NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final draft guidance

Exagamglogene autotemcel for treating transfusion-dependent beta-thalassaemia in people 12 years and over

1 Recommendations

1.1 Exagamglogene autotemcel (exa-cel) is recommended with managed access as an option for treating transfusion-dependent beta-thalassaemia in people 12 years and over:

- when a haematopoietic stem cell transplant (HSCT) is suitable, but a human leukocyte antigen-matched related haematopoietic stem cell donor is not available
- only if the conditions in the managed access agreement for exa-cel are followed.

1.2 This recommendation is not intended to affect treatment with exa-cel that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS healthcare professional consider it appropriate to stop. For children or young people, this decision should be made jointly by the healthcare professional, the child or young person, and their parents or carers.

Why the committee made these recommendations

Standard care for beta-thalassaemia includes blood transfusions and iron chelation therapy to remove excess iron in the blood. If people who have regular blood

transfusions are well enough, an HSCT is an option. Exa-cel is a possible cure when an HSCT is suitable but there is no human leukocyte antigen-matched stem cell donor.

Clinical trial evidence shows that exa-cel removes the need for blood transfusions in most people. But, in the trial, people were only followed up for a relatively short time, and exa-cel was not compared with any other treatment. Evidence from an indirect comparison shows that exa-cel reduces the need for transfusions compared with standard care. But the number of transfusions that most people have as part of standard care needs confirming.

As well as the uncertainties in the clinical evidence, there are several issues with the economic modelling, including:

- the model structure
- how long the treatment effect with exa-cel lasts
- how often people withdraw from exa-cel treatment before the infusion takes place
- the survival and quality-of-life outcomes used for people having exa-cel and standard care
- the frequency of complications.

Exa-cel has the potential to be cost effective compared with standard care. But the cost-effectiveness estimates are highly uncertain. This is because of the uncertainty in exa-cel's long-term effects and impact on quality of life, and in the outcomes for people on standard care. Some of the most likely cost-effectiveness estimates are higher than what NICE normally considers an acceptable use of NHS resources, even when accounting for exa-cel's potential impact on health inequalities. So, exa-cel is not recommended for routine use in the NHS.

Collecting more data through a managed access agreement may resolve some uncertainty in the evidence. So, exa-cel is recommended for use with managed access.

2 Information about exagamglogene autotemcel

Marketing authorisation indication

2.1 Exagamglogene autotemcel (Casgevy, Vertex Pharmaceuticals) is indicated for 'the treatment of transfusion-dependent β-thalassemia in patients 12 years of age and older for whom haematopoietic stem cell transplantation is appropriate and a human leukocyte antigen matched related haematopoietic stem cell donor is not available'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for exagamglogene autotemcel.

Price

2.3 The list price for exagamglogene autotemcel is £1,651,000 per course of treatment.

2.4 The company has a commercial arrangement (managed access agreement including a commercial access agreement). This makes exa-cel available to the NHS with a discount. The size of the discount is commercial in confidence.

3 Committee discussion

The evaluation committee considered evidence submitted by Vertex, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

Transfusion-dependent beta-thalassaemia

3.1 Thalassaemia is the name for a group of hereditary blood disorders caused by a genetic mutation. It reduces or prevents production of healthy red blood cells (RBCs) and haemoglobin. Beta-thalassaemia is when the

genetic mutation is in the haemoglobin subunit beta gene. Beta-thalassaemia major is the most severe type and people with it need regular RBC transfusions, which makes them transfusion dependent. People with thalassaemia intermedia may also need regular RBC transfusions and be considered transfusion dependent. Beta-thalassaemia is associated with varying degrees of anaemia, which causes tiredness, weakness, shortness of breath and pale skin. Transfusion-dependent beta-thalassaemia affects normal growth, skeletal and endocrine development, and quality of life. The regular blood transfusions can cause too much iron in the body, which leads to serious debilitating and life-threatening complications if not treated. At its most severe, it can lead to heart failure, liver complications, pulmonary hypertension and other complications related to thrombotic events. Beta-thalassaemia mainly affects people of Mediterranean, South Asian, South-East Asian and Middle Eastern ethnic origin. In the UK, the largest groups affected are of Pakistani, Indian and Bangladeshi ethnic origin. The patient experts explained that beta-thalassaemia has a significant financial, physical and psychological burden on people with the condition, their families and carers. A 2021 survey for the UK Thalassaemia Society found that 97% of people with thalassaemia have more than 1 secondary condition, 63% have more than 5, and 32% have more than 10. Around 80% of respondents reported a moderate to severe effect on their quality of life, with chronic pain, anxiety and depression. Chronic pain was also reported in people as young as 3 years. The patient experts highlighted the significant effect that intense blood transfusion regimens, and their associated side effects and complications, have on work, family and friends. The committee concluded that beta-thalassaemia is a debilitating and life-limiting condition. It also concluded that there is a high unmet need for effective treatments that improve outcomes and quality of life for people with the condition. It further noted the considerable impact that the condition has on families and carers of people with beta-thalassaemia.

