CADTH REIMBURSEMENT REVIEW

Patient and Clinician Group Input

exagamglogene autotemcel (TBC)

(Vertex Pharmaceuticals (Canada) Incorporated)

Indication: Exagamglogene autotemcel (exa-cel) is an autologous genome edited hematopoietic stem cell-based therapy indicated for the treatment of patients aged 12 years and older with: • sickle cell disease (SCD) with recurrent vaso-occlusive crises (VOCs)

May 13, 2024

Patient Group Input

Name of Drug: Exagamglogene Autotemcel

Indication: Sickle Cell Disease, Thalassemia Disorder.

Name of Patient Group: Global Action Network for Sickle Cell & Other Inherited Blood Disorders (GANSID) on behalf of its Canadian member organizations listed below:

1. Thalassemia Foundation of Canada

2. Sickle Cell Awareness Group of Ontario (SCAGO)

3. Sickle Cell Awareness Network of Saskatchewan

4. Sickle Cell Disease Association of Atlantic Provinces

Author of Submission: Lanre Tunji-Ajayi, M.S.M

1. About Your Patient Group

The GANSID is a global organization registered in the USA as a charitable organization and in Canada as a not-for-profit entity. It is governed by a board of directors and led by a CEO who runs the day-to-day operations of the organization. GANSID comprises of 60 member organizations across 20 countries

In Canada, the GANSID has 4 member organizations (listed above) which are autonomous in their operations.

Website: https://inheritedblooddisorders.world/

2. Information Gathering

Data was gathered through:

a). The survey of people affected by Sickle Cell and Thalassemia Disorders in Canada

b). One-on-One conversation with people affected by Sickle Cell and Thalassemia Disorders in and outside of Canada.

Sickle Cell Disease: The Sickle Cell Awareness Group of Ontario (SCAGO) conducted a survey of 45 individuals living with sickle cell disease and their caregivers. It also held a one-on-one interview/conversation with 10 peers living with sickle cell disease. Of the people surveyed, 57% have sickle cell disease and 43% are caregivers of people living with the disease.

Thalassemia Disease: The Thalassemia Foundation of Canada (TFC) conducted a survey of 80 people across Canada including the province of Quebec. 61 of which are individuals living with thalassemia disorder and 19 are caregivers of people living with thalassemia.

The GANSID also received comments from peers living with Sickle Cell and Thalassemia Disorders outside of Canada.

3. Disease Experience

Impact of Disease on Day-to-Day Life and Quality of Life of People Living with Sickle Cell and Thalassemia Disorders:

Sickle Cell Disease: The impact of sickle cell disease on patients' quality of life are varied and differ from individual to individual. In general, sickle cell disease will affect every aspect of the affected person's life. A few examples of how it may affect someone living with the disease are provided below:

a). It may cause damage to vital organs of the body such as the kidney, liver, heart. It may also cause blindness, deafness and premature death.

b). It may cause disruption in family life balance whereby the affected spent too much time on admissions in hospitals and may not be able to manage the disease along with work and family life expectations. This may cause conflicts at home leading to higher rates of separation and divorce in marriage.

c). Frequent hospitalizations leading to absenteeism in school and work, and resulting in lost education and job opportunities. It also reduces the opportunity for the affected to contribute meaningfully to their community and society.

d). Recurrent ischemic priapism is a common morbidity among men with sickle cell disease and based on research studies, men with sickle cell disease experiences higher sexual dysfunction compared to men without sickle cell disease. Priapism affects self-esteem and self-image of the affected, leading to additional psychosocial issues. You may learn more at the link here: https://ashpublications.org/bloodadvances/article/4/14/3277/461435/Men-with-sickle-cell-disease-experience-greater

e). Sickle Cell Disease affects fertility in males and females living with the disease.

f). Many of the respondents in the survey also advised that the disease is very tiring and this is especially true when pain medication doesn't work to effectively control their pain or when healthcare providers are second-guessing the severity of the pain they are experiencing.

g). People living with sickle cell disease are often stigmatized and labelled as drug-seeking in Canadian hospitals. Without the disease, many felt that they might not have witnessed the same level of discrimination from the Canadian health care system.

