Canada's Drug Agency
L'Agence des médicaments du Canada

Reimbursement Review

CDA-AMC Reimbursement Recommendation

(Draft)

Exagamglogene autotemcel (Casgevy)

Indication: For the treatment of patients 12 years of age and older with transfusion-dependent β-thalassemia (TDT)

Sponsor: Vertex Pharmaceuticals (Canada) Incorporated

Recommendation: Reimburse with Conditions

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Single Technology

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Recommendation

The CDA-AMC Canadian Drug Expert Committee (CDEC) recommends that exagamglogene autotemcel be reimbursed for patients 12 years of age and older with transfusion-dependent β-thalassemia (TDT) only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

TDT is a rare, autosomal recessive genetic hemoglobinopathy causing severe anemia and other comorbidities, which is managed using lifelong standard of care (SoC) treatment with red blood cell (RBC) transfusions and iron chelation therapy (ICT). While advances in therapies mean that patients whose SoC is optimized can have longer life expectancy than previously reported, patients with TDT have poorer health-related quality of life (HRQoL) compared with the general population. CDEC emphasized that there is a need for effective therapies that significantly reduce or eliminate the need for transfusions and improve HRQoL for patients with TDT.

One phase I/II/III single-arm, open-label, multisite, single dose study (CLIMB-111, N = 59 patients enrolled and 42 patients analyzed) assessed the efficacy and safety of a single intravenous (IV) infusion of exagamglogene autotemcel following mobilization and myeloablative conditioning in patients 12 to 35 years of age with TDT, who met specific transfusion and performance status criteria and were eligible for autologous hematopoietic stem cell transplant (HSCT). The results of the interim analysis demonstrated that a majority of patients (92.9% [95% confidence interval (CI)]: [80.5% to 98.5%]) had transfusion independence (TI) for 12 consecutive months (TI12) during follow-up. The results from the long-term extension (LTE) study, CLIMB-131, into which patients who had completed CLIMB-111 enrolled, reported that as of the data cutoff date (April 16, 2023), all 39 patients who met the primary endpoint remained transfusion independent for all subsequent follow-up; the mean duration of transfusion independence was 23.6 months (SD = 7.8), range (13.5 months to 48.1 months). Evidence for the impact on HRQoL from the applicable adult or pediatric populations in the trial demonstrated numeric score improvements at 6, 12 and 24 months post-infusion for the Functional Assessment of Cancer Therapy – Bone Marrow Transplant (FACT-BMT), Pediatric Quality of Life Inventory (PedsQL), and EuroQol Visual Analog Scale (EQ VAS) Adult and Non-adult measures. However, the clinical importance of the changes was unclear due to a lack of MIDs in patients with TDT.

Patient input noted that many patients with TDT face challenges in managing the illness including the time commitment for invasive and ongoing RBC transfusions, but with currently available treatments many are able to effectively control symptoms. However, the lifelong requirements and toxicities associated with SoC treatment, particularly ICT, still impact HRQoL. Patients indicated that there is a need for a treatment that would eliminate the need for transfusion, maintain hemoglobin (Hb) at a high enough level to function daily, and improve HRQoL. Despite the limitations inherent to the single-arm trial, CDEC concluded that exagamglogene autotemcel may meet the needs identified by patients, including TI.

Using the sponsor submitted price for exagamglogene autotemcel and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for exagamglogene autotemcel was $194,807 per quality-adjusted life-year (QALY) compared with standard of care. At this ICER, exagamglogene autotemcel is not cost-effective at a willingness to pay (WTP) threshold of $50,000 per QALY gained for patients aged 12 years and older with TDT. A price reduction is required for exagamglogene autotemcel to be considered cost-effective at this threshold.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Patients 12 years of age or older with a diagnosis of transfusion-dependent β-thalassemia, defined as: 1.1. Documented homozygous β-thalassemia or compound heterozygous β-thalassemia including β-thalassemia/hemoglobin E (HbE) 1.2. Received transfusions of packed RBCs of at least 100 mL/kg/year, or 10 units/year, during the previous 2 years	CLIMB-111 enrolled patients aged 12 to 35 who had received a diagnosis of β-thalassemia (including the hemoglobin E genotype) with either homozygous or compound heterozygous mutations; who had received transfusions of packed red cells consisting of at least 100 mL/kg/year (or 10 units/year) during the previous 2 years. Clinical experts consulted by CDEC noted that there should be no upper age limit for the reimbursement of exagamglogene autotemcel. The approved Health Canada indication is for the treatment of patients 12 years of age and older with TDT.	—
2. Karnofsky performance status of ≥ 80% for patients ≥ 16 years of age, or Lansky performance status of ≥80% for patients < 16 years of age	CLIMB-111 enrolled patients who had Karnofsky performance status of ≥ 80% for patients ≥16 years of age, or Lansky performance status of ≥ 80% for patients <16 years of age.	—
3. Patients must be eligible for autologous stem cell transplant as per the treating physician's judgment	CLIMB-111 enrolled patients with TDT who were eligible for autologous stem cell transplant as per the investigator's judgement.	—
4. Patients must not have an available and willing 10/10 HLA-matched related donor	CLIMB-111 excluded patients with an available 10/10 HLA-matched related donor.	—
5. Patients must not have any of the following: 5.1. Associated α-thalassemia and >1 alpha deletion or alpha multiplications 5.2. Prior or current history of malignancy 5.3. Sickle-cell β-thalassemia variant	CLIMB-111 excluded patients with any of these comorbidities.	—
6. Patients must not have previously received any of the following: 6.1. Prior allo-HSCT treatment 6.2. Prior gene editing therapy or editing product	There is no evidence to support the use of exagamglogene autotemcel in patients who have received prior gene editing therapy or editing products.	—
Prescribing		
7. Exagamglogene autotemcel should only be prescribed by a hematologist with expertise in TDT.	This is meant to ensure that exagamglogene autotemcel is prescribed only for appropriate patients and adverse events are managed in an optimized and timely manner.	Exagamglogene autotemcel should be administered in specialized centres with adequate infrastructure, resources, and expertise to facilitate treatment with CRISPR/Cas9 gene

Reimbursement condition	Reason	Implementation guidance
		editing therapy. The exagamglogene autotemcel treatment process requires mobilization and myeloablative conditioning prior to treatment infusion which CDEC noted may require additional support.
8. Treatment with exagamglogene autotemcel is a 1-time therapy	At this time, re-treatment with with exagamglogene autotemcel has not been established as an efficacious strategy and is not considered standard of care.	—
Pricing		
9. A reduction in price	The ICER for exagamglogene autotemcel is $194,807 per QALY gained when compared with standard of care. A price reduction of 55% would be required for exagamglogene autotemcel to achieve an ICER of $50,000 per QALY gained compared to standard of care. The estimated price reduction is associated with high uncertainty because of limitations in the economic model that could not be addressed. Additional price reduction may be necessary to achieve cost-effectiveness if transfusion independence is not sustained indefinitely, and due to infrastructure costs associated with establishing specialized treatment centres.	—
Feasibility of adoption		
10. The economic feasibility of adoption of exagamglogene autotemcel must be addressed	At the submitted price, the incremental budget impact of exagamglogene autotemcel is expected to be greater than $40 million in year 3.	—
11. The organizational feasibility must be addressed so that jurisdictions have the infrastructure in place to implement treatment with exagamglogene autotemcel	CDEC acknowledges that the availability of specialized centres with adequate infrastructure and resources to administer exagamglogene autotemcel therapy in Canada is a barrier that needs to be addressed, and hence additional resources are likely to be required by transplant centres to accommodate patients with TDT.	—

HSCT = hematopoietic stem cell treatment; ICER = incremental cost-effectiveness ratio; TDT = transfusion-dependent β-thalaessmia;

