Public slides – part 1 (Redacted)

Lead team presentation

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

1st Evaluation Committee Meeting

Highly Specialised Technology, 28 September 2017

Lead team: Jeremy Manuel, Sarah Davis, Vincent Kirkbride

Companies: GlaxoSmithKline

Chair: Peter Jackson

Evidence review group: York Technology Assessment Group

NICE team: Thomas Strong, Ian Watson, Sheela Upadhyaya

Disease background

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

- Enzyme defect (adenosine deaminase) leads to build up of toxic metabolites with organ dysfunction
- Severe combined immune deficiency due to inability to produce functional lymphocytes
- Has effect on other organ systems, including hepatic, lung, renal, lymphoma, skeletal abnormalities and neurological
  - Neurological abnormalities include cognitive, behavioural and neurosensory deficits
- One of the sub types of severe combined immune deficiency (SCID)
  - ADA-SCID accounts for 10-15% of all types of SCID
- Ultra rare autosomal recessive monogenic inherited immune disorder
- Incidence 1:200,000 to 1:1 million
  - Company estimates 3 patients per year

Disease background

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

- Disease features
  - Increased susceptibility to infections
  - Failure to thrive
  - Chronically debilitating and risk of death unless immune function is restored
- Age of presentation
  - Usually diagnosed in early infancy
  - 10-15% have delayed onset (6-24 months)
  - Smaller percentage diagnosed after 4 years (late/adult onset)
- Diagnosis and early care
  - Lymphocyte count, immunoglobulin assay, biochemical and genetic testing
  - Specialist immunology and infectious disease teams two supra-regional centres
  - Clinical management antibiotics, antiviral, antifungal therapy and immunoglobulin replacement therapy
  - Stay in isolation until suitable donor identified

ADA-SCID
Current treatment options

Pegylated adenosine deaminase (PEG-ADA)

- Enzyme replacement therapy (no marketing authorisation in the UK) which can be used as a bridge until hematopoietic stem cell transplantation (HSCT)
- Outside the UK some people have long-term PEG-ADA treatment

HSCT – Matched Related Donor (MRD) – 1st choice

- A donor must be found with the same human leukocyte antigens (HLA) to avoid the transplanted cells rejecting the host (Graft versus host disease [GvHD])
- 25% chance that a sibling donor (**MSD**) inherits identical HLA typing, 1 in 200 chance a parent has identical HLA-typing
- Only 20-25% of infants have a suitable MRD available