Clinical management

Treatment options

3.2 The clinical experts explained that people with transfusion-dependent beta-thalassaemia need lifelong RBC transfusions. But continued use of RBC transfusions causes too much iron to build up in major organs, leading to disability or death. Iron chelation therapy removes excess iron and is a key component in managing symptoms and enabling regular transfusions. But the treatments are very toxic and unpalatable, meaning people may have difficulty adhering to the treatment schedule. The clinical experts explained that the only potentially curative treatment option for transfusion-dependent beta-thalassaemia is a haematopoietic stem cell transplant (HSCT). But, normally, only people under 18 years and who have a matching donor are considered for a transplant. The patient experts highlighted that there were only 12 transplants in the UK in 2021 to treat thalassaemia. They added that, when an HSCT is not suitable or a donor is not available, current treatment options are limited. Also, they are highly disruptive to people's lives and can cause considerable side effects. The patient experts also shared experiences of some people who have suboptimal RBC transfusion regimens. The clinical experts explained that RBC transfusions are the only treatment available in England when an HSCT is not suitable. This is because newer treatments that reduce the volume of blood needed in transfusions are not available. The clinical experts added that current treatment options lead to considerable disease burden, with morbidity and mortality that is more than five-times worse than in the general population. They highlighted that some people can develop immune responses to transfused blood if it is first given after age 2 years. This affects blood availability for life. They also added that RBC transfusions have a significant effect on daily life. This is because they can take up to 8 hours, and can be needed as often as every 2 or 3 weeks. The committee concluded that current treatment options are very limited for people with transfusion-dependent beta-thalassaemia when an HSCT is suitable but there is no matched donor. It

also concluded that these treatments are very burdensome, needing frequent hospital visits and causing significant side effects that are very difficult to live with.

Treatment positioning of exagamglogene autotemcel (exa-cel)

3.3 The company positioned exa-cel to be a treatment when an HSCT is suitable but there is no matched donor. It explained that exa-cel reactivates the expression of gamma-globin mRNA, and increases fetal haemoglobin levels in RBCs. This stops the effects of decreased or absent beta-globin. The treatment process involves collecting blood stem cells from the person having exa-cel and sending them to a manufacturing facility. There, the CD34+ cells are isolated and the CRISPR associated protein 9 is used to edit the BCL11A gene before the cells are frozen. The edited cells are returned to the body in a single infusion. The patient and clinical experts agreed with the company's positioning of exa-cel. They also explained that exa-cel could potentially be a curative treatment for people with otherwise limited treatment options. This would significantly reduce the side effects of current treatments. They also added that processes for collecting stem cells are common in the NHS. But they thought that a moderate amount of training and additional staff would be needed to implement exa-cel. The committee concluded that the company's proposed positioning of exa-cel in the treatment pathway was appropriate. It also concluded the company had appropriately defined standard care as a comparator.

Clinical effectiveness

CLIMB-THAL-111 trial

3.4 The main clinical evidence for exa-cel came from the CLIMB-THAL-111 trial. This was a multiphase (1, 2 and 3) single-arm open-label trial. It investigated the efficacy of exa-cel in people aged 12 to 35 years with transfusion-dependent beta-thalassaemia. The trial recruited 59 people, and 42 were followed for 16 months or more after exa-cel infusion. The

median cohort age was 20 years and 50% were women. The trial was carried out across multiple sites globally, including 2 sites in the UK. The primary outcome measure was the proportion of people who had transfusion independence for at least 12 months (from now, TI12). This was defined as having a weighted haemoglobin average of 9 g/dl or above and not having RBC transfusions for 12 months. At the latest data cut, 39 out of 42 people (92.9%; p<0.0001) had the TI12 outcome. The company outlined that the 3 people who did not meet the TI12 outcome were transfusion free for 10.3, 7.0 and 2.8 months at data cut-off. The committee concluded that the results of CLIMB-THAL-111 were generalisable to the UK. It also thought that the results showed promise for potentially life-changing outcomes for people with transfusion-dependent beta-thalassaemia.

Economic model

Company's modelling approach

3.5 The company developed a Markov model with 4 mutually exclusive health states to estimate the cost effectiveness of exa-cel compared with standard care. These were transfusion dependent, transfusion reduction, transfusion independent and death. Each of the 3 transfusion health states included 4 mutually exclusive iron-level health substates (high, medium, low and normal). Iron levels were modelled for 3 iron-level measures: serum ferritin, liver iron and cardiac iron. Chronic complications were modelled based on iron levels. They were cardiac complications, liver complications, hypogonadism, diabetes and osteoporosis. People started in the transfusion-dependent health state with abnormal iron levels (high, medium or low) and had either exa-cel or standard care. People in the exa-cel arm could move to transfusion-reduction, transfusion-independent or death health states. People having standard care remained in the transfusion-dependent health state or moved to the death health state. Transfusion status informed iron levels, which then informed complications and the associated effects on mortality, quality of life,

resource use and costs. This chain of clinical variables together estimated outcomes in each arm. The company applied a single mortality rate comprising general population mortality plus excess mortality to all people. The EAG thought that the company's model was not suitable for decision making. This was because the Markov model structure did not capture patient history, which is crucial to track individual outcomes. To compensate for no individual tracking, the model relied on multiple complex chains of evidence, leading to unclear assumptions and significant uncertainty. The company explained that it had amended its model during technical engagement to address the EAG's concerns, and had removed complication-related mortality. But the company argued that this change substantially underestimated excess mortality seen in the company's Burden of Illness study. This study estimated 1.19 deaths per 100 person-years for people with transfusion-dependent beta-thalassaemia compared with 0.2 for the general population. So, the company increased the standardised mortality rate for the transfusion-dependent health state in the model. This was to account for the removal of complication-related mortality and to reflect the excess mortality seen in practice. The exact standardised mortality rate is commercial in confidence, so cannot be reported here. The patient and clinical experts explained that the chains of evidence used in the model were not uncertain. This was because the link between transfusion dependence, iron overload and mortality in thalassaemia is well established. They added that transfusion independence relieves almost all disease burden, improving quality of life and mortality, as predicted in the model. The EAG explained that the removal of complication-related mortality improved the face validity of the model, but that significant uncertainties remained. The first was that applying a common mortality rate for all people leads to an over-accumulation of people with complications in both treatment arms. The second was that the distribution of iron levels was static and remained unchanged throughout the model. This lacked face validity because mortality increases for people with higher iron levels. This means

that people in the model with high iron levels should have died over the model time horizon, shifting the distribution of iron levels over time to lower levels. The EAG agreed that it was important to capture the effect of complications on outcomes and resource use. But it noted that this could not be achieved in a Markov model without using assumptions that would undermine the model's credibility. So, the EAG explored alternative modelling options (see section 3.6). The committee concluded that the company's model may not have accurately modelled the interaction between iron overload, complications and mortality. It would expect changes in iron levels to inform complications, and affect mortality and quality of life.

