SMC2709

exagamglogene autotemcel dispersion for infusion (Casgevy®)

Vertex Pharmaceuticals (Europe) Ltd

04 April 2025

The Scottish Medicines Consortium (SMC) has completed its initial assessment of the evidence for the above product using the ultra-orphan framework:

Indication under review: for the treatment of transfusion-dependent beta-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.

Key points:

- Transfusion-dependent beta-thalassaemia (TDT) is a chronic and severely disabling condition which has a significant impact on quality of life. Patients require lifelong regular blood transfusions which place a substantial burden on patients and carers. Chronic blood transfusions can lead to serious complications due to iron overload, including multiorgan damage, which may be life-threatening if untreated.
- In a single-arm, open-label study, the majority of patients with TDT who received exagamglogene autotemcel (exa-cel) were transfusion independent for ≥12 months (93% at interim analysis). This effect was sustained through the 24-month follow-up period. There were three patients who did not achieve this outcome, all of whom subsequently stopped red blood cell (RBC) transfusions.
- The clinical evidence was limited by small patient numbers, uncontrolled data and a limited follow-up period. Although the available results are promising, uncertainty remains about the long-term efficacy and safety of exa-cel. Final study results and further results from a long-term study are awaited.
- Small quality of life benefits were observed with exa-cel, as measured by EQ-5D-5L, but the clinical relevance of generic assessments are uncertain. Clinically relevant improvements in other patient reported outcomes (FACT-BMT and PedsQL) were observed.
- A model-based health economic evaluation indicates that exa-cel is associated with a quality-adjusted life-year gain compared with standard of care using a 3.5% discount rate. However, the following issues increased uncertainty in the results: the modelling of iron levels; utility values; mortality risks; complication risks; baseline RBC transfusion count; the TDT patient weight ratio; and long-term transfusion independence. The treatment's cost in relation to its health benefits is high.

Chair
Scottish Medicines Consortium

1. Clinical context

1.1. Background

Exagamglogene autotemcel (hereafter referred to as exa-cel) is a patient-specific, cell-based therapy consisting of haematopoietic stem and progenitor cells that have been collected from the patient and edited ex vivo using CRISPR/Cas9 gene editing technology. Following the standard for autologous haematopoietic stem cell transplantation (mobilisation, apheresis and myeloablation), these cells are infused back into the patient resulting in increased foetal haemoglobin production. In patients with beta-thalassaemia, foetal haemoglobin can compensate for the lack of normal adult haemoglobin and increase red blood cell (RBC) levels.

It is an advanced therapeutic medicinal product (ATMP).

The minimum recommended dose of exa-cel is 3 x 10^6 $CD34^+$ cells/kg administered as a one-time, single dose intravenous infusion. See the Summary of Product Characteristics (SPC) for details.[1-3]

1.2. Nature of condition

Beta-thalassaemias are a group of inherited autosomal recessive disorders caused by genetic mutations that reduce or eliminate the expression of beta-globin, which results in a reduced or lack of production of adult haemoglobin in RBC. Beta-thalassaemia is caused by a spectrum of mutations which are commonly assigned a severity index depending on the degree of incomplete (β+) or absent (β0) beta-globin expression. The condition mainly affects people of Mediterranean, South Asian, Southeast Asian and Middle Eastern ethnic origin.

There are three main types of beta-thalassaemia: thalassaemia major (homozygous or compound heterozygous for β+ or β0 genes) which presents early in life with severe anaemia and symptoms and requires regular transfusions; thalassaemia intermedia (mostly homozygous or compound heterozygous) which presents later in life with less severe anaemia and symptoms however some patients will require regular transfusions; and thalassaemia minor (mostly heterozygous) which is usually mild or asymptomatic. These types can be further classified into transfusion-dependent or non-transfusion-dependent beta-thalassaemia, depending on clinical severity and blood transfusion requirements.