Thalassemia Disease: The impact of thalassemia disorder is most felt by people living with transfusion dependent beta thalassemia major. Based on the survey conducted by the Thalassemia Foundation of Canada, this subset of Thalassemia patients has to go through recurring transfusion treatment which could be exhaustive in its own. Furthermore, the survey respondents advised that:

h). They need to orientate all facets of their life towards their transfusion cycle. A respondent stated that they need to budget 7-10 days of good health post-transfusion towards the maintenance and upkeep of family, and yet they still need to find pockets of time where one can do things that also bring joy.

i). The disorder has made them unable to participate in family activities. This could bring feelings of guilt and disrupt family dynamics.

j). Thalassemia and the continuous blood transfusion program contribute to lower self-esteem and psychological well-being of peers with Thalassemia.

k). They experience less energy to carry out day-to-day activities, exercise and attend social functions, especially as it gets closer to the time for transfusion

l). Excess iron from the frequent transfusion treatment could lodge in vital organs of the body causing damage to these vital organs and as such, patients with Thalassemia do not only go through continuous blood transfusion regimen, they also must go through iron chelation therapies.

While some patients do well on oral chelation therapies, there are those that require desferal as their chelation treatment option. Desferal must be administered subcutaneously over a period of 10-12 hours each evening. Even for

those that can take the oral chelation therapies, other side effects such as nausea, gastrointestinal issues, rash, kidney issues and lowering of white blood cells can be problematic and even dangerous.

In addition to iron chelation, a multitude of other routine diagnostic tests are required and thalassemia patients must receive multi-disciplinary care, preferably at a specialized treatment centre.

m). Having a low hemoglobin prior to transfusion also affects all aspects of life due to chronic fatigue

Impact of Disease on Day-to-Day Life and Quality of Life of Caregivers of People living with Sickle Cell and Thalassemia Disorders:

Sickle Cell Disease:

Sickle Cell Disease does not only affect the individual living with the disease but also their families and friends. Caregivers and other family members advise that due to their loved ones living with this disease, they themselves suffer from:

a). Emotional and psychological deficits. Many blame themselves for passing the gene to their child, and they experience guilt feelings, especially when their child is going through the episodic pain crisis associated with the disorder.

b). Disruption in family balance life. Given the unpredictability of the complications association with the disease, planned family activities including vacations are sometimes cancelled at the last minute.

c). Inability to work at all or full time due to their child's frequent hospitalizations as a result of the disease.

d). Depression and anxiety due to their child's illness resulting in low quality of life.

Thalassemia Disorder:

The caregivers of people with thalassemia are very much affected by the disorder and they provided that:

e). When parents of children with thalassemia receive the gut-wrenching news that their child has thalassemia disorder (usually when the child is at a very young age), they are overwhelmed with feelings of guilt that they have passed this on to their child genetically and then spend the next 18+ years caring for their child that has intense medical needs, which requires time off work and causes extensive worrying and stress. Some find it daunting, especially those new to the country who don't speak French/English and those who don't know how to navigate the healthcare system.

f). They suffer emotional pain when watching their child endure being poked multiple times to get an IV in. A respondent advised that he could see his son tensed up when he has to get his IV in.

g). They go through exhaustion due to multiple appointments including routine blood transfusions for their child. For many, the blood transfusion schedule is monthly while for others it could be less or more frequent than every 4 weeks.

h). They may incur financial stress due to time off work and out of pocket expenses for medications, travel to the hospital, etc.

i). The disorder could put stress on the whole family and also hinder family activities including vacations.

j). It is stressful to have to take time off from work multiple times a month for transfusions, and other appointments such as: MRIs, hearing and eye tests required for their child's treatment

4. Experiences with Currently Available Treatments

Thalassemia Disorder:

a). Impact on personal and social life- Patients and family members spent long days at the hospital during transfusions and other appointments, impacting time and energy left for other family and life activities.

b). Time- Iron chelation is an essential treatment for patients with thalassemia who are on continuous blood transfusion. While many do well on oral chelators, there is the subset of patients that do well on desferal which also require additional appointment and travel time to the hospital.

c). Treatment procedure- Caregivers advised that their children are not very fond of the essential but painful needle poking before an IV could be put in for treatment.