Alternative modelling approaches

3.6 Because the EAG thought that the company's model was not suitable for decision making (see section 3.5), it explored alternative modelling approaches to the company's base case. They were:

- a patient-level simulation model
- a Markov model with no complications included
- a Markov model with 1 complication included.

The EAG highlighted the advantages and disadvantages of each approach, but decided to adopt a Markov model with no complications in its base case. It favoured this approach because it was transparent. But it emphasised that this was not its preferred model, just the most reasonable model that could be achieved in the time available for this evaluation. The EAG highlighted that its base-case model underestimated the burden of complications and was biased in favour of the standard-care arm and against exa-cel. But the model was internally consistent (unlike the company's base case). Also, the direction of bias was known and could be accounted for in decision making. The EAG decided against a patient-level simulation model because of the likely lack of evidence to link iron levels to complications. Also, the effect of complications may not be

known, and that model would have been very complex and time consuming to implement. Finally, the EAG decided against a Markov model that included 1 complication. This was because it would still have relied on an uncertain chain of evidence, despite being simple and capturing some of the complication burden. The company argued that it was crucial to model the effect of complications to accurately estimate the associated costs and disutility. It added that removing complications in the EAG's base case significantly underestimated excess mortality associated with complications and the benefits of exa-cel. The company also shared figures comparing the proportion of people modelled with complications in its base case, and figures from the literature. It noted that the modelled figures were realistic but lower than those in Jobanputra et al. (2020; a study selected for comparison). The EAG explained that excess mortality was accounted for in its model by changing the standardised mortality rate for the transfusion-dependent health state in the model to 2.5. It added this value was used in the discontinued NICE technology appraisal guidance on betibeglogene autotemcel for treating transfusion-dependent beta-thalassaemia to account for excess mortality. The committee concluded that the company's and EAG's base-case models were associated with considerable uncertainty. It noted a fundamental need of the model was to capture the interaction between iron overload, complications and mortality. The committee thought that neither the company's nor EAG's base-case model adequately did this. The company's model did not accurately reflect how complications affect outcomes and the EAG's did not model complications. The committee concluded that it would like to see a clinically validated model that accurately captures the interaction between iron levels, complications and mortality. It added that this should be explored alongside the period of managed access (see section 3.19) because this would provide the timeframe necessary to change the model. But, for now, the committee concluded that its preference was for the company's model structure because it included complications, unlike the EAG's model. It also

preferred the standardised mortality rate for the transfusion-dependent health state used by the company. The committee decided to state these preferred assumptions to support its decision making. But it noted that these assumptions should only be considered as preferred given the context of this evaluation. The committee concluded that the modelling was very uncertain but provided an incremental cost-effectiveness ratio (ICER)-based estimate that it could consider. The uncertainty was considered by the committee in its decision making (see section 3.20). The committee would like to see, as part of the evaluation after managed access, a model that more accurately captures the interaction between iron overload, complications and mortality (see section 3.5 and section 3.20).

Long-term treatment effects

3.7 The company's model assumed that all people treated with exa-cel had permanent transfusion independence. The company explained that this assumption was supported by CLIMB-THAL-111. The EAG questioned the assumption, noting that CLIMB-THAL-111 had limited follow up, so it may have been inappropriate to relate trial outcomes to lifetime outcomes. It also noted that people who have had HSCTs can have very late relapses, which may also happen with exa-cel. The EAG's base case retained the assumption of permanent transfusion independence, but it explored 2 scenarios based on estimates from the literature. One used a relapse rate of 2.19% (Santarone et al. 2022) and the other a relapse rate of 10.00% (the Institute for Clinical and Economic Review report on betibeglogene autotemcel 2022). The company explained that there is no biological plausibility that the exa-cel genetic edit is reversible. It noted that Santarone et al. was specific to HSCT, a modality with a key difference to CRISPR gene editing. Also, the Institute for Clinical and Economic Review report cited 2 experts, one of which suggested a 0% relapse rate. The patient and clinical experts outlined to the committee that transfusion independence at 24 months is highly predictive of a permanent treatment effect. They recalled that nobody who has become

transfusion independent has reverted to transfusion dependence. The committee concluded that there was uncertainty with the long-term treatment effects of exa-cel because of the relatively short-term follow up of CLIMB-THAL-111. But it understood from the clinical experts that the long-term efficacy of exa-cel was more certain after 2 years. So, it concluded that a 0% relapse rate for exa-cel should have been used in the model. But it noted uncertainty with this assumption that it would like to see explored with further data collection.

Non-reference case discount rate

3.8 The company stated that exa-cel met the criteria for the non-reference case discount rate of 1.5%. The committee acknowledged that all of the following criteria in the NICE process and methods guide (section 4.5.3) must be met for a 1.5% discount rate to be used:

- The technology is for people who would otherwise die or have a very severely impaired life.
- It is likely to restore them to full or near-full health.
- The benefits are likely to be sustained over a very long period.

The company argued that the first criterion was met because people with transfusion-dependent beta-thalassaemia had a mortality rate 5 times higher than the general population. The company's Burden of Illness study recorded a mean age of death of 55 years. The EAG was concerned that the evidence represented historical treatment practice and included people for whom exa-cel would be ineligible. The patient and clinical experts disagreed, saying that the company's estimate was too high for most people. They added that people typically die in their 30s, or live into their 40s but with severely impaired quality of life because of complications and treatment side effects that get worse with age. The EAG commented that the quality-of-life effects referenced by the company are not as severe as claimed (see section 3.10).