Transfusion-dependent beta-thalassaemia (TDT) is the most severe form and is characterised by severe anaemia, requiring lifelong RBC transfusions. Transfusions are usually given every 2 to 5 weeks to maintain pretransfusion haemoglobin levels at 9.5 to 10.5 g/dL. Regular transfusions are effective in managing symptoms of TDT but they result in iron overload which can lead to serious complications that may be fatal if untreated, including effects on cardiac, liver, skeletal and endocrine systems. Iron chelation therapies (desferrioxamine, deferiprone and deferasirox) are usually required to remove excess iron in the blood. These therapies carry a number of potential adverse effects, including growth and bone disorders, neutropenia including agranulocytosis, gastrointestinal disturbances and renal and liver dysfunction, and

there are issues with adherence. Currently, allogeneic haematopoietic stem cell transplant (allo-HSCT) is the only potentially curative treatment available. However, access to transplants is limited due to inherent risks of the procedure (including graft-versus-host disease and graft failure), lack of suitable donors (ideally a matched sibling which may only be available to <25% of patients) and other restrictive eligibility criteria, including young age. With currently available treatment, it is estimated that only 55% of patients survive to the age of 30 years.[2-9]

TDT is a chronic and severely disabling condition and has significant impact on patients' and carers' quality of life. The requirements for lifelong transfusions, iron chelation therapy and monitoring as well as symptoms of the disease itself, including chronic pain and fatigue, have significant impacts on patients' daily functioning. Patients may be affected in terms of their ability to work, participate in education and plan social and leisure activities. There are also impacts on relationships and emotional wellbeing.

Clinical experts consulted by SMC considered that exa-cel fills an unmet need offering a one-off treatment, avoiding the need for life-long transfusions.

2. Impact of new technology

Comparative efficacy

There are no direct comparative efficacy data and key clinical evidence for exa-cel in TDT comes from the single-arm CLIMB THAL-111 study, details of which are presented in Table 2.1.

Table 2.1 Overview of relevant study[2, 3, 10]

Criteria	CLIMB THAL-111
Study design	Multicentre, ongoing, open-label, single-arm, phase I/II/III study.

Eligible patients	• 12 to 35 years of age.
	• Diagnosis of TDT as defined by:
	  ○ Documented homozygous or compound heterozygous beta-thalassaemia including beta-thalassaemia / haemoglobin E (HbE).
	  ○ History of at least 100 mL/kg/year or 10 units/year of packed RBC transfusions in the 2 previous years.
	• Eligible for autologous stem cell transplant as per investigator's judgement but with no available 10/10 HLA-matched related donor.
	• Karnofsky performance status (for patients ≥16 years of age) or Lansky performance status (for patients <16 years of age) of ≥80%.

Treatments	Single minimum dose of exa-cel of at least 3.0 x 10^6 $CD34^+$ cells/kg of body weight via intravenous infusion following standard for autologous haematopoietic stem cell transplantation (mobilisation, apheresis and myeloablation).
Primary outcome	The proportion of patients achieving transfusion independence (TI12), defined as maintaining weighted average Hb ≥9 g/dL without RBC transfusions for ≥12 consecutive months any time after exa-cel infusion.

	The evaluation of TI12 started 60 days after last RBC transfusion for post-transplant support or TDT disease management.
Secondary outcomes	• Proportion of patients achieving transfusion independence (defined as maintaining Hb ≥9 g/dL without RBC transfusions) for ≥6 consecutive months (TI6) (key secondary outcome). • Duration transfusion-free (for patients who achieved TI12). • Relative reduction from baseline in annualised volume of RBC transfusions (for patients who did not achieve TI12). • Absolute and relative monthly reduction from baseline in RBC transfusion volume, units and episodes.
Statistical analysis	Efficacy analyses were performed in the PES, which included all patients who received an exa-cel infusion and were followed up for ≥16 months and for ≥14 months after completion of the RBC transfusions for post-transplant support or TDT disease management. This is a subset of the FAS (defined as all patients who received exa-cel infusion). The familywise type I error rate was controlled using an alpha spending approach for tests at the interim and final analysis and sequential testing of the primary and key secondary outcome.

Abbreviations: FAS = full analysis set; Hb = haemoglobin; HLA = human leukocyte antigen; PES = primary efficacy set; RBC = red blood cell; TI6 = transfusion independence for ≥6 months; TI12 = transfusion independence for ≥12 months; TDT = transfusion-dependent beta-thalassaemia.

Prespecified interim analyses were performed at data cutoffs September 2022 and January 2023. An additional updated interim analysis (data cutoff April 2023), that was not prespecified, was performed for regulatory purposes and are the key results presented in the company submission. However, as this analysis was not prespecified, results are considered descriptive only. At this analysis, 54 patients had received exa-cel and 42 patients had sufficient follow-up to be included in the primary efficacy set (PES). Of these 42 patients, 39 (93%) achieved transfusion independence for ≥12 months. See Table 2.2 for further details.[2, 3, 10, 11]

Table 2.2. Summary of selected efficacy results from CLIMB THAL-111 (PES) at data cut-off April 2023[2, 3, 11]

