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Reimbursement Recommendation

Exagamglogene Autotemcel (Casgevy)

Indication: For the treatment of patients 12 years of age and older with sickle cell disease with recurrent vaso-occlusive crises

Sponsor: Vertex Pharmaceuticals (Canada) Incorporated

Final recommendation: Reimburse with conditions

Summary

What Is the Reimbursement Recommendation for Casgevy?

Canada's Drug Agency (CDA-AMC) recommends that Casgevy be reimbursed by public drug plans for the treatment of sickle cell disease (SCD) with recurrent vaso-occlusive crises (VOCs), if certain conditions are met.

Which Patients Are Eligible for Coverage?

Casgevy should only be covered to treat patients aged 12 years or older with a diagnosis of severe SCD (defined as documented severe SCD genotype and a history of at least 2 severe VOC events each year for the last 2 years). Patients aged 12 to 16 years must have normal transcranial Doppler (TCD) velocity in the middle cerebral artery and the internal carotid artery. Patients aged 12 to 18 years should not have had 2 or more abnormal TCD results. Patients also need to meet specific performance status criteria, be eligible for an autologous stem cell transplant, not have a willing 10/10 HLA-matched related donor available, and should not have previously received an allogenic-hematopoietic stem cell transplant (allo-HSCT) or gene therapy. Additionally, patients must not have a history of cancer or significant immune disorders.

What Are the Conditions for Reimbursement?

Casgevy should only be reimbursed if prescribed by a hematologist with expertise in SCD, if it is not a re-treatment (Casgevy is a one-time treatment), and if the cost of Casgevy is reduced.

Why Did CDA-AMC Make This Recommendation?

- The hallmark clinical feature of SCD is the presence of VOCs, which are episodes of sudden, severe pain. There is a need for effective treatments for patients with severe SCD who often experience repeated VOCs.
- Evidence from a clinical trial showed that most patients did not have severe VOCs for at least 12 months. In a long-term follow-up study, most of these patients continued to be free of severe VOCs. Additionally, patients reported improvement in their health-related quality of life (HRQoL).
- Based on the CDA-AMC assessment of the health economic evidence, Casgevy does not represent good value to the health care system at the public list price. A price reduction is therefore required.

Summary

- Based on public list prices, Casgevy is estimated to cost the public drug plans approximately $59 million over the next 3 years. However, the actual budget impact will depend on the number of patients who receive Casgevy, which will be influenced by the number of treatment centres and bed capacity.

Additional Information

What Is SCD?

SCD is a rare genetic condition caused by mutations in the beta-globin gene, which leads to the production of sickle-shaped red blood cells (RBCs). These sickle cells can block blood flow in small vessels, causing pain crises known as VOCs. Patients often experience severe pain and may suffer from ongoing organ damage, increased health care needs, and higher mortality rates. This affects patients' daily lives and the lives of their caregivers. In Canada, SCD affects approximately 1 in 4,200 people.

Unmet Needs in SCD

There is a need for effective treatments that can reduce complications of severe SCD, lessen the long-term treatment burden of severe SCD, and improve HRQoL.

How Much Does Casgevy Cost?

Casgevy is expected to cost approximately $2,800,000 per administration per patient.

Recommendation

The Canadian Drug Expert Committee (CDEC) recommends that exagamglogene autotemcel be reimbursed for the treatment of patients aged 12 years or older with SCD with recurrent VOCs, only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

SCD is a chronic rare genetic disease where mutations in the beta-globin gene result in an increased production of sickle hemoglobin. VOCs are the hallmark clinical feature of SCD and involve the abrupt onset of severe, acute, and debilitating pain. CDEC emphasized that there is a need for effective therapies for patients with severe manifestations of SCD, who typically present with recurrent VOCs, which are associated with ongoing organ damage, high health care utilization, and mortality.

One phase I, II, and III single-arm, open-label, multisite, single-dose study, the CLIMB-121 study (N = 63 patients enrolled and 30 patients analyzed), assessed the efficacy and safety of a single IV infusion of exagamglogene autotemcel following mobilization and myeloablative conditioning in patients aged 12 to 35 years with severe SCD who have recurrent VOCs (i.e., at least 2 protocol-defined severe VOC events per year for the 2 years before enrolment). The results of the interim analysis demonstrated that a majority of patients (96.7%; 95% confidence interval [CI], 82.8% to 99.9%) did not experience any severe VOCs for at least 12 consecutive months during follow-up. In addition, all 30 patients in the analysis did not have any hospitalizations for severe VOCs for at least 12 consecutive months. The results from the long-term extension (LTE) CLIMB-131 study — into which patients who had completed the CLIMB-121 trial enrolled — indicated that as of the data cut-off date (June 14, 2023), for the 29 patients who did not have any severe VOCs for at least 12 consecutive months, the mean VOC-free duration was 22.4 months (standard deviation [SD] = 7.2; range, 14.8 months to 45.5 months); 1 patient who did not have any severe VOCs for at least 12 consecutive months had a single VOC in the CLIMB-121 trial approximately 20.2 months after exagamglogene autotemcel infusion. Evidence for the impact on HRQoL from the Adult Sickle Cell Quality of Life Measurement Information System (ASCQ-Me) indicated that the magnitude of the change from baseline through month 24 observed with exagamglogene autotemcel may be considered clinically meaningful for the emotional, pain, social functioning, and stiffness impact subscales, as well as for the pain episode frequency subscale.

Patient input noted that for patients with severe manifestations of SCD who are ineligible for HSCT, or who do not experience a response to, cannot tolerate, or have difficulty accessing current therapies, there is an unmet need for effective treatments that reduce disease complications, decrease burdens of long-term treatment, and improve HRQoL. Despite the limitations inherent to the single-arm trial, CDEC concluded that exagamglogene autotemcel might meet the needs identified by patients.

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 $116,300 per quality-adjusted life-year (QALY) gained compared with standard of care (SOC). At this ICER,

exagamglogene autotemcel is not cost-effective at a $50,000 per QALY willingness-to-pay threshold for patients aged 12 years and older with SCD and recurrent VOCs. A price reduction is required for exagamglogene autotemcel to be considered cost-effective at a $50,000 per QALY threshold.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Patients aged 12 years or older with a diagnosis of severe SCD, defined as: 1.1. documented severe SCD genotype (beta^S/beta^S, beta^S/beta^0, or beta^S/beta$^+$) 1.2. history of ≥ 2 severe VOC events per year during the previous 2 years.	The CLIMB-121 trial enrolled patients aged 12 to 35 years who had received a diagnosis of severe SCD. Clinical experts consulted by CDEC noted that there should be no upper age limit for the reimbursement of exagamglogene autotemcel for patients with SCD. The approved Health Canada indication is for the treatment of patients aged 12 years or older with SCD.	In the CLIMB-121 trial, a severe VOC was defined as any of the following events, while receiving appropriate supportive care (e.g., pain management plan, hydroxyurea if indicated): • acute pain event requiring a visit to a medical facility and administration of pain medications (opioids or IV nonsteroidal anti-inflammatory drugs) or red blood cell transfusions • acute chest syndrome • priapism lasting > 2 hours and requiring a visit to a medical facility • splenic sequestration.
2. Patients aged 12 to 16 years must have normal TCD velocity in the middle cerebral artery and the internal carotid artery.	For patients aged 12 to 16 years, the CLIMB-121 trial enrolled patients with normal TCD velocity in the middle cerebral artery and the internal carotid artery.	—
3. Patients aged 12 to 18 years must not have a history of 2 or more abnormal TCD exam results, where an abnormal TCD reading is defined as TAMMV ≥ 200 cm/sec for nonimaging TCD and ≥ 185 cm/sec for imaging TCD.	Patients aged 12 to 18 years with a history of abnormal TCD exam results (TAMMV ≥ 200 cm/sec for nonimaging TCD and ≥ 185 cm/sec for imaging TCD) were excluded from the CLIMB-121 trial. The clinical experts noted to CDEC that TCD is part of standard care for patients with SCD, and that some patients could have an isolated abnormal TCD result at some point during their lives, but that this would likely resolve with transfusion therapy and not be detected on subsequent TCD tests.	—
4. Patients must have a Karnofsky performance status score ≥ 80% for patients aged ≥ 16 years, or Lansky performance status score ≥ 80% for patients aged < 16 years.	The CLIMB-121 trial enrolled patients who had a Karnofsky performance status score ≥ 80% for patients aged ≥ 16 years, or a Lansky performance status score ≥ 80% for patients aged < 16 years.	—
5. Patients must be eligible for autologous stem cell transplant as per the treating physician's judgment.	The CLIMB-121 trial enrolled patients with SCD who were eligible for autologous stem cell transplant as per the investigator's judgment.	—