The company explained that the second criterion was met because exa-cel improves survival, reduces the risk of complications and comorbidities, and eliminates the need for transfusions or iron chelation. The patient and clinical experts noted that complications and comorbidities associated with standard care would be reversed. So, quality of life would be expected to return to that of the general population. The EAG disagreed with the assertion that complications would be entirely reversible, especially when irreversible damage was present before an exa-cel infusion. It noted that associated morbidities would likely continue even if exa-cel was a functional cure. The clinical experts challenged this view by explaining that only people who are well enough would meet the eligibility criteria for exa-cel treatment. So, most of the comorbidities could be reversed.

The company thought that the third criterion was met because there is no biological mechanism or reason for exa-cel to lose its treatment effect. The clinical experts explained that graft-versus-host disease seen with HSCTs is not relevant to exa-cel because it uses the person's own edited cells. They added that any issues with an exa-cel infusion would occur within 6 to 12 months. So, graft success at 2 years would represent a permanent effect. The EAG noted that the short-term follow up of CLIMB-THAL-111 led to uncertainty about the permanence of treatment effect, long-term quality of life and survival. It also queried the long-term effect of 10% to 40% of thalassaemia cells remaining after infusion. The company explained that 20% of cells need to be edited to cause a treatment effect, but exa-cel edits 80% of cells.

The committee concluded that the first criterion for using a 1.5% discount rate was met. This was because the company and the experts had shown that people would otherwise die or have a severely impaired life. When considering the second criterion, the committee noted considerable uncertainty with the likelihood of exa-cel returning people to full or near-

full health. It understood from the experts that exa-cel would reduce the need for blood transfusions. But it was not clear whether persistent damage from complications and comorbidities would be reversed by exa-cel. The committee thought that the second criterion could be met, but it was uncertain. It noted that the short-term follow up of the clinical-effectiveness evidence compounded the uncertainty. So, it said that it would like to see this explored with further data collection (see section 3.19). For the third criterion, the committee thought it plausible that exa-cel's benefits were sustained over a very long time. But it noted that this was very uncertain because of the limited follow up of clinical evidence. So, it said that it would like to see this explored with further data collection (see section 3.19). So, the committee concluded that not all criteria had been met and that a 3.5% discount rate should be used. It agreed that exa-cel may meet criteria 2 and 3, but wanted to see longer-term follow-up data to understand the longer-term effects of exa-cel.

Other inputs and assumptions in the model

3.9 The EAG raised additional concerns with the company's model:

- the assumption that people on standard care cannot become transfusion independent
- the definition of transfusion independence used
- including withdrawals from exa-cel treatment before the infusion takes place
- the number of transfusions for people having standard care.

The company assumed in its model that people having standard care could not become transfusion independent (see section 3.5). It justified this assumption by doing a matching adjusted indirect comparison (MAIC). The MAIC compared the exa-cel arm from CLIMB-THAL-111 with the standard-care arm from the BELIEVE trial. This included placebo plus best supportive care in people 18 years and over with transfusion-dependent beta-thalassaemia. Individual patient data from

CLIMB-THAL-111 was reweighted to make key baseline characteristics comparable with aggregated data from the BELIEVE trial comparator arm. This showed that 86.5% of the people who had exa-cel were transfusion independent at 6 months compared with 0% of people at 3 months in the standard-care arm. The EAG noted that these results were expected. It also noted that a focus on transfusion reduction outcomes instead of transfusion independence would have been more informative. The EAG noted that BELIEVE did not report usable transfusion reduction outcomes. But it did report that, in 4.5% of people, transfusion burden was reduced by at least a third in weeks 13 to 24. The clinical experts explained that a reduced transfusion burden is not necessarily because of people's condition improving. Rather, they said that it tends to mean people are having fewer transfusions for other reasons, including non-adherence to a transfusion regimen. They added that standard-care treatments cannot lead to transfusion reductions or independence.

The EAG noted that the company's model used a different outcome definition for transfusion independence than CLIMB-THAL-111. The trial outcome (TI12) was defined as having a weighted haemoglobin average of 9 g/dl or above and not having RBC transfusions for 12 months. But the model defined transfusion independence as being transfusion free starting 60 days after the last blood transfusion. The EAG thought that this outcome was easier to reach than the trial's outcome, as shown by the 3 people who did not meet the trial definition yet were considered transfusion independent in the model. The EAG's base case used the TI12 definition in its model. The patient and clinical experts explained that both definitions are correct and reflect the early- and long-term natures of response. The company noted that the 3 people identified by the EAG as not meeting TI12 were transfusion free for 10.3, 7.0 and 2.8 months respectively at data cut-off. It also added that 60 days is the time it takes for most transfused cells to be destroyed. So, after this time, haemoglobin levels will be maintained by a person's own cells. It means that 60 days is

a suitable timepoint for measuring transfusion independence.

For treatment withdrawals from exa-cel, the EAG explained that the company's model did not capture people who withdrew before the infusion. It noted that this excludes a significant period of time between cell cycle collection and pre infusion, when people can withdraw from treatment and will have incurred pretreatment costs. The company's response to this issue was confidential, so cannot be reported here.

The EAG also thought that the modelled number of transfusions for people having standard care were too high. The company included 16.4 transfusions per year based on CLIMB-THAL-111 data. But the EAG used data from Shah et al. (2021) in its base case (13.7 transfusions). This used UK data, whereas people in the trial may not have fully reflected people in the UK for whom exa-cel would be suitable. The company argued the Shah et al. data was not generalisable to the UK. This was because genotype proportions were not reported and 25% of people in the study would not have been eligible for CLIMB-THAL-111. It also noted that gene therapy would most likely be for people with severe thalassaemia and increased numbers of transfusions. The EAG expressed uncertainty with the company's assertion that disease severity is a key determinant of having treatment with exa-cel because future health is also likely an important factor. The patient and clinical experts added that RBC transfusions are typically given every 3 to 4 weeks, equating to between 13.0 and 17.3 per year. They also noted that transfusion needs increase as people age, or develop antibodies or secondary conditions.