	Exa-cel (n=42)
Median follow-up, months	22.8
Primary outcome:	
Proportion of patients achieving transfusion independence[a] for ≥12 consecutive months (TI12), n (%)	39 (93%)
Secondary outcomes:	
Proportion of patients achieving transfusion independence[a] for ≥6 consecutive months (TI6), n (%)	39 (93%)

Mean duration transfusion-free[b] , months	(n=39) 23.6
Mean relative reduction from baseline in annualised volume of RBC transfusions[c] , %	(n=3) 88%
Mean relative monthly reduction from baseline in RBC transfusion episodes at 12 months[b], %	(n=39) 98%

[a] transfusion independence defined as maintaining Hb ≥9 g/dL without RBC transfusions; [b] In patients who achieved TI12; [c] In patients who did not achieve TI12.
Abbreviations: Hb = haemoglobin; NA = not available; PES = primary efficacy set; RBC = red blood cell.

Following exa-cel administration, there were sustained increases in total and foetal haemoglobin from 3 months. Mean total haemoglobin increased to 11.4 g/dL at month 3 and was maintained above 12 g/dl from 6 months to the April 2023 cutoff. Foetal haemoglobin increased to 7.7 g/dL at 3 months and was maintained above 10 g/dL.[10]

Patient reported outcomes included EQ-5D-5L (for patients ≥18 years old), EQ-5D-Y (for patients <18 years old), Functional Assessment of Cancer Therapy-Bone Marrow Transplant (FACT-BMT) (for patients ≥18 years old) and Paediatric Quality of Life Inventory (PedsQL) (for patients <18 years old). These questionnaires were used at screening and then every month from months 3 to 24 or end of follow-up. Overall, the results suggested there were small improvements in patient reported outcomes, as measured by EQ-5D-5L, and clinically relevant improvements in FACT-BMT and PedsQL.[10, 12]

Patients who completed the 24 months' follow-up or discontinued the CLIMB THAL-111 study were invited to enrol in an ongoing long-term, follow-up, phase III study (CLIMB-131). The study was designed to evaluate the long-term efficacy and safety of exa-cel for a total of up to 15 years after administration of exa-cel in CLIMB THAL-111 and CLIMB SCD-121 (a study in patients with sickle cell disease). At the unplanned interim analysis (data cutoff April 2023), 23 patients from CLIMB THAL-111 had enrolled in CLIMB-131 and longest follow-up was around 48 months. Overall, the limited results suggest that once achieved, transfusion independence was generally maintained.[2, 3, 13]

Limited further details are available from later data cutoffs. Data from March 2024, after enrolment and dosing in CLIMB THAL-111 was complete (n=56) and 43 patients had completed the 2-year follow-up in CLIMB THAL-111 and had enrolled in the longer term CLIMB-131 study (median overall follow-up of 33.3 months), found that 94% (49/52) of evaluable patients achieved the primary and key secondary outcomes (TI12 and TI6); the mean transfusion-free duration was 31.0 months. Further data after a median follow-up of 38.1 months found that 98% (53/54) of evaluable patients achieved TI12 and the mean transfusion-free duration was 34.5 months.[11, 14]

Indirect evidence

In the absence of direct evidence versus the relevant comparator, the submitting company performed an unanchored matching adjusted indirect comparison (MAIC) to compare exa-cel with standard of care (SoC) comprising RBC transfusions and iron chelation therapy. The MAIC

compared the efficacy of exa-cel, using data from the CLIMB THAL-111 study, with SoC, using data from the BELIEVE study (comparison SoC plus either erythroid maturation agent or placebo), for the treatment of TDT. The outcome assessed was the proportion of patients achieving transfusion independence for ≥6 months (for exa-cel) or any 3 months (for SoC).[3, 15] The results were not directly used in the economic analysis but informed the assumption that patients receiving SoC retain their baseline transfusion status, frequency and volume and iron distribution.

Comparative safety

CLIMB THAL-111 is a single-arm study and no comparative safety data are available. Refer to the SPC for details.

At the interim analysis (data cutoff April 2023), 54 patients had received exa-cel at a median dose of 8.0 x 10^6 $CD34^+$ cells/kg; median follow-up was 22.8 months (range 2.1 to 51.1). All patients reported a treatment-emergent adverse event (AE), and most of these (98%) were considered related or possibly related to busulfan conditioning and 26% of patients reported an AE related or possibly related to exa-cel. Patients reporting a grade 3 or above AE was 89% and patients reporting a serious AE was 35%: 3.7% of serious AEs were considered related or possibly related to exa-cel and 17% to busulfan. The most commonly reported AEs of any grade were febrile neutropenia (61%), headache (56%), stomatitis (52%), thrombocytopenia (46%), anaemia (44%), mucosal inflammation (43%), nausea (43%) and vomiting (41%).