Sickle Cell Disease:

Most people with sickle cell disease in Canada are on modifying therapies such as hydroxyurea (HU) and blood transfusion treatments.

d). Hydroxyurea- This is a standard therapy for sickle cell disease. It is supplied in capsule form in Canada and would require compounding into suspension for younger patients. Unfortunately, not every pharmacy is able to support families in compounding the drug into liquid suspension. As such, family members may have to do the compounding themselves- which might not be as accurate as it should be done. Furthermore, they may also be exposed to inhaling the drug, resulting in potential health hazard for them.

e). Blood Transfusion- Peers with sickle cell disease on continuous blood transfusion face challenges around taking time off work to attend their routine transfusion appointments.

f). Limited Treatment Option- There is a subset of patients with sickle cell disease that the current treatment options do not work for and unfortunately, these patients will continue to experience preventable morbidities and premature death except there are new treatments that they could be try.

5. Improved Outcomes

Thalassemia Disorders:

Based on the survey conducted by the TFC, respondents' expectations for the new treatment include:

a). Improved Quality of Life- Families would like to no longer be transfusion dependent. A respondent also provided that they would want their daughter to spend life as normal as their peers.

b). Low Risk & Post-Treatment Support- Respondents expect this treatment to be accessible, efficacious, well researched, with a reasonable balance of risk to reward, and good support infrastructure post treatment.

c). Access- Families expect that it will be covered by the Provincial Drug Programs, and be an available option to anyone who is a good candidate for it regardless of economic means.

d). Cure- The new treatment to cure Thalassemia with no need for further transfusions.

e). Safety and Efficacy- The new treatment will be safe and effective.

Sickle Cell Disease:

Based on the survey and interview conducted by the SCAGO, respondents' expectations for the new treatment include:

f). Risks and Side Effects- Families are happy for a cure, however, they expect the benefits of the cure to outweigh the risks and side effects. According to some respondents, the long-term safety of these therapies should be explored and the proponents of these treatments must provide empirical evidences of outcomes and long-term effect on participants.

Many of the respondents would also like to see that the new treatment has reduced risks especially around immune systems and fertility.

g). Ease of Access- Families expected the new treatment to be accessible to individuals who desire to explore it as a treatment option regardless of financial means.

h). Improved Health Outcomes- Families expect the new therapy to eliminate the pain crisis and end-organ damage experienced by people living with the disease.

i). Lasting solution for all: Families expect the new treatment to cure sickle cell disease and free all from any complications relating to the debilitating disease.

6. Experience with Drug Under Review

Sickle Cell Disease: None of the patients surveyed or interviewed by the SCAGO had experience with the drug under review.

Thalassemia Disorder: None of the patients surveyed by the TFC had experience with the drug under review

7. Companion Diagnostic Test

None of the patients surveyed and interviewed had experience with the drug nor biomarker testing regarding the drug under review

8. Anything Else?

As a global organization supporting people affected by hereditary blood disorders, the GANSID believes that the world is in exciting times where sickle cell and thalassemia disorders are concerned.

This is especially true with many pharma having increasing interest in hemoglobinopathies and developing innovative cure therapies in this space. However, access to these therapies may be hindered due to funding for the therapies from country level health systems.

The GANSID is of the opinion that the lifetime costs of sickle cell and thalassemia disorders to the persons living with these life-altering diseases and their family members (not limited to the cost of treatment, admissions in hospitals, loss of school and work times, loss of productivity in society, disrupted family life balance, and mental health deficits) is far more expensive than the cost of the new treatment.

As such, the GANSID is submitting to CADTH that it is in the best interest of the people with sickle cell and thalassemia disorders as well as the Canadian Health System to ensure:

- the safety of the new treatment;

-access to the new therapy by patients who are good candidate for it.

Appendix: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH reimbursement review process, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group

Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.

No

1. Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.

   No

2. List any companies or organizations that have provided your group with financial payment over the past 2 years AND who may have direct or indirect interest in the drug under review.

Table 1: Financial Disclosures

Check Appropriate Dollar Range with an X. Add additional rows if necessary.

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Vertex Inc			x	

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

Name: Lanre Tunji-Ajayi, M.S.M
Position: President/CEO
Patient Group: Global Action Network for Sickle Cell & Other Inherited Blood Disorders (GANSID)
Date: May 11th, 2024

Name of Drug: < exagamglogene autotemcel >

Indication: < Sickle cell disease (SCD) >

Name of Patient Group: <NotJustYou>

Author of Submission: <Ufuoma Muwhen>

1. About Your Patient Group

Describe the purpose of your organization. Include a link to your website.