The committee concluded that the company's MAIC provided some comparative evidence for exa-cel but that its usefulness was limited. But it agreed with the clinical experts and the company that people on standard care could not become transfusion independent or have a reduction in

transfusions. The committee also concluded that the TI12 outcome should have been used to measure transfusion independence in the model. This was because it was the primary outcome measure in CLIMB-THAL-111. It also concluded that the impact of exa-cel treatment withdrawals on estimated quality-adjusted life years (QALYs) should have been included in the model. The committee concluded that 16.4 RBC transfusions per year should be included in the model for the standard-care arm. This was based on CLIMB-THAL-111 data, and the patient and clinical expert testimony that transfusions typically occur more often than every 3 weeks. But the varying estimates made this uncertain and the committee would like to see further data collected.

Utility values

Source of utility values

3.10 CLIMB-THAL-111 collected EQ-5D data. The company argued that it was not suitable for decision making because it lacked face validity and that EQ-5D was not a disease-specific measure. Some people in the trial reported perfect health (utility value of 1). Baseline utility values in the trial were 0.89, which the company argued was higher than the UK general population average of 0.87. It explained that a utility increase of 0.19 was seen for 8 people, but that this would not be possible for everyone because of EQ-5D's ceiling effects. The patient and clinical experts explained that the EQ-5D utility values showed a large degree of adaptation by people, which may have influenced how they responded. They explained that people with thalassaemia have not known a life without the lifelong condition, so perfect health to them is different to someone without thalassaemia. This means that utility effects are underestimated, as shown by 67% of people with thalassaemia reporting perfect health using EQ-5D in Shafie et al. (2021). This is at odds with people's experience of the condition, as shown by 29.6% of people considering that EQ-5D-5L did not capture their experience of thalassaemia (Boateng-Kuffour et al. 2023). The patient experts also

explained that people feel like they cannot report their true feelings in quality-of-life questionnaires because of cultural pressures to not be seen as weak. The EAG noted that the model health-state utility values did not include utility effects from complications because disutility for these was modelled separately. So, the utility values experienced by people in the model would have been lower than inputted in the health states. The EAG disputed claims that EQ-5D was not suitable for decision making. It noted that a more accurate general population utility value was age and gender-matched to the trial population. This was 0.94 and higher than the trial population baseline of 0.89. The EAG also noted claims that EQ-5D misses key symptoms of thalassaemia were unsubstantiated, and are typical for other chronic conditions with fluctuating symptoms. The company decided to use utility values from Matza et al. (2020) in its base case. The study used time-trade-off interviews with people from the UK to estimate utility values for thalassaemia health states. So, the company used the following health-state utility values: 0.73 for transfusion dependence, 0.75 for transfusion reduction and 0.93 for transfusion independence. The clinical experts thought that these utility values had better face validity than the EQ-5D values, but noted that the transfusion reduction value may have been underestimated. The EAG noted that there was considerable uncertainty with the Matza et al. values. This was because the study did not follow the best practices outlined in a report by the NICE Decision Support Unit, and it was possible that descriptions of health states were value laden. The company's base case assumed a 0.2 utility decrement between transfusion-dependent and -independent health states. The EAG's base case used a smaller utility decrement for transfusion dependence that is commercial in confidence, so cannot be reported here. The committee questioned why the company used EQ-5D in its pivotal trial if it knew the measure was unsuitable. The company explained that there is no disease-specific measure that can be used for thalassaemia, and the ceiling effect was made clear once data was collected. It also noted that the trial protocol was confirmed a long time

ago, and other quality-of-life measures have since shown very different results compared with EQ-5D. The committee noted uncertainty with the Matza et al. utility values because of the possibility of value laden questions. It noted that, in the absence of a clear prognoses, the general public may associate a description of the complications with early death. It concluded that it would like to see more information on how the interviews in Matza et al. were conducted. But it understood that the company may not have access to this information because it did not do the study. The committee concluded that EQ-5D may be an appropriate measure to capture quality of life in people with thalassaemia. But it concluded that the utility values used in the EAG's base case seemed high. It concluded that this seemed inaccurate and the effect of transfusion dependence had been underestimated. So, it concluded that the Matza et al. utility values should be used but noted the uncertainty in how these values had been derived. It also noted general uncertainty in establishing the quality of life of people who were transfusion dependent and transfusion independent, given the long-term nature of the condition. The committee would like to see further data collected on health-related quality of life, including EQ-5D data.

Severity

Severity modifier calculations

3.11 The severity modifier allows the committee to give more weight to health benefits in the most severe conditions. Absolute and proportional QALY shortfalls should be calculated in line with the NICE process and methods guide (section 6.2.17) and the NICE Technical Support Document 23. The company estimated that a weight of 1.2 should apply to the QALY increments. But, in its calculation, the company used a 1.5% discount rate (see section 3.8) to calculate the shortfalls. The NICE process and methods guide (section 6.2.17) stipulates that shortfall calculations should include discounting at the reference case rate (3.5%). The committee was aware that the severity thresholds were not suitable for calculations using

different discount rates. Using the same reference case discount rate across evaluations ensures that the assessment of severity is applied in a consistent and fair manner. The committee noted that both the company's and EAG's QALY shortfall estimates calculated using a 3.5% discount rate were considerably less than the thresholds to meet the criteria for a severity modifier. The company's base case (with 3.5% discount rate) estimated an absolute QALY shortfall of 9.51 and a proportional QALY shortfall of 0.42. The EAG's base case estimated an absolute QALY shortfall of 3.78 and a proportional QALY shortfall of 0.17. The committee recalled the powerful testimony of the patient and clinical experts on what it is like to live with the condition, and the effects on families and carers (see section 3.1 and section 3.2). The committee noted that it agreed that criterion 1 for the non-reference case discount rate was met (see section 3.8). It considered whether the identified uncertainties in the evidence could have affected the calculations of the QALY shortfall. The committee recalled its preference for the Matza et al. (2020) utility values (see section 3.10). It noted that, although there was uncertainty in these estimates, the company's base case using these did not generate a shortfall that met a 1.2 QALY weight. It was reassured that the uncertainty would not change this decision. The committee also considered any impact from health inequalities. It noted that the condition disproportionately affects individuals with higher levels of deprivation and considered how this could have biased the estimates. It was reassured that this would not have led to an underestimate of the QALY shortfall. The company argued that the severity modifier:

- discriminates against conditions that get progressively worse over time
- will only be accepted in conditions with an immediate mortality risk instead of mortality that increases over time.

The committee was aware that the NICE process and methods guide (section 6.2.17) includes consideration of both absolute and proportional shortfall. It understood that the use of both measures of shortfall widens

the consideration beyond conditions with an immediate mortality risk. The committee took into account the quantitative estimates and any possible changes to these estimates due to any uncaptured benefits and uncertainties. It did not think that the threshold for a severity modifier was met.

Health inequalities

Identified health inequalities

3.12 The company, stakeholders, and patient and clinical experts raised health inequality concerns for people with transfusion-dependent beta-thalassaemia. This is because the condition mainly affects people from Mediterranean, South Asian, South-East Asian and Middle Eastern ethnic origin. In the UK, the largest groups affected are Pakistani, Indian and Bangladeshi ethnic origin (see section 3.1). The patient and clinical experts explained that outcomes for people with beta-thalassaemia vary across the country. They noted that survival estimates quoted during the committee meeting appeared to be overestimated and not reflective of the UK. They added that most people die in their 30s or 40s, and that people from Asian ethnic groups die considerably earlier than people from Mediterranean ethnic groups. But committee did not see data supporting these estimates. The experts noted that people's outcomes were not solely based on their ethnicity, but were because of deprivation and level of education. They explained that adherence to transfusions and iron chelation was difficult because of the number of hospital visits and side effects. The patient experts explained that most people need to use annual leave from their employment to make very frequent hospital visits. This leads to a huge financial burden, and barriers to maintaining employment and accessing care. The clinical experts explained that regional disparities in access to care should be mitigated by the National Haemoglobinopathy Panel in England. This panel has representatives from 4 coordinating centres in England. The experts explained that the panel's role is to hold the care network to account and to provide the

same access to expertise across the country. The committee asked the experts how access to exa-cel would help to reduce health inequalities. Firstly, the experts explained that people from ethnic minority groups (excluding White minority groups) find it very difficult to find matched donors for an HSCT. Access to exa-cel would give more people from ethnic minority backgrounds a treatment option with comparable outcomes to treatments available to people who find a suitable donor and have an HSCT. Secondly, the experts explained that exa-cel would substantially reduce the need for contact with the healthcare system, which is a significant barrier to care because of needing time off work and money for transport. They explained that exa-cel as a possible cure would drastically reduce the need to attend medical appointments so often, improving quality of life and access to care. The committee questioned whether a reluctance to take up new treatments would increase health inequalities by disproportionately affecting people who are not currently accessing optimal care. The patient experts explained that adherence issues are caused by the toxicity and significant burdens of current treatments. They added that adherence is also difficult because people are being told to follow intense regimens for the rest of their lives, leading to a waning of engagement. The committee understood that the following health inequalities were relevant to consider:

- Thalassaemia mainly affects people from Mediterranean, South Asian, South-East Asian and Middle Eastern ethnic minority groups and, in the UK, it is most prevalent in people from Pakistani, Indian and Bangladeshi ethnic backgrounds.
- Treatment outcomes vary considerably by ethnic background.
- Some treatment options with much improved outcomes are harder to access by people because of their ethnic background.
- Among people with thalassaemia, a disproportionate level may live with higher levels of deprivation, which generates barriers to access and exacerbates existing variability in care.

The committee concluded that there were clear health inequality concerns that needed to be taken into account in its decision making.

Accounting for health inequalities in decision making

3.13 The company accounted for health inequalities in its submission by doing a distributional cost-effectiveness analysis (DCEA). This stratified the eligible population by index of multiple deprivation (IMD). The company weighted the benefits and costs in each IMD group using a health inequality aversion parameter to create an equity-weighted ICER. This needs information on how much the UK population prefers extending quality-adjusted life expectancy for a person from a deprived population compared with someone with less deprivation. The company used an aversion parameter of 11, taken from Robson et al. (2017). The EAG preferred to use a value of 3.5, taken from a more recent estimate from Robson et al. (2023). The committee noted there were a range of possible weights in the literature, and the most appropriate for the UK setting is not universally agreed. The NICE technical team clarified that NICE's position is that the NICE process and methods guide does not allow for a quantitative modifier for health inequalities. NICE does not consider that there is sufficiently robust evidence to support using aversion weights as part of a DCEA. But, taken together, the NICE process and methods guide, statutory duties, principles and deliberative decision making provide the flexibility to take into account relevant considerations. So, the committee considered the company's quantitative assessments of health inequalities from the DCEA, without aversion weights. It noted that the evidence showed the potential scale of effect for the eligible population and the potential impact of new technologies on health inequalities. The EAG shared concerns around the inputs and methodology of the company's DCEA, including how ethnicity is accounted for and the use of IMD data. But the committee did not discuss these concerns in detail. The EAG also thought that exa-cel had the potential to increase health inequalities because of the technology's cost, and resulting opportunity cost. The committee considered this along with the company's evidence

and testimony from stakeholders and experts (see section 3.12). The committee gave careful consideration to:

- its obligations under the Health and Social Care Act 2012.
- the options available to it in the NICE process and methods guide and NICE's principles to account for health inequalities.