HSCT – Matched Unrelated Donor (MUD), 2nd choice due to risk of GvHD

- Database search conducted to find a registered donor who is HLA-matched

HSCT – Haploidentical donor, (no recent in UK), high risk of GvHD

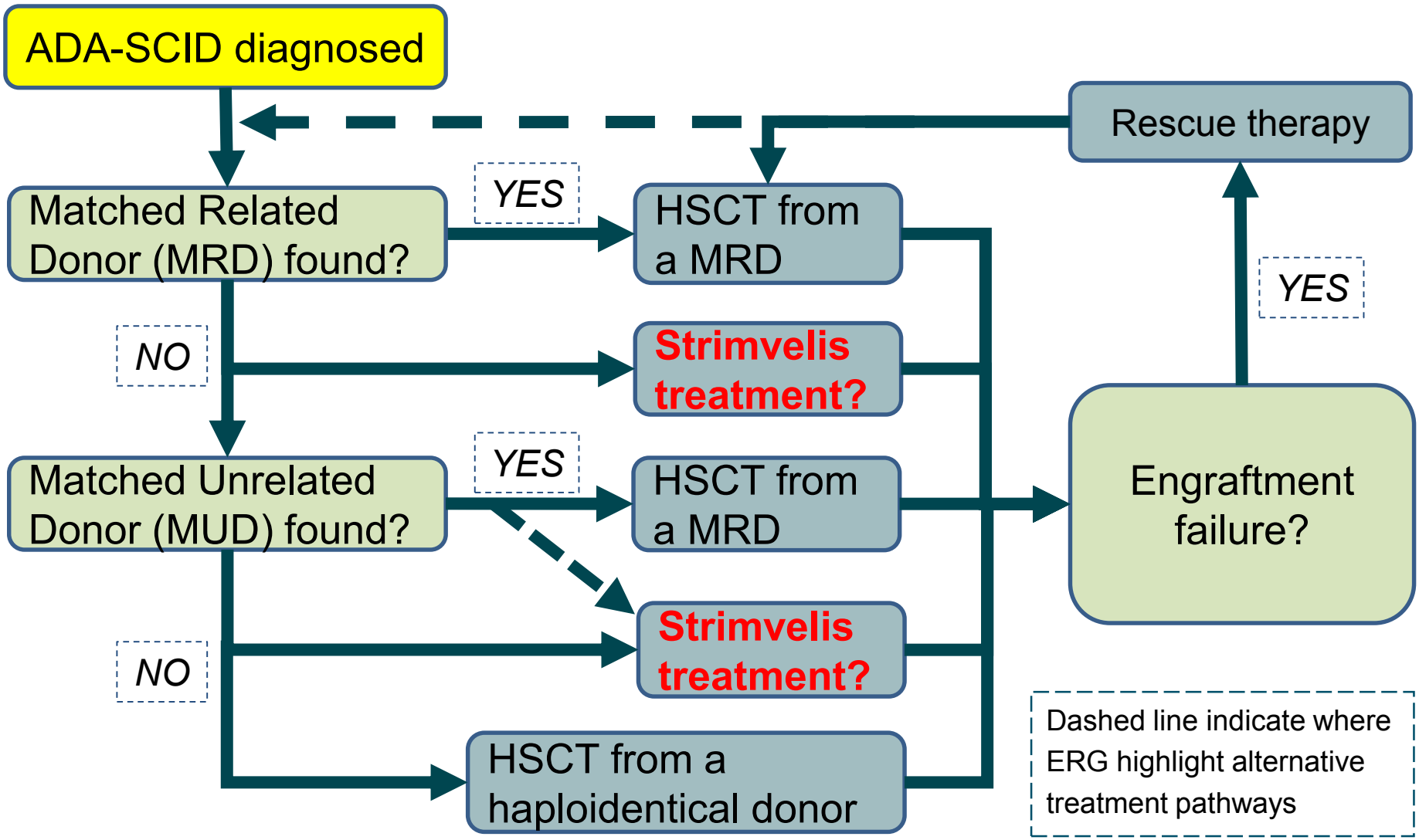
- A parent will always be at least 50% HLA-identical, and there is a 50% change that any sibling is at half matched.
- In the UK those unable to find a MUD are enrolled in trials for gene therapies

ADA-SCID

Impact of the disease

- Quality of life is impacted by recurrent infections due to fungal, viral, and opportunistic agents. Without treatment, patients die before school age.
- Neurological abnormalities, including cognitive deficits and hearing impairment, are common in patients with ADA-SCID
  - HSCT treatment 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 expected to be low - with increased need for hospitalisations, more intensive caregiving, and resulting emotional toll

Clinical pathway of care



⊙ ***Where will Strimvelis be used in the treatment pathway?***

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

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

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, 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

NHS England comments

- All patients with ADA-SCID treated at Newcastle Children's hospital or Great Ormond Street hospital (GOSH). No variation in clinical practice
- Where no suitable donor is available (~ 2 people a year) patients are treated under the gene therapy trial 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

*GOSH gene product is currently being tested in clinical trials, and is not a comparator for this evaluation

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]

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 ≥6 months of treatment with PEG-ADA OR PEG-ADA discontinued due to intolerance OR enzyme replacement therapy 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

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]
	Black	2 (11%)	[redacted]
	Asian	1 (6%)	[redacted]
[redacted]			

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

- ***Is the population generalisable to English clinical practice?***
- ***Should the NPP data be included in the evidence synthesis?***

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%)	No PEG-ADA reintroduction information; 1/15 received 2nd HSCT
Haploidentical donor Hassan 2012 (full cohort)	13/30 (43%)	Not reported
Haploidentical donor Hassan 2012 (2000-2009 cohort)	5/7 (71%)	No PEG-ADA data; 2/7 did not engraft • 1 received gene therapy • 1 had 2 HSCTs and then died