A serious AE considered related or possibly related to exa-cel was reported in two patients: one patient with haemophagocytic lymphohistocytosis, acute respiratory distress syndrome, idiopathic pneumonia syndrome and headache and one patient with delayed engraftment and thrombocytopenia.[1]

No cases of graft failure, graft-versus-host disease or graft rejection were reported.

Overall, exa-cel was generally safe and well tolerated, and the safety profile was generally consistent with that expected from busulfan conditioning and HSCT, with no additional exa-cel specific concerns identified. The SPC notes that neutrophil engraftment failure may occur after HSCT. Regulators also noted that some potential long-term safety risks, including off-target gene editing and clinical consequences, are unknown and will be followed up in the postmarketing setting.[1-3]

Clinical effectiveness issues

The key strengths and uncertainties of the clinical case are summarised below.

Key strengths:

- In the CLIMB THAL-111 study, the majority of patients with TDT (93% at the interim analysis and 98% at the latest data cut of patients continuing in CLIMB-131) who received exa-cel were transfusion independent for ≥12 months. This effect was sustained through the 24-month follow-up period. There were three patients who did not achieve this outcome, all of whom have since stopped RBC transfusions; at the

latest data cut, these patients had been transfusion-free for 21.6, 14.3 and 3.4 months respectively. These results are promising and clinically relevant.[2, 3, 11]

- The introduction of exa-cel could offer a potentially curative treatment for patients with TDT who have limited treatment options. Patients with TDT are anaemic and require lifelong blood transfusions and iron chelation therapy to manage their symptoms, which places a substantial treatment burden on patients and their carers.
- Clinical experts consulted by SMC considered that exa-cel is a therapeutic advancement, offering transfusion independence and avoiding the need for iron chelation therapy.
- Overall, exa-cel was generally well tolerated. Most AEs were considered related to busulfan conditioning and HSCT, and no exa-cel specific concerns were identified.[2, 3]

Key uncertainties:

- The CLIMB THAL-111 and CLIMB-131 studies are ongoing and the overall duration of follow-up is limited to a median of 38.1 months at the latest data cut-off. Therefore, there is uncertainty about the durability of the treatment effect of a one-off exa-cel infusion. Data from CLIMB THAL-111 and the ongoing long-term follow-up study, CLIMB-131, suggest that transfusion independence is generally maintained but further results are awaited. The impact of transfusion independence on the onset of TDT associated complications and mortality is also uncertain. In addition, regulators noted that long-term safety risks, including gene editing-related oncogenesis, are still unknown.
- There were several methodological limitations with CLIMB THAL-111. The study was single-arm and open-label which may introduce bias. The study included small patient numbers, although this would be expected in such a rare condition. Furthermore, there were several protocol amendments as the study evolved from a phase I/II study, including changes to the primary outcome, timing of efficacy assessment and eligibility criteria. There were also limitations with the statistical methodology as the first interim analysis was not conducted, suggesting that analyses may have been data driven, and it is unclear whether type I error was appropriately controlled at subsequent analyses. All these limitations increase uncertainty in the results.[2]
- Exa-cel was granted a conditional marketing authorisation by the MHRA. The specific obligations, to provide further efficacy and safety data from the final clinical study report from CLIMB THAL-111 and an interim clinical study report from CLIMB-131 by August 2026, may address some of the key uncertainties in the clinical evidence presented. However available data will remain uncontrolled.[2, 3]
- Quality of life benefit of exa-cel is uncertain. The submitting company claimed that baseline EQ-5D-5L levels in CLIMB THAL-111 were similar to the UK general population despite the high morbidity associated with TDT, which they suggest reflects patients' adaptation to their condition. Therefore, they considered that this generic measure does not fully capture the impact of TDT and is not responsive to changes in this

population. Nevertheless, the results from the unplanned interim analysis (data cutoff April 2023) suggest there were small improvements in quality of life, as measured by EQ-5D-5L, and clinically relevant improvements in FACT-BMT and PedsQL.[16]