It recalled section 6.2.36 of the NICE process and methods guide. This states that additional considerations can be made by the committee, especially when they are broader social considerations. It noted one such consideration is NICE's social value judgement principle 9, which aims to reduce health inequalities. This states that NICE must give due regard to reducing inequalities and aim to produce guidance that aims to reduce and not increase identified health inequalities. The committee concluded that the eligible population for exa-cel experience health inequalities and that exa-cel likely reduces or mitigates them. So, it considered what reasonable adjustments it could make to avoid disadvantaging a relevant population. The clinical and patient experts also explained that social and structural barriers may prevent people engaging in research, so affecting the generation of high-quality evidence. This had likely also been compounded by a relative lack of funding for research in transfusion-dependent beta-thalassaemia. So, the committee was willing to accept a higher degree of uncertainty in the clinical-effectiveness evidence for exa-cel. It also concluded that an appropriate reasonable adjustment to account for health inequalities was to adjust its acceptable ICER (see section 3.17). But the committee was aware of the opportunity cost of doing so. This would mean displacing resources in the NHS for care for other people. So, it concluded that adjustments to the acceptable ICER would need to be carefully considered.

Other factors

Innovation

3.14 The company, and patient and clinical experts explained that exa-cel is an innovative treatment. This is because it provides a potential cure for people who currently have limited effective treatments options. They added that exa-cel is a one-time infusion treatment that uses cutting-edge gene therapy. It has advantages compared with regular transfusions, which need frequent hospital appointments and burdensome iron chelation therapy. The company also thought that exa-cel will substantially reduce the need for contact with the healthcare system, which is a significant barrier to care. The committee concluded that exa-cel is an innovative treatment and it explored how benefits were captured in its preferred model structure (see section 3.6). It did recognise that the innovative and complex nature of exa-cel affected the ability to generate high-quality evidence. This could be because of small sample sizes in clinical trials and restrictions on trial design because of the inability to randomise participants. It also noted the views of the patient experts that people can be reluctant to engage in research for innovative and complex treatments. The committee also recalled the health inequalities experienced by the eligible population (see section 3.12) and thought that this may affect evidence generation. So, the committee was willing to accept a higher degree of uncertainty in the clinical-effectiveness evidence for exa-cel.

Equalities

3.15 The committee recognised that equalities issues had been raised during the evaluation. Several issues were identified by stakeholders:

- a high prevalence of beta-thalassaemia in people from ethnic minority groups, including from Mediterranean countries like Greece and Turkey, South Asia, Southeast Asia, the Middle East and Africa
- decreased life expectancy and health-related quality of life in people of Asian and South-East Asian origin with the condition compared with people of other ethnic origins

- difficulty accessing donor blood for people from ethnic minority groups because of a shortage of matched blood stocks and the lack of available treatments that reduce the need for blood transfusions
- that people with beta-thalassaemia could be considered disabled under the Equality Act 2010
- that treatment with exa-cel may need treatment with busulfan (or other drugs), which may affect fertility.

The committee was aware that most of the equalities issues raised were closely related to the health-inequalities issues it had previously considered (see section 3.13). It thought that the equalities issues had been fully captured in the evidence, economic modelling and committee considerations. For each issue, the following considerations were made:

- The committee understood concerns with the high prevalence of beta-thalassaemia for people from specific ethnic minority groups, but it noted that this is not an equalities issue that is within the remit of the committee.
- The committee thought that decreased life expectancy for people from specific ethnic origins was partially addressed in the model, but it took this into account deliberatively.
- The committee considered the limited availability of donor blood for people from specific ethnic minority backgrounds as an equalities issue that the availability of exa-cel could address, so it took this into account in its decision making.
- The committee understood that some people with beta-thalassaemia can be considered as disabled under the Equality Act 2010, and it thought that this was captured in cost-effectiveness estimates.
- The committee noted that the summary of product characteristics for exagamglogene autotemcel identifies that infertility has been seen with myeloablative conditioning (such as busulfan), so fertility preservation options should be considered.

The committee noted the reasonable adjustments that it had made in developing its recommendations. For example, it recognised the potential barriers to generating high-quality evidence because of health inequalities. It also accepted a higher degree of uncertainty in the clinical evidence (see section 3.13 and section 3.14). The committee also increased the acceptable ICER with which exa-cel would be considered cost effective (see section 3.17). The committee considered the equality issues, noting that its recommendations apply to everyone covered by the marketing authorisation indication for exa-cel for beta-thalassaemia. It concluded that its recommendations do not have a different impact on people protected by equalities legislation than on the wider population.

Cost-effectiveness estimates

Committee's preferred assumptions

3.16 The committee concluded that its preferred assumptions for the cost-effectiveness modelling of exa-cel compared with standard care were:

- the company's preferred model structure (see section 3.6)
- the company's preferred standardised mortality rate for the transfusion-dependent health state (see section 3.6)
- 0% relapse rate for exa-cel transfusion independence (see section 3.7)
- a 3.5% discount rate (see section 3.8)
- utility values from the company's base case and Matza et al. (2020; see section 3.10)
- the definition of transfusion independence used in the trial (see section 3.9)
- inclusion of the effect of exa-cel treatment withdrawals (see section 3.9)
- 16.4 RBC transfusions per year for the standard-care arm (see section 3.9)
- that the severity modifier is not met (see section 3.11).

The committee noted significant uncertainties with most of its preferred assumptions. It considered these uncertainties when determining its acceptable ICER (see section 3.17).

