (baseline) data would suggest otherwise, i.e. that patients at greater risk or more difficult to treat were in fact included in the programme.	Not a factual inaccuracy.

that the patients put forward for these early studies with this experimental therapy, in these programmes, might have already exhausted alternative therapeutic options. In the integrated population, four patients had already received unsuccessful haplo transplants and 15/18 had received PEG-ADA prior to receiving Strimvelis. Therefore, it cannot be concluded that patients at greater risk were systematically excluded – patients were considered for therapy based on their referral to the centre in Milan.			

Issue 8 Appropriateness of viral infection as a prognostic factor for outcome in gene therapy

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
It is noted (Summary page 12) that '… advice from the clinical advisor to the ERG that the presence of viral infection may be prognostic, it is unclear the extent to which the data can be generalised to patients presenting with viral infection'. Viral infection status at baseline has not been shown to be a prognostic marker for gene therapy. In contrast to gene therapy, patients receiving an allogenic transplant undergo high intensity chemo conditioning followed by immunosuppressives	Suggest to note that although viral infection status may be considered to be a prognostic marker for the treatment with HSCT, the same is not shown to happen with gene therapy. All references to the importance of viral status as a prognostic marker for GT should be removed.	Viral infection status at baseline is considered prognostic for allogenic transplants (HSCT) but has not been proven for autologous transplants, such as Strimvelis,	Not a factual inaccuracy. This is based on advice from the clinical advisor to the ERG.

post-transplants which may result in a greater risk for viral reactivation. Although there were no patients with active viral infection at screening in the Strimvelis clinical programme, subjects did have a history of EBV/CMV infection and there were adverse events of viral reactivation post Strimvelis. It is therefore reasonable to expect that the outcomes of the clinical programme will reflect clinical practice.			

Issue 9 Outcomes of interest: undervaluing of overall survival as an outcome of interest

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
In the Summary section (page 15) it is noted that '… the overall survival outcome overestimates the effectiveness of the intervention since those who experienced a Strimvelis treatment failure but did not die due to receiving an alternative treatment (such as PEG-ADA or HSCT) are still counted as a treatment success. Intervention-free survival was lower for Strimvelis ([redacted]) and in the view of the ERG provides a better assessment of clinical effectiveness'. Overall survival is the key clinical	Request that wording which suggests that overall survival is an overestimation of the effectiveness of Strimvelis is removed or put into context alongside IFS. In addition, ensure that the appropriate numbers for rescue transplant are used in the ERG preferred base case, i.e. assuming 83.3% (15/18) patients do not require a rescue transplant after Strimvelis.	The relevance given to the issue is misleading. It is important consider both survival and IFS. All patients in the Strimvelis programme (and comparable gene therapies) have survived even when they required a rescue HSCT. As there is no information to exclude an eventual protective effect of previous GT influencing the success of rescue HSCT, questioning survival data should be made with caution. Based on current evidence, Strimvelis is a tool to reach high likelihood of survival in managing ADA-SCID, which ultimately is the	Not a factual inaccuracy.

outcome of interest to clinicians, patients and their carers. To date, no patient who has received Strimvelis, or similar gene therapy for ADA-SCID, has died. Once a patient survives, intervention-free survival becomes of relevance, and should be considered on a like-for-like basis when compared across therapies, using the same definition. But, the importance of overall survival should not be diluted as this remains the key outcome for parents considering treatment options for their child.		first objective when treating children with ADA-SCID. Further, the need for rescue intervention is fully considered in the economic analysis.	

Issue 10 Mean age of the Strimvelis integrated population

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The mean age of the Strimvelis Integrated Population was incorrect in the ERG report (Section 5.2.3, p 73). Per manual computation of the data in Table C21 (p 85) of the Strimvelis dossier, mean age should be 2.25.	Change the mean from 2.1 years to "2.25 years."	Numerical factual inaccuracy	Not factual inaccuracy, mean age as calculated from table C21 is 2.094444 which we rounded up to 2.1 years. The mean of 2.25 years you suggest appears to require double counting patient [redacted] (who received 2 doses of Strimvelis). We used age at first dose of Strimvelis for this patient to avoid double counting.

Issue 11 Median follow-up time for Strimvelis not accurate

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The median follow-up time in the Strimvelis Integrated Population is "6.95" in the ERG report (pp 13 and 45), but it was "6.9" in the Strimvelis dossier (Section 4.1, p 26).	The median should be made consistent with the dossier (6.9).	Numerical factual inaccuracy	This is not a factual inaccuracy. We checked the data again and the median follow up time of 6.95 reflects the data presented in table C21. Given the slight inconsistency in median values between the table and the text we chose to use the values that reflected the table.

Issue 12 Incorrect representation of the relative safety profiles of Strimvelis and comparator procedures

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
In the Summary section (page 14) it is noted that 'Adverse events were largely similar for Strimvelis, HSCT from a MUD and HSCT from a haploidentical donor', which is incorrect. As noted throughout the CS, GvHD (which does not occur with autologous transplants, i.e. such as gene therapy with Strimvelis) carries a considerable amount of mortality and morbidity which cannot be ignored when assessing the safety profile of the technology and the intervention.	Suggest first sentence under the "Adverse events" title is changed to "Adverse events of a neurological origin were similar for Strimvelis, HSCT from a MUD, and HSCT from a haploidentical donor. However, in terms of GvHD, which is absent for Strimvelis, the safety profile of Strimvelis is favourable compared to that of HSCT, as GvHD is associated with significant mortality and morbidity.	The report should reflect the evidence available.	This is not a factual inaccuracy. In addition, the same paragraph in which the quote is taken from states:' The major difference between Strimvelis and HSCT in terms of adverse events was that some patients experienced Graft versus Host Disease (GvHD) after HSCT, whereas no patients experienced this adverse event following Strimvelis.' So we think your concerns have already been addressed in the report.

Issue 13 Long-term safety of gene therapy

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
In the Summary section (page 15) it is noted that '… a potential risk of gene therapy identified in other SCID patients is the risk of leukaemia'. The report does not include a background to appropriately contextualise the risk of oncogeneis in ADA-SCID patients undergoing gene therapy. As noted in the company's	Additional text should be added to explain that caution should be used when extrapolating the risks of oncogenesis from historical reports in other diseases where different vectors were used, else should be removed altogether.	The report should present an accurate picture of the evidence available, otherwise it undervalues the safety profile demonstrated by Strimvelis to date.	Not a factual inaccuracy.

response to the clarification questions, since 2000 up to the Marketing Authorisation approval, data on 60 patients who have received gene therapy for the treatment of ADA-SCID have been published: Strimvelis (N=18), other comparable gamma-retroviral vectors (N=22), and lentiviral vectors (N=20) [Farinelli, 2014; Gaspar, 2015; Cicalese, 2016] (see Appendix 7 of the original submission for the full list of individual publications) and there has been no incidence of leukaemia or myelodysplasia reported following gene therapy for ADA-SCID. Haematological malignancies have indeed been reported during trials for X-linked SCID, chronic granulomatous disease, and Wiskott-Aldrich syndrome that used MLV-like vectors with slightly differing envelope proteins and/or gene expression systems, but multiple references in the scientific literature hypothesise that leukaemia risk after retroviral gene therapy is multifactorial. The background disease of ADA-SCID may play some role in the safety record to date, as ADA is known as a 'house-keeping' protein. Strimvelis continues to have additional monitoring by the European			

Medicines Agency (EMA) through mandated pharmacovigilance reporting (Periodic Benefit-Risk Evaluation Reports [PBRERs], Periodic Safety Update Reports [PSURs] and Drug Safety Update Reports [DSURs]) and Risk Management Plans (RMP). To date, the EMA has granted that Strimvelis continues to have a positive benefit:risk profile for patients with ADA-SCID who do not have an HLA-matched related donor available. The Strimvelis integrated population have been followed for a considerable period of time, and will continue to do so in a Registry.			