Reimbursement condition	Reason	Implementation guidance
6. Patients must not have an available and willing 10/10 HLA-matched related donor.	The CLIMB-121 trial excluded patients with an available 10/10 HLA-matched related donor.	—
7. Patients must not have prior or current history of malignancy or myeloproliferative disorder or a significant immunodeficiency disorder.	The CLIMB-121 trial excluded patients with any of these comorbidities.	In the CLIMB-121 trial, there was no specific protocol definition of "significant immunodeficiency disorder" and this exclusion was based on clinical judgment of the health care practitioner. The clinical experts noted to CDEC that "significant immunodeficiency disorder" could include any significant disorder in adaptive or innate immunity (e.g., common variable immunodeficiency, *GATA2* deficiency, chronic granulomatous disease).
8. Patients must not have previously received any of the following: 8.1. prior allo-HSCT treatment 8.2. prior gene-editing therapy or editing product.	There is no evidence to support the use of exagamglogene autotemcel in patients who have received prior allo-HSCT treatment or prior gene-editing therapy or editing products.	—
Prescribing		
9. Exagamglogene autotemcel should only be prescribed by a hematologist with expertise in SCD.	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-editing therapy. The exagamglogene autotemcel treatment process requires mobilization and myeloablative conditioning before treatment infusion, which CDEC noted may require additional support.
10. Treatment with exagamglogene autotemcel is a one-time therapy.	At this time, re-treatment with exagamglogene autotemcel has not been established as an efficacious strategy and is not considered standard of care.	—
Pricing		
11. A reduction in price.	The ICER for exagamglogene autotemcel is $116,300 per QALY gained compared with standard of care, based on the sponsor's analysis. A price reduction of at least 39% would be required for exagamglogene autotemcel to be considered cost-effective at a willingness-to-pay threshold of $50,000 per QALY gained. The estimated price reduction is associated with high uncertainty because of limitations in the economic model that could not be	—

Reimbursement condition	Reason	Implementation guidance
	addressed. Additional price reduction may be necessary to achieve cost-effectiveness if reductions in VOCs and SCD-related complications are not sustained indefinitely, and due to infrastructure costs associated with establishing specialized treatment centres.	
Feasibility of adoption		
12. 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.	—
13. 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; hence, additional resources are likely to be required by transplant centres to accommodate patients with SCD.	—

allo-HSCT = allogenic-hematopoietic stem cell treatment; ICER = incremental cost-effectiveness ratio; SCD = sickle cell disease; TAMMV = time-averaged mean of the maximum velocity; TCD = transcranial Doppler; VOC = vaso-occlusive crisis.

Discussion Points

- **Criteria for significant unmet need are met:** CDEC noted 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 resulted in very low certainty due to the absence of a comparator arm, considering the rarity and severity of SCD and the absence of clinically effective alternatives that meet the unmet need for prevention of VOCs, 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 experts noted to CDEC that patients with severe manifestations of SCD typically present with recurrent pain crises, ongoing organ damage, and high health care utilization, which in turn have a substantial impact on their daily life and that of their caregivers. The natural trajectory is generally poor and patients are unlikely to improve spontaneously. The disease has a substantial negative impact on life expectancy and a limited number of effective therapeutic options are available, which require an ongoing commitment to therapy for continued benefit. Second-line and subsequent-line therapies include HSCT, which is the

preferred treatment option in younger patients who have a matched sibling donor who is eligible and willing to donate. The clinical experts highlighted, however, that only approximately 10% of patients in their practice have a matched related donor, resulting in HSCT not being considered widely available or accessible. The clinical experts also noted that nonmatched donations for HSCT are still considered experimental and should only be conducted within a clinical trial. In the context of this information, CDEC concluded that there is not likely to be substantial overlap between patients with SCD eligible for allo-HSCT and patients with SCD eligible for exagamglogene autotemcel, except in specific cases.

- **Generalizability:** CDEC discussed the generalizability of the results from the single-arm CLIMB-121 study with regard 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-121 only enrolled patients between the ages of 12 and 35 years means the effectiveness of treatment in patients older than 35 years is unknown; however, they agreed that patients older than 35 years who otherwise would be eligible for treatment should be eligible to receive exagamglogene autotemcel.
- **SOC in the CLIMB-121 trial:** CDEC noted that there is a lack of information regarding the treatments received during the 2 years before enrolment (i.e., the baseline period), so it was not possible to confirm whether patients enrolled in the study had an adequate trial of first-line treatments before receiving exagamglogene autotemcel. It is therefore unknown if SOC was optimized in the CLIMB-121 trial.
- **Cost of managing SCD:** CDEC discussed uncertainty in the cost of treating VOCs and SCD-related complications. The sponsor's analysis suggests that patients will have approximately 100 fewer VOCs over their lifetime, resulting in cost savings that will partially offset the acquisition cost of exagamglogene autotemcel. The sponsor's analysis assumes that all VOCs and complications are treated in an inpatient setting; however, clinical expert feedback received by CDA-AMC indicated that some events may be managed at home or in the outpatient setting. The exclusive use of inpatient costs for managing SCD-related events in the model may overestimate costs associated with SOC, biasing results in favour of exagamglogene autotemcel.
- **Price reduction:** CDEC discussed the uncertainty in the economic analysis, notably the lack of long-term data and lack of robust comparison to SOC. The estimated cost-effectiveness is strongly influenced by the large predicted gain in life-years and QALYs for patients who receive exagamglogene autotemcel compared to SOC. The committee noted that there is a lack of robust and long-term comparative evidence to support the assumed duration of reductions in VOCs and the resulting changes in resource utilization, survival, and QALYs. As such, the sponsor's model may overestimate the incremental benefits of exagamglogene autotemcel relative to SOC (considering that 99% of the incremental QALYs were based on extrapolation). The estimated price reduction of at least 39% is therefore associated with high uncertainty because of limitations in clinical 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 reductions that reflect these costs may be needed to achieve cost-effectiveness.
- **Budget impact:** CDEC discussed uncertainty in the estimated budget impact of reimbursing exagamglogene autotemcel for patients aged 12 years or older with SCD with recurrent VOCs. 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 SCD on patients and the limitations of existing therapies. CDEC acknowledged how exagamglogene autotemcel has the potential to address unmet needs for people with SCD, a condition that disproportionately impacts groups experiencing health inequities (including people who are racialized —most commonly those who are Black — and immigrants). The committee also discussed the potential safety impacts of exagamglogene autotemcel treatment (including the impacts of myeloablative conditioning on fertility). They also highlighted the importance of robust consent conversations to ensure patients understand the uncertain long-term benefits as well as known and theoretical risks, and that they have reasonable expectations of the treatment (e.g., understanding that it may not cure SCD or reverse end-organ damage). CDEC also discussed the importance of addressing potential intersecting barriers related to geography, cost, and systemic racism to equitably accessing specialized treatment centres, undergoing prolonged hospitalization, and accessing fertility preservation.
- **Ethical and equity considerations for health systems and implementation:** CDEC discussed how the high cost of exagamglogene autotemcel raises concerns regarding health care system sustainability in the context of finite resources and the absence of long-term evidence. CDEC discussed the need for lifelong follow-up of patients and the collection of long-term safety and efficacy data, which they acknowledged may require addressing limited epidemiological information and registry data on SCD 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 (including trained personnel and bed capacity to accommodate a lengthy hospital stay). The committee discussed how health system capacity constraints are expected to severely limit the number of eligible patients that can be treated each year. They noted that it is unclear whether transplant centres have additional personnel and inpatient

beds required to accommodate patients eligible for treatment with exagamglogene autotemcel. CDEC discussed the importance of establishing fair, consistent, and ethically defensible prioritization processes as well as intrajurisdictional and interjurisdictional agreements for ensuring equitable access to the therapy.