- Patients >35 years old were excluded from CLIMB THAL-111. Therefore, efficacy and safety in these patients in clinical practice is uncertain. CLIMB THAL-111 also excluded patients with severely elevated iron in the heart or advanced liver disease and with a Karnofsky/Lansky status of <80% as patients are required to be suitable for myeloablative conditioning and HSCT. In addition, approximately 30% of study patients had a splenectomy at baseline and approximately 40% of patients were of Asian origin, which may affect the generalisability to the Scottish population.[1, 2]
- There were no direct comparative data versus SoC, consisting of regular blood transfusions and iron chelation therapy. Although the MAIC results were not used in the economic analysis, the submitting company considered that they supported the assumption that patients receiving SoC maintain their baseline status. The MAIC indicated that no SoC patients were transfusion independent for 12 weeks. However, in the BELIEVE study, two patients were transfusion independent for 8 weeks, raising concern that the MAIC inadequately captured the transfusional status of SoC patients. There were also differences between the studies that could not be matched in terms of baseline characteristics and outcomes assessed. Despite the uncertainties in the MAIC, clinical experts consulted by SMC considered that the assumption that patients on SoC maintain their baseline status was reasonable.

3. Impact beyond direct health benefits and on specialist services

Exa-cel could offer a one-time potentially curative treatment, which is advantageous for patients and carers. Current treatment consists of lifelong blood transfusions to manage the effects of severe anaemia, as well as iron chelation and monitoring to prevent transfusion related iron overload. This places a substantial burden on the service, patients and carers. The symptoms and treatments for TDT have an impact on all areas of life, including work, travel, leisure and social activities, relationships and emotional wellbeing. Exa-cel may allow patients to achieve transfusion independence, thereby removing the need for regular blood transfusions, iron chelation and the associated impacts on day-to-day life. Patients may be able to participate in daily activities, including work and education, without disruption due to fluctuating cycles of fatigue associated with transfusion schedules, time planning around medical appointments and transfusion side effects. There may also be positive impacts on family and carers, as they would no longer have to provide transport to transfusion and pretransfusion appointments, and may potentially address feelings of depression, anxiety and worry due to complications associated with chronic transfusions. Exa-cel is manufactured from the patients' own stem cells, thereby removing the need for suitable donors and reducing the risks associated with allo-HSCT.

There will be significant service implications associated with administering exa-cel. There may be increased monitoring requirements following exa-cel infusion, and additional staff and training may be required to administer exa-cel. The capacity for specialist services to deliver treatment may be limited depending on availability of specialist centres.

The extremely high upfront acquisition cost for this single-dose treatment is likely to have significant service implications and is associated with financial risk to the service if the long-term predicted clinical benefits do not materialise.

4. Patient and carer involvement

The following information reflects the views of the specified Patient Group.

- We received a patient group submission from the UK Thalassaemia Society, which is a charitable incorporated organisation.

- UK Thalassaemia Society has not received any pharmaceutical company funding in the past two years.

- Living with thalassaemia can present major challenges for patients and carers. Treatment and management of the condition has a significant lifelong impact on everyday life for both the patients and their care givers due to the high clinical burden, societal stigma and disruption of life activities.

- Regular transfusion is the mainstay of treatment for patients with TDT; however, it brings with it iron overload, increased and often irreversible end-organ toxicity, and adverse effects of iron chelators. While there are generally high rates of success when a human leukocyte antigen (HLA)-identical sibling donor is available, the outcomes of hematopoietic stem cell transplantation (HSCT) are usually not as successful with less well-matched allogeneic donors.

- A substantial unmet clinical need exists for curative treatments for patients with TDT. Exa-cel is seen as a significant step forward in disease modifying treatment options to improve patient outcomes which haven't changed in the last decades. It may provide a curative option for patients who are suitable for HSCT but do not have an HLA-matched donor.

- Patients who received exa-cel as part of a clinical trial reported benefits to their quality of life.

5. Value for money

5.1. Economic case

The submitting company presented an economic analysis, summarised in Table 5.1.

