Exagamglogene autotemcel for treating transfusion-dependent beta-thalassaemia [ID4015]

This is not a HST topic – this STA is being considered by the HST committee due to scheduling and capacity

For public and projector – commercial in confidence information is redacted [redacted]

HST technology appraisal committee assessing ID4015 as a single technology appraisal [14 February 2024]

Chair: Dr Paul Arundel

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External assessment group: Centre for Reviews and Dissemination (CRD) and Centre for Health Economics (CHE) Technology Assessment Group – University of York

Technical team: Owen Swales, Claire Hawksworth, Jasdeep Hayre

Company: Vertex

Committee meeting format

Part 1 – Meeting in public	Part 2a – Meeting in private with committee, EAG, NHSE, company, experts	Part 2b – Meeting in private with committee only
• Disease background • Technology and treatment pathway • Expert perspectives • Equality considerations • Decision problem • Key clinical evidence • Summary of economic model • Summary of key issues	• Key issues in further detail • Confidential clinical effectiveness data • Views from EAG and experts • Managed access proposal	• Committee preferences • Cost-effectiveness results • Committee recommendation

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Background on beta-thalassaemia

Causes and classification

- Thalassaemia is a group of hereditary blood disorders caused by genetic mutation of the HBB gene
- Characterised by reduced production of haemoglobin and absence of healthy red blood cells
- People have alpha- or beta-thalassaemia; beta-thalassaemia major is the most severe type and requires regular RBC transfusions (transfusion-dependent)
- People with severe forms of thalassaemia intermedia may also be considered transfusion-dependent

Symptoms and prognosis

- All cases have anaemia, tiredness, weakness, shortness of breath and pale skin
- Regular blood transfusions cause too much iron in the body, leading to serious complications if not treated
- Iron chelation therapy to treat excess iron can lead to considerable toxicity and side effects
- Severe cases lead to heart failure, liver complications, pulmonary hypertension or thrombotic events
- Only possible cure is a HSCT (but only 10 to 30% of eligible people find a matching donor)
- Normal growth, skeletal and endocrine development and quality of life are impaired
- People with transfusion-dependent thalassaemia have reduced life expectancy compared to UK population

Epidemiology

- 1,000 people with beta-thalassaemia major and 260 with beta-thalassaemia intermedia in England (2020/1)
- Mainly affects people with a Mediterranean, South Asian, South East Asian and Middle Eastern background
- Highest UK prevalence in ethnic minority groups, mainly people with Pakistani, Indian, Bangladeshi backgrounds

Abbreviations: HBB, haemoglobin subunit beta; HSCT, haematopoietic stem cell transplant; RBC, red blood cell

Patient perspectives (1)

Thalassaemia and current treatments significantly impact quality of life

Submissions from UKTS, Anthony Nolan

- Key symptoms – fatigue, tachycardia, breathlessness, chronic pain, cognition issues and weakness; impacts energy levels, wellbeing and daily activities
- People experience bone deformities, improper transfusion regime, delayed growth and fertility issues- impacts self-esteem and quality of life
- Significant emotional and social impact on patients and their families
- Current treatment options are limited, highly disruptive and lead to side effects
- There were 12 stem cell transplants in the UK to treat thalassaemia in 2021
- Reduced life expectancy – quoted as 30 years
- Variation in care between areas with high prevalence and larger ethnic minority populations, compared with areas of low prevalence
- People deserve access to potential curative therapies which allow transfusion independence

Abbreviations: UKTS, UK Thalassaemia Society

Patient perspectives (2)

Survey results highlight the impact on patients

Submissions from patient experts

- *"It's quite a lot for a parent to go through…if I'm on a fulltime job and I have appointments, my employer, he's going to say, "Well, find another job. I can't give you five, six times a month off so that you could do your appointments"*
- *So, self-employed is low income…sometimes you work. Sometimes you sit in the house. Most of the time, you are in appointments. So, there is no support for thalassaemia patients."*
- *"Every night, as I watched the sunset, I would cry in anticipation of the pain I knew was coming. My parents had to hold me down as I squirmed and tried to escape. It was a traumatic experience."*
- *"Another difficult aspect that I face now is witnessing the impact of my condition on my family, friends, and community. The guilt, fear, and uncertainty they experience after every transfusion, infection, complication, and the constant adjustments they make to accommodate my needs weigh heavily on me."*