Issue 14 Inappropriate reference to a potential risk of gene silencing

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 54 and 55 it is noted 'There is also a theoretical risk of gene silencing leading to a loss of therapeutic benefit although this requires further study to confirm the risk in ADA-SCID patients'. GSK does not understand why this is referred and what is the basis for this 'theoretical risk'. Based on median follow up of 6.9 years and maximum follow up of 13 years, no event indicative of	Either more details are presented justifying the relevance of this or this reference to gene silencing should be removed.	It is not clear what risk the ERG is referring to and, as no evidence or references are presented to justify its relevance for ADA-SCID and Strimvelis, it should be removed not to create an unwarranted perception of uncertainty.	Not a factual inaccuracy. We have added further detail in the errata.

clinically significant gene silencing was evident in the Strimvelis clinical programme.			

Issue 15 Rate of rescue transplant after Strimvelis

Description of problem	Description of proposed amendment	Justification for amendment	
In the analysis presented in the ERG preferred base case it is referred that 14/17 (82.3%) in the Strimvelis Integrated Population experienced intervention-free survival (i.e. did not require either ≥ 3 months of PEG-ADA treatment or HSCT), which would not totally translate to 'need for rescue transplant in the model'. Although in the modelling exercise presented in the CS we incorrectly excluded Patient [redacted]. This was highlighted in the company response to the ERG's clarification questions: Patient [redacted] should be included in the economic analysis as not having had a rescue transplant (as noted in the response to the clarification questions). This is because, although PEG-ADA immediate post-procedure data is absent, GSK is confident after confirming with the TIGET team that this patient did not receive a rescue transplant, which is ultimately the	For the purpose of the economic analysis, it should be considered that 15/18 (83.3%) patients in the Integrated Population did not require a rescue transplant rather than 14/17 (82.3%). Sensitivity analysis could be conducted to test the impact of excluding Patient [redacted], who had a lower dose than what would be required today, i.e. using 88,2% (15/17).	The data presented is inaccurate. This was an oversight in the CS, but was highlighted in the response to the clarification questions. As it has been detected, the base case should be updated to reflect it. Otherwise, the misrepresentation of the available evidence would result in an overestimation of the need for rescue transplant after Strimvelis, which will negatively impact the cost-effectiveness of Strimvelis.	Not a factual inaccuracy. The company submission assumes that patients who received long-term PEG-ADA following gene therapy in the Strimvelis population would have been treated with a rescue transplant in the UK. A lack of data on PEG-ADA usage therefore prevents an assessment of whether a patient may have received a rescue transplant in UK practice.

outcomes considered in the model. This would result in 83.3% (15/18) surviving without the need for a rescue transplant. If, in addition, Patient [redacted] had a lower dose (which would not happen again today) and went on to have a rescue transplant. If the calculation is corrected to account for both these patients (adding Patient [redacted] and excluding Patient [redacted]), the proportion of patients in the Strimvelis Integrated Population not requiring a rescue transplant would be 88,2% (15/17).			

Issue 16 Use of back-up bone marrow cells

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 47 it is noted that 'The company reported that one patient received a contaminated product, three patients received back up bone marrow cells due to events after Strimvelis. However, in an additional request for clarification the company stated that two patients had a contaminated drug product so the data provided appeared inconsistent'. The information provided is accurate. [redacted] patients had contaminated drug product, but [redacted] received	Add clarification to Section 4.2.5. Two patients had contaminated drug product, and 1 required receipt of back-up bone marrow and delete any reference to inconsistency in the CS. The remainder of the text should be re-worded to include the correct information. Similarly, the section related to the potential costs around the use of back-up bone marrow cells should be corrected.	It is important that the Appraisal Committee received the correct information regarding the use of back-up bone marrow cells, particularly when it is suggested by the ERG these may represent additional costs.	Corrected in errata.

back-up bone marrow as a result of this. The [redacted] received the drug product along with antibiotic at the investigator discretion with no known AEs or SAEs resulting from this. [redacted] did not receive their back-up bone marrow. Out of the [redacted] subjects who received cells due to events after Strimvelis, [redacted] received back up bone marrow, and [redacted] received their CD34 negative fraction, which is a considerably less costly procedure than a full transplant given whilst the patient is hospitalized for the procedure. In addition, it is believed that some of these issues would not occur today given the improvements made in the clinical protocol for the procedure since the Strimvelis programme started.			

Issue 17 Unwarranted suggestion the QoL data from the Strimvelis Programme is inconsistent with the safety profile observed in the trials

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
In page 51 it is noted that '… quality of life data is potentially inconsistent with other data showing that 17/18 patients experienced a neurological, CNS or hearing impairment'. GSK	The comment around potential inconsistencies should be removed and quality of life and activities of daily living data taken at its face validity.	The suggestion of inconsistency is unsupported and may provide the wrong perception that these data are not valid.	Not a factual inaccuracy.

believes comment is inappropriate given that these data were collected directly from patients receiving Strimvelis and are consistent with all the children attending school expected for their age. In addition, on the same page, the ERG speculates on the fact that most children were reported as not participating in sports may potentially be reflective of impairment of health. Tthis was in fact mainly due to the wishes of parents as stated in the CS.			

Issue 18 Incorrect representation of evidence presented in the CS – data on carer quality of life

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
It is noted (Summary page 12) that '…The outcomes are all addressed in the clinical evidence presented except for carer quality of life.',which is inaccurate. The carer quality of life has been presented in the CS in Section 7, page 34 to ERG as AiC. This research abstract has been accepted and will be presented in an upcoming congress in Nov 2017. Title: The burden and impact on the patient, caregiver and Family. A qualitative research	Request removal of 'except for carer quality of life'.	Factual inaccuracy, these data have been provided.	Not a factual inaccuracy. The data presented on page 34 is based only on carers of patients who had received treatments other than Strimvelis, carers of patients who had any involvement with GSK gene therapy trials were excluded from the study. Page 12 refers to the outcomes specified in the decision problem, which relate to treatment with Strimvelis. No data on carer quality of life after

in USA, Italy, France and UK.			treatment with Strimvelis is presented in the submission.

Issue 19 IVIG discontinuation

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
In the last paragraph of page 48, the ERG report states the company submission stated that 9 Strimvelis patients discontinued IVIG, but the company response stated 11 patients discontinued IVIG. This is incorrect. The company submission stated that 9 patients in the Pivotal Population and 2 in the supportive studies discontinued IVIG. This adds up to match the 11 for the whole Integrated Population reported in the company response to the clarification questions.	Change text in Section 4.2.6 to “11 patients in the Integrated Population discontinued IVIG (65%)” and remove text discussing the 9 patients or suggesting any inconsistency in the CS regarding this.	Inaccurate interpretation of the presented data.	Corrected in errata.

Issue 20 Percentage of PEG-ADA of duration >3 months previous to procedure

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG reports that 67% received PEG-ADA of duration >3 months previous to the treatment with Strimvelis (Section 5.2.3, p 73), but based on Table C21 (p 85) of the Strimvelis dossier, there are 13/18 patients who had PEG-ADA for >3 months, which is equivalent to 72.2%.	Change the percentage from 67% to "72.2%."	Numerical factual inaccuracy.	Number has been changed in errata.

Issue 21 NPP inaccurately classified as a 'study'

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 42 it is noted that 'No critical appraisal was conducted for the study of the Named Patient Programme'. This is inappropriate because the NPP is not a study.	The word 'study' should be removed as this is innacurate.	Noting the NPP as a study wrongly indicates that the NPP is part of the Strimvelis clinical programme and therefore at the same level in terms ofavailability and quality of evidence.	Not a factual inaccuracy. The company submission, Section 9.2.4 refers to the NPP as a study: 'Since the NPP is an investigator-sponsored study' as does Appendix 6.