Table 5.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility analysis.
Time horizon	A lifetime time horizon of 79 years was used in the model, with a starting age of 21 years.
Population	The patient population included in the economic evaluation was defined as patients with TDT, who are 12 years of age and older and are eligible for an autologous stem cell transplantation (SCT) and without an HLA-matched donor.
Comparators	The comparator was standard of care (SoC), assumed to comprise lifelong red blood cell (RBC) transfusions and iron chelation therapy (ICT).
Model description	A Markov model was used. The Markov model had four mutually exclusive health states: transfusion independent (TI), transfusion reduction (TR), transfusion dependent (TD), and death. The three transfusion health states contained four mutually exclusive iron level statuses: normal and the non-normal levels of high, medium and low. Three measures of iron levels were included in the model: serum ferritin (SF), myocardial T2*, and liver iron (LIC). Non-mutually exclusive chronic cardiac, liver, hypogonadism, diabetes, and osteoporosis complications were included in the model.
Clinical data	CLIMB THAL-111 was the main source of clinical efficacy evidence for exa-cel (D120 data cut, April 2023, with a median of 22.8 months of follow-up). For exa-cel, key clinical inputs were the response (after treatment phase) parameters. The proportion with TI (92.9%) was from the proportion of PES patients who were TI12 (transfusion independence for at least 12 consecutive months) at the time of the D120 cut-off. The remaining were the proportion with TR (7.1%), based on having stopped RBC transfusions and been transfusion-free 60 days after last RBC transfusion. In addition, the percentage of RBC transfusion reduction for TR patients was from the CLIMB THAL-111 Trial PES. Baseline clinical inputs of patient demographics, complications, and RBC transfusions (annual of 16.5 per patient) were drawn from the CLIMB THAL-111 study (FAS population), with iron levels and the ICT distribution informed by a chart review study of nine UK NHS centres by Shah et al. 2021.[17] The submitting company noted that Shah was used in preference to the CLIMB THAL-111 baseline values because the study excluded patients with high T2* and LIC at baseline, whereas patients could have potentially developed high T2* and LIC over the course of their lifetime had they remained on SoC. Mortality risks were from a selection of literature sources suggesting TDT patients remain at increased risk of early death. These were applied as standardised mortality ratios (SMRs) in each transfusion health state. Complication risks for cardiac complications, liver complications, osteoporosis, diabetes, and hypogonadism were from a selection of literature sources.
Extrapolation	SoC patients entered the model in the TD health state and remained in this state for the model time horizon. Hence, SoC patients experienced no reduction in baseline

	RBC transfusions or the amount of ICT, with no changes to baseline non-normal iron levels. Exa-cel patients progressed through a series of tunnel states to reflect the treatment, iron normalisation and ongoing phases. In the 12-month treatment phase, exa-cel patients entered the model in the TD health state, with baseline non-normal iron levels, RBC transfusions and amounts of ICT. In the 60-month iron normalisation phase, exa-cel patients either remained TD (0%) or transitioned to the TR (7.1%) or TI (92.9%) health states. Patients that remained TD had the same number of RBC transfusions, patients that achieved TR had a reduction in RBC transfusions and patients that achieved TI had no further RBC transfusions. In this phase, iron levels changed according to transfusion status, with patients in the TD health state retaining baseline non-normal iron levels, patients in the TR health state experiencing a one-level reduction in non-normal iron levels, and patients in the TI health state achieving normal iron levels. Throughout this phase the amount of ICT was the same as baseline until iron normalisation. In the ongoing phase, patient transfusion status and iron levels remained the same from the end of the iron normalisation phase until the end of the model horizon. Complications were extrapolated using rates and risk equations to estimate the rate of developing complications based on iron levels and transfusion status. Once a complication occurs, the patient had the complication until death. All patients were at risk of death. In the base model mortality risk was estimated based on transfusion status SMRs of 1.25 for TI, 3.01 for TR, and 4.76 for TD.
Quality of life	The transfusion health state utility values were obtained from a vignette study.[18] These values were 0.93 for TI, 0.75 for TR, and 0.73 for TD. The submitting company opted to use the vignette study utility values over any derived from the EQ-5D-5L data from CLIMB THAL-111 due to primarily to ceiling effects. Transplantation-related, ICT-related, and complication disutilities were included. Health state utilities in the model were adjusted for age and gender.[19] Caregiver disutilities were considered as a scenario and assumed that caregivers of TDT patients less than or equal to 26 years of age experience a utility decrement based on the patient's transfusion status.
Costs and resource use	Costs included treatment acquisition, administration (covering pre-transplant, transplant and post-transplant), RBC transfusions, ICT, and adverse events. Disease monitoring, complications and other condition costs, and terminal costs were also included in the model. A scenario analysis also included societal costs.
PAS	A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a discount was offered on the list price.

5.2. Results

SMC would wish to present the with-PAS cost-effectiveness results. However, SMC is unable to publish these results due to commercial in confidence concerns regarding the PAS.

*Other data were also assessed but remain confidential.**

5.3. Sensitivity analyses

A range of sensitivity and scenario analyses were considered, and descriptions of these key scenarios are provided in Table 5.2. A distributional cost-effectiveness analysis (DCEA) was part of the submission. The DCEA assessed the equity impact of exa-cel across different socioeconomic groups. As part of the analysis, cost-effectiveness results were weighted based on an inequality aversion parameter.