*Defined for Strimvelis as no post-treatment PEG-ADA of ≥3 months, SCT, or death
Hassan 2012 - largest data source on outcomes of HSCT for ADA-SCID currently available
Source: adapted from page 94-95, Company submission

⊙ ***What is the committee's view on the relevance of the survival outcomes?***

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

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

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
  - Weight of one 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

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

- Safety of Strimvelis in line with an ADA-SCID population that has undergone busulfan conditioning and undergoing immune reconstitution
- Adverse events were mostly grade 1 and 2
- All adverse events were resolved
- No Graft versus Host disease was observed
  - No immune rejection is expected as Strimvelis is an autologous treatment
  - Company consider the lack of GvHD to be a key benefit of Strimvelis treatment over HSCT
- Severe infections significantly reduced after gene therapy relative to baseline rates
- No events indicative of leukemic transformation or myelodysplasia reported
- No issues around immunogenicity were evident

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

Adverse events
EMA assessment report

The EMA notes:

- 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
- The use of other gamma-retroviral vectors has been associated with insertional mutagenesis in 3 different gene therapy trials
- The long-term carcinogenic potential of Stimvelis could not be determined at the time of EMA assessment

- 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

⊙ **How does committee view the long-term risks of Strimvelis treatment?**

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 provided the terms used in reporting such as acute, chronic, severe, or specific grades
- Several infections, including infections resulting in deaths, were reported but details were limited in many cases
  - 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 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.

⊙ ***What is the impact of Strimvelis on HRQoL compared to HSCT?***

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 a prognostic factor for Strimvelis treatment
  - 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

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: ERG presented expert opinion and evidence that survival after HSCT has improved 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

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?

Lead team presentation

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

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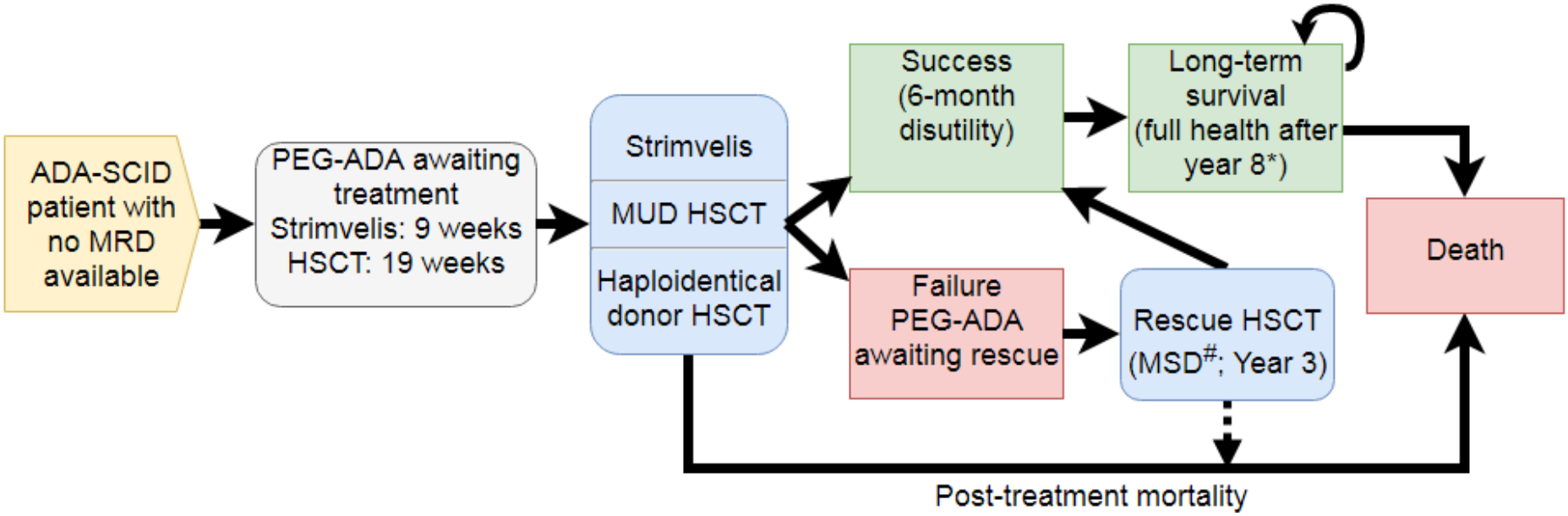
Highly Specialised Technology, 28 September 2017