NotJustYou is a Sickle Cell Support Organization that is devoted to creating support systems that provide tools and resources for individuals and families affected by sickle cell disease. Our mission is to be an easily accessible, broad support network that educates, motivates, and celebrates individuals and families affected by sickle cell disease.

Our vision is to shed celebratory light on sickle cell disease, and provide a sense of hope for affected individuals.

Website: https://notjustyou.ca/

2. Information Gathering

CADTH is interested in hearing from a wide range of patients and caregivers in this patient input submission. Describe how you gathered the perspectives: for example, by interviews, focus groups, or survey; personal experience; or a combination of these. Where possible, include **when** the data were gathered; if data were gathered **in Canada** or elsewhere; demographics of the respondents; and **how many** patients, caregivers, and individuals with experience with the drug in review contributed insights. We will use this background to better understand the context of the perspectives shared.

Focus groups from January – May 2024 (4 groups of 5-10 patients, 2 caregivers)

One-on-one conversations with patients from 2022-2024 (25 patients, 3 caregivers)

Personal patient experience

3. Disease Experience

CADTH involves clinical experts in every review to explain disease progression and treatment goals. Here we are interested in understanding the illness from a patient's perspective. Describe how the disease impacts patients' and caregivers' day-to-day life and quality of life. Are there any aspects of the illness that are more important to control than others?

For 16 years, I battled this condition alongside my family, experiencing numerous traumatic episodes and navigating the challenges it posed to our everyday lives. Sickle cell disease not only affected me physically but also took a toll on my mental and emotional well-being, as well as that of my loved ones. The constant vigilance and fear of crises robbed me of many of the simple joys of life and compelled me to create NotJustYou—a beacon of hope for those facing similar struggles.

In 2016, I underwent a reduced intensity bone marrow transplant, an experience that profoundly shaped my perspective on treatment and resilience. The transplant process itself was both physically and emotionally demanding. From initial consultations to the post-transplant period, every step was full of uncertainty and challenges. Having undergone this process, I understand firsthand the

importance of accessible and effective treatments for sickle cell disease. Moreover, I recognize the critical intersection between sickle cell disease, mental health, and reproductive health, areas often overlooked in discussions surrounding this condition. The financial burden associated with treatment further exacerbates the challenges faced by individuals and families affected by sickle cell disease, underscoring the urgent need for innovative solutions.

4. Experiences With Currently Available Treatments

CADTH examines the clinical benefit and cost-effectiveness of new drugs compared with currently available treatments. We can use this information to evaluate how well the drug under review might address gaps if current therapies fall short for patients and caregivers.

Describe how well patients and caregivers are managing their illnesses with currently available treatments (please specify treatments). Consider benefits seen, and side effects experienced and their management. Also consider any difficulties accessing treatment (cost, travel to clinic, time off work) and receiving treatment (swallowing pills, infusion lines).

Hydroxyurea: whilst effective, has seen to be ineffective or loose it's efficacy in some patients. Some patients struggle to mediation compliance

NSAIDS: some-what effective, many patients find these medication are not strong enough for pain management

Oral opioids: whilst effective for pain-management, addiction is always a risk factor, along with skin challenges and constipation.

Red-cell exchange: effective, but not a good long-term treatment as patients tend to need them more frequently and take longer to recover from each exchange over time

Reduced Intensity Haploidentical Bone Marrow Transplantation: effective, but not accessible due to lack of donors. Many patients have concerns with side effects such a fertility.

5. Improved Outcomes

CADTH is interested in patients' views on what outcomes we should consider when evaluating new therapies. What improvements would patients and caregivers like to see in a new treatment that is not achieved in currently available treatments? How might daily life and quality of life for patients, caregivers, and families be different if the new treatment provided those desired improvements? What trade-offs do patients, families, and caregivers consider when choosing therapy?

Patients consistently express their desire for better access to treatment, information, and comprehensive support services, highlighting the pressing demand for advancements in the field. Beyond effectiveness for relieving primary symptoms AND less adverse side effects than tradtional bone marrow transplants, but the new treament should be accompanied by wrap-around supports (access to treatment information, mental health, reproductive health, and financial support) as they undergo and recover from treatment.

6. Experience With Drug Under Review

CADTH will carefully review the relevant scientific literature and clinical studies. We would like to hear from patients about their individual experiences with the new drug. This can help reviewers better understand how the drug under review meets the needs and preferences of patients, caregivers, and families.