Discussion Points

- **Criteria for significant unmet need are met:** CDEC considered that there were limitations in the comparative evidence and single-arm trial which resulted in a very low certainty of evidence. Given the uncertainty in the clinical evidence, CDEC deliberated on exagamglogene autotemcel considering the criteria for significant unmet need described in section 9.3.1 of the Procedures for CDA-AMC Reimbursement Reviews. While the Grading of Recommendations Assessment, Development and Evaluation (GRADE) assessment of all outcomes assessed were of very low certainty due to the absence of a comparator arm, considering the rarity and severity of TDT and the absence of clinically effective alternatives which meet the unmet need for transfusion independence, CDEC concluded that the available evidence reasonably suggests that exagamglogene autotemcel has the potential to reduce morbidity and/or mortality associated with the disease.
- **Need for new therapies to address unmet needs:** The clinical expert consulted by CDEC indicated that optimized SoC can provide longer life expectancy than previously reported, and luspatercept may reduce the need for transfusion in adult patients. However, SoC does not provide TI. The clinical expert noted that allogenic HSCT with a human leukocyte antigen (HLA)-matched sibling donor is SoC for pediatric patients and a curative treatment, but is only an option in about 20% of patients and not routinely done in adults. The clinical experts also noted that non-matched donors for HSCT are still considered experimental and should only be conducted within the context of a clinical trial. The clinical experts noted that from their perspective, allo-HSCT would likely be considered first for patients who are eligible, and patients for whom allo-HSCT is not an option and/or who are struggling on their current SoC would be primarily considered for exagamglogene autotemcel. In the context of this information, CDEC concluded that there is not likely to be substantial overlap between patients with TDT eligible for allo-HSCT and patients with TDT eligible for exagamglogene autotemcel, except in specific cases.
- **Generalizability:** CDEC discussed the generalizability of the results from the single-arm CLIMB-111 study with regards to the age of patients eligible for treatment. The approved Health Canada indication did not specify an upper age limit, and the clinical expert consulted by CDEC agreed with the lower age limit but emphasized that there should not be an upper age limit, rather that eligibility for treatment should be conducted on a case-by-case basis. CDEC noted that the fact that CLIMB-111 enrolled only patients between the ages of 12 and 35 mean the effectiveness of treatment in patients over the age of 35 is unknown, however agreed that patients over 35 years of age who otherwise would be eligible for treatment should be eligible to receive exagamglogene autotemcel.
- **Comparability of the results:** CDEC discussed the comparability of the results from the single-arm CLIMB-111 study to valid comparators. An indirect comparison analyzed exagamglogene autotemcel compared to luspatercept and SoC; allo-HSCT was not included as a comparator. The indirect evidence comparison was subject to considerable limitations and no concrete conclusions could be drawn about the comparative effectiveness of exagamglogene autotemcel.
- **Price reduction:** CDEC discussed the uncertainty in the economic analysis. The estimated cost-effectiveness is strongly influenced by results from the model that suggest a large quality-adjusted survival benefit for patients treated with exagamglogene autotemcel compared to standard of care. The model results also suggest that the high cost of exagamlogene autotemcel is partially offset by the avoided costs of transfusion over a patient's lifetime. The Committee noted the absence of robust and long-term comparative evidence to support the assumed duration of transfusion independence and the resulting gains in resource utilization, LYs, and QALYs, the sponsor's model may overestimate the incremental benefits and underestimate the incremental costs of exagamglogene autotemcel relative to standard of care. The estimated price reduction is associated with high uncertainty because of limitations in the evidence informing the economic model that could not be addressed; as such, further price reductions may be required.
- **Total costs to the health care system:** CDEC noted that there are considerable anticipated start-up costs associated with establishing specialized treatment centres that can administer exagamglogene autotemcel. These start-up costs are not reflected in either the economic evaluation or the budget impact analysis. The overall economic impact of reimbursing exagamglogene autotemcel will be affected by these costs, and total costs to the health care system will be higher. Additional price reduction which reflect these additional costs may be needed to achieve cost-effectiveness.
- **Budget impact:** CDEC discussed uncertainty in the estimated budget impact of reimbursing exagamglogene autotemcel for patients 12 years and older with TDTs. The estimated budget impact is highly sensitive to the number of patients who receive exagamglogene autotemcel, which will be influenced by the number of treatment centres, bed capacity, and uptake of exagamglogene autotemcel. If more patients receive exagamglogene autotemcel than anticipated by the sponsor, the budget impact of reimbursing exagamglogene autotemcel will be higher than expected.
- **Ethical and equity considerations:** CDEC discussed the impact of TDT on patients, the limitations of existing therapies, and the potential safety impacts of exagamglogene autotemcel treatment (including the impacts of myeloablative

conditioning on fertility). The committee also discussed geographic, socioeconomic, psycho-emotional, and age-related disparities in accessing standard TDT care. The committee also highlighted the importance of robust consent conversations to ensure patients understand the uncertain long-term benefits, known and theoretical risks, and have reasonable expectations of the treatment (e.g., as it may not cure TDT nor reverse end-organ damage). CDEC also discussed the importance of addressing potential geographic and cost-related barriers to equitably accessing specialized treatment centres, undergoing prolonged hospitalization, and accessing fertility preservation.

- **Ethical and equity considerations for health systems implementation and prioritization**: CDEC discussed how the high cost of exagamglogene autotemcel raises concerns regarding health care system sustainability in the context of finite resources and absence of long-term evidence. CDEC discussed the need for life-long follow-up of patients and collection of long-term safety and efficacy data, which they acknowledged may require addressing limited epidemiological information and registry data on TDT in Canada. The committee acknowledged that the implementation of exagamglogene autotemcel will be complex and resource intensive, especially considering the requirement for accredited transplant centre resources. The committee discussed how health system capacity constraints are expected to severely limit the number of eligible patients that can be treated each year. CDEC discussed the importance of establishing fair, consistent, and ethically defensible prioritization processes and intra- and interjurisdictional agreements for ensuring equitable access to the therapy. They acknowledged that people with TDT may have difficulty accessing the therapy if they are prioritized below people with other diseases requiring access to transplant resources.

Background

Transfusion-dependent β-thalassemia (TDT) is a rare, autosomal recessive genetic hemoglobinopathy and the more severe form of β-thalassemia. Without the support of RBC transfusions, patients with TDT develop severe anemia due to ineffective erythropoiesis, as well as comorbidities such as splenomegaly, bone marrow expansion with accompanying bone pain, progressive bone deformities, extramedullary erythropoiesis, and iron overload. Newborn screening (NBS) initiatives allow identification of affected individuals before symptom onset and allow access to specialty care and initiation of red blood cell (RBC) transfusions prior to development of severe complications. The main goals of managing TDT in Canada include ameliorating the negative effects of anemia through lifelong, regular packed RBC transfusions (typically every 2-4 weeks, beginning in infancy) which aim to maintain a pre-transfusion Hb between 90 to 100 g/L, and reducing iron overload due to transfusions and TDT with iron chelation therapy (ICT); both treatments represent the standard of care (SoC). Other potential treatment options to accompany transfusion for adult patients with TDT include luspatercept, an erythroid maturation agent approved for the treatment of anemia in adults with TDT which stimulates erythroid response. The clinical experts consulted by CDA-AMC noted that if transfusion and ICT are optimized, with newer iron chelation therapies available patients with TDT can have life expectancy beyond the mean ages of death that have been previously reported for this disease. Allogenic hematopoietic stem cell transplant (HSCT) is the only curative treatment available for patients with TDT; HSCT with a human leukocyte antigen (HLA)-matched sibling donor is considered the SoC for children with TDT and is recommended to be discussed as a treatment option before puberty. Per the clinical experts consulted by CDA-AMC, HSCT with an HLA-matched donor is an option in about 20% of patients.

Although a rare disease in Canada, the number of individuals with β-thalassemia is evolving. It may also continue to rise in the Western world due to continued immigration from endemic regions including the Mediterranean, Asian, Indian, and Middle Eastern regions. Within the jurisdictions relevant to the CDA-AMC submission, there were an estimated 1,900 patients with TDT.

Exagamglogene autotemcel has been approved by Health Canada for for the treatment of patients 12 years of age and older with TDT. Exagamglogene autotemcel is a cellular therapy consisting of autologous CD34+ human stem and progenitor cells (HSPCs) edited by clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated protein 9 (Cas9) technology. It is available as a single dose for infusion containing a suspension of CD34+ cells in one or more vials and the minimum dosage recommended in the product monograph is 3 x 10^6 viable CD34+ cells per kilogram.

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of 1 phase I/II/III single-arm, open-label trial in patients with TDT between 12 and 35 years of age, who had received transfusions of packed RBCs consisting of at least 10 units per year during the previous 2 years, who met specific Karnofksy or Lansky performance thresholds and who were eligible for autologous stem cell transplant as per investigator judgement; 1 long-term extension; and 1 indirect treatment comparison
- patients' perspectives gathered by 2 patient groups, Thalassemia Foundation of Canada (TFC) and the Global Action Network for Sickle Cell & Other Inherited Blood Disorders (GANSID)
- input from public drug plans that participate in the CDA-AMC review process
- Input from 3 clinical specialists with expertise diagnosing and treating patients with TDT
- input from 1 clinician group, Canadian Hemoglobinopathy Association/ L'Association canadienne d'hémoglobinopathie (CanHaem)
- a review of the pharmacoeconomic model and report submitted by the sponsor
- a review of relevant ethical issues related to exagamglogene autotemcel

Perspectives of Patients, Clinicians, and Drug Programs

Patient Input

CDA-AMC received 2 patient group submissions from the Thalassemia Foundation of Canada (TFC) as well as the Global Action Network for Sickle Cell & Other Inherited Blood Disorders (GANSID), a global organization with 4 member organizations: TFC, Sickle Cell Awareness Group of Ontario (SCAGO), Sickle Cell Awareness Network of Saskatchewan and Sickle Cell Disease Association of Atlantic Provinces. TFC collected information via prior surveys conducted in 2022 and a new survey launched across Canada in April 2024, collecting responses from 80 respondents across 5 provinces (British Columbia, Alberta, Manitoba, Ontario and Quebec). GANSID's submission was based on the TFC survey and comments from peers living with thalassemia disorders outside of Canada.

Common patient symptoms noted in the inputs were severe anemia, lethargy, tiredness, feeling short of breath and feeling weak. The input noted that thalassemia can also cause other health issues including loss of bone density (e.g., osteopenia or osteoporosis) and higher risk of liver cancers, etc. Many patients experience growth delays, bone deformities and other physical changes due to anemia, iron chelation side effects and hormone insufficiency. Furthermore, the chronic nature of thalassemia, with its lifelong treatment requirements and potential complications, can lead to emotional distress in patients, and patients may experience feelings of anxiety, depression, or fear about their health and future. Due to misconceptions about the condition, thalassemia patients may also face stigma and discrimination in various aspects of their lives, such as education, employment, and social interactions.

Thalassemia patients and their caregivers face various challenges in managing the illness, but with currently available treatments, many are able to effectively control symptoms and improve quality of life and life expectancy. When asked about their main expectations for gene therapy, patient expectations included transfusion independence, maintaining Hb at a high enough level to function daily, safe and effective, and improved HRQoL including freedom to travel, work and spend time where they wished.

There were 2 patients had experience with exagamglogene autotemcel in the United States through clinical trials, and their family members shared their experiences with TFC. Both patients had come off blood products and their blood parameters were normal, which according to family members, was life changing. TFC asked about the respondents to identify as many concerns regarding gene therapy as they wanted, and patients and caregivers responded with concerns around cost and affordability of treatment (75%), length of treatment and/or recovery (71%), chemotherapy (61%), as well as eligibility due to older age.

Clinician Input

Input From Clinical Experts Consulted by CDA-AMC

The information in this section is based on input received from a panel of 3 clinical specialists consulted by CDA-AMC for the purpose of this review.