Economic evidence
Sarah Davis

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

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 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 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

*Hassan 2012 - largest data source on outcomes of HSCT for ADA-SCID currently available

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

Key company clinical variables

Variable		Strimvelis	MUD	Haploidentical
6-month OS		100% (18/18)[a]	67% (10/15)[b]	71% (5/7)[b]
>6-month OS		Assumed equal to general population		
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]
	Chronic GvHD	0%	3.6% (1/28)[c]	0% (0/9)[c]

[a]based Strimvelis integrated population (does not included NPP population)
[b]based on Hassan 2012 data
[c]based on pooled incidence of GvHD from the literature
Source: Table D5, page 158-167, Company submission

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 per living patient	[redacted]	£59,541	£59,541
Total cost per treatment/patient	[redacted]	**£462,498**	**£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
Source: Adapted from Table 17, page 99, ERG report

Utilities

Variable	Company value	Source / Justification
Pre-treatment	0.98	For simplicity, assumed no disutility whilst waiting for treatment on PEG-ADA
0-6 months post-treatment	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
IVIG disutility	No disutility	Likely to have little impact as assumed the rates are equal
Severe infection	No disutility	
Acute GvHD	One-off loss of 0.41	Values calculated from GvHD in lymphoma patients (Swinburn 2015), adjusted by assumed durations
Chronic GvHD	One-off loss of 1.44	

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

Base case results

	Total costs	Total QALYs	Incr. costs	Incr. QALYs (undiscounted)	ICER
Company – base case (deterministic)					
Strimvelis	£1,059,425	41.4	-	-	-
MUD	£565,170	27.8	£494,255	13.6 (23.2)	**£36,360**
Haplo	£888,757	29.7	£170,668	11.7 (19.9)	**£14,645**

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
  - *ERG believe the deterministic ICERs are suitable for decision-making*

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 years)	MLS*0.8 (63.9 years)
Strimvelis vs HSCT from a MUD		
Utility Score by Age * 1	**£36,360**	£40,987
Utility Score by Age * 0.8	£45,475	£51,266
Strimvelis vs HSCT from a Haploidentical donor		
Utility Score by Age * 1	**£14,645**	£16,508
Utility Score by Age * 0.8	£18,352	£20,694

Source: Adapted from table D26, page 214, company submission; base case is bold and underlined

⊙ ***Is it plausible that people regain full health following treatment?***
⊙ ***Should a lower utility or life-expectancy be used in decision-making?***

Scenario analyses

- At clarification the company provided a “secondary” scenario analysis with updated unit costs for PEG-ADA and IVIG, cost to the NHS for providing travel to Milan, and ambulance costs to and from the airports
- PEG-ADA cost had the largest impact on ICER: +£72 Strimvelis versus MUD ICER and + £7,619 Strimvelis versus Haploidentical donor
- *ERG prefers this analysis, and incorporate these assumptions into its preferred base case*

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	-
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)

- The company assumed 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

⊙ ***Are the patient numbers for Strimvelis plausible?***

ERG Comments
Key concerns

1. **Treatment costs are overestimated for HSCT and underestimated for Strimvelis**
   - ERG identified alternative unit costs, and preferred the scenario where travel costs to Italy were 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

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, while the majority of patients did receive ERT prior to gene therapy
- There may be a lower wait time for HSCT in clinical practice with the possibility of cord blood matches
- 9 week PEG-ADA duration for Strimvelis is less than observed in the pivotal study 'pre-treatment phase' (average 25 weeks)
- ERG prefers to use equal PEG-ADA duration for all treatments

⊙ ***What are the most plausible pre-treatment PEG-ADA durations?***

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
- ERG preferred analysis reduces the duration of chronic GvHD to 2 years, although the impact on the ICER is much smaller than delaying rescue transplant

		-1 years	Base case	+1 years	+ 2 years
Timing of rescue transplant	MUD	£30,699	**£36,360**	£41,971	£47,456
	Haplo	£20,822	**£14,645**	£8,414	£2,147
Duration of chronic GvHD	MUD	£36,421	**£36,360**	-	-
	Haplo	£14,645	**£14,645**	-	-