How did patients have access to the drug under review (for example, clinical trials, private insurance)? Compared to any previous therapies patients have used, what were the benefits experienced? What were the disadvantages? How did the benefits and disadvantages impact the lives of patients, caregivers, and families? Consider side effects and if they were tolerated or how they were managed. Was the drug easier to use than previous therapies? If so, how? Are there subgroups of patients within this disease state for whom this drug is particularly helpful? In what ways? If applicable, please provide the sequencing of therapies that patients would have used prior to and after in relation to the new drug under review. Please also include a summary statement of the key values that are important to patients and caregivers with respect to the drug under review.

<Enter Response Here>

7. Companion Diagnostic Test

If the drug in review has a companion diagnostic, please comment. Companion diagnostics are laboratory tests that provide information essential for the safe and effective use of particular therapeutic drugs. They work by detecting specific biomarkers that predict more favourable responses to certain drugs. In practice, companion diagnostics can identify patients who are likely to benefit or experience harms from particular therapies, or monitor clinical responses to optimally guide treatment adjustments.

What are patient and caregiver experiences with the biomarker testing (companion diagnostic) associated with regarding the drug under review?

Consider:

- Access to testing: for example, proximity to testing facility, availability of appointment.
- Testing: for example, how was the test done? Did testing delay the treatment from beginning? Were there any adverse effects associated with testing?
- Cost of testing: Who paid for testing? If the cost was out of pocket, what was the impact of having to pay? Were there travel costs involved?
- How patients and caregivers feel about testing: for example, understanding why the test happened, coping with anxiety while waiting for the test result, uncertainty about making a decision given the test result.

<Enter Response Here>

8. Anything Else?

Is there anything else specifically related to this drug review that CADTH reviewers or the expert committee should know?

Vertex Pharmaceuticals has been an invaluable ally in NotJustYou's mission to empower individuals and families affected by sickle cell disease. Their unwavering support has extended into active engagement and collaboration in our advocacy efforts. Vertex has demonstrated a genuine commitment to amplifying our impact and advancing the cause of sickle cell awareness and treatment. Their dedication to knowledge mobilization and patient-centric innovation has greatly enriched our programs and initiatives, enabling us to reach a broader audience and deliver meaningful support. It is imperative that Vertex Pharmaceuticals' groundbreaking treatment receives approval in Canada, as it represents a significant step forward in improving the lives of sickle cell disease patients across the country

Appendix: Patient Group Conflict of Interest Declaration

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4. List any companies or organizations that have provided your group with financial payment over the past 2 years AND who may have direct or indirect interest in the drug under review.

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Vertex Pharmaceuticals		X		

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Name: Ufuoma Muwhen
Position: Chief Executive Officer
Patient Group: NotJustYou
Date: May 13, 2024

Name of Drug: Exagamglogene Autotemcel
Indication: Sickle Cell Disease

Name of Patient Group: Sickle Cell Awareness Group of Ontario (SCAGO)
Author of Submission: Lanre Tunji-Ajayi, M.S.M

1. About Your Patient Group

The Sickle Cell Awareness Group of Ontario (SCAGO) is a leading charitable patient organization providing evidence-based support to families with children, adolescents, and adults, with sickle cell disease across the four regions of the province. It supports clinical research and engages in psycho-social research, health promotion, patient and care providers' education, community awareness, and the development of best practices guidelines.

It engages in evidentiary advocacy on their behalf with the government, schools, and the healthcare system to improve the lives of Ontarians living with sickle cell disease (SCD)—and ultimately to find a universal cure for this devastating disease.

Website: www.sicklecellanemia.ca

2. Information Gathering

Data was gathered through survey of people affected by sickle cell disease in Canada and through one-on-one interviews of patients. People that completed the survey include 45 individuals living with sickle cell disease and their caregivers. We also had a one-on-one interview with 10 peers with sickle cell disease. Of the people surveyed, 57% have sickle cell disease and 43% are caregivers.