Issue 22 Available information on NPP that was not reported

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
In the summary section it was noted that the follow up time for the NPP and the inclusion/exclusion criteria had not been reported. This information is available, but was not	[redacted]	Ensure that all information is made available to the Committee.	Not a factual inaccuracy. We disagree that information on follow up time and inclusion/exclusion criteria

previously requested from GSK. The NPP was only reported in the Appendix and not part of the main analyses and therefore it was not deemed to be critical information. Median follow up for the NPP as calculated for the most recent PBRER on 25 May 2017 [redacted]. There were inclusion/exclusion criteria in the NPP guidance document to support appropriate use by applying physicians. Patients will be considered eligible for treatment where the following criteria apply: 1. ADA-SCID patients for whom an HLA–identical healthy sibling donor is not available as suitable bone marrow donor. The decision to treat the patients with alternative transplantation strategies will be taken independently, before the patient is taken into consideration for treatment in this named patient program. 2. Patients of pediatric age (< 18 years of age).Patients for whom their parents or legal guardians have signed the Informed Consent. <u>and at least one of the following criteria:</u> 4i. Patients who have received			were not requested: 1)Follow up time: A3 of the ERG's request for clarification asked GSK for data on the NPP in the format of Table 1 (p23) of the Cicalese et al. 2016 paper. Since Table 1 in the Cicalese et al 2016 paper includes duration of follow up time we expected that if such information was available it would have been provided. However the table in response to question A3 did not provide this information. 2) Inclusion/exclusion criteria: A4 of the ERG's request for clarification also requested further details on the NPP to be presented in the same format as in the main clinical effectiveness section on the Strimvelis Integrated Population. Given that information was provided on inclusion/exclusion criteria for the Strimvelis Integrated Population we expected if that information was available to GSK it would have been provided in response to this

enzyme replacement therapy (PEG-ADA) for at least 6 months before enrolment and displayed at least two of the following immune parameter alterations: - Absolute lymphopenia (<1500/µl) - Absolute T lymphopenia (<1000/ µl) - Requirement for IVIg infusion - Deficit of serum immunoglobulins (IgM or IgA or subclasses of IgG) or lack of antibody response to vaccination. 4ii. Patients who have received enzyme replacement therapy (PEG-ADA), and in whom the drug was discontinued due to intolerance, allergy, or autoimmune manifestations. 4iii. Patients for whom enzyme replacement therapy (PEG-ADA) is not a life-long therapeutic option (e.g. from countries in which the drug is not available). Patients will be considered unsuitable for treatment if any of the following apply: 1. Positive test for human immunodeficiency virus (HIV) or any other agent listed in the current EU Cell and Tissue Directive			request.

2. Current or previous history of leukaemia or myelodysplasia 3. History of previous gene therapy 4. Patients suffering from any other clinical condition that in the treating physician's opinion is dangerous for the patient to participate in this named patient program.			

Issue 23 Incomplete representation of the data available in the literature – Haploidentical outcomes

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
In the summary section (page 14) it is noted that 'Following HSCT from a haploidentical donor (2000-2009 subgroup), 2/7 did not engraft, resulting in one patient receiving gene therapy and the other patient starting PEG-ADA followed by two rescue transplants before death'. This does not fully reflect the key outcomes of interest noted in the scope, i.e. overall survival and intervention free survival. Separately it is noted that a further two patients died – in total there were three deaths, and one further unsuccessful Haplo transplant followed by a subsequent gene therapy procedure. The same should happened whenever these are discussed (e.g. page 22).	The text should read something in the lines of: 'Out of the 7 Haplo transplants between 2000-2009, 2 patients died. A further 2 did not engraft – 1 had a subsequent GT; the other had PEG-ADA and two rescue transplants, and then died. Overall, 3/7 had a successful Haplo transplant'.	The overall (and comparable) picture of outcomes following Haplo HSCT should be provided to the Appraisal Committee.	This not a factual inaccuracy. In addition, information on overall survival following Haplo HSCT is provided in the previous paragraph.

Issue 24 ADA-SCID considered to be comparable to other less difficult to treat types of SCID

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 22 it is noted that 'The CS claims that ADA-SCID is perceived in the clinical community as more difficult to treat than other types of SCID,[3] although the ERG notes that the cited paper says there is "no objective data to support this notion".' This is not a fair representation of the view expressed in the cited paper which notes 'In contrast poor outcome was observed after HCT from HAPLO donors (Tables 2 and 3). In this series, unconditioned HAPLO T cell–depleted transplantations had a high rate of graft failure or rejection, which contrasts markedly from the data for similar transplantations performed in SCID-X1.20 In general, patients with ADA-SCID are severely lymphopenic, lacking both T and natural killer cells, so that the basis of nonengraftment is unlikely to relate to immunologic rejection. Alternative explanations may include the inability of the ADA-deficient marrow stromal microenvironment to support engraftment of wild-type HSCs, and this is supported by in vitro murine data which show that	The statement should be removed or, alternatively, be expanded to include a balanced perspective of the views expressed in the referred manuscript. This should also include the perspective provided by clinical experts.	ADA-SCID is different from other types of SCID and the data from other types of SCID are not transferable o ADA-SCID. This is a view that is expressed in the literature as well as commonly taken by experts in the field. Not differentiating between the two may lead to inappropriate extrapolation and consideration of incorrect estimates relating to the HSCT success rates in ADA-SCID.	Not a factual inaccuracy. The quote from the cited paper has been taken from the same sentence as the claim in the CS and therefore gives a balanced reflection of the view in the paper.

mesenchymal stromal cells from ADA_/_ mice have a decreased ability to support colony formation compared with mesenchymal stromal cells from wildtype mice.21 This hypothesis most probably relates to the support of progenitor cells, because, although unconditioned MSD/MFD transplantations with infusions of whole marrow are able to engraft, under these conditions the engraftment is mainly of more mature cells. Further experimental evidence is required to study this question in more detail. In the HAPLO and MUD setting conditioned transplantations also have poor outcome, and this may relate to the inability to withstand toxicity associated with the conditioning regime or the delayed T-cell reconstitution, which may prevent clearance of viral infection.' We would naturally welcome the opinion of clinical advisors who treat patients across diseases.			

Issue 25 Percentage of UK HSCTs reported in Hassan et al

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The percentage (44%) of HSCTs provided in the UK of the HSCTs reported in Hassan et al. is	Change the percentage from 44% to "41.5%."	Numerical factual inaccuracy.	Number corrected in errata.

incorrectly presented in the ERG report (Section 5.2.6.2, p 78). The number reported is 44/106, which is 41.5%.			

Issue 26 Time on PEG-ADA between diagnosis and procedure

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
In the Summary section (page 17) it is noted that 'The ERG consider that the available evidence does not support the assumption that Strimvelis will reduce the use of PEG-ADA prior to transplant'. This is incorrect and referred to throughout the document as well as included as an assumption in the ERG preferred base case. The available information from English clinical practice in the management of ADA-SCID (which is different from other conditions requiring transplant) does indicate that time on PEG-ADA for Strimvelis is likely to be considerably less than that observed for HSCT In addition, as per Kohn 2017 paper and clinical advice received by the ERG, the recommendation was to continue PEG-ADA up to the point of HSCT, or for 1 month after if using (lenti)GT. For Strimvelis, it is stopped 10-22 days beforehand. This was overlooked	The ERG preferred base case should include a shorter duration of PEG_ADA prior to transplant for Strimvelis compared with HSCT in line with the assumptions used in the GSK model.	We believe that our assumed shorter duration of PEG-ADA pre-procedure for Strimvelis compared with HSCT is more reflective of likely clinical practice, as suggested by the clinical expert advising the ERG.	Not a factual inaccuracy.

in the GSK model for simplicity and both arms were conservatively expected to carry on PEG-ADA up to the point of procedure.			

Issue 27 Use of PEG-ADA before HSCT

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 77 it is noted that 'The ERG notes that many patients with ADA-SCID did not receive ERT prior to HSCT, including 83/106 (78%) of those reported in Hassan 2012.[3] In contrast the majority of patients in the Strimvelis Integrated Population did receive ERT prior to gene therapy (15/18; 83%). As UK centres contributed 44 patients to the Hassan study, even with the extreme assumption that all of the 23 patients that did receive ERT were from the UK, this would give a maximum rate of PEG-ADA use of 23/44 (52%) prior to HSCT. The ERG note that there is little data on the use of PEG-ADA as secondary therapy following a failed HSCT, with Gaspar 2009 reporting use in fewer than 10% of patients.[30] Thus there is uncertainty not only regarding the duration of PEG-	Correct the statement to align the evidence with the point where ERT may be used. Note that according to clinical advice received the current practice is to give PEG-ADA as a bridging treatment between diagnosis and an HSCT procedure. Also, note that in some cases patients may be on PEG-ADA for longer whilst attempting to find a donor which is likely to improve the case for Strimvelis.	The cited evidence needs to be related to the correct context so that appropriate conclusions can be made. Otherwise, unwarranted confusion may be created.	Not a factual inaccuracy.