2021 UKTS survey (n=not known):

- 97% of people have > 1 secondary condition, 63% ≥ 5; 32% ≥ 10
- 83.3% of people have had chronic bone and joint pain, even in children aged 3
- 86.4% of people report a moderate to severe impact on quality of life
- 78.2% of people report anxiety, depression, and fear due to condition

Abbreviations: UKTS, UK Thalassaemia Society

Clinical perspectives

Exa-cel is a potential cure, current treatments cause significant burden

Submissions from UKFHD and RCP & BSH

- Treatments lead to considerable burden of disease, high degree of morbidity and mortality; mortality rate over 5x the general population
- People develop an immune response to transfused blood when transfusions are given after the age of 2 – impacts blood availability for life
- Repeated transfusion leads to iron accumulation in major organs, which lead to death or disability unless treated (with toxic and unpalatable treatments)
- Transfusion therapy is the only treatment in England – newer treatments reducing the volume of blood patients require are not available
- Successful treatment with exa-cel would mean no more transfusions or iron chelation therapy, monitoring of endocrine, growth, audiology, ophthalmology; excess iron could rapidly be removed by safe and cheap venesection
- The processes for collecting stem cells exist and are common in the NHS but a moderate amount of training and additional staff would be required

"With this treatment, [people] would have normal haemoglobin levels, thus they would have no chronic and fluctuating fatigue symptoms and the burden of hospital appointments and impact on their life would be significantly reduced"

Abbreviations: BSH, British Society for Haematology; RCP, Royal College of Pathologists; UKFHD, UK Forum on Haemoglobin Disorders

Equality considerations

Consultees raised several equality issues related to beta thalassemia:

- A positive recommendation for exa-cel may decrease existing health inequalities related to ethnicity, and the protected characteristic of race, because there is:
  - a high prevalence of beta thalassaemia in people with a Mediterranean (including Greek and Turkish), South Asian, Southeast Asian, Middle Eastern and African background
  - difficulty accessing donor blood for people from ethnic minority groups, because of a shortage of ethnically-matched blood stocks and alternative treatments that reduce need for blood transfusions
  - decreased life expectancy and health-related quality of life for people with beta thalassemia with South Asian and Southeast Asian ethnicity compared with people from other ethnic minority groups
- Lack of treatment options and well-funded services, exacerbated by variable care across the country-particular burden on people from low socio-economic backgrounds
- Necessary pre-treatment or conditioning with busulfan (or others) may affect fertility