Background

SCD is a chronic, rare, genetic disease in which mutations in the beta-globin gene result in an increased production of sickle hemoglobin, giving the usually round RBCs a sickle-like shape. Clinical manifestations arise as the sickle cells disrupt circulation in the small blood vessels. VOCs are the hallmark clinical feature of SCD and involve the abrupt onset of severe, acute, and debilitating pain. The natural trajectory is generally poor. The clinical experts highlighted an unmet need in patients with severe manifestations of SCD, who typically present with recurrent VOCs, which are associated with ongoing organ damage, high health care utilization, and mortality. This, in turn, has a substantial impact on patients' daily life and that of their caregivers.

Prevalence data in Canada suggest that SCD affects 1 in 4,200 individuals. The current disease-modifying therapy in SCD includes hydroxyurea, which is used off-label to reduce complications and mortality, and transfusions, which are recommended for specific complications of SCD. Neither of these are curative therapies, and to date they remain the only treatment options currently available for many patients. HSCT is a curative therapy, having the best overall and event-free survival outcomes in the few young patients who have a matched sibling donor who is available and willing to donate.

Exagamglogene autotemcel is approved by Health Canada for the treatment of patients aged 12 years and older with SCD with recurrent VOCs. Exagamglogene autotemcel is a cellular therapy consisting of autologous $CD34^+$ hematopoietic stem and progenitor cell edited by CRISPR-Cas9 technology. Exagamglogene autotemcel is provided as a one-time single dose for IV infusion containing a suspension of $CD34^+$ cells. The minimum recommended dose according to the product monograph is 3×10^6 viable $CD34^+$ cells/kg.

Sources of Information Used by the Committee

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

- a review of 1 phase I, II, and III single-arm, open-label trial in patients aged 12 to 35 years with severe SCD who have recurrent VOCs, and 1 long-term extension study
- patients' perspectives gathered by 4 patient groups, the Sickle Cell Awareness Group of Ontario (SCAGO), the Sickle Cell Disease Association of Canada (SCDAC), the Global Action Network for Sickle Cell and Other Inherited Blood Disorders (GANSID), and NotJustYou
- input from public drug programs that participate in the Reimbursement Review process

- input from 3 clinical specialists with expertise diagnosing and treating patients with SCD
- input from 2 clinician groups, the Canadian Hemoglobinopathy Association (CanHaem) and Cell Therapy Transplant Canada (CTTC)
- 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 4 patient groups submission from SCAGO, SCDAC, GANSID, and NotJustYou. Information-gathering methods included focus groups, one-on-one conversations, surveys with patients and caregivers, and a virtual webinar on gene therapy.

Patient groups highlighted that SCD has a significant impact on every aspect of an individual's life. The multiple unpredictable complications — such as severe painful attacks, fatigue, and organ damage — pose a substantial physical and mental burden. The clinical manifestations of the disease can be quite severe and may require frequent hospitalizations, leading to absenteeism from school or work and disruptions in family life. Social stigma, fertility issues, and the burden of managing a complex painful condition have been emphasized as important sources of emotional suffering. Families also often face significant strain, which can be amplified in some instances by the financial burden of medical expenses. As such, patients placed a high value on avoiding VOCs and hospital visits, improving quality of life, facilitating access to treatment, and ensuring long-term safety.

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.

The clinical experts highlighted a significant unmet need in patients with severe manifestations of SCD. These patients typically present with recurrent pain crises, ongoing organ damage, and high health care utilization, which in turn have a substantial impact on their daily life and that of their caregivers. However, access to SOC therapies can be limited and challenging across the country, due to inconsistent coverage between jurisdictions and difficulties in obtaining blood products for a lifetime of chronic transfusions, as the Canadian blood donation pool is not always representative of most people living with SCD. Second-line and curative therapies include HSCT, which has the best outcomes in young patients who have a matched sibling donor available and willing to donate. According to the clinical experts, however, having a donor is a significant barrier for most patients, who are left with very limited therapeutic options despite substantial morbidity.

The clinical experts expect that exagamglogene autotemcel will be positioned as second-line or later-line therapy in patients with severe manifestations of SCD for whom matched sibling HSCT is not an option, and who did not have an optimal response or who became resistant to hydroxyurea or RBC transfusions; in patients who cannot access these therapies for lack of coverage, unavailability of blood supply, or due to remoteness of living area from tertiary centres; or in patients for whom these therapies are intolerable or contraindicated. These patients were identified by the clinical experts as having the greatest unmet need.

SCD is considered a rare disease; the prevalence of patients who would be considered candidates for exagamglogene autotemcel treatment is therefore limited. However, the clinical experts noted that there are limited health care resources and significant health care capacity issues at the time of this review. Individual patient prioritization is expected to be done by transplant experts, upon referral by the hemoglobinopathy specialist, as they have the necessary expertise to assess and identify patients who are the most likely to benefit from treatment while having a sufficiently good health status to sustain the toxicities of myeloablative conditioning. The clinical experts indicated that socioeconomic factors also often play an important role in the management of patients with SCD, and that nonclinical features could have a bearing in the selection of patients to receive exagamglogene autotemcel. These would include socioeconomic and geographic barriers, in addition to psychological status of the patient and support network.

Treatment with exagamglogene autotemcel requires an initial inpatient course, with a length of stay averaging 1 month. Patients should ideally be supported throughout hospitalization and follow-up by a multidisciplinary team, which would also include a pain specialist and a psychologist or social worker. Upon discharge, the treating hemoglobinopathy specialist and the multidisciplinary team would then resume outpatient care, with additional follow-up by cell therapy specialists. The clinical experts emphasized that patients are expected to be very involved in the discussion around the risks, benefits, and practicalities of exagamglogene autotemcel to make an individualized and informed decision about treatment.

Clinician Group Input

CDA-AMC received 2 clinician group submissions from CanHaem and CTTC.

Both groups noted that SCD is the most common monogenetic rare disease, currently affecting more than 5,000 individuals in Canada. The input highlighted the severity of clinical manifestations, leading to significant morbidity and early death. Goals of therapy are to improve quality of life, decrease cumulative disease burden, and maximize life expectancy. Consequently, a clinically meaningful response to treatment according to the input received would include absence of VOCs; improved quality of life; independence of transfusion; absence of treatment-related neoplasms; and stability of cardiovascular, renal, and pulmonary function.

Several unmet needs were identified from the input, including the fact that despite the effectiveness of HSCT, most patients do not have access to this treatment as they do not have a matched sibling donor. Other available treatments do not consistently stop disease progression and ongoing organ damage, and all of these are associated with important toxicities. Considering the overall limited number of therapies, the input highlighted that additional therapeutic options are needed.

The place in therapy of exagamglogene autotemcel suggested by the 2 clinician groups was consistent with the input provided by the clinical experts consulted by CDA-AMC. Therapy must be delivered in the inpatient setting, in specialized treatment centres with experience in myeloablative therapy and/or cellular therapy, and with specialty services from a multidisciplinary team.

The input noted that patients with SCD are at higher risk of myeloid malignancies, and that busulfan has been associated with myeloid malignancies and solid tumours in this patient population. The input also noted the need for equitable access regardless of a patient's geographic distance from treatment centres, which can sometimes mean relocation. The clinician groups recognized the high risk of infertility and suggested that the cost of fertility preservation be included in price negotiations.