ADA use, but also the rate of PEG-ADA use. Clinical advice to the ERG indicated that most patients in the UK would be expected to receive PEG-ADA while awaiting transplant. The ERG therefore accepts the simplifying assumption that patients will receive PEG-ADA for the duration of the wait until transplant, but cautions that this likely overestimates any savings from reducing the duration of time between diagnosis and transplant procedure'. This text is inappropriately comparing different things. One is the use of ERT as a bridge which, as noted in the clinical expert advice given to the ERG, is given to everybody; another is the use of previous use of ERT in the Strimvelis trials which relates to both long term and bridging ERT (as expected by the fact GT was only tested in failing patients); and yet another is the chronic use of ERT in the UK as quoted through Gaspar et al. The model considers only bridging ERT for which there is no uncertainty in terms of rates, so the ERG's caution is not appropriate. Regarding duration, as noted earlier by the ERG there may be cases that patients remain longer on ERT whilst waiting to			

find a more suitable donor, so if anything the potential for saving would be underestimated and not overestimated.			

Issue 28 Number of patients with Grade I/II GvHD (MUD donor)

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
In Table 10 of the ERG report (p 82), the number of Grade I/II GvHD was indicated as 5. However, in the CS (Table C28), only suggested 4 patients have Grade I/II GvHD, as the grade for the patient from Gennery 2001 was not specified.	Change total from 5 to "4" and add a row in the table for GvHD with grade not reported.	Ensure accuracy and faithful representation of the evidence presented.	Not a factual inaccuracy. Event is reported as 'mild' and is included by company in denominator when calculating rates of overall GvHD and rates of Grade III/IV GvHD. This implies that the company treated the event as a Grade I/II GvHD event for these calculations. Characterising this event as 'Grade unknown' would alter the denominator and imply recalculation of both the rate of Grade III/IV events and the company model results.

Issue 29 Irrelevance of newer Haplo techniques for the stated decision problem

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 22 it is noted that 'The clinical advisor also suggested that with current methods and techniques results achieved with MRDs are not necessarily better	Suggest to remove the statement as it is not relevant for the decision problem and the EBMT guidelines, which are expected to be followed in England by the two specialty	Caution should be used when referring to options which are not relevant for the stated decision problem around ADA-SCID as they can wrongly suggest a picture	Not a factual inaccuracy.

than those with MUD or haploidentical donors. However, these techniques are very recent and not yet reflected in published data. In addition, these improvements are not based exclusively on ADA-SCID patients'. GSK does not agree these should even be referred to in the document as these are new techniques that may have been explored experimentally in other diseases and types of patients, and are not relevant for the decision problem as stated in the scope. As noted by NICE at the scoping meeting, the decision problem should focus on current clinical practice and not future hypothetical scenarios. HSCT from an Haplo donor has not been conducted in ADA-SCID patients in the England in the last 15 years. These newer Haplo techniques have never been used in ADA-SCID patients in England and, given the EBMT guidelines which considered all the evidence and expertise available and placed HSCT from haploidentical donors after HSCT from matched related donors > gene therapy > HSCT from matched unrelated donors, are unlikely to be used (let alone to become standard of care) in	centres, should be referred to instead.	which may not be relevant to England or the population in question.	

ADA-SCID patients.			

Issue 30 Misrepresentation of literature – Kohn et al

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 26 of the report it is noted that 'Kohn & Gaspar's overview of the management of ADA-SCID,[19] though not exclusively UK based, also confirms that HSCT from an MRD is the current standard of care where possible, with ERT, HSCT from a MUD or haploidentical donor, or gene therapy as options for those without an MRD'. This is a misrepresentation of the cited manuscript, which clearly suggests gene therapy as an option before MUD and Haplo as stated in its summary 'Based on growing evidence of safety and efficacy from gene therapy, we propose a treatment algorithm for patients with ADA SCID that recommends HSCT from a matched family donor, when available, as a first choice, followed by gene therapy as the next option, with allogeneic HSCT from an unrelated or haplo-identical donor or long-term ERT as other options'. This is the current expert thinking on the best way to manage patients with ADA-	The text should be reworded to reflect the conclusions of the cited manuscript, i.e. 'Kohn & Gaspar's overview of the management of ADA-SCID,[19] though not exclusively UK based, also confirms that HSCT from an MRD is the current standard of care where possible, followed by gene therapy as the next option, with allogenic HSCT from a MUD or Haplo or long-term ERT as other options.'	It is important that the expected pathway after Strimvelis is made available, is presented to the Appraisal Committee and correctly substantiated. For this, the preference stated by English clinical experts in the literature and through their participation in the development of the EBMT Guidelines should be fully acknowledged by the ERG.	Not a factual inaccuracy. All listed treatments are covered in the cited paper. Additionally, this section of the ERG report cites the paper in support of the current clinical pathway set out by the company in the submission (which does not include gene therapy). The ERG report later states in section 2.2.4 that the new pathway of care presented by the company, including gene therapy, reflects the EMBT/ESID guidelines.

SCID and also in line with the EBMT guideline and should be clearly made visible.			

Issue 31 Inappropriate reference to a potential future comparator

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 30 and 31 reference is made to ongoing gene therapy trials in the UK: 'There is an ongoing trial in the UK for an alternative gene therapy delivered via a lentiviral vector (NCT01380990). While this is not yet available as a comparator, patients in the UK may enter into the trial and it has the potential to be a relevant comparator in the future. GSK believes that although the information that a gene therapy is being trialled is relevant, the information presented is irrelevant to the decision problem and is out of scope. Comparators were agreed and a scope was developed; in the scoping meeting it was agreed that hypothetical future situations should not be seen relevant for the decision to be taken. GSK notes that this lentiviral gene therapy has not yet had its benefit-risk profile assessed by Regulatory Authorities, is unlicensed, has a shorter safety	Suggest to note that the reference to the potential of NCT01380990 to be a future compartor should be removed. In addition, when referring to the available data on it, it should be noted that 'This lentiviral gene therapy has not yet had its benefit-risk profile assessed by Regulatory Authorities, is unlicensed, has a shorter safety profile, and very limited data publically available in peer-reviewed journals'.	The HST appraisal process should be adhered to and comparators limited to those in the final scope. Speculative suggestions on possible future comparators should not be considered or expected to have an impacton the decision to be taken.	Not a factual inaccuracy. The ERG report does not include lentiviral vector gene therapy as a comparator and is consistent with the final scope.

profile, and very limited data publically available in peer-reviewed journals,. In any case, the fact that 100% survival was observed in these trials should increase confidence on the survival of Strimvelis which is a fully licensed product.			

Issue 32 Inaccuracy in reporting the literature on HSCT

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 46 it is noted that 'A similar subgroup analyses by year for HSCT from a MUD was not available from that dataset which particularly limits the comparison between this treatment and Strimvelis'. The mention to an analysis by year' is incorrect given that for Haplo the analysis was conducted by decade.	The text should be corrected to note 'by decade' rather than 'by year' and the span of the study should be mentioned.	This may induce confusion, particularly when the span of the study is not mentioned in the report, which is relevant to understand that any improvement observed over time was observed over the course of several decades, not years.	Typo corrected in errata.