Health inequalities are revisited in later slides as a key issue

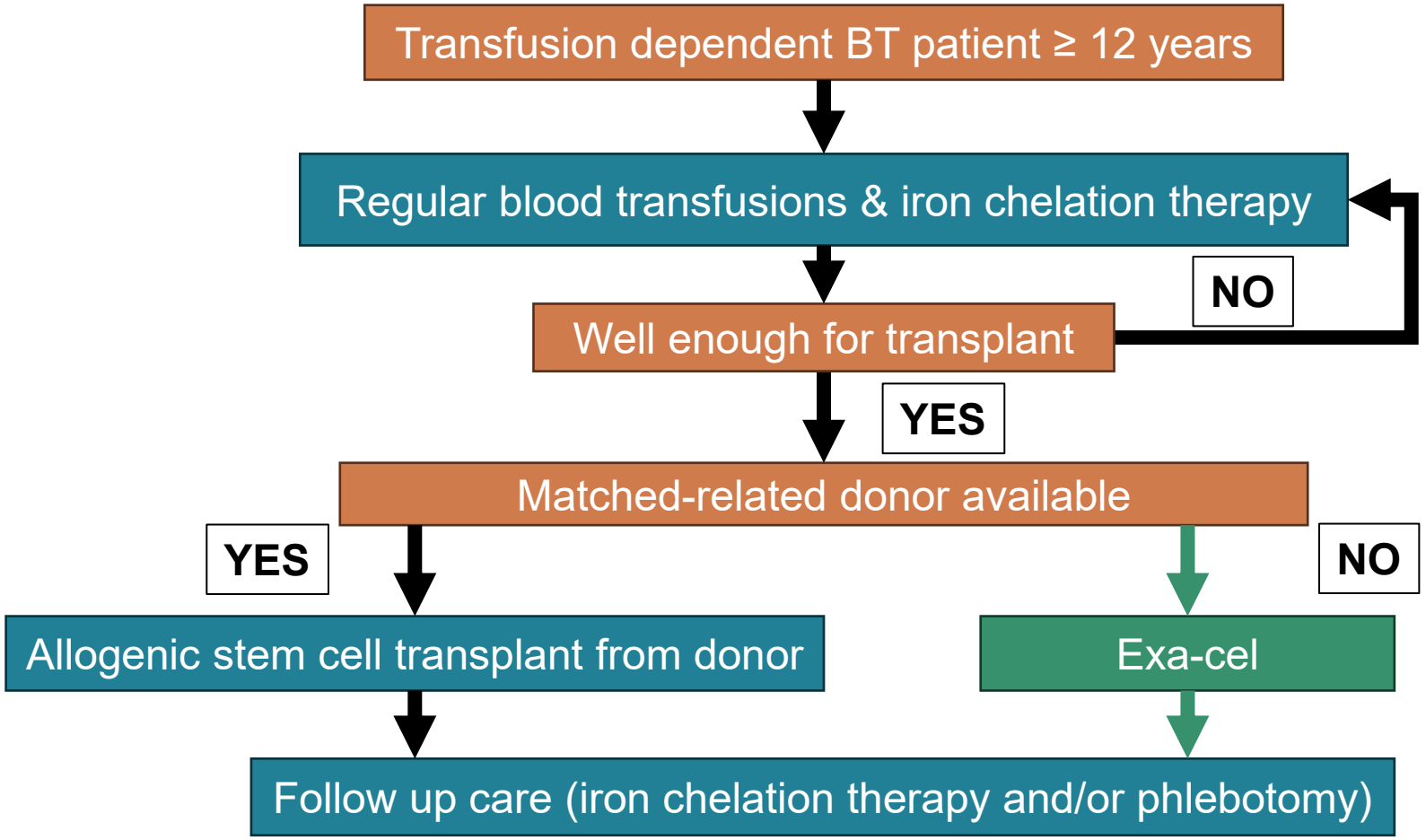
Exagamglogene autotemcel (exa-cel) (Casgevy, Vertex)

Marketing authorisation	For the treatment of transfusion-dependent beta-thalassaemia in patients 12 years of age and older and for whom a human leukocyte antigen (HLA)-matched related haematopoietic stem cell (HSC) donor is not available (November 2023)
Mechanism of action	Reactivates expression of gamma (γ)-globin mRNA, which increases foetal haemoglobin levels in circulating red blood cells, easing effects of decreased or absent beta-globin in transfusion-dependent beta-thalassemia
Administration	One-time, single dose intravenous infusion. Exa-cel treatment process involves 4 key stages: • **Stage 1:** screening and pre-mobilisation • **Stage 2:** blood stem cells collected **(apheresis)** sent to manufacturing facility → CD34+ cells isolated → CRISPR/Cas9 edited → cells frozen and tested → cells returned for infusion • **Stage 3A+B:** preparative chemotherapy → **exa-cel infusion** • **Stage 4A+B:** post-infusion in-hospital follow-up during engraftment and discharge → RBC washout period (60-day period after the last RBC transfusion for post-transplant support or TDT disease management) → post-engraftment follow-up for approx. 2 years The minimum recommended dose of exa-cel is 3 × 10^6 CD34+ cells/kg. Treatment consists of a single dose for infusion containing a dispersion of viable CD34+ cells in one or more vials. A back-up collection of ≥2 × 10^6 CD34+ cells/kg is required.
Price	List price: [redacted] for a course of treatment

Abbreviations: Cas9, CRISPR associated protein 9; RBC, red blood cell; TDT, transfusion-dependent thalassaemia

Treatment pathway

Exa-cel would be used in people who have no matched-related donor for a HSCT



Is this how exa-cel would be used in practice?