Acceptable ICER

3.17 The NICE process and methods guide notes that, above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. But it will also take into account other aspects including difficulties with evidence generation for innovative and complex technologies and health inequalities. The committee considered the options available to it to account for these additional factors. It recalled its conclusion about the innovative and complex nature of exa-cel meaning that it was willing to accept a higher degree of uncertainty in the evidence (see section 3.14). It also recalled its conclusion on health inequalities and the reasonable adjustments to its acceptable ICER (see section 3.13). So, the committee concluded that it was willing to take health inequality into account in its decision making by accepting a higher cost-effectiveness estimate than it otherwise would have done.

Committee's preferred cost-effectiveness estimate

3.18 The ICER reflecting the committee's preferences (see section 3.16) was above the range considered cost effective. So, the committee concluded that exa-cel could not be recommended for routine commissioning. The exact ICER included a confidential price for exa-cel and cannot be reported here. The committee thought that some differing assumptions were plausible. It considered an optimistic scenario that included a 1.5% discount rate (see section 3.8). It also considered a pessimistic scenario that included:

- the cost for people who withdrew from exa-cel pre infusion

- the EAG's preferred utility values (EQ-5D data)
- a 10% relapse rate for transfusion independence in people who have had exa-cel
- an assumption of 13.7 RBC transfusions per year for standard care based on Shah et al. (2021).

The ICER for the pessimistic scenario was above the committee's preferred cost-effectiveness range. The ICER for the optimistic scenario was below the committee's preferred cost-effectiveness range. The committee considered that further data collection might help identify different appropriate assumptions. So, it agreed that exa-cel demonstrated plausible cost effectiveness.

Managed access

Consideration of managed access suitability

3.19 Having concluded that exa-cel could not be recommended for routine use, the committee considered whether it could be recommended with managed access for treating transfusion-dependent beta-thalassaemia. It identified the key uncertainties for which additional data collection would be useful:

- the durability of the treatment effect of exa-cel (relapse rate)
- whether people return to full health after exa-cel or whether complications persist
- utility values for exa-cel and standard care for the transfusion-dependent and transfusion-reduced health states
- the rates of complications for exa-cel and standard care
- the number of RBC transfusions per year for standard care
- the number of exa-cel treatment withdrawals before the transfusion is given
- mortality and life expectancy for exa-cel and standard care.

The committee compared this with the data the company intended to collect according to its current managed access proposal:

- additional data for CLIMB-THAL-111 from the CLIMB-131 follow-up study
- additional exa-cel safety and clinical-effectiveness data from the European Society for Blood and Marrow Transplantation Registry.

The company provided an updated managed access proposal after the first committee meeting. The committee agreed that some of the uncertainties were likely to be resolved with managed access, such as

- the rates of complications or adverse events for people having exa-cel
- the number of people who withdraw pre infusion.

The committee also considered that the trial data would provide additional follow up on people who have had exa-cel. It agreed that this would reduce uncertainty about the durability of the treatment effect, particularly because people would be followed up for longer than 2 years. It also thought that it would reduce uncertainty about whether people return to full health, and provide additional EQ-5D data. The committee acknowledged that it may be difficult to collect data on all of its uncertainties, especially those relating to the standard-care arm. It also noted the limitation of the managed access timeframe, and that some uncertainties, such as life expectancy, were unlikely to be resolved. The committee also discussed the plausible potential for exa-cel to be cost effective. The committee considered its preferred assumptions (see section 3.16), along with an optimistic and a pessimistic scenarios (see section 3.18). It considered the range of ICERs, and agreed that the optimistic scenario was plausible and within the range considered an acceptable use of NHS resource (see section 3.17).

Conclusion

Recommendation

The committee recalled the uncertainties it identified with the company's cost-effectiveness evidence. It thought that a model was needed that more accurately models the interaction between iron overload, complications and mortality. It also thought that more evidence to generate more robust cost-effectiveness estimates was needed. It recalled that both the EAG's and company's base cases were associated with high uncertainty. But it decided to assess cost-effectiveness estimates with this uncertainty and with reasonable adjustments to its acceptable ICER because of the innovative and complex nature of exa-cel and to account for health inequalities. The committee concluded that exa-cel met the criteria to be considered for a recommendation with managed access. It recommended exa-cel for use with managed access, if the conditions in the managed access agreement are followed. It recommended it as an option for transfusion-dependent beta-thalassaemia in people 12 years and over, when an HSCT is suitable but there is no human leukocyte antigen-matched related haematopoietic stem cell donor. When the guidance is next reviewed, the company should use the committee's preferred assumptions (unless new evidence indicates otherwise), as set out in section 3.16. Also, it should provide a model that more accurately models the interaction between iron overload, complications and mortality (see section 3.6).

4 Implementation

4.1 When NICE recommends a treatment as an option for use with managed access, NHS England will make it available according to the conditions in the managed access agreement. This means that, if a patient has transfusion-dependent beta-thalassaemia and a haematopoietic stem cell transplant is suitable but a human leukocyte antigen-matched related haematopoietic stem cell donor is not available, and the healthcare professional responsible for their care thinks that exa-cel is the right treatment, it should be available for use, in line with NICE's recommendations and the criteria in the managed access agreement.

Further information can be found in the Innovative Medicines Fund principles.

4.2 Funding for this treatment will be available through the Innovative Medicines Fund when positive final draft guidance is released.

4.3 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance when the drug or treatment, or other technology, is approved for use with managed access. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, for use with managed access, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final draft guidance or agreement of a managed access agreement by the NHS in Wales, whichever is the later.

5 Evaluation committee members and NICE project team

Evaluation committee members

This topic was evaluated as a single technology evaluation by the highly specialised technologies evaluation committee. Because of this, some members of the technology evaluation committees were brought in to provide additional expertise to the committee. The highly specialised technologies evaluation committee and the 4 technology evaluation committees are standing advisory committees of NICE.

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

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

Chair

Dr Paul Arundel

Chair, highly specialised technologies evaluation committee

NICE project team

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

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