According to the expert panel, the major goals of therapy in TDT are to prolong life, reduce severity of symptoms, and improve HRQoL. The curative standard of care for TDT is HSCT, and therefore patients with an available HLA-matched sibling donor (approximately 20% of patients) are recommended for this treatment. The experts noted that most patients in this situation will be recommended to undergo transplant as early as possible if there is an HLA-matched sibling, as outcomes are generally better for patients less than 17 years old and there is less risk of organ damage from iron overload in younger patients. Patients without an HLA-matched donor or who decide not to undergo HSCT would receive lifelong blood transfusions on an approximately monthly basis, with iron chelation to address iron overload. The experts noted that other risks of transfusion include developing allo-antibodies to transfusion, transfusion reactions, transfusion-transmitted infections, and the potential for vascular access issues. Current treatment goals for transfusion focus on maintaining a hemoglobin (Hb) level of 9.5 to 10.5g/dL and maintaining liver iron, measured by ferriscan, of 2 to 3mg/g or 2 to 5mg/g. Luspatercept is used in adult patients, however the experts noted that a minority of patients (20%) respond to it and if they do, treatment would reduce, but not eliminate, the need for transfusion. The longitudinal nature of therapy and commitments associated with traveling to receive transfusion therefore remains an unmet need for patients. The experts noted that removing the need for transfusions would likely allow for considerable improvement in HRQoL, particularly as the life expectancy for patients with TDT can be beyond the mean ages of death that have been previously reported for this disease, with optimized transfusion and iron chelation. They noted that the majority of organ damage due to TDT comes from end organ damage and toxicity associated with iron overload; adherence to iron chelation can be difficult for some patients, and also becomes difficult to deliver as patients age, requiring a combination of agents. In addition, adult patients who may not have had newer iron chelation agents available earlier in their lives may have accrued end organ damage from iron overload. Therefore, there also remains an unmet need in some patients if there are challenges in optimizing chelation either due to patient age, clinical characteristics, or adherence concerns.

The expert panel noted that exagamglogene autotemcel would potentially change the treatment paradigm as it may modify the disease course to provide transfusion independence for patients for whom HSCT is not a treatment option. The experts felt that patients should have tried transfusion and iron chelation prior to exagamglogene autotemcel, but patients should not need to try luspatercept before exagamglogene autotemcel because not all patients respond to this treatment and the expected results from treatment are different (i.e., luspatercept does not eliminate the need for transfusion). Families who are eligible but who do not opt for HSCT may be considered for exagamglogene autotemcel, however the experts noted these patients may not choose exagamglogene autotemcel either due to concerns around myeloablative conditioning. The experts felt that discussions for exagamglogene autotemcel would likely be approached similarly, and involving similar specialists, to discussions around HSCT.

The expert panel noted that TDT diagnosis is generally done to the molecular level for patients at most centres, therefore patients who might be candidates for exagamglogene autotemcel would be readily identifiable. The experts felt that the patient population they would consider for exagamglogene autotemcel therapy would align with the lower age range and the inclusion criteria for the pivotal trial. They felt strongly that there should not be an upper age limit for therapy, but suitability and choice for exagamglogene autotemcel should be determined on a case-by-case basis. Patients they might consider prioritizing for therapy would be those who are not responding to their current therapy or whose HRQoL is impacted by their current therapy. It would also need to be established that such patients did not have end-organ damage severe enough to negatively affect the safety of myeloablative therapy. The experts noted that patient and family preference would likely be the biggest determinant to identify those patients who would not be suitable candidates for exagamglogene autotemcel.

The experts stated they typically see their patients every 3 to 6 months and assessments include whether they are meeting transfusion targets (i.e., sufficient transfusion to suppress endogenous RBC production) and whether iron overload is a concern (typically assessed using magnetic resonance imaging [MRI]). For the experts, a clinically meaningful response would be whether patients were transfusion independent with a Hb level of 9g/dL or more. Another potentially important outcome would be if patients need less than 6 transfusions per year (decreased from approximately 12 per year), as well as any changes in HRQoL and

decreases in iron overload or need for chelation from that patient's baseline. They noted that these changes would be meaningful even if patients hadn't reached transfusion independence.

As exagamglogene autotemcel is a one-time treatment, criteria for discontinuation would be less applicable, however the experts noted that patients may choose to stop the exagamglogene autotemcel process after mobilization but before myeloablative conditioning. When asked whether exagamglogene autotemcel might be redone if its efficacy were to wane in the future, the experts felt that a second round of myeloablative conditioning would be hard for patients, although not impossible for pediatric patients if there was a strong reason.

The experts noted that the management of TDT in general requires a hematologist and they emphasized that the mobilization, myeloablative conditioning and exagamglogene autotemcel infusion would need to be undertaken at an accredited transplant facility. Following this, patients could be transferred back to their hemoglobinopathy care provider. Being followed by specialist at a centre of excellence (i.e., a clinic with a hematology specialist in thalassemia as well as trained nurses); the experts estimated there were approximately 17 such centres across Canada. A hematologist who has an understanding of the disease would be important for ongoing care. They also noted that patients undergoing transplant use an autologous transplant centre and their follow-up consists of appointments with both the transplant hematologist and their TDT hematologist, so it was likely that exagamglogene autotemcel patients could be followed in a similar manner. They emphasized that patients receiving exagamglogene autotemcel should receive long-term follow-up.

Clinician Group Input

CDA-AMC received 1 clinician group submission from the Canadian Hemoglobinopathy Association/ L'Association canadienne d'hémoglobinopathie (CanHaem). CanHaem is a not-for-profit organization that was established in 2013 and is composed of healthcare providers of individuals in Canada with hemoglobinopathies. CanHaem's proposed submission was drafted by a CanHaem physician member and then shared amongst other members (including the CanHaem chair) for review.

The clinician group agreed with the expert panel on the need for lifelong, multidisciplinary care required for patients with TDT and the general impact of the disease on patients' lives and HRQoL, and that with optimized care, patients with TDT may have a near-normal life expectancy. In addition to the limitations of SoC therapies noted by the clinical expert panel, they also highlighted that emerging disease-related complications are now appreciated in the aging thalassemia population including increased risk of hepatocellular carcinoma, as well as renal, cardiac and hepatic failure, all of which are related to the chronic toxicity of iron. The clinical group agreed with the clinical experts on the patients who might be considered candidates for exagamglogene autotemcel and also agreed that there should not be an upper age limit for eligibility. The clinician group input noted that outcomes for efficacy should be the same as those in the pivotal clinical trial, including HRQoL measures. They agreed with the clinical expert panel that patients should receive long-term follow-up and their care for the exagamglogene autotemcel treatment process should be handled by facility experienced with stem cell collection, administration of myeloablative chemotherapy and specialized hematologic care. The clinician group emphasized the need for equity in the availability of exagamglogene autotemcel, particularly for patients living in geographically remote areas, as well as the need to offer fertility preservation as part of the treatment process.

Drug Program Input

Input was obtained from the drug programs that participate in the CDA-AMC reimbursement review process. The following were identified as key factors that could potentially impact the implementation of a CDA-AMC recommendation for exagamglogene autotemcel:

- considerations for initiation of therapy
- considerations for continuation or renewal of therapy
- generalizability of trial populations to the broader populations in the jurisdictions
- care provision issues

The clinical experts consulted by CDA-AMC provided advice on the potential implementation issues raised by the drug programs.

Table 2: Responses to Questions from the Drug Programs

Implementation issues	Response
Considerations for initiation of therapy	
Patients were eligible for the pivotal trial if they had: • Received a diagnosis of β-thalassemia (including the hemoglobin E genotype) with either homozygous or compound heterozygous mutations • Had received transfusions of packed red cells consisting of at least 100 mL/kg/year (or 10 units/year) during the previous 2 years **Question for the clinical experts:** Would these criteria from the pivotal trial be appropriate for reimbursement purposes?	The clinical experts and CDEC agreed that that diagnosis of TDT would be sufficient for a patient to be eligible for exagamglogene autotemcel, but a patient who is struggling with response to their current therapy, having challenges to the chelation therapy whose HRQoL is impacted would be more likely to be prioritized for exagamglogene autotemcel.
Would any additional laboratory tests be required for reimbursement purposes based on the pivotal trial inclusion or exclusion criteria?	The clinical experts and CDEC agreed that testing for associated α-thalassemia including > 1 alpha deletion or alpha multiplications, which was done in the pivotal trial, would be additional testing. It was also noted that the percentage of cells with edited alleles would also be additional testing after treatment.
Eligibility criteria for the pivotal trial required patients to be 12 to 35 years of age. The submission notes that "if patients with TDT who are over 35 years of age are deemed fit for treatment with exagamglogene autotemcel, there is no plausible biologic mechanism to limit access to exagamglogene autotemcel to those no older than 35 years". **Question for the clinical experts:** Should patients older than 35 be eligible to receive exagamglogene autotemcel?	CDEC agreed with the clinical experts that there should not be a hard upper age limit for exagamglogene autotemcel therapy as patients with TDT who are well-chelated and well-transfused have increased life expectancy than those who are not and may tend to reach the higher percentiles of the general population. Patients' ability to tolerate myeloablative conditioning should be assessed and their eligibility for treatment should be at the discretion of the treating physician.
Exagamglogene autotemcel is proposed as a one-time treatment. Are there any instances where a second dose would be considered appropriate?	CDEC agreed with the clinical experts that at this time a second dose of exagamglogene autotemcel would not be considered appropriate.
Considerations for continuation or renewal of therapy	
The submission notes that "patients with TDT who participated in CLIMB-111 were asked to enroll in the long-term follow-up study CLIMB-131, where they will be followed for up to 15 years post-infusion. The primary and key secondary endpoints evaluated in CLIMB-111 will continue to be evaluated in CLIMB-131." **Question for the clinical experts:** How should clinically meaningful response be defined using objective parameters?	CDEC agreed with the clinical experts that the only indicator of a clinically meaningful response would be transfusion independence, this with Hb level of 9 g/dL or more. The clinical experts also noted to CDEC that response should be assessed at the standard care assessments which are usually every 3 to 6 months.
How long should follow-up last to confirm a clinically meaningful response is maintained?	The clinical experts noted to CDEC that patients should receive lifelong follow-up; to confirm clinical response, ideally 5 years follow-up, but 2 years would be a reasonable surrogate to suggest a sustained response.
Generalizability	
The pivotal trial listed numerous exclusion criteria, but there are no related contraindications or warnings/precautions to therapy listed in the product monograph for most of these. The submission notes that "patients with an available HLA-matched related donor were excluded from the pivotal clinical trials due to ethical concerns around including patients with a viable treatment option in a trial for a treatment without proven efficacy or safety at the time. However, based on the results of CLIMB-111 this may no longer be a valid concern."	The clinical experts noted to CDEC that excluding patients with an available HLA-matched donor sibling is reasonable, but based on the science, any patient who is above the lower limit of the age range used in the pivotal trial, who can safely undergo the autologous transplant as per their clinical team, should be eligible for exagamglogene autotemcel. CDEC recommended that patients who have an available and willing 10/10 HLA-matched related donor, have associated α-thalassemia and >1 alpha deletion or alpha multiplications, prior