Drug Program Input

Input was obtained from the drug programs that participate in the Reimbursement Review process. The following were identified as key factors that could potentially impact the implementation of a 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 for the review 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	

Eligibility criteria for the pivotal trial required patients to have:
• severe SCD, defined by the occurrence of at least 2 VOC events per year during the 2-year period before screening, while receiving appropriate supportive care (e.g., pain management plan, hydroxyurea). A VOC event included any of:
  ◦ acute pain event requiring a visit to a medical facility and administration of pain medications (opioids or IV nonsteroidal anti-inflammatory drugs) or red blood cell transfusions
  ◦ acute chest syndrome
  ◦ priapism lasting > 2 hours and requiring a visit to a medical facility
  ◦ splenic sequestration
• documented beta^{S}/beta^{S}, beta^{S}/beta^{0} thalassemia, or beta^{S}/beta^{+} thalassemia.
Would the aforementioned criteria from the pivotal trial be
	The clinical experts noted to CDEC that these criteria are fair. However, they noted that there are patients with severe phenotypes who would not be captured by the criteria. For example, the clinical experts highlighted those patients who had severe VOCs but whose symptoms are now well controlled with chronic red blood cell transfusions. Considering the burden of transfusions for the patients, caregivers, and health care system, the clinical experts suggested that these patients should not be excluded from the reimbursement criteria. The clinical experts also noted that stroke is considered a severe manifestation that may be included in the reimbursement criteria.
	While the treatment is not entirely comparable to bone marrow transplant, the clinical experts indicated that the selection criteria for bone marrow transplant may be a benchmark to balance the risks and benefits of therapy regarding the conditioning risks with exa-cel.
	The clinical experts confirmed to CDEC that no additional laboratory tests would be required for reimbursement purposes

Implementation issues	Response
appropriate for reimbursement purposes? Would any additional laboratory tests be required for reimbursement purposes based on the pivotal trial inclusion and exclusion criteria?	based on the pivotal trial selection criteria. CDEC recommended that exa-cel be reimbursed for those with a documented severe SCD genotype (beta^{S}/beta^{S}, beta^{S}/beta^{0}, or beta^{S}/beta^{+}) and history of at least 2 severe VOC events per year during the previous 2 years, with the VOC defined according to the pivotal trial inclusion criteria.
Eligibility criteria for the pivotal trial required patients to be aged 12 to 35 years. The sponsor noted that "if patients with SCD or TDT who are over 35 years of age are deemed fit for treatment with exa-cel, there is no plausible biologic mechanism to limit access to exa-cel to those no older than 35 years." Should patients older than 35 years be eligible to receive exa-cel?	CDEC and the clinical experts considered that patients older than 35 years of age should be eligible to receive exa-cel, as several patients beyond 35 years are likely to benefit from treatment. Therefore, CDEC recommended that that age should not be an absolute cut-off for reimbursement, but rather whether the patient is deemed fit for treatment with exa-cel.
The product is proposed as a "one-time treatment with potential for a functional cure." Are there any instances where a second dose would be considered appropriate?	The clinical experts considered it very unlikely that transplant specialists would recommend a second round of myeloablative conditioning chemotherapy. CDEC recommended that exa-cel be a one-time treatment.
Considerations for continuation or renewal of therapy	
Therapy will not be continued, per se, as exa-cel is a single-administration therapy. However, there may be a need to confirm long-term response. The sponsor noted, "Patients with SCD with recurrent VOCs who received exa-cel in CLIMB-121 were asked to enrol in the long-term follow-up study CLIMB-131 (NCT04208529), where they will be followed for up to 15 years post exa-cel infusion." How should "clinically meaningful response" be defined using objective parameters? How long should follow-up last to confirm a clinically meaningful response is maintained?	The experts suggested to CDEC that clinically meaningful response be monitored by clinicians, based on routine evaluations. These would include mainly quality of life assessments and health care utilization in terms of emergency department visits and hospitalizations. Biochemical monitoring of treatment effect may also be performed by measuring hemoglobin and fetal hemoglobin percentages, which are objective measures that can be collected peripherally. However, the clinical experts indicated that these remain surrogate outcomes of lesser importance compared to clinical outcomes. The proportion of bone marrow, genetically modified cells may theoretically inform on maintenance of effect over time; the clinical experts mentioned, however, that there is no agreed-upon threshold to be reached. The clinical experts also noted that there is a current paucity of long-term data, and complications from myeloablative conditioning may present late (thus the 15-year follow-up in the CLIMB-131 study). CDEC heard from the clinical experts that long-term data collection and patient registries for SCD are needed and would be of great value, as there are still evidence gaps regarding the long-term efficacy and safety of exagamglogene autotemcel. CDEC also noted that jurisdictions may wish to discuss with the sponsor the need for a registry for patients with SCD.
Generalizability	
The pivotal trial listed numerous exclusion criteria, but there are no related contraindications, warnings, or precautions to the therapy listed in the product monograph for most of these.	The clinical experts and CDEC agreed that patients who were previously treated with HSCT should not be candidates to receive exa-cel, as having a second round of myeloablative

Implementation issues	Response
The sponsor noted: "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-121 and CLIMB-111 demonstrating that exa-cel results in improved clinical outcomes (by significantly reducing VOCs in patients with SCD and by demonstrating transfusion independence in patients with TDT), this may no longer be a valid concern." Which, if any, of the pivotal trial exclusion criteria should be used for determining eligibility for treatment?	conditioning chemotherapy would be contraindicated. In clinical practice, exa-cel would be positioned after HSCT in younger patients who have a matched sibling donor who is eligible and willing to donate, considering the lack of long-term efficacy and safety data. Therefore, the clinical experts indicated that these patients should not be eligible for exa-cel at the time of this review. CDEC recommended that patients with an available HLA-matched donor sibling should not be eligible for treatment with exa-cel. The clinical experts also noted that patients who are ineligible for transplant or who present with unacceptable end-organ damage, at the discretion of the transplant physician, should not be candidates to receive exa-cel.
Eligibility criteria for the pivotal trial required patients to be aged 12 to 35 years, 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." Will there be interest in using exa-cel in those younger than 12 years? If so, should such patients be considered for reimbursement?	The clinical experts noted that there would likely be interest in using exa-cel in patients younger than 12 years. However, they also noted that there are several risks and uncertainty surrounding this treatment, which may limit the number of young patients to whom it may actually be offered. Some issues may resonate stronger in a younger population, such as the loss of fertility and the contraindication to receiving another gene therapy in the future. CDEC noted that there is no evidence available in patients who are younger than 12 years and that it is outside of the Health Canada indication.
Care provision issues	
The sponsor noted: • SCD and TDT are generally diagnosed through newborn screening (NBS) programs. Therefore, most cases in Canada would have already been detected via NBS and would have been referred to a reference centre to receive care. As most patients would have already received a confirmed SCD/TDT diagnosis before pursuing exa-cel treatment, these tests should not require additional health care resources specific to diagnosis the condition for the purpose of receiving exa-cel. • 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 exa-cel. Patients not diagnosed via NBS could also have their blood drawn and sent to a laboratory for testing, with review by a	The clinical experts noted to CDEC that they agree with the sponsor's assessment of diagnosis testing newborns. They indicated that newborn screening is an important diagnostic tool for identifying babies born in Canada with hemoglobinopathies. Newborn screening uses a spot screening test, which is widely available and tests for a number of conditions. Abnormal newborn screens suggestive of hemoglobinopathies are sent for confirmation with hemoglobin electrophoresis. If positive, genetic testing is often also performed. Screening and diagnosis of hemoglobinopathies would occur regardless of exa-cel eligibility. Sensitivity and specificity of blood spot testing is excellent for SCD. For adults, however, the clinical experts noted to CDEC that some people would not have had access to newborn screening, such as newcomers to Canada or those who were born before the implementation of newborn testing. These patients may be identified after they develop symptoms, or during routine screening. This is with hemoglobin electrophoresis, which is reviewed and interpreted by an expert (hematologist or hematopathologist). Genetics is often conducted to provide further information. Hemoglobin electrophoresis is widely available.