Issue 33 Irrelevant and potentially misleading reference to a study of HSCT in other therapy area

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 46 (and later on page 78) it is noted that 'Although data for improvements in HSCT from a MUD are not currently available specifically for ADA-SCID patients, a study assessing outcomes in children with non-malignant	Remove this information as it is potentially misleading.	Reference to survival rates in unrelated diseases is inappropriate. The choice of this particular study over others which indicate small or no improvement in HSCT success, may in itself lead to bias.	Not a factual inaccuracy.

diseases observed an increase in 5-year overall survival from 72% (in 1992-2002) to 93% (in 2003-2013)'. This is inappropriate as treatment success and survival rates vary considerably across diseases. In fact, this is demonstrated by the very example given where the rates for 1992-2002 presented are similar to those observed in ADA-SCID only a decade later, i.e. 2000-2009. It's not noted how or why the referenced study was identified as many other examples, such as that of late infantile metachromatic leukodystrophy where 5-year survival rates for HSCT have remained greatly unchanged over the years, could have been presented.			

Issue 34 Reference of a QoL study without providing sufficient details to ascertain its relevance

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 52 a QoL study is cited, but no details are provided on how the study was identified, what information collected, and no quality assessment of the research is provided.	If the study is to be cited, it should be noted how it was identified as well key details of the research. In addition, the quality assessment of the study should be reported.	To ensure robustness in study selection and inclusion.	Not a factual inaccuracy. The QoL studies cited on page 52 were identified by the company and provided with their submission (in sections 7.1, 10.1.6 and 10.1.7 of the company submission).

Issue 35 ERG considerations on the potential longer duration of PEG-ADA use limited only to rescue transplants

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 71 it is noted that '… for some patients duration of PEG-ADA may be longer than is characterised in the model. The implication is that QALYs may be overestimated and health care resource use underestimated for patients requiring rescue transplants'. It may indeed be the case that duration of PEG-ADA before HSCT is longer than characterized in the model. However, this will not only impact the model outcomes attributable to the rescue transplant, but also the costs and QALY associated with the first HSCT procedure.	The word 'rescue' should be removed and the statement should read '… be overestimated and health care resource use underestimated for patients requiring transplants'.	The ERG should present a balanced view of varying assumptions in a holistic manner. Otherwise it may compromise the integrity of the analyses and these will lack validity.	Not a factual inaccuracy.

Issue 36 ERG concerns on currency fluctuation

Description of problem	Description of proposed amendment	Justification for amendment	
On page 94 it is stated that 'The second uncertainty is the exchange rate at the time of purchase. The ERG has concerns that this uncertainty is not addressed in the CS but deserves consideration'. GSK has approached NHS England who stated that they are aware of this	Amend the text to contextualise the ERG concern through the inclusion of the remarks of NHS England made to GSK.	It is important to contextualise the concerns raised by the ERG in terms of likelihood and impact, based on all the information that has been made available to the ERG.	Not a factual inaccuracy.

and comfortable with contracting the fixed price in local currency. From their experience, exchange rates can go up or down and they are not concerned about it. The process would be similar to how NHS England have contracted for Proton Beam Therapy.			

Issue 37 Inclusion criteria for systematic literature search

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Dates (01Jan2000 to 20May2016) were an inclusion criterion in the literature search per the Strimvelis dossier, but these were omitted from the ERG table of inclusion criteria for the literature search (Table 1, p 34).	Add “date 01Jan2000 to 20May2016” to Table 1 of the ERG report.	Ensure accuracy and faithful representation of the search methodology presented.	Not a factual inaccuracy, the date of the search is provided in the text of section 4.1.1.

Issue 38 Typos on referencing

Description of problem	Description of proposed amendment	Justification for amendment	
On Table 9 (page 81) there are a couple of typos in the reference for MUD (‘Hassen et al 2012’) and Haplo (‘Hassan et al 2002’).	It should read ‘Hassan et al 2012’.	Ensure the references are properly noted.	Typos corrected in errata.

Issue 39 Information that should be marked as Commercial in Confidence

Description of problem	Description of proposed amendment	Justification for amendment	
Rates related to the rates observed in the NPP (page 81) should be marked as CiC.	Mark as CiC.	Ensure data intellectual property is not compromised.	CiC marking updated accordingly.

Issue 40 Place of Strimvelis in the treatment pathway for ADA-SCID patients

Description of problem	Description of proposed amendment	Justification for amendment	
In the Summary section (page 17) it is noted that 'The ERG was concerned that the model failed to characterise alternative points in the treatment pathway at which a decision to use Strimvelis may be taken. The company model applies only to younger patients in whom the decision is taken immediately following diagnosis and before any search for a MUD is undertaken'. GSK does not understand the concerns expressed by the ERG. In our perspective and based on clinical advice received, the economic model fully reflects current English practice where patients are likely to present earlier and therefore should be seen as valid to assess the cost-effectiveness of Strimvelis. The model is also reflective of the new EBMT (European Group for Blood	Request that the text in the ERG report concerning the structure of the model and pathway of care be modified to clarify that, although the model considers only the use of Strimvelis in patients that have recently been diagnosed, that is indeed the place in the pathway where Strimvelis is likely to be used in England. The ERG report should also reflect better the existence of the newly published guidelines, which will be adhered to in England, that prescribe that gene therapy should be considered ahead of any non-MRD HSCT. As result, the ERG's suggestion that a search for a MUD may be undertaken before gene therapy is not supported by the guidelines and should therefore be removed from the report.	The statement that the ERG has concerns around the structure of the model raises unwarranted doubt on the validity of the model to assess the cost-effectiveness of Strimvelis in the context of English clinical practice. We also note it is somewhat surprising that the guidelines which are expected to be followed in England and clearly position Strimvelis as a second option ahead of any non-MRD HST are not mentioned in the report when discussing the treatment pathway.	Not a factual inaccuracy.

and Marrow Transplantation)/ ESID (European Society for Immunodeficiencies) guidelines, which place Strimvelis after a MSD but before a MUD or haploidentical donor. It should be noted that both Andy Gennery (Newcastle) and Bobby Gaspar (Great Ormond Street) actively participated in the development of these guidelines and GSK has received clinical advice that this recommendation will be followed in England. Hence, we believe there would be no clinical reason for a non-MRD donor (MUD or Haplo) to be prioritised over Strimvelis and, therefore, no need to perform a search for a MUD ahead of being treated with gene therapy. In addition, although the need to travel may impact the family's decision to travel to Milan to receive gene therapy, if the option of receiving gene therapy through the NHS exists, this is less unlikely to be an issue when choosing between Strimvelis and HSCT given the marked difference in survival and the risks associated with HSCT. Use of Strimvelis after failure from a MUD is also very unlikely given that the intensity of the conditioning regimen necessary for a MUD would make it difficult for patients to receive gene therapy afterwards.			

Issue 41 Mixed comparator based on first line MUD and 2nd line Haplo

Description of problem	Description of proposed amendment	Justification for amendment	
On page 75 it is noted that 'The comparison of Strimvelis with HSCT from a MUD is appropriate if the availability of a MUD is known before choosing between gene therapy and HSCT. This is inconsistent with company's assumption that this information is not available at the point of the treatment decision. To inform decisions made without knowledge of the availability of MUD the relevant comparator may be a weighted combination of MUD for the proportion of patients that find a suitable donor, with haploidentical donor restricted to those who fail to find an appropriate MUD'. Clinical advice received after the scope had been issued suggested Haplo has not been used in the last 15 years and that is the reason why it was not deemed to be very relevant to the current context of English practice. In any case, although adjusting the model to include a comparator mix of MUD and Haplo would benefit Strimvelis, the way this is worded seems to suggest that a mixed comparator	A short note should be added to the sentence to clarify that a mixed comparator would improve the case for Strimvelis.	Adding that note would prevent confusion on the potential impact such an option would have on the ICER.	Not a factual inaccuracy

would be detrimental to Strimvelis.			