Implementation issues	Response
Question for the clinical experts: Which, if any, of the pivotal trial exclusion criteria should be used to determine eligibility for treatment?	or current history of malignancy, sickle-cell β-thalassemia variant, prior allo-HSCT treatment, or prior gene editing therapy or edting product should not be eligible for exagamglogene autotemcel.
Eligibility criteria for the pivotal trial required patients to be 12 to 35 years of age, and the product monograph states, "No data in patients less than 12 years of age are available to Health Canada; therefore, Health Canada has not authorized an indication of pediatric use in patients less than 12 years of age." **Question for the clinical experts:** Will there be interest in using exagamglogene autotemcel in those younger than 12 years? If so, should such patients be considered for reimbursement?	CDEC agreed with the clinical experts that given the lack of safety data in patients who are younger than 12 years of age, exagamglogene autotemcel should not be considered in these patients.
Care provision issues	
The sponsor notes: • TDT is generally diagnosed through NBS programs. Therefore, most cases in Canada would have already been detected via NBS and would have been referred to a reference center to receive care. Since most patients would have already received a confirmed diagnosis prior to pursuring exagamglogene autotemcel treatment, these tests should not require additional healthcare resources specific to diagnose the condition for the purposes of receiving exagamglogene autotemcel. • There may be individuals who receive a diagnosis later in life either because NBS was not available in their province at the time of their birth or because they have immigrated from a country without a widespread NBS program. For this patient population, individuals presenting clinical symptoms would undergo a similar clinical diagnostic process to that of NBS, which involves being referred for a blood spot screening test by their treating physician. This aligns with the current standard of care for patients showing clinical manifestations suggesting hemoglobinopathies. These patients would thus undergo this diagnostic test regardless of their eligibility status for exagamglogene autotemcel. • Patients not diagnosed via NBS could also have their blood drawn and sent to a laboratory for testing, with review by a hematopathologist (this is how most hemoglobinopathies are diagnosed later in life). **Question for the clinical experts:** Is the above accurate from a diagnostic standpoint?	The clinical experts noted to CDEC that what the sponsor noted from a diagnostic standpoint is accurate.
Is the blood spot screening test referenced by the sponsor widely available, in use in Canada, and most importantly, reliable and accurate?	The clinical experts noted to CDEC that bloodspot is widely used although not universal, and it is reliable.
The sponsor notes: • Exagamglogene autotemcel is associated with a new treatment journey; however, most of the steps of the exagamglogene autotemcel treatment pathway are already being performed by experienced and dedicated	The clinical experts indicated noted to CDEC that in general, transplant centres are stretched thin and this would be an added service, so the impact will not be minimal as an added number of patients will become eligible for services that these centres offer, and many transplant centres in the country are funded exclusively

Implementation issues	Response
teams in potential ATCs in Canada (e.g., for HSCT), and thus, clinicians and health care providers are familiar with the required processes. • While the treatment processes increase slightly with exagamglogene autotemcel patients, additional healthcare resources are not expected to be needed since they will largely rely on processes and healthcare teams that are currently in place. **Question for the clinical experts:** Is the above accurate from an implementation/ resources standpoint?	for patients with malignancies. It would lead to increased work for the transplant teams in particular. On the hemoglobinopathy side the process would be similar for exagamglogene autotemcel as is currently done for HSCT, however there would be additional discussion and education required for families which will require additional resources, and which would ideally be built into the process. Overall, there would need to be dedicated resources to the transplant teams, thalassemia teams, and for TDT patients so they do not compete with other patients (e.g., cancer patients who may have time-sensitive transplant requirements) so that the treatment may be available but also that patients will have access to it.

ATC = authorized treatment centre; HRQoL = health-related quality of life; HSCT = hematopoietic stem cell transplant; NBS = newborn screening; TDT = transfusion-dependent β-thalassemia.

Clinical Evidence

Systematic Review

Description of Studies

CLIMB-111 is an ongoing Phase I/II/III single arm, multi-site, single dose trial which enrolled a total of 59 patients aged 12 to 35 who had TDT. Transfusion dependence was defined as a history of at least 100mL/kg/year or 10 units/year of packed red blood cell (RBC) transfusions in the past 2 years prior to enrolment. The primary objective of CLIMB-111 was to evaluate the safety and efficacy of a single dose of autologous CRISPR/Cas9 modified CD34+ human HSPCs, otherwise known as exagamglogene autotemcel. CLIMB-111 contained 3 pre-specified interim analysis (IA) points – IA1, IA2 and IA3 – and data from IA3 was submitted based on a data cutoff on January 16, 2023. Additional supplemental data from a further data cutoff on April 16, 2023 was also supplied by the sponsor and used in the report where available. The study took place at 13 sites in 5 countries including 2 sites in Canada.

Key inclusion criteria required patients to be between the ages of 12 and 35, inclusive; have a diagnosis of TDT; be eligible for autologous stem cell transplant; and have functional status greater than specific thresholds for two different scales, depending on patient age. Key exclusion criteria included patients who had a willing and healthy 10/10 HLA-matched donor per investigator judgement, patients with any illness or clinical condition that, in the opinion of the investigator, might confound the results of the study or pose an additional risk to the patient, and prior recipients of allo-HSCT.

The primary outcome was the proportion of patients achieving transfusion independence (TI) for at least 12 consecutive months (TI12), and the key secondary outcome was the proportion of patients achieving TI for at least 6 consecutive months (TI6). TI was defined as maintaining weighted average Hb 9 g/dL or greater without RBC transfusions. The evaluation of TI12 and TI6 commenced 60 days after the last RBC transfusion for post exagamglogene autotemcel infusion support or TDT disease management. Secondary outcomes were total Hb and HbF concentrations, the proportion of alleles with the intended genetic modification in the CD34+ cells of the bone marrow and the peripheral blood, and changes from baseline in HRQoL assessed by the Functional Assessment of Cancer Therapy – Bone Marrow Transplant (FACT-BMT) and EuroQol Quality of Life Scale – 5 Dimensions – 5 Levels of Severity (EQ-5D-5L) in adults, as well as the Pediatric Quality of Life Inventory (PedsQL) and EuroQol Quality of Life Scale – 5 Dimensions – Youth (ED-5D-Y) measures in pediatric patients. Additional secondary outcomes included the duration of TI with weighted average Hb of 9g/dL or greater in patients with TI12, and the time to the last RBC transfusion for patients with TI12.

As of the data cutoff on April 16, 2023, a total of 59 patients were enrolled, 54 had received an infusion of exagamglogene autotemcel, and 42 patients were included in the primary efficacy set (PES). A total of 23 (39.0%) of patients had completed CLIMB-111; the mean (standard deviation [SD]) duration of follow-up was 19.2 (6.97) months. Baseline characteristics were broadly similar between the PES and the full analysis set (FAS). The majority of patients (59.5% in the PES) expressed a β^0/β^0-like genotype of TDT. In the PES, the average age was 21.6 years old; 31.0% of patients were pediatric patients (12 years or older and less than 18

years old), and 69.0% were adult patients were between the ages of 18 and 35. Of note, the study did not enrol any Black or African American, [redacted] patients. In addition, the study did not enrol any patients with the [redacted] thalassemia genotypes.

Efficacy Results

Proportion of Patients with TI12

The proportion of patients who achieved TI12 following infusion of exagamglogene autotemcel and as of the April 16, 2023 data cutoff was 92.9% (95% CI: 80.5% to 98.5%) in the PES. Among patients with TI12, the time from the exagamglogene autotemcel infusion to the last RBC transfusion was 28.0 days (range: 11.0, 91.0). The mean (SD) duration of TI to date was 23.6 (7.8) months.

Proportion of Patients with TI6

Following infusion with exagamglogene autotemcel, the proportion of patients in the PES who achieved TI6 as of the data cutoff was 92.9% (95% CI: 80.5% to 98.5%).

Fetal Hemoglobin Levels

Clinical experts consulted by CDA-AMC note that in TDT patients, almost all of total Hb is expected to be HbF after exagaoglogene autotemcel infusion, and total Hb should be maintained above 9 g/dL.Total HbF concentrations at 6 months post exagamglogene autotemcel infusion (mean [SD]) were 10.8 (2.8)g/dL. At 12 months post exagamglogene autotemcel infusion, the observed mean (SD) concentration of HbF was 11.5 (2.5)g/dL, and at 24 months post exagamglogene autotemcel infusion, the observed mean (SD) concentration of HbF was 11.5 (2.7)g/dL.

Total Hb Concentration

The total Hb concentrations targeted by SoC are 9 to 10 g/dL.[1] At 6 months post exagamglogene autotemcel infusion, the observed mean (SD) Hb concentration was 12.1 (2.0)g/dL. At 12 months post exagamglogene autotemcel infusion, the observed mean (SD) Hb concentration was 12.8 (2.1)g/dL. At 24 months post exagamglogene autotemcel infusion, the observed mean (SD) Hb concentration was 12.9 (2.4)g/dL.

Proportion of Alleles with the Intended Genetic Modification in the CD34+ Cells of the Bone Marrow

At 6 months post exagamglogene autotemcel infusion, the observed mean (SD) proportion of CD34+ cells with the intended genetic modification was 78.48 (11.39)%. At 12 months post exagamglogene autotemcel infusion, the observed mean (SD) proportion was [redacted]. At 24 months post exagamglogene autotemcel infusion, the observed mean (SD) proportion was [redacted].