Table 5.2: Scenario analyses

	Parameter	**Base case**	**Scenario**
1	Discount rate (costs and outcomes)	3.5%	1.5%
2	Societal benefits	Excluded	Included
3a	Annual RBC transfusions	16.5	8.0 (Minimum. Transfused every 5 to 6 weeks).
3b			13.62 (Company BoI study)
3c			20.8 (Transfusion every 2 to 3 weeks)
4a	Units of blood per RBC transfusion	2.2	Lower bound 1.4
4b			Upper bound 3.2
5	TI patient complication risks	General population	2 times risk of general population of
6	Caregiver disutility	Excluded	Included
7	Interaction between disutilities of complications	Multiplicative	Maximising
8	Utility values	Base case	0.1 decrement between TI and TD
9a	TD SMR	4.76	Lower bound 2.89
9b			Upper bound 6.63
10a	TI SMR	1.25	Lower bound 1
10b			Upper bound 1.74
11a	Weight ratio of TDT/general public	Central estimate	Lower bound

11b			Upper bound
12	DCEA	Excluded	Included
C1	3a and 4a		Minimum annual RBC transfusion and units of blood per RBC transfusion
C2	3c and 4b		Maximum annual RBC transfusion and units of blood per RBC transfusion

Abbreviations: BoI = Burden of illness; DCEA = distributional cost-effectiveness analysis; RBC = red blood cell; SMR = standardised mortality ratio; TD = transfusion dependent; TDT = Transfusion-dependent β-thalassaemia; TI = transfusion independent.

5.4. Key strengths:

- Deterministic sensitivity analysis parameters were varied through their 95% confidence intervals or 20% variation around the mean, which is appropriate.
- The set of costs included in the economic evaluation are likely appropriate.
- The SoC comparator, comprising lifelong red blood cell (RBC) transfusions and iron chelation therapy (ICT) was appropriate.

5.5. Key uncertainties:

- There was uncertainty in the utility values used. Firstly, the company opted to use utility values from a vignette study, with the EQ-5D-5L derived utilities from CLIMB THAL-111 excluded. The submitting company noted the reasons for excluding the CLIMB THAL-111 utilities included ceiling effects in the observed EQ-5D-5L data and that the EQ-5D-5L could not accurately capture symptoms of functional impact of TDT. However, a scenario using CLIMB THAL-111 health state utilities was unavailable and comparison with those applied from the vignette study was unavailable. The conclusion that the EQ-5D-5L cannot capture symptoms of TDT should also be seen with the caveat that this was not derived from a formal synthesis of peer reviewed literature. Secondly, the decrement of 0.2 between the TI and TD health state utilities was wider than a previous preference in a UK HTA for TDT (NICE ID968) of approximately 0.1 (Scenario 8). Thirdly, the comorbidity disutilities in the model were applied multiplicatively, but there is methodological uncertainty in this area, and an alternative conservative approach was considered (Scenario 7). As utility values were identified as some of the most sensitive parameters in one-way deterministic sensitivity analysis, reducing uncertainties in the utility values would increase confidence in the economic results.
- The number of baseline RBC transfusions may be subject to uncertainty. The base case applied an annual set of transitions of 16.5 based on the CLIMB THAL-111 study, but the UK chart review study by Shah et al. 2021 indicated a lower baseline number of RBC transfusions of 13.7. Given that SoC patients remain at baseline RBC transfusions for

their entire lifespan, variation to the baseline RBC transfusion count can be expected to impact incremental costs and QALYs scenarios were available showing the ICER impact of alternative baseline RBC transfusions (Scenarios 3a, 3b and 3c). Furthermore, as the units of blood per transfusion was identified as sensitive parameter in deterministic sensitivity analysis, scenarios varying this parameter and combining it with alternative RBC transfusion count were considered (Scenarios 4a, 4b, Combined Scenario 1 and Combined Scenario 2).