Issue 42 ERG judgement on the fact different time to treatment across subgroups are not accounted for in the economic model

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 70 it is noted that 'If a reduction in wait time is an important factor in either the choice of treatment or in establishing the value for money of Strimvelis, then these factors could have been reflected in the model structure, for example by including branches with different expected wait times (e.g.to indicate the existence of a cord blood match in the bone marrow registry), or with the use of subgroups (e.g. to indicate longer expected wait times in certain ethnic groups)'. GSK would like to clarify that the scope provided to us included 'bone marrow transplant' and that the submission followed the scope as required therefore GSK did not have the chance to explore the implications of the possibility of receiving cord blood. Time between diagnosis and treatment remains an important issue due to both the costs of bridging with PEG-ADA and also the impact the	The reference to cord blood should be removed as it is considered to be out of scope. A note should be added explaining that, although the inclusion of subgroups for whom it may take longer to find a donor could be interesting, there are no data available to inform such structure.	It is important the scope is adhered to and the appraisal follows the process stated for the HST appraisals. It is also important that the Appraisal Committee is aware that economic models are a simplification of reality and that some of the structural limitations of the economic model submitted are due to lack of information and not due to any other factors.	The mention of cord blood reflects advice received by the ERG from a UK clinical expert in treating ADA-SCID. The clinical advisor to the ERG indicated that transplant from cord blood would be used in UK practice. The data from Hassan 2012 support this as 9 patients received HSCT from umbilical cord blood.(ERG report Section 3.3, p30). The ERG do not include HSCT from a cord blood as a separate comparator to HSCT from adult bone marrow, but note its potential relevance to clinicians treating patients with ADA-SCID if it is informative to wait time.

time and uncertainty whilst waiting for a donor is expected to have on the family. Different structures were indeed considered to account for potential variations across patients. However, given the low prevalence of ADA-SCID the data that could eventually inform such parameters is not available, so those branches could not be populated.			

Issue 43 ERG suggestion the cost for screening for a MUD should be considered for Strimvelis

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 109 it is stated that 'The ERG note that some patients may utilise Strimvelis after having completed a search for a MUD. These may include patients unwilling to travel to Milan unless no appropriate MUD is found or until failure of a first-line MUD. For these patients the decision to use Strimvelis will not avoid the search costs for a MUD, but the company model structure assumes this search is avoided for all patients'. As noted before, the scenario of families not being willing to travel to Milan is very extreme and certainly not expected to be the norm,	The statement should be removed (and the ERG concerns around the position of Strimvelis in the treatment pathway resolved). This action should be taken across the whole document where these concerns are mentioned and the scenario analysis provided on page 125 should be removed.	This draws unwarranted doubt over the model results and should therefore be corrected. The scenario analysis presented on this matter by adding the cost of screening for MUD to the Strimvelis arm is incorrect, inadequate, and misleading.	Not a factual inaccuracy. This reflects clinical advice to the ERG that some patients and their families may be unwilling to travel. It also reflects the evidence included in the Strimvelis Integrated Population where patients received Strimvelis after failed HSCT. The license for Strimvelis does not preclude its positioning after HSCT.

particularly when the decision is between Strimvelis and HSCT. In the scenario positioning Strimvelis after a failed MUD, GSK does not understand the suggestion and believes it is not technically appropriate to attach the cost of screening for a MUD failure to Strimvelis. If Strimvelis was to be used after a MUD failure the comparison should be made versus the possible options at that time, i.e. a MUD or an Haplo requiring a new MUD search, so the exact same comparison strategy would still apply.			

Issue 44 Type of HSCT when rescue transplant is required

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 71 it is noted that The ERG believes that following an unsuccessful transplant not all patients would find a MSD to provide a rescue transplant. In practice many rescue transplants come from a MUD (and potentially even haploidentical donor), and this may be especially likely in patients for whom the decision was made to use gene therapy before a search for a MUD was complete'. This assumption is unfounded. If a MSD/MRD is	The statement suggesting an eventual rescue transplant is likely to come from a MUD or Haplo is inconsistent with the available data and should therefore be corrected or removed. It should also be noted that all patients needing a rescue transplant after Strimvelis have had a MSD/MRD. In addition, it should be noted the expected impact on the cost-effectiveness of Strimvelis if it were assumed that patients who received a first MUD are more likely to get an Haplo than a MUD as a rescue transplant. Naturally, the ERG preferred base case also needs to be corrected to reflect this, i.e. by not assuming an eventual rescue transplant will	Although it is acknowledged there is some uncertainty around the trype of transplant received for a rescue it is inadequate to extrapolate in a direction that is completely inconsistent with what the available evidence would suggest.	Not a factual inaccuracy. The ERG do not consider that all rescue transplants will come from a MUD. However, the ERG consider that given the small sample size it is not unreasonable to consider that not all rescue transplants will come from a MSD. The ERG analysis also reflects that even where rescue transplant is from a MSD there will be some mortality risk and risk of infection and GvHD.

available, as it was the case for all the patients in the Strimvelis programme requiring a rescue, it will always be used in preference to a MUD or an Haplo which, we note again, has not been performed in England in the last 15 years. In addition, rescue transplants from a younger MSD are likely to become more prevalent as new techniques allow selecting the embryo before birth to ensure the child is born with no genetic predisposition for ADA-SCID. The ERG then further states that 'The ERG therefore considers that the type of rescue therapy could differ between patients initially allocated to gene therapy and those initially allocated to HSCT, as the former would be more likely than the latter to identify a suitable MUD for rescue transplant, having not already exhausted that option'. Although we believe that the assumption on the basis on the statement is incorrect – there is nothing precluding a patient from having a rescue MUD after a first MUD and, given rescue transplant will normally happen after 2 to 3 years once the patient is stabilized, there is a considerably amount of time to find a suitable donor –, we would expect that if	come from a MUD. Different proportions of type of rescue (MSD, MUD, Haplo) should also be explored in sensitivity analyses for each of the initial procedures.		

patients who have had a first MUD require an Haplo in case of rescue this would in fact improve the cost-effectiveness case for Strimvelis.			

Issue 45 Cost of screening for patients deemed ineligible for Strimvelis

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 69 it is noted that '… if Strimvelis were approved it may be expected that a proportion of patients would incur the cost of an initial baseline assessment for gene therapy but would not subsequently receive treatment with Strimvelis'. Although it is correct that screening may deem a patient ineligible for Strimvelis, both the incidence and the cost of this is expected to be very low. In addition, this issue is more likely to happen in older patients and therefore should be minimised in the case of the English reality.	An indication of the likelihood of this happening as well as the resulting relatively low cost of screening per treated patient should be added to the statement.	Although this is factually correct, attention should be given to placing the issue in the context of the decision being made. The added cost of this is negligible extremely small compared to the overall cost of treatment and therefore has no impact whatsoever in the analyses.	Not a factual inaccuracy

Issue 46 Uncertainty around key model parameters

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
In the Summary section (page 18) it is noted that 'Given the small sample sizes used to inform the	Given the very significant impact the rates of rescue transplant appear to have on the ICERs, the direction and magnitude of the	The rate of rescue appears to have as great an impact on the ICER (but in a different direction) as the	Not a factual inaccuracy

key model parameters, each additional patient treated can have a large influence on estimates of overall survival, rates of successful engraftment and rates of rescue transplant'. Although this statement is correct, it should be noted that ADA-SCID is an ultra-rare disease for which the uncertainty will not be resolved. However, this uncertainty also exists around the small samples related to HSCT and may be both overestimating (as stated numerous times by the ERG report) as well as underestimating the cost-effectiveness of Strimvelis. In our submission the values we have chosen were dictated by the available data even when such an approach might negatively impact Strimvelis. This is the case, for instance, for the rates of rescue transplant which, based on clinical advice, should in practice be expected to be at least as good as MUD. Although, in principle we believe that the correct approach is to use the available data and then assess plausibility based on clinical advice and test the impact of each input by the means of sensitivity analyses, bias should not be introduced by testing only inputs that tend to favour comparators. It	observed changes in the ICER should be given its due relevance across the report. Based on clinical advice, we understand that it is expected the rates of rescue for Strimvelis are expected to be at least as low as those for MUD. To account for this uncertainty a full set of sensitivity analyses should be conducted, including a two-way sensitivity analysis increasing both survival and rate of rescue transplant in MUD.	difference in procedural survival and it is based on even lower numbers, so it is important that sensitivity analyses around it are discussed in more detail in the report. otherwise the report focuses only on the uncertainty that may increase the ICERs and compromise its balance by disregarding parameters that are likely to favour Strimvelis.	

should be noted that the rescue transplant numbers for MUD are based on an extremely small sample (n=7), which is considerably smaller than the Strimvelis sample, where a single additional case of rescue would increase the rate of rescue transplant significantly. In addition, based on clinical advice and as noted before, reductions in the intensity of conditioning regimens observed in HSCT over the last decades may mean a smaller chance of engraftment and consequently a higher rate of rescue transplant after a MUD. In the Summary section (page 18) it is noted that 'The results were sensitive to alternative assumptions regarding the rate of rescue transplant'. However, contrarily to the assumptions around survival (supported by a considerably greater number of patients both in the Strimvelis and other gene therapy programmes) this was not fully explored by the ERG. In essence, the way in which rates of rescue transplant affect the results is not fully and appropriately reported.			