Proportion of Alleles with the Intended Genetic Modification in the Peripheral Blood

At 6 months post exagamglogene autotemcel infusion, the observed mean (SD) proportion of CD34+ cells with the intended genetic modification was [redacted]. At 12 months post exagamglogene autotemcel infusion, the observed mean (SD) proportion was [redacted]. At 24 months post exagamglogene autotemcel infusion, the observed mean (SD) proportion was [redacted].

Functional Assessment of Cancer Therapy-Bone Marrow Transplant

FACT-BMT is a quality of life measure for cancer patients 18 years or older undergoing bone marrow transplant. Total scores range from 0 to 164, with higher scores indicating greater quality of life. Results were not reported at 6 months post exagamglogene autotemcel infusion. At 12 months post exagamglogene autotemcel infusion, the observed mean (SD) change in scores from baseline was 7.4 (23.0) points. At 24 months post exagamglogene autotemcel infusion, the observed mean (SD) change in scores from baseline was 13.9 (21.4) points.

Pediatric Quality of Life Inventory

PedsQL scores range from 0 to 100 and describe general quality of life in children; the total score is the mean of all items and higher scores represent greater quality of life. At 6 months post exagamglogene autotemcel infusion, the observed mean (SD) change from

baseline in scores was 10.8 (10.2) points. At 12 months post exagamglogene autotemcel infusion, the observed mean (SD) change from baseline in scores was 12.0 (10.3) points. At 24 months post exagamglogene autotemcel infusion, the observed mean (SD) change from baseline in scores was 12.3 (17.4) points.

EuroQol Quality of Life Scale – 5-dimensions VAS

EQ-5D VAS is a self-reported health rating using a 20-cm visual analog scale (VAS) that ranged from 0 (worst imaginable health state) to 100 (best imaginable health state) points with higher scores indicating better HRQoL. At 9 months post exagamglogene autotemcel infusion, the observed mean (SD) change from baseline was [redacted] points. At 12 months post exagamglogene autotemcel infusion, the observed mean (SD) change from baseline was 7.9 (16.7) points. At 24 months post exagamglogene autotemcel infusion, the observed mean (SD) change from baseline was 10.7 (18.6) points.

Non-Adult EuroQol Quality of Life Scale – Visual Analog Scale

The EQ VAS used for pediatric patients was identical to that used in adults in the trial. Based on the January 16, 2023 data cut, at 6 months post exagamglogene autotemcel infusion, the observed mean (SD) change from baseline was [redacted] points. At 12 months post exagamglogene autotemcel infusion, the observed mean (SD) change from baseline was [redacted] points. At 18 months post exagamglogene autotemcel infusion, the observed mean (SD) change from baseline was [redacted] points.

Harms Results

During the course of the entire study to date, a total of 58 (98.3%) patients had any adverse events (AEs). A total of 56 (94.9%) patients had any AE during the time from enrolment until the day before exagamglogene autotemcel infusion, which included myeloablative conditioning. A total of 100% of patients had any AE during the time period from the day of exagamglogene autotemcel infusion to either M24 visit or the EOS visit. The most common AEs from the time of enrolment to the day before exagamglogene autotemcel infusion were nausea (44.1% of patients) headache (39.0% of patients), bone pain (33.9% of patients), vascular site access pain (28.8% of patients), and vomiting (20.3% of patients). The most common AEs to date from the day of exagamglogene autotemcel infusion to the M24 or EOS study visit were febrile neutropenia (61.1% of patients), headache (55.6% of patients), stomatitis (51.9% of patients), thrombocytopenia (46.3% of patients), anemia (44.4% of patients), mucosal inflammation (42.6% of patients), nausea (42.6% of patients), and vomiting (40.7% of patients).

A total of 9 (15.3%) patients had any serious adverse event (SAE) during the time from enrolment until the day before exagamglogene autotemcel infusion, which included myeloablative conditioning. A total of 26 (44.1%) of patients had any SAE during the time period from enrolment to either their month 24 (M24) or end of study (EOS) visit. The SAEs that occurred in 2 or more patients during the study to date were venoocclusive liver disease, pneumonia, COVID-19, hypoxia, thrombocytopenia, upper respiratory tract infection, nausea, vomiting, and bacteremia.

To date, no patients withdrew from the study drug or withdrew from the study due to AEs after exagamglogene autotemcel infusion. A total of 3 withdrawals prior to exagamglogene autotemcel infusion were reported; reasons included [redacted]. To date, no deaths had been reported in the study.

To date, all 54 (100.0%) patients had achieved neutrophil engraftment. The median (range) time to neutrophil engraftment was 29.0 (12 to 56) days. A total of 53 patients achieved platelet engraftment; the median (range) time to engraftment was 44.0 (20 to 200) days. Engraftment syndrome was not reported. Delayed engraftment was reported as a SAE in 1 patient during the time between exagamglogene autotemcel infusion and M24 or EOS visit.

Other AEs of special interest included 41 (69.5%) of patients who reported AEs of infection or infestation and 33 (55.9%) patients experienced febrile neutropenia. A total of [redacted] types of bleeding AEs were reported: gingival bleeding in 6 (10.2%) patients, [redacted]. Veno-occlusive liver disease SAEs occurred in 5 (8.5%) patients. [redacted] No information was reported regarding hemophagocytic lymphohystiocytosis, engraftment syndrome, infections and infestations classified as SAEs, bleeding classified as SAEs, or anaphylaxis. The submission noted that no malignancies had been reported in patients after exagamglogene autotemcel infusion in the study to date. No information was provided on off-target editing.

Critical Appraisal

There are several internal validity limitations to note. Firstly, CLIMB-111 is a single-arm trial with no blinding, randomization or allocation concealment, and therefore the study population may have unknown confounders and the results observed may not be able to be entirely attributable to the study drug. While a well-designed RCT that allows for causal inferences to be drawn with greater certainty than a single-arm treatment design is preferred, especially for decisions in health technology assessment (HTA) and reimbursement, the use of a single-arm study in this scenario is understandable, but nevertheless results in the GRADE assessment of certainty being very low, without evidence for grading up as is typical for single-arm studies. CLIMB-111 underwent several protocol changes including conversion to a Phase I/II/III trial, which has implications for the sample size and measurement of outcomes that may increase the heterogeneity of the results because of the confirmatory expectations of the Phase III designation. The European Medicines Agency (EMA) review of exagamglogene autotemcel for TDT highlighted that 1 patient in CLIMB-111 had achieved the primary outcome at the time some of these key amendments were made. The EMA accepted that – while not ideal for internal validity – this likely had little effect on the overall validity or results of the study. Nonetheless, the number of important protocol and statistical analysis revisions for a study that does not have a true confirmatory Phase III design adds to the very low certainty of the evidence. The results submitted from CLIMB-111 are an interim analysis based on the PES; interim analyses may overestimate the true effect of treatment. Furthermore, the PES is potentially a select population because it reflects only those patients who completed the exagamglogene autotemcel treatment process in the time since the study began. Reporting all the study results to date based only on the PES could bias the effect estimate against a null hypothesis, favoring the intervention. In addition, the alpha-spending methods used patient denominators to derive the alpha values for the IA1, IA2 and IA3 interim analyses, an approach which is considered more data-driven and there is potential to adjust for and not adjust for type 1 error based on the fluctuating thresholds. The first and second interim analyses were not done; the statistical analysis for IA3 recycled the alpha from the previous unused alpha spends but the appropriateness of this is questionable and would not necessarily result in a sufficiently conservative threshold. Furthermore, a response rate of 50% was used as the null threshold for the primary testing hypothesis, which was considered by the clinical experts consulted by CDA-AMC to be low. There are also no adjustments for multiplicity in the secondary and exploratory outcomes and reduces the ability to draw firm conclusions on the results from these analyses. There are also limitations regarding outcome ascertainment. The HRQoL measures are subjective and the single-arm, open-label nature of the study may bias the reporting of these results. There is also no rationale provided for the flexibility of the potential start and finish of the TI monitoring period within the 2 years of follow-up, and the clinical relevance of the TI6 outcome is somewhat uncertain especially whether it represents TI12 and longer-term outcomes. The use of a flexible outcome window increases the risk of overestimating the true effect. Furthermore, the analysis noted that the efficacy analyses were based on patients' available data before death or loss to follow-up. As the submission did not describe whether any patient results were carried forward, there is a risk of additional uncertainty in the results. With regards to the duration of TI reported for those patients with TI12 (a secondary outcome), patients were required to maintain a weighted average Hb of 9g/dL or greater; however no rationale was provided for choosing a weighted average and there is a possibility that absolute Hb values below this would erroneously contribute to the proportion of TI responders.

There are some external validity limitations to note. The transfusion criteria used in the inclusion criteria were an internationally accepted cutoff for severe transfusion dependence; the study results are therefore only generalizable to patients with this degree of transfusion dependence. In addition, the clinical experts felt the age range was narrow and felt strongly that there should not be an upper age limit, but rather the suitability of patients for the therapy should be determined on a case-by-case basis as is done for HSCT; however, the age cutoff in the trial means the results are not necessarily generalizable outside of these age ranges. In addition, the exclusion criteria for any comorbidity which may impact outcomes or suitability for therapy does not specify comorbidities, and the available evidence was insufficient to assess with certainty whether patients in CLIMB-111 were on optimal SoC prior to initiating exagamglogene autotemcel. This may reduce the generalizability of these study results to all patients with TDT who may be considered for exagamglogene autotemcel therapy. In addition, the exclusion critiera for α-thalassemia, multiple alpha deletions, and sickle cell thalassemia means that results of the study do not apply to situations of co-inheritance of multiple types of thalassemia. Furthermore, the frequency of follow-up visits and laboratory measures undertaken in the trial may not reflect those in clinical practice, and therefore the results may not be wholly extrapolatable to clinical settings. In addition, the relatively short follow-up duration of patients in the trial is a concern for both efficacy and safety assessments; the mean follow-up after exagamglogene autotemcel infusion of 19 months (SD = 7) was not sufficient so far to inform the issues of potential waning of effect over time, as well as longer-term toxicities such as the potential occurrence of malignancies. Lastly, the clinical experts noted that while SoC is

generally similar across higher socioeconomic status (SES) countries, CLIMB-111 did not take place in any lower SES countries where thalassemias are endemic, and patient outcomes in these settings or the clinical status of patients who have recently immigrated to Canada from these countries may be different than those observed in the trial.