Implementation issues	Response
hematopathologist (this is how most hemoglobinopathies are diagnosed later in life). Is the aforementioned information accurate from a diagnostic standpoint? Is the blood spot screening test referenced by the sponsor widely available, in use in Canada, and most importantly, reliable and accurate?	
The sponsor noted: • Exa-cel is associated with a new treatment journey; however, most of the steps of the exa-cel treatment pathway are already being performed by experienced and dedicated 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 exa-cel patients, additional health care resources are not expected to be needed as they will largely rely on processes and health care teams that are currently in place. Are the aforementioned notes accurate from an implementation and resource standpoint?	The clinical experts noted to CDEC that they did not agree with the sponsor's assessment. The clinical experts highlighted that most centres are geared toward treating patients with malignant disease, and that very few centres have established nonmalignant funding sources and ancillary services. While the number of patients receiving exa-cel treatment is likely to be small, the source of funding for the use of resources aside from the drug cost is currently unclear. The clinical experts listed, for example, red blood cell exchange, stem cell collection, treatment with Plerixafor, and admission to inpatient ward for 1 month.

exa-cel = exagamglogene autotemcel; HLA = human leucocyte antigen; HSCT = hematopoietic stem cell transplant; NBS = newborn screening; SCD = sickle cell disease; TDT = transfusion-dependent beta thalassemia; VOC = vaso-occlusive crisis.

Clinical Evidence

Systematic Review

Description of Studies

One study was reviewed: the CLIMB-121 study (N = 63 patients enrolled and n = 30 patients analyzed) is a single-arm, phase III, ongoing, multicentre study designed to evaluate the efficacy and safety of exagamglogene autotemcel, administered after a single-agent myeloablative conditioning chemotherapy, for the treatment of SCD in patients between the ages of 12 and 35 years who have severe disease with recurrent VOCs (i.e., at least 2 protocol-defined severe VOC events per year for the previous 2 years before enrolment).

The primary outcome was the proportion of patients who had not experienced any severe VOCs for at least 12 consecutive months from 60 days after the last RBC transfusion and up to 2 years after exagamglogene autotemcel infusion. A severe VOC was defined in the CLIMB-121 study as any of the following events: acute pain event that required a visit to a medical facility and administration of pain medications or RBC transfusions, acute chest syndrome, priapism lasting more than 2 hours and requiring a visit to a medical facility, or splenic sequestration. On-trial VOC events were adjudicated by an independent external end point adjudication committee.

Secondary outcomes in the study included hospitalizations and RBC transfusions, as well as HRQoL, which was assessed using the Adult Sickle Cell Quality of Life Measurement Information System (ASCQ-Me). ASCQ-Me is a disease-specific measurement system that includes questions for adults to describe their functioning and well-being. Five question sets assess emotional, social functioning, pain, stiffness, and sleep impact; higher scores indicate improved HRQoL. For the pain episode questions (which include pain frequency and pain severity scores) and the SCD Medical History Checklist (SCD-MHC), lower scores indicate less severe pain. The minimal clinically important difference (MCID) was considered a reduction in score of 5 for pain episodes and an increase of 5 for impact subscales.

The mean age at baseline was 22 years, with 6 patients (20%) younger than 18 years. A total of 26 patients (87%) were Black or African American, 1 patient (3%) was white, and 3 patients (10%) were other. The predominant genotype was beta^{S}/beta^{S}, which is considered a severe phenotype. Within the prior 2 years, patients in the CLIMB-121 study had a mean annualized rate of 3.9 severe VOCs (SD = 2.1). The mean annualized rate of inpatient hospitalizations for severe VOCs was 2.7 (SD = 2.0), resulting in a mean annualized duration of hospitalizations of 17.1 days (SD = 14.3). Patients were annually transfused a mean of 8.4 units (SD = 14.9) of RBCs for an SCD-related indication.

Efficacy Results

The primary outcome pertaining to the absence of severe VOCs for at least 12 consecutive months was considered the preferred clinical end point. In the CLIMB-121 study, 29 of 30 patients (96.7%) who were followed for at least 16 months after exagamglogene autotemcel infusion reached the primary outcome and did not experience any severe VOCs for at least 12 consecutive months. In the 2 years preceding enrolment in the CLIMB-121 study, patients had a mean annualized rate of 3.9 severe VOCs (SD = 2.1). Results reached statistical significance against a prespecified but nonjustified sponsor-selected 50% response rate. The magnitude of the response was considered clinically meaningful by the clinical experts. There is, however, substantial uncertainty surrounding those findings, considering the limitations of the study and the fact that stroke events were not included in the definition and captured in the trial despite being considered a severe manifestation of SCD. In the absence of comparative data, the evidence is therefore very uncertain about the effect of exagamglogene autotemcel on severe VOCs when compared with any comparator.

Secondary outcomes pertaining to health care utilization were hospitalizations and RBC transfusions, which are highly resource-intensive treatments. These were deemed particularly relevant as they have a substantial impact on patients' and caregivers' daily lives. All 30 patients in the analysis did not require hospitalizations for severe VOCs for at least 12 consecutive months. In the 2 years preceding enrolment, patients had a mean annualized rate of 2.7 hospitalizations (SD = 2.0). No patient received RBC transfusions for indications related to SCD throughout the 12-month period following the exagamglogene autotemcel infusion. In the 2 years before enrolment, the mean annualized units of RBCs transfused was 8.4 (SD = 14.9). The magnitude of the response for both outcomes was considered clinically meaningful by the clinical experts. However, there is substantial uncertainty surrounding those findings. In the absence of comparative data, the evidence is very uncertain about the effect of exagamglogene autotemcel on health care utilization when compared with any comparator.

Hematological outcomes were considered as surrogate outcomes of efficacy and therefore, not as clinically meaningful to inform treatment decisions according to the clinical experts. Results suggest that there was sufficient and stable allelic editing following exagamglogene autotemcel infusion to induce fetal hemoglobin levels above the 20% threshold in all 30 patients, thus significantly changing the phenotype. However, in the absence of comparative data, the evidence is very uncertain about the effect of exagamglogene autotemcel on hematological outcomes when compared with any comparator.

HRQoL was assessed using the disease-specific ASCQ-Me measurement system. The magnitude of the mean improvement from baseline through month 24 observed with exagamglogene autotemcel across the 7 subscales ranged from 3.3 (SD = 13.3) to 21.0 (SD = 7.7), which was considered clinically meaningful by the clinical experts, especially regarding emotional impact, social functioning, and pain. However, substantial uncertainty surrounds those findings, considering the overall limitations of the trial and the subjectivity of the HRQoL assessments. In the absence of comparative data, the evidence is very uncertain about the effect of exagamglogene autotemcel on HRQoL when compared with any comparator.

Gaps in the Evidence

The short follow-up duration of 20.1 months (SD = 10.37) in the trial was highlighted as a major evidence gap, as it does not inform whether there could be a waning of efficacy leading to a loss of response over time. Limitations to generalizability include the fact that available evidence was insufficient to assess with certainty whether patients in the study had an adequate trial of first-line treatments, although exagamglogene autotemcel would be positioned as second-line or later-line therapy in clinical practice. In addition, patients who had important health care utilization that was consistent with chronic pain were excluded from the study, although they might also benefit from treatment to prevent further deterioration in their condition. However, the magnitude of the response to exagamglogene autotemcel in these patients is unknown.

Harms Results

All patients who received exagamglogene autotemcel in the CLIMB-121 study experienced at least 1 adverse event (AE). Serious adverse events (SAEs) were also relatively common, the safety profile being generally consistent with that associated with myeloablative busulfan conditioning and underlying disease according to the clinical experts. A total of 6 patients discontinued the study due to inability to achieve a full dose of exagamglogene autotemcel. One death was reported due to respiratory failure after COVID-19 infection in a patient with pre-existing lung disease and reported busulfan lung injury. The time to engraftment was an AE of special interest, and while it was considered relatively long by the clinical experts, no association was reported between infection events and time to neutrophil engraftment, or between bleeding events and time to platelet engraftment.

From the small number of patients and short follow-up duration, in the very controlled setting of the clinical trial, the clinical experts indicated that the overall harms profile of the exagamglogene autotemcel treatment process in the CLIMB-121 study did not raise any particular safety signals.

Gaps in the Evidence

There are important evidence gaps in the safety assessment of exagamglogene autotemcel that limit interpretation of the findings. The short follow-up duration could not provide information on longer-term toxicities such as malignancies. These were highlighted as a significant concern by the clinical experts due to the increased baseline risk of leukemia in patients with SCD, and the increased risk of developing secondary malignancies associated with busulfan and with the possibility of off-target editing. Although none of these notable harms were reported in the CLIMB-121 study, the follow-up duration was insufficient to assess the risk properly.