Source: adapted from page 46, company response to clarification

⊙ ***When are people likely to have a rescue transplant?***

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 also 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 [redacted] people will not be eligible (but will incur testing cost)

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

2. Position in pathway
Alternative treatment pathways

- Strimvelis is assumed not to include search for MUD
  - ERG considers some people would have Strimvelis after search for a MUD and would therefore incur costs of search
- 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

⊙ ***Do alternative treatment pathways need to be considered?***

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 believes that the assumption that people have full life expectancy 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

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
- 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

⊙ ***What are the most plausible rates of rescue therapy?***

3. Overestimation of health gains
Rescue therapy (II)

- Rescue transplant was assumed to come from MSD, with 100% success and survival, and no risk of GvHD or severe infection – 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
  - This overestimates the mortality in patients assigned to HSCT
- ERG preferred assumption that people would receive a MUD transplant, and incur chance of GvHD, severe infections, and further failure to engraft

⊙ ***What form of rescue treatment will people have?***
⊙ ***Will rescue treatment have similar outcomes to initial treatment?***

3. Overestimation of health gains
Health-related quality of life

- Model assumes that people have utility equal to the general population pre-treatment and 8 years post-treatment, and with no disutility in relation to severe infections or IVIG administration
- The ERG considers that prior to transplantation the HRQL of patients awaiting treatment may be lower than that of the general population
- ERG prefer to include the 0.75 weight for IVIG disutility included in the company sensitivity analysis
- ERG identified long-term disutilities for bilateral permanent hearing impairment and emotional and behavioural dysfunction
  - Given uncertainties in the utilities for emotional and behavioural dysfunction, the ERG prefers to include only hearing impairment disutilities

⊙ ***Will utilities post-treatment be equal to the general population?***
⊙ ***What utilities should be included in the modelling?***

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

⊙ ***What is the committee's view of the ERG's changes to the model?***
⊙ ***Are there any issues raised which require further exploration?***

ERG preferred analysis

		Strimvelis versus HSCT			
		Inc. costs	**Inc. QALY (undiscounted)**	**ICER**	**Δ ICER**
Company base case	MUD	£494,255	13.6 (23.2)	£36,360	-
	Haplo	£170,668	11.7 (19.9)	£14,645	-
ERG preferred analysis	MUD	£811,195	9.3 (15.9)	£86,815	+£50,455
	Haplo	£184,686	11.1 (18.8)	£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 total QALY gain – and hence any QALY weighting
- Strimvelis must reduce mortality by over 25 percentage points

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

*adjusted threshold based on the QALY weighting applied to the undiscounted QALY gain
Source: adapted from table 32, page 120-121, ERG report; ERG preferred analysis bolded and underlined

⊙ ***What is the most plausible difference in overall survival?***

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 criterion 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 may be reasonable according to NICE guidance

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

⊙ ***Is a 1.5% discount rate appropriate?***

ERG Comments

Sensitivity to product price

- Product cost of Strimvelis is uncertain because:
  - potential fluctuations in the exchange rate
  - costs incurred in Italy still under negotiation between NHSE and 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

⊙ What uncertainties around product price need to be taken into account?

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
- Setting rates of rescue therapy to be equal to the Strimvelis rate would increase MUD rate from 10% and decrease haploidentical rate from 40%
- The ICER is sensitive to this change, because of costs of PEG-ADA before rescue therapy

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

ERG Comments

Alternative treatment pathway scenario

- Strimvelis would incur the costs of searching for a MUD if:
  - People explore having a MUD HSCT before deciding to use Strimvelis
  - People have Strimvelis as a rescue therapy after HSCT
- ERG note that, if a search were not conducted, Strimvelis should be compared to weighted mix of MUD and haploidentical transplants
  - The ICER would be lower than for Strimvelis vs MUD alone

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

⊙ **Should search costs for a MUD be included for Strimvelis?**

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
  - Elements often observed in MAAs are already naturally in place for Strimvelis
  - Strimvelis is only indicated for patients with ADA-SCID without an MRD – eligibility is already restricted to those patients that can benefit the most
  - Company expects referrals only from 2 specialist hospitals – 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 – 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

⊙ ***What QALY weighting should be used for decision-making?***

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

⊙ ***Do any equality issues need to be taken into account?***

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?