GRADE Summary of Findings and Certainty of the Evidence

For pivotal studies and RCTs identified in the sponsor's systematic review, GRADE was used to assess the certainty of the evidence for outcomes considered most relevant to inform CDA-AMC's expert committee deliberations, and a final certainty rating was determined as outlined by the GRADE Working Group.

Although GRADE guidance is not available for noncomparative studies, the CDA-AMC review team assessed pivotal single-arm trials for study limitations (which refers to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias to present these important considerations. Because the lack of a comparator arm in CLIMB-111 does not allow for a conclusion to be drawn on the effect of the intervention versus any comparator, the certainty of evidence for this GRADE assessment started at very low certainty with no opportunity for rating up.

When possible, certainty was rated in the context of the presence of an important (nontrivial) treatment effect; if this was not possible, certainty was rated in the context of the presence of any treatment effect (i.e., the clinical importance is unclear). In all cases, the target of the certainty of evidence assessment was based on the point estimate and where it was located relative to the threshold for a clinically important effect (when a threshold was available) or to the null.

The following list of outcomes was finalized in consultation with expert committee members:

- Clinical outcomes:
  - Proportion of patients with transfusion independence for 12 consecutive months (TI12)
  - Proportion of patients with transfusion independence for 6 consecutive months (TI6)
  - Total HbF
  - Total Hb Concentration
- HRQoL outcomes:
  - Change from baseline to 24 months in FACT-BMT scores
  - Change from baseline to 24 months in PedsQL scores
- Harms:
  - All-cause mortality
  - Proportion of patients with engraftment (platelet and neutrophil)
  - Time to engraftment (platelet and neutrophil)
  - AEs in 25% or more patients and SAEs in 2 or more patients

Table 3: Summary of Findings for Exagamglogene autotemcel for Patients With Transfusion-Dependent β-Thalassemia

Outcome and follow-up	Patients (studies), N	Effect	Certainty [a]	What happens
Transfusion and Hematologic Outcomes				
Patients achieving TI for at least 12 consecutive months (TI12) Follow-up: any 12-month period 60 days after last RBC transfusion up to 2 years after exagamglogene autotemcel infusion	42 (1 single-arm study)	Patients with TI12: n = 39 (929 per 1,000 patients) 92.9% (95% CI: 80.5% to 98.5%)	Very Low [b,c,d]	The evidence is very uncertain about the effect of exagamglogene autotemcel on the proportion of patients achieving TI12 when compared with any comparator.
Patients achieving TI for at least 6 consecutive months (TI6) Follow-up: any 12-month period 60 days after last RBC transfusion up to 2 years after exagamglogene autotemcel infusion	42 (1 single-arm study)	Patients with TI6: n = 39 (929 per 1,000 patients) 92.9% (95% CI: 80.5% to 98.5%)	Very Low [b,c,d]	The evidence is very uncertain about the effect of exagamglogene autotemcel on the proportion of patients achieving TI16 when compared with any comparator.
Total HbF (g/dL) Follow-up: 24 months	42 (1 single-arm study)	Mean (SD) total HbF: 11.5 (2.7) Change from baseline: NR (95% CI: NR to NR)	Very Low [c,d]	The evidence is very uncertain about the effect of exagamglogene autotemcel on the total HbF when compared with any comparator.
Total Hb concentration (g/dL) Follow-up: 24 months	42 (1 single-arm study)	Mean (SD) total Hb: 12.9 (2.4) g/dL Change from baseline (95% CI): NR, (NR, NR)	Very Low [c,d]	The evidence is very uncertain about the effect of exagamglogene autotemcel on the total Hb concentration when compared with any comparator.
HRQoL and Symptom Outcomes				
Change in FACT-BMT scores from baseline Follow-up: 24 months	29 (1 single-arm study)	Mean (SD): 13.9 (21.4)	Very Low [c,d]	The evidence is very uncertain about the effect of exagamglogene autotemcel on the change from baseline in FACT-BMT scores when compared with any comparator.
Changes in PedsQL scores from baseline Follow-up: 24 months	12 (1 single-arm study)	Mean (SD): 12.3 (17.4)	Very Low [c,d]	The evidence is very uncertain about the effect of exagamglogene autotemcel on change from baseline in PedsQL scores when compared with any comparator.
Harms				

Outcome and follow-up	Patients (studies), N	Effect	Certainty [a]	What happens
All-cause mortality Follow-up: 24 months	59 (1 single-arm study)	Patients who died: n = 0 (95% CI: NR to NR)	Very Low [d, e]	The evidence is very uncertain about the effect of exagamglogene autotemcel on all-cause mortality when compared with any comparator.
Patients with engraftment (neutrophil and platelet)	54 (patients who had undergone myeloablative conditioning in 1 single arm study)	Patients with neutrophil engraftment: n = 54 (1,000 per 1,000 patients) Patients with platelet engraftment: n = 53 (981 per 1,000 patients)	Very Low [d, e]	The evidence is very uncertain about the effect of exagamglogene autotemcel on the proportion of patients with engraftment when compared with any comparator.
Time to engraftment (neutrophil and platelet)	54 (patients who had undergone myeloablative conditioning in 1 single arm study)	Median (range) time to neutrophil engraftment: 29 (12 to 56) days Median (range) time to platelet engraftment: 44 (20 to 200) days	Very Low [d, e]	The evidence is very uncertain about the effect of exagamglogene autotemcel on the time to neutrophil or platelet engraftment when compared with any comparator.
AEs (in ≥ 25% of patients) and SAEs (in ≥ 2 patients)	59 (1 single arm study)	AEs: n = 58 (983 per 1,000 patients) SAEs: n = 26 (441 per 1,000 patients)	Very Low [d, e]	The evidence is very uncertain about the effect of exagamglogene autotemcel on AEs, SAEs and AEs of special interest when compared with any comparator.

AE = adverse event; Hb = hemoglobin; FACT-BMT = Functional Assessment of Cancer Therapy – Bone Marrow Transplant; HbF = fetal hemoglobin; HRQoL = health-related quality of life; PedsQL = Pediatric Quality of Life Inventory; RCT = randomized controlled trial; SAE = serious adverse event; TI = transfusion independence;

Note: All serious concerns with study limitations (which refers to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias are documented in the table footnotes.

[a] In the absence of a comparator arm, conclusions about efficacy relative to any comparator cannot be drawn and certainty of evidence started at very low. None of the outcome were rated up because of serious study limitations (see specific footnotes).

[b] Serious study limitations. The flexibility of the start and finish dates of the TI monitoring period during the 2-year follow-up risks overestimating the treatment effect. Updates to the outcomes made to the study protocol after enrolment and with no rationale provided cause an unknown risk of bias.

[c] Serious indirectness. According to clinical experts consulted by CDA-AMC, the age limit in the trial is not likely to represent all patients with TDT who may be considered for exagamglogene autotemcel therapy, and the list of comorbidities in the exclusion criteria is not known.

[d] Serious study limitations. The interim analysis provided results only for the primary efficacy set (PES), which is potentially a select sample as it represents those patients who have completed the study to date, as opposed to the full enrolled sample. Information on the outcomes based on the full treatment experience is therefore lacking.

[e] Serious imprecision. The study captured a very small number of events, and the study duration is unlikely to be long enough to fully capture the outcome.

Source: Details included in the table are from the sponsor's Summary of Clinical Evidence,[2] Clinical Addendum Update[24] and additional information provided by the sponsor.

Long-Term Extension Studies

The sponsor submitted one LTE study for this review. CLIMB-131 is an ongoing, multi-site, open-label, rollover study designed to evaluate the long-term safety and efficacy of exagamglogene autotemcel in patients who received treatment in CLIMB-111 and who completed or discontinued the study. The primary objective was to evaluate the long-term safety of exagamglogene autotemcel.

Description of Studies

All patients who completed or discontinued CLIMB-111 after exagamglogene autotemcel infusion and signed and dated the informed consent form were invited to participate in the CLIMB-131 study, with no exclusion criteria. Patients did not receive any study drug. All medication taken from the signing of the consent form for CLIMB-131 through the data cut-off date (April 16, 2023) were recorded. CLIMB-131 is planned to provide an additional 13 years follow-up, totaling 15 years follow-up after exagamglogene autotemcel infusion.

The primary safety endpoints for the CLIMB-131 study included new malignancies, new or worsening hematologic disorders, all-cause mortality, all SAEs (to be recorded up to 5 years after infusion) and exagamgloene autotemcel-related AEs and SAEs. The secondary endpoints summarized in this section for the CLIMB-131 study included the same outcomes that were assessed in CLIMB-111, with the exception of TI6 and TI12. Of note, HRQoL results were not reported past 24 months in the submission.

Analysis sets for patients with TDT in CLIMB-131 were the same as for the CLIMB-111 study. All data from the extension studies were analyzed descriptively using summary statistics. Continuous variables were summarized using the following descriptive number of patients (n), mean, SD, median, minimum and maximum values. For certain continuous variables, such as Hb and HbF, additional summary statistics including the 1st, and the 3rd quartiles were presented. Categorical variables were summarized using counts and percentages. Baseline value, unless specified otherwise, was defined as the baseline in the CLIMB-111 study.

Missing data was not imputed, and all data were evaluated as observed. Patients who discontinued the study were listed with the reasons for withdrawal. The submission noted that starting after the month 24 visit, only AEs related or possibly related to exagamglogene autotemcel, SAEs, new malignancies, and new or worsening hematologic disorders were recorded.