Critical Appraisal

Several limitations affected our confidence in the findings and led to a risk of bias across all outcomes assessed in the trial. The first is the absence of a control group, precluding the ability to draw any conclusions regarding the true effect of exagamglogene autotemcel compared to any comparator. As per the GRADE assessments, in the absence of a comparator group, conclusions about efficacy relative to any comparator cannot be drawn and the certainty of evidence is set at *very low*, as is typical for single-arm studies. The second limitation is the lack of information regarding the treatments received during the 2 years before enrolment (i.e., the baseline period), so that the review team could not confirm whether patients in the study had an adequate trial of first-line treatments before receiving exagamglogene autotemcel. Therefore, what the baseline actually represents in terms of treatments received and compared is unknown. The third limitation is the assessment of subjective outcomes such as VOCs and HRQoL in a single-arm trial, which is susceptible to influencing the investigator's assessment in favour of the drug. Finally, the review team noted that the sponsor made several changes to the planned study conduct once the trial was ongoing. This adds to the overall uncertainty; however, the impact on the results and on the risk of bias cannot be quantified.

Regarding generalizability, based on demographics and disease characteristics, the study population was considered mostly representative of patients with SCD seen in clinical practice who would be candidates for exagamglogene autotemcel.

GRADE Summary of Findings and Certainty of the Evidence

Methods for Assessing the Certainty of the Evidence

For pivotal studies and randomized controlled trials 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 (referring 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 the CLIMB-111 study 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 target of the certainty of evidence assessment was defined based on the presence or absence of an important effect based on thresholds identified in the literature whenever possible or informed by the clinical expert consulted for this review.

Results of GRADE Assessments

Table 3 presents the GRADE summary of findings for exagamglogene autotemcel.

The selection of outcomes for GRADE assessment was based on the sponsor's Summary of Clinical Evidence, consultation with clinical experts, and input received from patient and clinician groups and public drug plans. The following list of outcomes was finalized in consultation with expert committee members:

- clinical outcomes of SCD — VOCs:
  - patients who have not experienced any severe VOCs for at least 12 consecutive months
- health care resource utilization:
  - patients free from inpatient hospitalization for severe VOCs sustained for at least 12 months
  - reduction in units of RBC transfusions
- hematological outcomes:
  - patients with sustained fetal hemoglobin ≥ 20% for at least 12 consecutive months
  - proportion of alleles with intended genetic modification present in $CD34^+$ cells of the bone marrow
- patient-reported outcomes:
  - change over time in Adult Sickle Cell Quality of Life Measurement Information System
- harms outcomes:
  - patients with engraftment (neutrophil and platelet)
  - time to engraftment (neutrophil and platelet)
  - AEs and SAEs
  - mortality.

Table 3: Summary of Findings for Exagamglogene Autotemcel for Patients With SCD

Outcome follow-up at interim analysis data cut-off (June 14, 2023)	Patients (studies), N	Effect	Certainty[a]	What happens
Clinical outcomes of sickle cell disease VOCs				
Patients who have not experienced any severe VOCs for ≥ 12 consecutive months[b]	N = 30, new drug (1 single-arm trial)	n = 29 (967 per 1,000 patients) Reduction from baseline (95% CI): 96.7% (82.8 to 99.9)	Very low[c]	The evidence is very uncertain about the effect of exagamglogene autotemcel on severe VOCs when compared with any comparator, in the absence of comparative data.
Health care resource utilization				
Patients free from inpatient hospitalization for severe VOCs sustained for ≥ 12 months[b]	N = 30, new drug (1 single-arm trial)	n = 30 (1,000 per 1,000 patients) Reduction from baseline (95% CI): 100.0% (88.4 to 100.0)	Very low[d]	The evidence is very uncertain about the effect of exagamglogene autotemcel on hospitalization for severe VOCs when compared with any comparator, in the absence of comparative data.
Reduction in units of red blood cell transfusions	N = 30, new drug (1 single-arm trial)	Baseline mean (SD): 8.4 (14.9) Reduction from baseline (95% CI): 100.0% (100.0 to 100.0)	Very low[d]	The evidence is very uncertain about the effect of exagamglogene autotemcel on red blood cell transfusions when compared with any comparator, in the absence of comparative data.
Hematological outcomes				
Patients with sustained HbF ≥ 20% for ≥ 12 consecutive months	N = 30, new drug (1 single-arm trial)	n = 30 (1,000 per 1,000 patients)	Very low[d]	The evidence is very uncertain about the effect of exagamglogene autotemcel on HbF when compared with any comparator, in the absence of comparative data.
Proportion of alleles with intended genetic modification present in $CD34^+$ cells of the bone marrow	N = 30, new drug (1 single-arm trial)	Mean (SD) at: Month 6, [redacted] Month 12, [redacted] Month 24, [redacted]	Very low[d]	The evidence is very uncertain about the effect of exagamglogene autotemcel on intended allelic genetic modification when compared with any comparator, in the absence of comparative data.

Outcome follow-up at interim analysis data cut-off (June 14, 2023)	Patients (studies), N	Effect	Certainty[a]	What happens
Patient-reported outcomes				
Change over time in ASCQ-Me, emotional impact	N = 30, new drug (1 single-arm trial)	Change from baseline, mean (SD) at: Month 12, 9.4 (8.9), N = 23 Month 24, 10.3 (10.9), N = 16	Very low[d]	The evidence is very uncertain about the effect of exagamglogene autotemcel on the ASCQ-Me emotional impact subscale when compared with any comparator, in the absence of comparative data.
Change over time in ASCQ-Me, pain impact	N = 30, new drug (1 single-arm trial)	Change from baseline, mean (SD) at: Month 12, 5.2 (8.6), N = 23 Month 24, 9.1 (10.5), N = 16	Very low[d]	The evidence is very uncertain about the effect of exagamglogene autotemcel on the ASCQ-Me impact subscale when compared with any comparator, in the absence of comparative data.
Change over time in ASCQ-Me, social functioning impact	N = 30, new drug (1 single-arm trial)	Change from baseline, mean (SD) at: Month 12, 13.7 (11.7), N = 22 Month 24, 16.4 (11.0), N = 16	Very low[d]	The evidence is very uncertain about the effect of exagamglogene autotemcel on the ASCQ-Me social functioning impact subscale when compared with any comparator, in the absence of comparative data.
Change over time in ASCQ-Me, stiffness impact	N = 30, new drug (1 single-arm trial)	Change from baseline, mean (SD) at: Month 12, 3.6 (10.5), N = 23 Month 24, 6.6 (10.5), N = 16	Very low[d]	The evidence is very uncertain about the effect of exagamglogene autotemcel on the ASCQ-Me stiffness impact subscale when compared with any comparator, in the absence of comparative data.
Change over time in ASCQ-Me, sleep impact	N = 30, new drug (1 single-arm trial)	Change from baseline, mean (SD) at: Month 12, 4.4 (7.0), N = 23 Month 24, 4.7 (8.0), N = 16	Very low[d]	The evidence is very uncertain about the effect of exagamglogene autotemcel on the ASCQ-Me sleep impact subscale when compared with any comparator, in the absence of comparative data.
Change over time in ASCQ-Me, pain episode frequency	N = 30, new drug (1 single-arm trial)	Change from baseline, mean (SD) at: Month 12, −19.3 (8.1), N = 24 Month 24, −21.0 (7.7), N = 17	Very low[d]	The evidence is very uncertain about the effect of exagamglogene autotemcel on the ASCQ-Me pain episode frequency subscale when compared with any comparator, in the absence of comparative data.
Change over time in ASCQ-Me, pain episode severity	N = 30, new drug (1 single-arm trial)	Change from baseline, mean (SD) at: Month 12, −3.6 (12.2), N = 24 Month 24, −3.3 (13.3), N = 17	Very low[d]	The evidence is very uncertain about the effect of exagamglogene autotemcel on the ASCQ-Me pain episode severity subscale when compared with any comparator, in the absence of comparative data.