Abbreviations: BT, beta-thalassaemia; HSCT, haematopoietic stem cell transplant

Decision problem

Company included non-reference case economic analysis, to be discussed later

	Final scope	Company	EAG comments
Population	TDT where there is no HLA-matched related donor	TDT ≥ 12 years for whom an HLA-matched related HSCT donor is not available (as per MA)	Agree
Intervention	Exa-cel	Exa-cel	No deviation from scope
Comparators	Best supportive care	Best supportive care	No deviation from scope
Outcomes	Company queried the inclusion of some outcomes, but the EAG noted that the outcomes were included in the company's submissions and supporting documents anyway		
Economic analysis	As per reference case	Exa-cel qualifies for the 1.5% discount rate and severity modifier, EQ-5D not suitable in TDT	Incorrect to use: • Discount rate of 1.5% • Non-EQ-5D utility values
Subgroups	People with beta thalassaemia major and intermedia, if possible	No absolute cut-off between the two phenotypes; transfusion independence can vary over time	Agree, in line with TIF guidelines

Company reweighted QALYs via a non-reference case DCEA analysis to estimate the impact on health inequality

To discuss as a key issue later…

Abbreviations: DCEA, distributional cost-effectiveness analysis; HLA; human leukocyte antigen; HSCT; haematopoietic stem cell transplant; MA; marketing authorisation; TDT, transfusion-dependent thalassaemia; TIF, Thalassaemia International Federation

Clinical effectiveness

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CLIMB THAL-111 trial

Design	Phase 1/2/3 single-arm, open-label, multicentre, single-dose study Primary efficacy set (April 2023 data cut) – 120 days post-marketing authorisation application requested by regulatory authorities
Population	People aged 12 to 35 years with TDT **PES:** Median cohort age (20 years), Female (50.0%) Enrolled: 59 → 54 had exa-cel infusion → 53 completed initial RBC transfusion washout → 42 followed for ≥ 16 months after exa-cel infusion and ≥ 14 months after RBC transfusion
Intervention	Exa-cel
Comparators	None (single arm study)
Primary outcome	Proportion of patients achieving transfusion independence for at least 12 months (TI12)
Key result	92.9% (39 of 42, 95% CI: 80.5%, 98.5%) [p<0.0001]
Locations	US (5 sites), Canada (2 sites), UK (2 sites), Germany (3 sites), Italy (1 site)
Used in model?	Yes - baseline characteristics and exa-cel clinical outcomes

Abbreviations: CI, confidence interval; D120, Day 120; Hb, haemoglobin; HbF, foetal haemoglobin; PES, primary efficacy set; RBC, red blood cell; TDT, transfusion-dependent thalassaemia

Indirect treatment comparison

Comparison with BELIEVE SoC data informs transfusion independence assumption in the model

BELIEVE trial:

- Double-blind, randomised, placebo-controlled Phase 3 trial (Luspatercept + BSC versus placebo + BSC)
- People ≥ 18 years of age with TDT
- BELIEVE trial not used in the model, but used to inform the indirect treatment comparison

Matching adjusted indirect comparison (MAIC)

MAIC:
IPD from CLIMB THAL-111 was re-weighted to make key baseline characteristics comparable with aggregated SoC data from BELIEVE

→

Due to small sample of patients in CLIMB THAL-111 (n=24), MAIC matched on genotype, median of annualised RBC units at baseline and median age

→

% of patients TI3 in BELIEVE compared to % of patients TI6 in CLIMB THAL-111

CLIMB THAL-111 TI6 evaluation started 60 days after last RBC transfusion, BELIEVE evaluation started Day 1 after treatment

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Abbreviations: beti-cel, betibeglogene autotemcel; BSC, best supportive care; IPD, individual patient data; RBC, red blood cell; SoC, standard of care; TDT, transfusion-dependent thalassaemia; TI(3 or 6), transfusion independent (for 3 or 6 months)

Indirect treatment comparison results

SoC cannot lead to transfusion independence

Proportion of patients who were TI3 in SoC arm of BELIEVE and TI6 with exa-cel (data not in model)

	SoC (n=112)	Exa-cel unweighted (n=27)	Exa-cel re-weighted (ESS=13)
Proportion (95% CI)	0.0% (-,-)	88.9% (70.8%, 97.6%)	86.5% (56.7%, 96.9%)

Company

- ITC shows no TD patients on SoC can spontaneously revert to TI or TR without active intervention
- Model assumes people on SoC retain baseline transfusion status/frequency/volume and iron distribution
- Conservative assumption for paediatric patients, SoC requirements likely to increase as they grow