Efficacy Results

A total of 23 patients had completed the 2-year follow-up after exagamglogene autotemcel in the CLIMB-111 study and rolled over into CLIMB-131. To date, no patient had discontinued from CLIMB-131.

Total Hemoglobin and Fetal Hemoglobin

At 36 months post exagamglogene autotemcel infusion, the observed mean (SD) concentration of HbF was [redacted] and [redacted]. At 48 months post exagamglogene autotemcel infusion, the observed mean (SD) concentration of HbF was [redacted] and [redacted].

Proportion of Alleles with the Intended Genetic Modification in the CD34+ Cells of the Bone Marrow

At 36 months post exagamglogene autotemcel infusion, the observed mean (SD) proportion of CD34+ cells with the intended genetic modification was [redacted]. At 48 months post exagamglogene autotemcel infusion, the observed mean (SD) proportion was [redacted].

Proportion of Alleles with the Intended Genetic Modification in the Peripheral Blood

At 36 months post exagamglogene autotemcel infusion, the observed mean (SD) proportion of CD34+ cells with the intended genetic modification was [redacted]. At 48 months post exagamglogene autotemcel infusion, the observed mean (SD) proportion was [redacted].

Health-related Quality of Life

HRQoL assessments were conducted for patients with TDT included EQ-5D-5L/EQ-5D-Y, FACT-BMT, and PedsQL. Due to a paucity of long-term PRO data collected as of the January 12, 2023 data cutoff, PRO data for the CLIMB-131 study is not reported herein.

Transfusion Independence

All patients who achieved TI12 continued to remain transfusion independent in the CLIMB 111 study. These benefits were sustained through the CLIMB 131 study. The mean (SD) duration of TI to date was 23.6 (7.8) months with a range of 13.5 to 48.1 months, starting 60 days after the last RBC transfusion for post-transplant support or TDT disease management.

Harms Results

As of April 16, 2023, a total of 23 patients with TDT were rolled over in the CLIMB-131 study after completion of the Month 24 visit. The overall duration of follow-up (including follow-up in CLIMB-131) for these patients ranged from 25.2 to 51.1 months after exagamglogene autotemcel infusion. No deaths have occurred during the CLIMB-131 study. [redacted]. No new safety findings were observed for 23 patients enrolled in the CLIMB-131 study including no evidence of new malignancies or new or worsening hematologic disorders long-term after exagamglogene autotemcel infusion.

Critical Appraisal

The CLIMB-131 study was an open-label extension designed to evaluate the long-term efficacy and safety of exagamglogene autotemcel in treating patients with TDT. However, the same study design, study population and outcome ascertainment limitations noted in the critical appraisal for CLIMB-111 also apply to the LTE. In addition, the available data for CLIMB-131 is limited to a greater extent due to the fact that it is an interim analysis which only a fraction of patients have completed at the time of the submission, which hampers the ability to draw definitive long-term conclusions until the follow-up is complete. The same limitations regarding external validity of the LTE (including the age and comorbidity exclusion criteria) which were identified in CLIMB-111 also apply to the LTE. Additionally, the study did not report HRQoL results for the CLIMB-131 period as of the data cut-off date, therefore long-term data on HRQoL is lacking. Another important limitation is the fact that no harms were reported after month 24 unless they were judged related to the study drug, which is an important limitation as relation to the study drug can be a subjective measure, and therefore complete harms reporting in the LTE is lacking.

Indirect Comparisons

Description of Studies

The sponsor submitted a matching-adjusted indirect comparison (MAIC) based on the data cut up to January 16, 2023 to assess the relative safety and efficacy of exagamglogene autotemcel and luspatercept as well as SoC, this defined as RBC transfusions and ICT.[36] The objective of the indirect comparisons were to provide comparative efficacy data for exagamglogene autotemcel versus appropriate comparators (luspatercept and SoC).

The feasibility of conducting an indirect comparison against the comparators of interest was considered separately for each comparator. Relevant baseline covariates identified as the key effect modifiers and/or prognostic factors were selected using a targeted literature review and clinical expert consultation (N = 7 clinical experts). Variables were ranked in order of importance and were confirmed by clinical consensus. A maximum of 3 adjustment variables were used at one time. The adjustment variables were as follows:

- Genotype (proportions of patients with β^0/β^0 vs non-β^0/β^0 genotype)
- Baseline annualized units or volume (mL/kg) of transfusions
- Age
- Sex

- Race/ethnicity (white versus non-white).

Patients from CLIMB-111 were reweighted according to the methodology proposed by Signorovitch et al.[37] The outcome assessed in the MAICs was the proportion of patients with TI6 (for CLIMB-111) and TI3 (for BELIEVE).

Efficacy Results

The report identified that there were qualitative differences between the two studies in several areas including study design, inclusion and exclusion criteria, and the timing of outcome ascertainment. The results of the quality assessment for BELIEVE reported that 2 domains were assessed as 'no', suggesting that the evidence was a low to moderate rating overall on the basis of the NICE quality appraisal checklist.

Exagamglogene autotemcel Versus Standard of Care

The individual patient data from CLIMB-111 were statistically adjusted to match the aggregate population characteristics of BELIEVE using genotype, baseline units of RBC transfusions, and age. The results showed a numeric difference in the proportion of patients with TI6 in CLIMB-111 (proportion [95% CI]: 90.0 [64.7, 97.8]) relative to the proportion of patients with TI3 on SoC (proportion [95% CI]: 0 [NR, NR]).

Exagamglogene autotemcel Versus Luspatercept

Adjustment was performed on genotype, baseline units of RBC transfusions, and age. A total of 4.0% patients in the luspatercept arm of BELIEVE had TI3, and 93.2% of patients in the adjusted CLIMB-111 arm had TI6. The rate ratio (RR) for the proportion of patients with TI was 23.3 (95% CI: 12.2 to 44.7).

Harms Results

Harms were not analyzed in the indirect comparison.

Critical Appraisal

The systematic literature review (SLR) which informed the indirect treatment comparisons is subject to some limitations, including that the results of the quality assessment were not provided for CLIMB-111 and therefore the risk of bias is not known.

There are several important limitations in the MAIC analysis to note. The MAICs were unanchored, which requires the assumption that all possible treatment effect modifiers and prognostic factors are controlled for, which is an assumption largely considered impossible to achieve and therefore adds uncertainty to the results.[38] The analysis solicited expert input to help provide a list of possible factors to include in the weighting, but limited weighting on 3 of them; a clear rationale for this was not given. Furthermore, the submission did not include details on the baseline characteristics that were not included in matching, therefore it is unknown whether there are other sources of heterogeneity in the patient population. In addition, the homogeneity assessment identified several potentially important differences between CLIMB-111 and BELIEVE which remain even after trimming patients from CLIMB-111 who would not match the BELIEVE study population. Firstly, the two studies had a different study design (BELIEVE was a double-blind randomized controlled trial [RCT] while CLIMB-111 was a single-arm Phase I/II/III) and weighting would not account for this difference. Secondly, different timing of outcome evaluation would not be controlled by weighting. CLIMB-111 was evaluated over a longer timeframe than BELIEVE, with 2 years follow up while BELIEVE lasted for 48 weeks. This suggests that the study populations and the results as reported are likely not able to satisfy the comparability assumptions required for an unanchored MAIC. An additional limitation to the MAIC methodology is a small effective sample size (ESS) after matching which imparts instability to the results. In addition, there is no summary provided of the distribution of weights from the matching, so it is unknown whether there were extreme weights applied to any of the patient data in CLIMB-111. Overall, these limitations impact a high degree of uncertainty in the results, and it is challenging to draw firm conclusions on the basis of the analysis.

There are additional limitations to the generalizability of the MAIC and the similarity of the comparator treatments which are important to note. Firstly, the clinical expert panel highlighted that luspatercept does not generally lead to TI, and approximately 20% of patients respond to it; it is not known whether the subgroup within the BELIEVE trial who reached TI differs from the main study population in meaningful ways. Furthermore, patients randomized to the SoC arm of BELIEVE would, by definition, be unable to

reach TI as transfusions are an integral part of the SoC for TDT. Other generalizability limitations include that the comparative results cannot be generalized to pediatric patients. Lastly, the MAIC did not analyze harms outcomes, therefore comparative data on the safety of treatments remains unknown. Overall, this suggests that the comparators used in the MAIC may not be wholly similar to one another, and makes it challenging to make meaningful conclusions about the comparative efficacy of luspatercept, SoC, and exagamglogene autotemcel for the outcomes that were measured in the indirect comparison.

Ethical Considerations

Patient group, clinician group, clinical expert, and drug program input, as well as relevant literature were reviewed to identify ethical considerations regarding the use of exagamglogene autotemcel for the treatment of patients aged 12 years and older with TDT.