Outcome follow-up at interim analysis data cut-off (June 14, 2023)	Patients (studies), N	Effect	Certainty[a]	What happens
Harms				
Patients with engraftment (neutrophil and platelet)	N = 44, new drug (1 single-arm trial)	Neutrophil: n = 44 (1,000 per 1,000 patients) Platelet: n = 43 (977 per 1,000 patients)	Very low	The evidence is very uncertain about the effect of exagamglogene autotemcel on neutrophil engraftment when compared with any comparator, in the absence of comparative data.
Time to engraftment (neutrophil and platelet)	N = 44, new drug (1 single-arm trial)	Neutrophil, median (range): 27 days (15 to 40) Platelet, median (range): 35 days (23 to 126)	Very low	The evidence is very uncertain about the effect of exagamglogene autotemcel on neutrophil and platelet engraftment when compared with any comparator, in the absence of comparative data.
AEs (in ≥ 25% of patients) and SAEs (in ≥ 2% of patients)	N = 44, new drug (1 single-arm trial)	AEs: n = 44 (1,000 per 1,000 patients) SAEs: n = 20 (455 per 1,000 patients)	Very low	The evidence is very uncertain about the effect of exagamglogene autotemcel on AEs, SAEs, and AEs of special interest when compared with any comparator, in the absence of comparative data.
Mortality	N = 44, new drug (1 single-arm trial)	n = 1 (23 per 1,000 patients)	Very low[e]	The evidence is very uncertain about the effect of exagamglogene autotemcel on mortality when compared with any comparator, in the absence of comparative data.

AE = adverse event; ASCQ-Me = Adult Sickle Cell Quality of Life Measurement Information System; CI = confidence interval; HbF = fetal hemoglobin; PES = primary efficacy set; SAE = serious adverse event; SCD = sickle cell disease; SD = standard deviation; VOC = vaso-occlusive crisis.

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

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

[b]Statistical testing for these outcomes was adjusted for multiplicity in the trial. Statistical testing for all other outcomes was not adjusted for multiplicity in the trial; therefore, findings for these other outcomes should be considered as supportive evidence.

[c]Serious study limitations: The flexibility of the start and finish dates of the patients who have not experienced any severe VOCs for at least 12 consecutive months 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.

[d]Serious study limitations: The interim analysis provided results only for the PES, which is potentially a select sample as it represents those patients who have completed a set follow-up time in 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.

Sources: SCD Clinical Overview Addendum. Details included in the table are from the sponsor's Summary of Clinical Evidence.

Other Considerations

SCD can be considered a rare disease for which a number of patients have a significant unmet need for effective treatments. The clinical experts highlighted that patients with severe manifestations of SCD typically present with recurrent pain crises, ongoing organ damage, and high health care utilization, which in turn have a substantial impact on their daily life and that of their caregivers. The natural disease trajectory is generally poor, as it has a substantial negative impact on life expectancy, and a limited number of effective therapeutic options are available.

According to the clinical experts, this unmet need may be met by the drug under review. They indicated that exagamglogene autotemcel is not suitable for all patients with SCD; some patients respond well to standard first-line therapies and these patients would not be candidates for this treatment. In clinical practice, exagamglogene autotemcel would likely be a second-line or later-line therapy in patients with severe manifestations of SCD for whom HSCT is not an option, and who did not have an optimal response or who became resistant to hydroxyurea or RBC transfusions; in patients who cannot access these therapies for lack of coverage, unavailability of blood supply, or due to remoteness of living area from tertiary centres; or in patients for whom these therapies are intolerable or contraindicated.

Long-Term Extension Studies

Description of Studies

At the time of this review, 1 long-term extension study is in progress: the CLIMB-131 study is an ongoing prospective, multisite, observational study evaluating the long-term safety and efficacy of exagamglogene autotemcel in patients who received this treatment in the parent study, the CLIMB-121 study. It is planned that patients will be followed for a total of up to 15 years after exagamglogene autotemcel infusion. The primary objective of the CLIMB-131 study is to evaluate the long-term safety of exagamglogene autotemcel. Because the CLIMB-121 study is ongoing, only a subset of patients with SCD has completed the parent study and enrolled in the CLIMB-131 study.

Efficacy Results

As of the data cut-off date (June 14, 2023), the median follow-up duration after exagamglogene autotemcel infusion across the CLIMB-121 and CLIMB-131 studies was 19.3 months (range, 0.8 to 48.1).

Patients who experienced the outcomes in the CLIMB-121 study: All patients who experienced either the absence of any severe VOCs, no inpatient hospitalizations for severe VOCs, or fetal hemoglobin levels greater than or equal to 20%, for at least 12 months in the primary efficacy set, remained VOC-free, hospitalization-free, and above the minimal fetal hemoglobin threshold throughout the available follow-up.

Overall evaluable population (CLIMB-121 and CLIMB-131 studies): A total of 43 out of 44 patients in the full analysis set population had at least 60 days of follow-up after the last RBC transfusion and were included in the June 2023 addendum; of these, 6 patients had adjudicated VOCs and 3 patients had inpatient hospitalization for VOCs through the duration of follow-up in the CLIMB-121 and CLIMB-131 studies. Of the 6 patients with adjudicated VOCs after the 60-day washout period, 1 patient experienced a VOC in the setting of parvovirus B19 infection, |

[redacted]. It is worth noting that each of the 6 patients with adjudicated VOCs that occurred after the 60-day RBC washout period had no observed difference in pharmacological response to exagamglogene autotemcel, with HbF percentage increases after exagamglogene autotemcel treatment comparable to other patients who had no VOCs, and each had high and stable percent allelic editing.

The proportion of total hemoglobin comprised of fetal hemoglobin (%) was maintained at generally ≥ 40% from month 6 to the overall duration of follow-up.

Harms Results

A total of 17 out of 44 patients (38.6%) had more than 24 months of follow-up and were included in the long-term extension with harms results reported. Of these, no deaths occurred during the CLIMB-131 study. [redacted] No new malignancies, new or worsening hematologic disorders, or complications related to SCD occurred during the CLIMB-131 study in patients from the CLIMB-121 study.

Critical Appraisal

The same study limitations regarding the single-arm and open-label nature of the CLIMB-121 study, as well as limitations related to generalizability, also apply to the long-term extension. In addition, the available data for the CLIMB-131 study used poor reporting and were limited due to the fact that they came from an interim analysis, which hampers the ability to draw definitive long-term conclusions until the follow-up is complete. Furthermore, the population in the primary efficacy set is potentially a select sample as opposed to the full enrolled sample, and data reported so far in the larger population bring uncertainty regarding the true magnitude of the treatment effect. Finally, long-term data on HRQoL and complete harms reporting in the long-term extension are lacking.

Indirect Comparisons

No indirect treatment comparisons were submitted by the sponsor.

Studies Addressing Gaps in the Evidence From the Systematic Review

No studies addressing gaps were submitted by the sponsor.

Ethical Considerations

Patient group, clinician group, clinical expert, and drug program input and relevant literature informed this review of ethical considerations regarding the use of exagamglogene autotemcel for the treatment of patients aged 12 years and older with SCD and recurrent VOCs. The ethical considerations identified include those related to the following.

Diagnosis, treatment, and experiences of SCD: SCD and its treatment are physically and psychosocially burdensome. Existing disease-modifying and curative therapies have limitations in efficacy and present risks, and may be inaccessible or intolerable for some. For people with SCD who are ineligible for allo-HSCT, and who do not respond to, tolerate, or have difficulty accessing current therapies, there is an unmet need for effective treatments that reduce disease complications, decrease burdens of long-term treatment, decrease health resource utilization, and increase quality of life. SCD disproportionately impacts people who are racialized, most commonly Black people. People impacted by intersecting factors related to race, disability, age, geography, income, immigration status, and opioid use may have more severe disease and higher unmet need for novel treatment options due to greater challenges in accessing and navigating standard care.