Issue 47 Cost and disutility impact of eventual long-term hearing impairment

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
It is noted on page 101 that 'A pragmatic search by the ERG found a UK study that estimated the increase in mean annual NHS (£83) and PSS (£1368.20) healthcare costs of £1,451 associated with bilateral permanent childhood hearing impairment'. Another manuscript on the same cohort was used to infer the disutility costs of potential hearing impairment developed by ADA-SCID patients in the long term. Given these estimates are used in the ERG preferred case with a sizeable impact on the ICER, we would welcome a full discussion of the studies and how these apply to the decision problem in question. GSK believes that the applicability of these estimates cannot be justified. Firstly, these studies relate to congenital prelingual deafness, which may carry greater costs than deafness with a postlingual onset. Secondly, these studies relate to moderate or greater impairment which is not aligned with what was observed in the Strimvelis programme. Thirdly,	Given these are inputs that may have a considerable impact on the cost-effectiveness estimates, we would welcome comments on the search strategy as well as a critique of the studies used, including a discussion of the robustness and their applicability to the decision problem in question. Although it is acceptable there is some degree of impairment, we do not think it is appropriate 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 programme.	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. The estimates selected to be used in the ERG preferred base case considerably overestimate the potential costs and health-related quality of life decrements associated with hearing impairment after the use of Strimvelis, and should be corrected.	Not a factual inaccuracy. As noted, the paper was identified in a pragmatic search and not a formal search.

these costs (which include speech therapy consultations, audiologist time, social worker time, etc) relate to costs incurred between the age of 7 and 9 years old and should not be assumed to be started at a very early age and carried into adulthood lasting for a lifetime. Similarly, it is questionable whether it is valid to extrapolate quality of life in children at 7 to 9 years old to ages below that and into adulthood. In addition, these costs and utility decrements are applied to 58.3% of the population, which is based on a sample of 12 patients who received HSCT. This is clearly misaligned with the considerably lower rate (11.11%, i.e. 2/18) of patients having bilateral deafness observed in the Strimvelis programme. Again, when using these inputs in the ERG preferred case, no consideration is given to aligning severity of the impairment (patients in the HSCT study experienced a range of severity from mild to severe impairment at different frequencies) with the potential cost and utility decrements.			

Issue 48 GvHD rates calculated in the submission

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
In the CS, conservatively only GvHD events that were assumed to be severe, i.e. Grade 3 or 4, were included in the analysis. As a result, the costs of treating acute Grade 3 or 4 GvHD were applied to the proportion of patients (3/28) with reported acute Grade 3 or 4 GvHD. For the proportion of patients (1/28) with reported chronic GvHD the cost of treating an acute GvHD was assumed for simplicity. As this cost is applied in year one only, as opposed to chronically for the full duration of chronic GvHD, this should be taken as a conservative assumption. On Page 55, the ERG report indicates that the fourth case was not reported as acute or chronic, which is incorrect as it was clearly reported as chronic in the literature. On Page 100, the ERG report indicates that the costs of Grade 3 or 4 GvHD were applied to the rate of all GvHD cases. This is incorrect. The costs of Grade 3 or 4 GvHD acute GvHD were applied only to the proportion of patients with confirmed Grade 3 or 4	Remove the last paragraph on page 55, which states that the rates used in the company submission lacked justification. Remove the paragraph on page 100 that states it was inappropriate to apply a cost of severe GvHD events to all grades as this was not done in the submission. Remove the sentence on Page 109 on applying the cost of severe GvHD events to events of any Grade. Adjust the ERG preferred base case to reflect the cost of severe GvHD and remove any other references to the inappropriate use of the cost of GvHD.	Ensure accuracy and faithful representation of the evidence presented as well as guarantee the ERG base case reflects the available data.	Not a factual inaccuracy. Table C28 reports four cases in total experiencing Grade 3 GvHD. Two of these events (both acute) are from Dvorak et al 2014, one event (also acute) from Grunebaum et al, 2006 and one event in Bhattacharya et al. 2005 (not recorded as acute or chronic in Table C28). It is unclear in the submission why this patient was counted as experiencing chronic GvHD. The ERG report does not contain an error regarding the cost of GvHD events. The cost of GvHD in the company model is calculated by multiplying the rate of any GvHD (32.1% for MUD and 33.3% for Haplo) by the cost of GvHD. If the company intended to multiply only the rate of Grade III/IV GvHD by the cost then the model they provided to the ERG and the results quoted in the company submission are incorrect.

GvHD in the case reports. This error in the ERG report is also repeated on page 109.			

Issue 49 Origin of respondents to survey where the GvHD disutility is derived from

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 88 it is stated that 'The expected duration of a GvHD event was informed by expert clinical advice whilst the utility value was taken from an international valuation survey that used time trade off to determine public preferences for health states relating to relapsing/refractory Hodgkin lymphoma'. It should be noted that these utility values were derived from data from an international study, but only the utility values corresponding to the subset of UK respondents were used in the model.	Add a note to clarify that only data from UK respondents was used in the model.	Ensure the origin of the input is described appropriately.	Not a factual inaccuracy.

Issue 50 Disutility applied to administration of IVIG

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG considered that the company's justification for omitting the health related quality of life impact of IVIG is inconsistent with their acceptance of physician survey as a source of the health-related quality of life value for HSCT. The CS did not consider lower disutility associated with IVIG due to the non-availability of robust utility data published recently. It fully explored the impact of including it in sensitivity analysis. While we used the results from a physician-based study (Swinburn 2015) to draw health-related quality of life, that study was designed as a utility elicitation study, with the methods and results presented in detail. In contrast, the reference suggested to be used for IVIG (Weeks et al (1991)) is a small utility study which was conducted as an *ad hoc* analysis to a cost-effectiveness study more than 25 years ago.	Suggest that, given the questions around the robustness of the data and the impact it has on the ICER, disutility due to IVIG should not be incorporated in the base case.	The use of such estimates has a significant impact on the ICER if included in the base case and therefore the validity and applicability of those data should be fully discussed.	Not a factual inaccuracy

Issue 51 Cost of travel to Milan

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 109 it is stated that 'The company base case omits travel costs that would be reimbursed by the NHS, although these were included in a separate scenario analysis'. These were not considered in the based case as, as noted in the CS, there is a chance for patients to apply for funding with the Telethon Foundation if receiving treatment in Milan. As noted by the ERG, those costs were included in a scenario analysis and the impact of adding them was deemed negligible.	A note explaining why these costs are not considered in the GSK's base case should be added.	It is important that a balanced view is presented and that the wording and tone of the document does appear biased against the case presented for Strimvelis.	Not a factual inaccuracy

Issue 52 ERG considerations around the potential need for an air ambulance for patients travelling to Milan

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 94 it is stated that 'The ERG considers that had the patient who required ambulance transport for treatment with Strimvelis been travelling from the UK, an air ambulance may have been required, and so travel costs may have been underestimated'. This assumption is not correct and GSK considers there is no reason for	The statement should be removed.	Ensure alignment with the evidence that is available.	Not a factual inaccuracy.

this concern. A few of the patient flew in to Milan for their treatment and none of them required air ambulance services. One patient, who had flown into Milan, did require an ambulance from Milan airport to the hospital but not air ambulance.			