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 and disutilities 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?

Public slides – part 1 (Redacted)

Lead team presentation

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

1st Evaluation Committee Meeting
Highly Specialised Technology, 28 September 2017

Patient Perspective
Jeremy Manuel

ADA-SCID

Impact on families and carers – company survey

Redacted

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 contribute to stress and anxiety and even guilt for parents
- Strimvelis treatment involves travel to Milan.
  - huge upheaval for a family
  - 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

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 – 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

Impact on families and carers
Treatment abroad with Strimvelis

- The Telethon Foundation started an anonymous formal assessment in July 2017
- 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 "just like home."
- The company notes that there are only 2 centres in the UK that perform paediatric HSCT (London and Newcastle)
  - Therefore families would still face lengthy treatments far from home
- With the availability of Strimvelis, patients and families will no longer face a long wait for treatment while searching for a MUD or have to make a choice to undergo HSCT that carries a significant mortality risk

Additional slides

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

1st Evaluation Committee Meeting
Highly Specialised Technology, 28 September 2017

Committee's preferred assumptions

Committee's preferred assumptions

3.5% discount rate

Scenario		Strimvelis versus HSCT				
		Inc. costs	Incr. QALY	Incr. QALY (undiscounted)	ICER	Δ ICER
ERG preferred analysis	**MUD**	**£740,930**	**5.5**	**15.9**	**£135,028**	**-**
	Haplo	**£238,681**	**6.5**	**18.8**	**£36,837**	**-**
Exclusion of NPP data	MUD	£626,013	6.0	17.3	£105,049	-£29,979
	Haplo	£123,764	7.0	20.2	£17,804	-£19,033
Exclusion of deafness costs	MUD	£731,635	5.5	15.9	£133,334	-£1,694
	Haplo	£227,923	6.5	18.8	£35,176	-£1,660
MUD survival set to 72.5%	MUD	£743,659	4.5	13.1	£164,281	+£29,253
	Haplo	£228,874	6.3	18.3	£36,186	-£650
Addition of excluded patient	MUD	£722,325	6.0	16.0	£129,829	-£5,199
	Haplo	£220,075	6.6	19.0	£33,569	-£3,267
Combined	MUD	£599,613	5.0	14.0	£120,506	-£14,523
	Haplo	£82,002	6.8	19.6	£12,106	-£24,731
Combined + equal rescue rates	MUD	£490,346	5.0	15.0	£91,910	-£43,118
	Haplo	£464,340	5.5	16.0	£84,172	+£47,336

Source: ERG model

Committee's preferred assumptions

1.5% discount rate

Scenario		Strimvelis versus HSCT				
		Inc. costs	Incr. QALY	Incr. QALY (undiscounted)	ICER	Δ ICER
ERG preferred analysis	**MUD**	**£811,195**	**9.3**	**15.9**	**£86,815**	-
	Haplo	**£184,686**	**11.1**	**18.8**	**£16,704**	-
Exclusion of NPP data	MUD	£666,137	10.2	17.3	£65,620	-£21,195
	Haplo	£39,627	11.9	20.2	£3,340	-£13,364
Exclusion of deafness costs	MUD	£795,161	9.3	15.9	£85,099	-£1,716
	Haplo	£165,950	11.1	18.8	£15,010	-£1,695
MUD survival set to 72.5%	MUD	£817,760	7.7	13.1	£106,101	+£19,286
	Haplo	£169,519	10.8	18.3	£15,721	-£983
Addition of excluded patient	MUD	£787,710	9.0	16.0	£83,138	-£3,677
	Haplo	£161,200	11.2	19.0	£14,410	-£2,295
Combined	MUD	£630,475	8.0	14.0	£74,430	-£12,385
	Haplo	-£22,804	11.5	19.6	Strimvelis Dominant	-
Combined + equal rescue rates	MUD	£491,053	9.0	15.0	£54,072	-£32,743
	Haplo	£465,071	9.4	16.0	£49,429	+£32,724

Source: ERG model