EAG comments

- Transfusion reduction more plausible outcome for SoC patients – ITC should have considered this
- BELIEVE did not report usable transfusion reduction outcomes, but some showed a small non-specific response: 4.5% of people had reduced transfusion burden ≥ 33% (weeks 13 to 24); 3.6% (weeks 37 to 48)
- Disagree with assumption that all SoC patients retain their baseline transfusion status

Abbreviations: CI, confidence interval; ESS, effective sample size; ITC, indirect treatment comparison; SoC, standard of care; TD, transfusion-dependent; TI, transfusion independent; TI(3 or 6), transfusion independent (for 3 or 6 months); TR, transfusion reduced

Cost effectiveness

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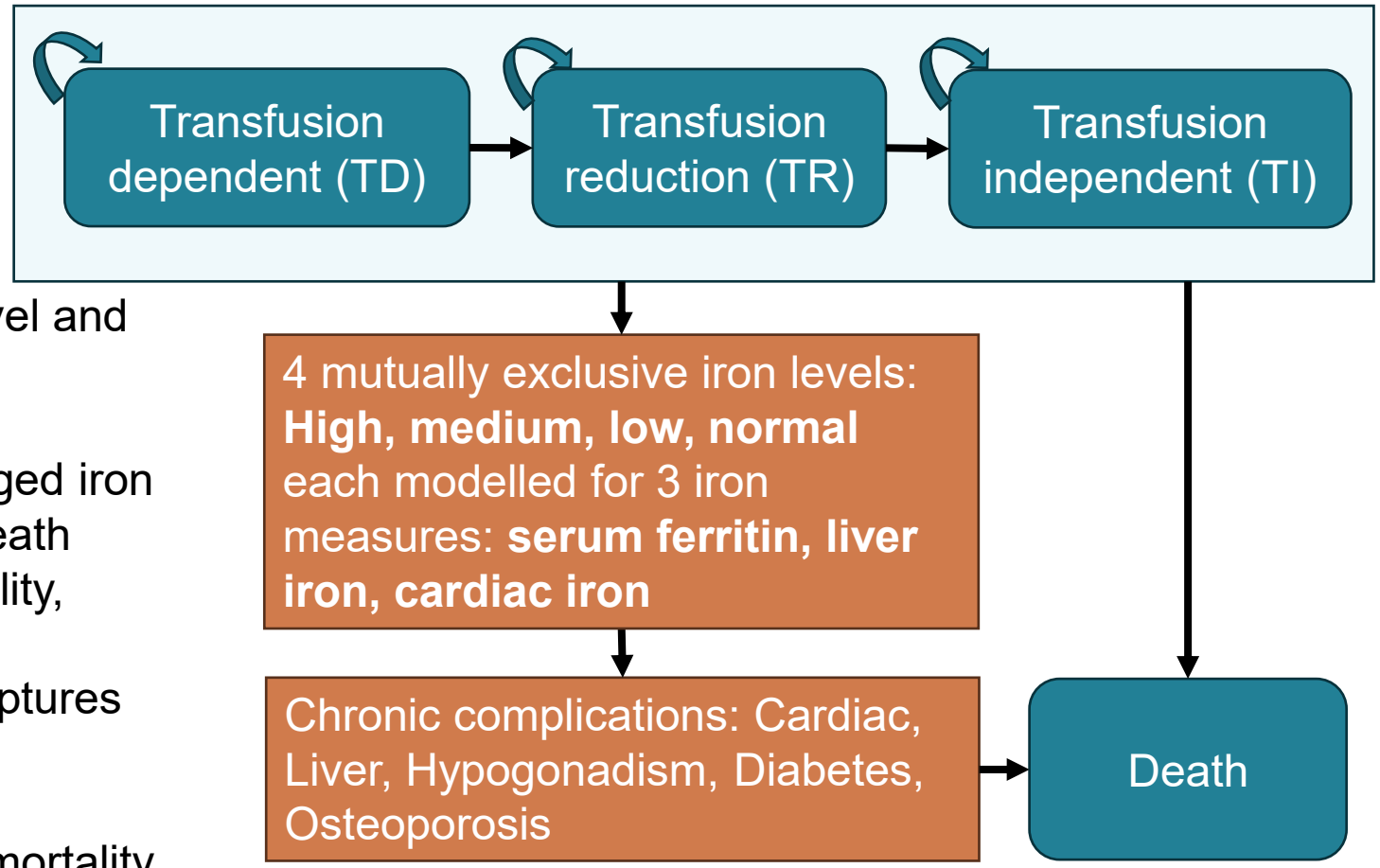
Company model structure