Issue 53 Source for cost of VCN test

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 99 it is noted that 'No reference is given in the submission or response to clarifications regarding the source of the unit cost or recommended VCN test schedule'. This was not requested earlier, but we can confirm the cost of VCN test was provided to GSK by TIGET.	Suggest removing the statement now that this information has been provided.	Ensure completeness of information.	Thank you for providing a source for the cost applied in the model. No change to the ERG report is required as this was not provided when the report was written and hence is not a factual inaccuracy.

Issue 54 Sensitivity analyses in the CS on the proportion who require a rescue transplant for HSCT from a Haploidentical donor

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
In Section 5.2.9.2 of the ERG report (p 104), the values explored in the 1-way sensitivity analysis for the percentage of patients receiving Strimvelis requiring a rescue transplant is	Change "0% compared to 17.6%" to "8.3% or 22.7% compared to 17.6%."	Ensure accuracy and faithful representation of the evidence presented.	There is no sentence stating "0% compared to 17.6%" on p104 and the sentence in fact reads as per the suggested correction.

incorrectly reported.			

Issue 55 ERG modelling – errors and inconsistencies

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
When reviewing the model provided by the ERG a few errors and inconsistencies were identified in addition to those already discussed earlier in this document: 1- Small inconsistencies were detected in the ICER values written in the report and those on the executable Microsoft Excel model received (£86,856 vs. the reported £86,815 for MUD and £16,751 vs. the reported £16,704 for Haplo). These also exist for the several sensitivity analyses reported. 2- Figure 6 presents negative ICERs, which are meaningless in their magnitude. We assume that the negative ICERs reflect that Strimvelis is dominant, but the presentation should be corrected to prevent any misunderstanding.	Suggest all of these to be corrected in addition to the other changes suggested in this document in order to generate a new ERG preferred base case that is more consistent with the decision problem and the reality of the use of Strimvelis in ADA-SCID patients.	These all affect the ERG preferred base case cost effectiveness, results of the sensitivity analyses, and the conclusions drawn around them. They should therefore be corrected.	1. The ERG model and results have been checked and confirmed and no corrections are required. 2. We agree that the negative ICERs should be replaced with 'Dominant' and a corrected Figure 6 is provided in the errata. 3-11. Not a factual inaccuracy. Where these repeat earlier comments from the company in this factual check, please see corresponding ERG response.

3- Using a weighted average for the cost of MUD where the cheaper bone marrow is assumed the source in the large majority (>82%) of cases is inconsistent with the previous ERG suggestion that time to find a donor is greatly reduced because of the use of cord blood. 4- The ERG considered that the company base case 'omitted potentially important costs associated with the use of Strimvelis…'. It should be noted that some of them amount to as little as £100 per surviving patient over a lifetime. 5- Despite the potential variation at an individual level, time on PEG-ADA should reflect the longer time on average needed to find a donor in the case of HSCT. 6- Cost and utility decrement attached to long term hearing impairment should be aligned with the frequency, duration, and severity observed in the			

Strimvelis programme. 7- Source of disutility associated with IVIG may lack robustness, so that should be explored only in sensitivity analysis. 8- Unit cost of GvHD should reflect the Grade to which the rates refer to, i.e. should be reverted to the cost of severe GvHD as presented in the CS. 9- The denominator used to calculate the rate of rescue transplant in the Strimvelis arm (as noted in Table 26) is incorrect. It should be 18 to reflect the Integrated Population as discussed earlier in this document. If the NPP was to be used in sensitivity analyses in addition to the Integrated Population, the denominator should be 22 and not 20 as noted in the table. This has an impact on the rates utilized and should be corrected. 10- Type of rescue always being a MUD does not reflect the available evidence or the expected reality. At a			

maximum, a mixture of MUD/MSD should be used. 11- It appears that when sensitivity analyses on the survival of MUD are conducted, the potential increase on MUD survival is not reflected in the outcomes from rescue transplants (when MUD is selected as the type of rescue transplant).			

ID926 Strimvelis ERG report errata

The amended pages are in the accompanying document 'ID926 Strimvelis ERG report post FAC amended pages'

Section 4.2.5, p46

A similar subgroup analyses by decade for HSCT from a MUD was not available from that dataset which particularly limits the comparison between this treatment and Strimvelis.

Section 4.2.5, p47

In response to an ERG request for clarification, the company stated that two patients had contaminated drug product (one of these received back up bone marrow as a result of this). Of the three patients who received cells due to an event after Strimvelis treatment, one patient received back up bone marrow and two patients received their CD34 negative fraction. [redacted]

Section 4.2.6, p48

The company submission reported that 11 Strimvelis patients had discontinued IVIG during follow up (8 before 3 years follow up and 3 after 3 years follow up).

Section 4.3, p54

In addition, as pointed out by our clinical advisor, there has been evidence[1] of silencing of gene expression in patients with chronic granulomatous disease (CGD) following gene therapy. Gene silencing can result in a loss of therapeutic benefit but further study is required to assess the risks in ADA-SCID patients.

Section 5.2.3, p73

The Strimvelis Integrated Population are older (mean 2.1 years at gene therapy), more frequently male (61%) and a proportion had already undertaken a HSCT prior to gene therapy (22.2%) or received PEG-ADA (83% PEG-ADA of any duration; 72.2% PEG-ADA of duration >3 months).

Section 5.2.6.2, p78

The source used to inform survival after HSCT is a retrospective survey of 16 international transplant centres, which included 44/106 (41.5%) HSCTs provided in the UK.

Table 9, p81

Table 1: Summary of primary efficacy data reported by the company

	Success, long term	Unsuccessful engraftment, PEG-ADA, awaiting	Death	Source

[1] Qasim W, Gennery AR. Gene therapy for primary immunodeficiencies: current status and future prospects. Drugs 2014; 74:963-969.

	survival	rescue transplant		
Strimvelis	14/17 (82.4%)	3/17 (17.6%)	0/17 (0%)	Strimvelis long-term integrated population study
MUD	9/15 (60.0%)	1/15 (6.7%)	5/15 (33.3%)	Hassan et al (2012)
Haploidentical	3/7 (42.9%)	2/7 (28.6%)	2/7 (28.6%)	Hassan et al (2012) [using 2000-2009 cohort]

Section 5.2.6.3, p81

The ERG notes that [redacted] in the Named Patient Programme required rescue therapy, and inclusion of these data would give a rescue transplant rate of [redacted] and a corresponding successful engraftment rate of [redacted].

Figure 6. p123

Figure 1: Two way sensitivity analysis for initial procedure survival rates showing ICER for Strimvelis compared to Haplo

Strimvelis Survival ↓ / Haplo Survival →	1.00	0.96	0.92	0.88	0.84	0.80	0.76	0.72	0.714
1.00	Dominant	Dominant	Dominant	£1,413	£6,707	£10,715	£13,856	£16,383	**£16,704**
0.98	Dominant	Dominant	Dominant	Dominant	£5,479	£9,942	£13,376	£16,101	£16,445
0.96	Dominant	Dominant	Dominant	Dominant	£4,024	£9,046	£12,830	£15,784	£16,153
0.94	Dominant	Dominant	Dominant	Dominant	£2,273	£7,996	£12,202	£15,424	£15,824
0.92	Dominant	Dominant	Dominant	Dominant	£124	£6,747	£11,473	£15,014	£15,449
0.90	Dominant	Dominant	Dominant	Dominant	Dominant	£5,238	£10,615	£14,542	£15,018
0.88	£1,218,861	Dominant	Dominant	Dominant	Dominant	£3,378	£9,592	£13,991	£14,517
0.86	£271,284	Dominant	Dominant	Dominant	Dominant	£1,027	£8,349	£13,342	£13,929
0.84	£160,825	£595,462	Dominant	Dominant	Dominant	Dominant	£6,810	£12,565	£13,227
0.82	£118,051	£210,925	Dominant	Dominant	Dominant	Dominant	£4,852	£11,617	£12,375

ERG base case*