Evidence used in the evaluation of exagamglogene autotemcel: Findings from the ongoing single-arm CLIMB-121 trial suggest that exagamglogene autotemcel demonstrates a potential clinically meaningful prevention of VOCs, hospitalizations, RBC transfusions, and improvements in HRQoL in patients with SCD who have recurrent VOCs. Exagamglogene autotemcel displays a short-term safety profile consistent with a treatment requiring myeloablative conditioning. However, there is uncertainty in the true effect of the treatment due to methodological limitations of the CLIMB-121 trial; the efficacy and safety of exagamglogene autotemcel beyond the current trial follow-up of 24 months; and generalizability to groups that clinical experts suggested may benefit from treatment but were not included in the clinical trial (i.e., people with severe disease but fewer than 2 VOCs in the previous 2 years, those aged 35 years and older, and those with chronic pain). Additionally, there is no evidence on comparative effectiveness and safety. The trial could not provide information on longer-term toxicities important to patients, such as the loss of fertility (a known risk of myeloablative conditioning), malignancies, and potential genotoxicities due to off-target gene editing. Given that exagamglogene autotemcel has been proposed as a one-time treatment with potential for lifelong 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 SOC and understanding opportunity costs.

Clinical use and implementation of exagamglogene autotemcel: Based on available evidence, the clinical experts would consider exagamglogene autotemcel given high unmet treatment need, severe morbidity, and premature mortality for people experiencing severe complications of SCD despite supportive care, and for whom allo-HSCT is not an option. As a gene therapy, exagamglogene autotemcel is associated with theoretical risks (e.g., genotoxicities due to off-target gene editing) and known risks of myeloablative conditioning (e.g., secondary malignancy and infertility). 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 to exagamglogene autotemcel 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 hold

reasonable expectations. Managing expectations is especially important considering that treatment with exagamglogene autotemcel may not cure SCD, will not reverse end-organ damage and related symptoms, and may preclude eligibility for re-treatment and future gene therapies. Addressing systemic racism and barriers to accessing standard SCD care may support equitable access to exagamglogene autotemcel. Equitable access may also be supported by addressing barriers to undergoing elements of the exagamglogene autotemcel treatment journey, which includes care in specialized centres, prolonged hospitalization, and long-term follow-up.

Health systems: Uncertainty regarding exagamglogene autotemcel's clinical effectiveness and safety and, in turn, cost-effectiveness, limits assessments of its value as a one-time therapy. Exagamglogene autotemcel has potential to meet unmet needs for people with SCD, a historically underfunded and underresearched condition that disproportionately impacts groups experiencing health inequities. Treatment with exagamglogene autotemcel is resource intensive, requiring pretreatment, 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. Clinical experts reported that, among people with SCD who are ineligible for allo-HSCT, they would prioritize those experiencing the most severe disease 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 and intrajurisdictional and interjurisdictional agreements are important for ensuring equitable access to exagamglogene autotemcel.

Economic Evidence

Cost and Cost-Effectiveness

Table 4: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	Patients aged 12 years and older with SCD with VOCs
Treatments	Exagamglogene autotemcel
Dose regimen	Single infusion of at least 3 × 10^6 CD34+ cells/kg
Submitted price	Exagamglogene autotemcel, 4 to 13 × 10^6 cells/mL: $2,800,000 per administration
Submitted treatment cost	$2,800,000 per administration
Comparator	SOC, composed of hydroxyurea, blood transfusions, or iron chelation therapy
Perspective	Canadian publicly funded health care payer

Component	Description
Outcomes	QALYs, LYs
Time horizon	Lifetime (78 years)
Key data source	Effectiveness of exagamglogene autotemcel informed by the CLIMB-121 study; effectiveness of SOC informed by data from the baseline period from the CLIMB-121 study
Key limitations	• The comparative efficacy of exagamglogene autotemcel relative to SoC is highly uncertain due to a lack of robust comparative data. The relative efficacy of exagamglogene autotemcel was informed by observations from patients who received exagamglogene autotemcel in the single-arm CLIMB-121 study compared observations from the same patients at baseline (assumed to represent SOC); however, there is uncertainty regarding the treatments received during the baseline period. • Allogenic HSCT was excluded by the sponsor as a relevant comparator, based on the assumption that patients who had an eligible donor would have received HSCT before reaching the age of eligibility for exagamglogene autotemcel (12 years). Canadian guidelines indicate that HSCT may be a treatment option for patients up to the age of 16 years; thus, HSCT may be a treatment option for some patients aged 12 to 16 years. The cost-effectiveness of exagamglogene autotemcel vs. allogeneic HSCT in this subgroup of patients is unknown. • The long-term effectiveness of exagamglogene autotemcel is uncertain owing to a lack of long-term follow-up data. The CLIMB-121 study and a long-term extension study (CLIMB-131) are both ongoing, but there is an absence of data beyond approximately 2 years of follow-up. Approximately 99% of the incremental QALYs predicted by the sponsor to be gained with exagamglogene autotemcel were on the basis of extrapolation. • The sponsor's model predicts an incremental gain of approximately 14 life-years with exagamglogene autotemcel. Survival was not an outcome in the CLIMB-121 or CLIMB-131 studies. While clinical expert feedback received by CDA-AMC agreed that it is reasonable to expect an extension of life with a reduction in VOCs, there remains uncertainty as to the magnitude of benefit. Owing to the multiple mortality adjustments applied by the sponsor in the model, CDA-AMC could not rule out the possibility of double counting of benefit, further increasing uncertainty with the magnitude of benefit predicted by the sponsor's model. • The sponsor's model included only inpatient cost associated with managing VOCs and other SCD-related complications. Clinical expert feedback received by CDA-AMC noted that a proportion of VOCs and complications can be managed at home or in an outpatient setting. The exclusive use of inpatient costs may overestimate the cost of managing SCD-related complications, thus biasing the results in favour of exagamglogene autotemcel. • The sponsor assumed that those who receive exagamglogene autotemcel would have either complete prevention of severe VOCs or have no change in the number of severe VOCs experienced. This is not supported by data from the CLIMB-121 study, in which a proportion of patients in the full analysis set experienced a reduction (but not prevention) in the number of severe VOCs.
CDA-AMC reanalysis results	• CDA-AMC was unable to address the lack of robust comparative clinical evidence and other identified limitations in the submitted economic evaluation. CDA-AMC could therefore not provide a more reliable estimate of the cost-effectiveness of exagamglogene autotemcel. • The sponsor's analysis suggests that exagamglogene autotemcel will prevent approximately 100 severe VOCs over a lifetime horizon and reduce the number and duration of SCD-related complications, resulting in cost savings of approximately $840,000 from VOCs and complications avoided. The sponsor anticipates that these cost saving will partially offset the acquisition cost of exagamglogene autotemcel ($2,800,000), resulting in an ICER of $116,300 per QALY gained compared with SOC (incremental costs = $1,913,894; incremental QALYs = 16.46). Based on the sponsor's analysis, a price reduction of approximately 39% would be required for exagamglogene autotemcel to be considered cost-effective at a willingness-to-pay threshold of $50,000 per QALY gained. • Almost all (99%) of the incremental gain in QALYs predicted by the sponsor's model was derived from

Component	Description
	extrapolation. If the magnitude of benefit between exagamglogene autotemcel and SoC is less than estimated by the sponsor or if costs of managing VOCs or SCD-related complications are lower than included in the sponsor's model, a higher price reduction may be needed.

CDA-AMC = Canada's Drug Agency; HSCT = hematopoietic stem cell transplant; ICER = incremental cost-effectiveness ratio; LY = life-year; QALY = quality-adjusted life-year; SCD = sick cell disease; SOC = standard of care; VOC = vaso-occlusive crisis.

Budget Impact

CDA-AMC identified the following key limitations with the sponsor's analysis: the number of patients with SCD with recurrent VOCs in Canada is uncertain, the number of people expected to receive exagamglogene autotemcel is uncertain and may be underestimated, the cost of RBCs is paid by Canadian Blood Services, and confidential prices of SOC. 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 aged 12 years and older with SCD with recurrent VOCs would be associated with a budget impact of $59,373,150 (year 1 = $0; year 2 = $15,444,927; year 3 = $43,928,392). 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: Five expert committee members did not attend.

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

Canada's Drug Agency
L'Agence des médicaments du Canada
Drugs. Health Technologies and Systems. Médicaments, technologies de la santé et systèmes.

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Questions or requests for information about this report can be directed to Requests@CDA-AMC.ca.