Markov model with four mutually exclusive health states

- Transfusion status informs frequency of transfusions and iron levels
- Cohort start in TD with abnormal iron levels (high/medium/low)
- Receive exa-cel or SoC:
  - Exa-cel – transition to TR (reduced iron level and transfusions), TI (normal iron level and no transfusions) and death
  - SoC – remains in TD health state (unchanged iron levels and transfusions) or transitions to death
- Iron level informs complications – affects mortality, quality of life, resource use and costs
- Applies a single mortality rate to everyone – captures general population and excess mortality

NOTE: Previously, complications caused excess mortality, but company removed this in response to TE



Abbreviations: SoC, standard of care; TE, technical engagement

How company incorporated evidence into model

CLIMB THAL-111 was the main evidence source for the model

Input	Assumption and evidence source
Baseline characteristics	CLIMB THAL-111 – patient characteristics, complications, transfusions Shah et al., 2021 – baseline iron levels, iron chelation therapy distribution
Intervention efficacy	CLIMB THAL-111 – treatment duration, withdrawal, success rate, response rates Clinical opinion – iron normalisation clinical parameters
Comparator efficacy	Assumption/MAIC – baseline transfusion status/frequency/volume and iron distribution retained over the course of the model time horizon
Utilities	Values from Matza et al., 2020 vignette study adjusted for changes over time, complications, SoC treatment received and caregiver utility (from the literature)
Costs	UK NHS and Personal Social Services costs and eMIT costs
Resource use	Clinical expert opinion, NICE ID968, dosing guidelines for treatments
Complications	Assumptions and literature – annual risk for complications
Mortality	CLIMB THAL-111, NICE ID968 and assumptions

Draft guidance was released for ID968 (betibeglogene autotemcel for treating transfusion-dependent beta-thalassaemia) but the appraisal was terminated by the company, citing its withdrawal from operations in Europe

Overview of key model outcomes

Inputs and assumptions that affect costs and QALYs

- **Exa-cel is modelled to affect QALYs by:**
  - Increasing overall survival and improving HRQoL:
    - Avoiding the need for RBC transfusions and iron chelation therapy
    - Preventing iron load related complications

- **Exa-cel is modelled to affect costs by:**
  - Higher acquisition costs
  - Greater immediate administration costs
  - Avoidance of disease related and complication related healthcare costs

- **Assumptions with the greatest ICER effect:**
  - The modelling approach and whether complications are explicitly modelled
  - The discount rate applied
  - HRQoL in patients who are transfusion-dependent
  - Permanence of treatment effect in transfusion independent people following treatment with exa-cel

Abbreviations: RBC, red blood cell; HRQoL, health related quality of life

Key issues that are not resolved

Model structure and non-reference case analyses have the largest ICER impact

Issues requiring committee decision	ICER impact	EAG view
Model: complications and mortality estimated from surrogate endpoints (transfusion status and iron levels)	Large	Model overestimates complications and mortality, suggest alternative
Use of non-reference discount rate (1.5%) in the model	Large	Criteria for 1.5% discount not met
Utility: EQ-5D not suitable, use Matza et al. 2020 values	Large	Use EQ-5D data, rejection not clear
Transfusion independence in the model: transfusion-free starting 60 days after the last blood transfusion	Med	Model definition easier to achieve than trial definition, use trial measure
Exa-cel treatment withdrawal in the model was assumed to happen just after apheresis (blood stem cells collected)	Med	Include costs of treatment withdrawals prior to infusion
Exa-cel's long-term efficacy in the model	Med	Assumed permanent treatment effect is uncertain
Frequency of red blood cell transfusions in the model	Med	Use figures that reflect UK population
Issues for committee consideration		
Estimating impact on health inequalities	N/A	Defer to NICE
Managed access	N/A	Defer to NICE

The meeting will now move to Part 2a

Meeting in private with committee, EAG, company, experts

- Key issues in further detail
- Confidential clinical effectiveness data
- Views from EAG and experts

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