- There was uncertainty in the economic case it is assumed that once patients progress to transfusion independence in the iron normalisation phase, they remain transfusion independent in the ongoing phase until the end of the model. Further clinical data to support long-term transfusion dependence would alleviate this uncertainty.
- There was uncertainty of the modelled impact of iron levels on mortality, quality of life and healthcare resource use and costs. Whilst iron levels directly affected complications, the impact of iron levels on mortality, quality of life and healthcare resource use and costs were not explicitly modelled as these outcomes were based on transfusion status alone (that is, iron levels were considered implicitly in these factors). In addition, the iron levels in the model remained static over time and could therefore not account for any iron level distribution changes over time if patients with higher non-normal iron levels would experience greater complications and mortality. Therefore, there remains some uncertainty in the explicit modelling of the relationships of iron levels for the given transfusion health states, and the effect of iron levels on modelled outcome factors affecting economic results. A potential improvement could be to consider a patient level simulation. However, this would increase data requirements and modelling complexity.
- The mortality risks in the model were subject to uncertainty. Firstly, these were applied as static SMR values for each transfusion health state, and were intended to reflect all-cause excess TDT mortality, including from complications and iron overload. However, these SMRs may not be reflective of the iron level distributions and complications over the modelled time horizon, and without longitudinal data cannot consider how SMRs could be impacted over time by a changing iron level distribution if high iron patients were to experience higher initial mortality and the distribution changed to lower iron levels over time. Secondly, the transfusion health state based SMRs were not derived from the key efficacy study, but were based on assumptions, with the TD SMR based on an observed mortality rates more than five times that of the matched UK general population. However, the generalisability of this to the modelled cohort of the economic evaluation may be uncertain. Finally, patients who achieve TI are assumed to have an SMR of 1.25 to reflect the potential mortality impact of myeloablative conditioning. However, this SMR may not sufficiently capture the history of complications and the mortality impact for a patient that has transitioned from TD through to TI from receiving exa-cel treatment. Although conservative bounds of the SMRs in sensitivity analysis did not highlight the mortality SMRs as key parameters of

interest, there were residual uncertainties in the parameters creating uncertainty in the economic case (Scenarios 9a, 9b, 10a and 10b).

- In the model the risks of complications among patients who reach a disease-free state from TDT (that is, patients who achieve TI and subsequent iron normalisation) were assumed to be the same as the risk of complications in the general (non-TDT) population. The submitting company justified this based on its clinical expert opinion. However, if the risks of comorbidities for treated independent patients persisted past TI this would reduce the incremental health benefits for exa-cel. A scenario was available applying a two times risk of general population in TI patients (Scenario 5).
- TDT patient weight in the model was derived from a fixed ratio calculated from the mean baseline weight of CLIMB THAL-111 trial patients (55.0 kg) over the matched age at baseline (21.3 years) mean body weight of the standard UK national reference (71.4kg) and was used in the weight-based dosing of ICTs. This was a sensitive parameter and scenario analysis considered the bounds of this parameter (Scenarios 11a and 11b).
- The company submitted a DCEA as part of the submission. This analysis was subject to uncertainties. Firstly, the equity-relevant subgroups were socioeconomic groups that were defined for the England population. The company did provide additional analyses using Scottish socioeconomic groups for the general population proportions only, but all other inputs were defined for England. Secondly, a key parameter affecting the equity-weighted ICER was the Atkinson inequality aversion parameter, which used a base case value of 11. Wider literature has reported lower Atkinson inequality aversion parameters of 1.4 and 3.5, which would increase the equity-weighted ICER towards the standard cost-effectiveness base case ICER. Finally, there is challenge in fully appraising the approach given the application of this new methodology in a UK HTA setting; the analysis was noted but not considered as base case analysis.

6. Costs to NHS and Personal Social Services

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

*Other data were also assessed but remain confidential.**

7. Guidelines and protocols

The Scottish Paediatric and Adult Haemoglobinopathy Network (SPAH) have published a number of guidelines on thalassaemia management, including the use of iron chelation, chronic transfusions, HSCT and management of endocrine complications.[5, 6, 20-22]

The United Kingdom Thalassaemia Society (UKTS) published "Standards for the Clinical Care of Children and Adults with Thalassaemia in the UK, 3rd Edition" in 2016.[4]

8. Additional information

8.1. Product availability date

08 August 2024

Table 8.1 List price of medicine under review

Medicine	Dose Regimen	Cost per treatment (£)
exagamglogene autotemcel	Minimum recommended dose of 3 x 10^6 $CD34^+$ cells/kg, administered as single dose intravenous infusion.	£1,651,000

Costs from the eMC Dictionary of Medicines and Devices Browser on 17 March 2025. Costs calculated using the full cost of vials/ampoules assuming wastage. Costs do not take any patient access schemes into consideration.

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This assessment is based on data submitted by the applicant company up to and including 14 March 2025.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC assessment report.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and

advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When a medicine is available through the ultra-orphan pathway, a set of guidance notes on the operation of the patient access scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC assessment report.

Assessment report context:

No part of the assessment summary on page one may be used without the whole of the summary being quoted in full.

This assessment represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.