The ethical considerations identified include those related to the following:

- **Treatment and experiences of TDT:** TDT and its treatment are physically and psychosocially burdensome and can adversely impact health-related quality of life. Some people with TDT may fulfill ambitions in education, work, and personal relationships and survive into their 60s when receiving optimal treatment and lifelong, multidisciplinary management. However, existing disease-modifying and curative therapies have limitations in efficacy, present risks, and may be inaccessible or intolerable for some. There is an unmet need for effective treatment for people with TDT who are not eligible for allogenic hemopoietic stem cell transplant (allo-HSCT) that eliminates or reduces burdens associated with lifelong RBC transfusions and ICT. Certain groups including those living far from specialized treatment centres, people experiencing financial hardship, adolescents, older people, and recent immigrants may experience disproportionate difficulty accessing and navigating effective treatment and care and may have higher unmet need for effective, one-time treatment options.
- **Evidence used in the evaluation of exagamglogene autotemcel:** Findings from the ongoing single-arm CLIMB-111 trial are consistent with a clinically meaningful impact on transfusion independence based on clinical expert input. Exagamglogene autotemcel also displays a short-term safety profile consistent with a treatment requiring myeloablative conditioning. However, there is uncertainty in: whether the effect observed is truly attributable to exagamglogene autotemcel due to methodological limitations in the CLIMB-111 trial; the efficacy and safety of exagamglogene autotemcel beyond the current trial follow-up of 24 months; and generalizability beyond the trial population (which excluded people aged 35 and older who the clinical experts noted may benefit from treatment, and people with co-inheritance of multiple types of thalassemia). Additionally, there is considerable uncertainty in indirect evidence comparing exagamglogene autotemcel to luspatercept and standard of care, and a lack of evidence to understand the value of exagamglogene autotemcel versus allo-HSCT for patients eligible for allo-HSCT. Given that exagamglogene autotemcel has been proposed as a one-time treatment with potential for life-long effects, this evidentiary uncertainty highlights the importance of robust consent conversations to support informed, autonomous decision-making and establish reasonable expectations, including for people underrepresented in the trial. Evidentiary uncertainty also has implications for health systems decision-making as it presents challenges for assessing the value of exagamglogene autotemcel relative to standard of care and understanding opportunity costs.
- **Clinical use and implementation of exagamglogene autotemcel:** Based on available evidence, the clinical experts would consider exagamglogene autotemcel given high treatment burden and unmet need for effective, one-time treatment options for people with TDT for whom allo-HSCT is not an option (especially those who do not respond to or have difficulty accessing or tolerating standard care). As a gene therapy, the use of exagamglogene autotemcel is associated with theoretical risks (e.g., genotoxicities) and known risks of myeloablative conditioning (e.g., secondary malignancy and infertility). Understandings of the level of transfusion independence required to deem exagamglogene autotemcel acceptable considering these risks may vary between and amongst clinicians and patients. This highlights the importance of shared decision-making processes eliciting individual patients' values. Clinician groups and clinical experts suggested that providing access to fertility preservation (as is common for patients undergoing oncological treatments that present risk of infertility) would help support equitable access and mitigate risks associated with infertility. Providers will need to facilitate thorough consent conversations to ensure patients and their families are aware of the benefits, risks, and evidentiary uncertainty related to exagamglogene autotemcel and have reasonable expectations. Managing expectations will be particularly important to prevent harms related to false hope, as treatment with exagamglogene autotemcel may not cure TDT, may not reverse end-organ damage and related symptoms, and may preclude eligibility for re-treatment and future gene therapies. The clinical experts and literature suggested that equitable access to exagamglogene autotemcel could be supported by addressing barriers to accessing standard TDT care, as well as barriers to accessing specialized treatment centres, undergoing prolonged hospitalization, and receiving long-term follow-up.

- **Health systems**: Uncertainty in evidence regarding exagamglogene autotemcel's clinical effectiveness and safety and, in turn, cost-effectiveness limits assessments of its value as a one-time therapy. Treatment with exa cel is resource-intensive, requiring pre-treatment, month-long hospitalization, and follow-up and administration by experienced personnel in authorized transplant and cell therapy centres. These factors, alongside current health systems capacity constraints, will severely limit the number of eligible patients that can be treated each year and necessitate prioritizing patients for access. To facilitate equitable access to exagamglogene autotemcel and other stem cell transplant-based therapies for people with hemoglobinopathies, the clinical experts proposed reserving a set number of transplant spots annually for people with TDT and sickle cell disease. Clinical experts reported that, among patients with TDT who are ineligible for all-HSCT, they would prioritize those with greatest difficulty responding to, tolerating, or accessing standard care who were still fit and eligible for treatment with exagamglogene autotemcel. As authorized treatment centres may only be situated in certain jurisdictions in Canada, consistent prioritization criteria, intra- and interjurisdictional agreements, and patient supports are important for ensuring equitable access to exagamglogene autotemcel.

Economic Evidence

Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	Patients aged 12 years and older with transfusion-dependent beta-thalassemia (TDT)
Treatment	Exagamglogene autotemcel
Dose regimen	Single infusion of at least 3 x 10^6 CD34+ cells/kg
Submitted price	Exagamglogene autotemcel, 4 to 13 × 106 cells/mL: $2,800,000 per administration
Submitted treatment cost	$2,800,000 per administration
Comparators	• Luspatercept • Standard of Care (SoC): blood transfusions and iron chelation therapy (deferoxamine, deferasirox, and deferiprone)
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (79 years)
Key data sources	• Exa-cel: CLIMB-111 study (phase 1/2/3 single-arm, single-dose open-label study) • Luspatercept: BELIEVE (phase 3, double-blind RCT) luspatercept plus SoC versus SoC alone • SoC: Efficacy assumed to be equal to baseline data from CLIMB-111
Key limitations	• The comparative clinical efficacy of exagamglogene autotemcel relative to comparators is very uncertain due to limitations with available clinical evidence including the single-arm design of CLIMB-111. The CDA-AMC clinical review suggested that the magnitude of benefit of exagamglogene autotemcel compared to luspatercept was highly uncertain due to important differences between the two trials in terms of study design, outcome ascertainment, and the validity of the comparators used in the sponsor's unanchored MAICs. • Allogeneic haematopoietic stem cell transplantation (HSCT) was excluded as a comparator in the analysis despite it being indicated for patients under 16 years of age. The cost-effectiveness of exagamglogene autotemcel versus allogeneic HSCT for patients with TDT aged 16 years and under is unknown. • The long-term effectiveness of exagamglogene autotemcel is uncertain owing to a lack of long-term follow-up data; results from the LTE were only available for a fraction of patients up to 48 months post-infusion. CDA-AMC acknowledges the ongoing nature of the CLIMB-111 and CLIMB-131 studies, however, there remains uncertainty in the long-term efficacy and safety of exagamglogene autotemcel.

Component	Description
	• The sponsor predicted a mortality benefit associated with exagamglogene autotemcel of 8 years, which is uncertain. Clinical experts consulted by CDA-AMC agreed that there are many factors that contribute to TDT-related mortality, including occurrence of complications; however, clinical expert feedback indicated that the model's predicted reduction in mortality due to fewer chronic complications appeared to be overestimated. In the absence of long-term survival data captured in the CLIMB-111 and CLIMB-131 trials, the exact mortality benefit associated with exagamglogene autotemcel is uncertain. • The population in the model does not accurately represent the proposed Health Canada indication as patients older than 35 were not enrolled in the CLIMB-111 trial. Results may be biased in favour of exagamglogene autotemcel as clinical expert feedback received by CDA-AMC noted that older patients with TDT tend to have increased likelihood of organ damage and complications due to the disease or its treatments. • Cost savings due to reduced healthcare resource utilization and frequency of complications with exagamglogene autotemcel are uncertain. Clinical experts consulted by CDA-AMC suggested that outpatient visits were likely overestimated in those who were transfusion dependent and transfusion reduced, likely biasing results in favour of exagamglogene autotemcel. Additionally, the inpatient cost associated with complication events is uncertain, as it implies all complications are treated in an inpatient setting. The assumption of inpatient treatment may overestimate the cost of treating complications, likely biasing results in favour of exagamglogene autotemcel. • Health state utility values lack face validity. The transfusion independent utility value derived from published literature suggests that patients who achieve transfusion independence have a higher quality of life than the average 20 to 24-year old Canadian.
CDA-AMC reanalysis results	• The CDA-AMC base case was derived by adjusting the mortality associated with cardiac complications and utility value associated with transfusion independence. CDA-AMC was unable to address uncertainty related to comparative clinical data, including the magnitude and duration of benefit for exagamglogene autotemcel and the predicted mortality benefit due to reduced chronic complications. Given the considerable limitations with the sponsor's MAIC and the CDA-AMC clinical review's conclusions that no concrete conclusions can be drawn from the indirect evidence about the comparative effectiveness of exagamglogene autotemcel, luspatercept was excluded from the CDA-AMC base case and included as a scenario analysis. • Results of the CDA-AMC base case suggest that exagamglogene autotemcel will be more effective (additional 10.7 QALYs) at an additional cost of $2,078,310 over the lifetime, resulting in an ICER of $194,807 per QALY compared to SoC. Exagamglogene autotemcel would require a price reduction of 55% to be considered cost-effective at a willingness-to-pay threshold of $50,000 per QALY. • Results were largely driven by the acquisition cost of exagamglogene autotemcel as well as the predicted gains in QALYs, LYs (8 years), and cost savings associated with reduced transfusions, ICT use, and chronic complications (total = $898,371). CDA-AMC notes that these findings are highly uncertain as most of the incremental QALYs were accrued in the extrapolation period (i.e., after 2 years). If the magnitude of benefit associated with exagamglogene autotemcel is less than estimated, then the ICER may be higher and a higher price reduction may be required to achieve cost-effectiveness.

HSCT = haematopoietic stem cell transplantation; ICER = incremental cost-effectiveness ratio; ICT = iron chelation therapy; LY = life years; QALY = quality adjusted life years; SoC = standard of care; TDT = transfusion-dependent beta-thalassemia.

Budget Impact

CDA-AMC identified the following key limitations with the sponsor's analysis: the market share for exagamglogene autotemcel is uncertain and may be underestimated, and the cost of RBC is paid by CBS. The CDA-AMC reanalysis was conducted from the perspective of the CDA-AMC participating drug plans. CDA-AMC reanalysis suggests that the reimbursement of exagamglogene autotemcel for the treatment of patients 12 years and older with TDT is associated with a budget impact of $64,614,557 (Year 1: $3,052,191; Year 2: $18,400,764; Year 3: $43,161,602). The estimated budget impact is sensitive to the number of patients who receive exagamglogene autotemcel.

CDEC Information

Members of the Committee:

Dr. Peter Jamieson (Chair), Dr. Sally Bean, Daryl Bell, Dan Dunsky, Dr. Trudy Huyghebaert, Morris Joseph, Dr. Dennis Ko, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Dr. Nicholas Myers, Dr. Krishnan Ramanathan, Dr. Marco Solmi, Dr. Edward Xie, and Dr. Peter Zed.

Meeting date: October 23, 2024

Regrets:

One expert committee member did not attend.

Conflicts of interest:

One expert committee member did not participate due to considerations of conflict of interest.