3. Disease Experience

Based on the feedback from the survey and the people we interviewed, the recurring themes around how sickle cell disease impacts patients' and caregivers' day-to-day life and quality of life are provided below:

a) SCD makes it difficult to perform basic activities even if patients would like to; the strain it has on family and friends… It's exhausting and more importantly, the intensity of the crisis and the type of management given at the hospitals are demoralizing most of the time.

b) Really tiring, sometimes pain could be controlled but there are times when pain medication doesn't work

c) SCD affects the quality of life of patients in different and numerous ways. It affects patients physically preventing them from going about day to day activities such as making a living, …getting an education, having a social life, and even forming and keeping relationships. For caregivers, it could also considerably deplete their resources financial, psychological, metal etc.

d) The frequency of crisis is a major factor to control

e) SCD affects ability to engage in sports and other physically demanding activities because of tiredness, pain, and fear of having a crisis. For me, minimizing pain and increasing energy are the two most important aspects I'd like to control.

f) Sickle cell disrupts my daily life as it makes me uncertain about my plans and commitments. I could be a normal healthy person this minute and fall apart the very next minute. The most important aspect requiring attention is the urgency at which healthcare workers attend to patients. There should be a standard protocol that requires that SCD patients should not be left unattended to. Sometimes, I have to wait for over 6 hours in indescribable pain and that's very bad. That requires a lot of attention and control.

4. Experiences with Currently Available Treatments

Please find below a few of the responses from the feedback we pulled from the survey and the people we interviewed:

a) Exhausting, a lot of appointments, dialysis, a lot of pills and pain, sick of it! feel like giving up sometimes but I don't… I try to stay positive

b) My son currently takes hydroxyurea so it manages the illness. It increases his fetal haemoglobin and keeps him crisis free since he was 14 years old. He is now 22 years old. He previously had crises three times which impacted his schooling.

c) It hasn't been easy as it is time/ finance consuming and yet no affordable cure in sight

d) I have been able to manage the disease well with opioid therapy and Hydroxyurea therapy. With both treatments, I don't experience major side effects so this has motivated me to continue. However, the cost and, at some point, accessing Hydroxyurea was a challenge. I've been taking Hydroxyurea consistently for 10 years so I've become habituated to swallowing the pill. Nevertheless, the demand for regular bloodwork is something I have not grown accustomed to. It requires taking time to travel to clinic, paying for parking, and leaving with scarred veins. Despite these concerns, I am generally managing well, with the treatment options provided to me.

e) I still partake in clinical trials because I have not found a medication that works for me. My body reacts very badly to Hydroxyurea and I still have not found a suitable treatment plan. Currently, I use vitamins and supplements and I have to go slowly with everything going on in my life so that I do not fall apart completely. I have experienced lots of benefits from using Glutamine as it reduces fatigue and helps keep my energy level steady. I also use a Yam vitamin supplement. Both supplements are not free and are not covered under my insurance. Even finding a health insurance policy that was willing to cover me as a person with SCD was a big hassle as most companies refuse to cover people with pre-existing health conditions.

5. Improved Outcomes

a) Cure for the disease... When choosing therapy, if the benefits outweighs the risks and side effects, then it is worth trying.

b) Current available treatments such as BMT, Stem Cell transplant and Gene editing can be made accessible and affordable to individuals who desire to explore these treatments. Long term safety of these therapies should to explored and the proponents of these treatments must provide empirical evidences of outcomes and long- term effect on participants.

c) Diminishing risks such as a weakened immune and risk of fertility issues.

d) New agents that would reduce the frequency of crisis experienced by sufferers.

6. Experience with Drug Under Review

None of the patients we surveyed or interviewed had experience with the drug under review. However, the key values that are important to patients and caregivers with respect to the drug under review are that the drug:

a) Would bring about a rebirth and patients would be pain free and able to live a normal life.

b) Reduce hospital visits, pain/pills.

7. Companion Diagnostic Test

None of the patients surveyed and interviewed had experience with the drug nor biomarker testing regarding the drug under review

8. Anything Else?

Some of the surveyed hoped that the reimbursement application for this therapy goes through to ensure that patients with sickle cell disease that might not qualify for Stem Cell Transplantation will have another chance of being cured.

Some others think that the therapy should be available to all patients with sickle cell disease regardless of if they have a donor to support them with stem cell transplantation or not.

1 Appendix: Patient Group Conflict of Interest Declaration

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and who provided it.

No

2. Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.

   Yes, worked with the Global Action Network for Sickle Cell & Other Inherited Blood Disorders to put the survey together

3. List any companies or organizations that have provided your group with financial payment over the past 2 years AND who may have direct or indirect interest in the drug under review.

2 Table 1: Financial Disclosures

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Name: Lanre Tunji-Ajayi, M.S.M

Position: President/CEO

Patient Group: Sickle Cell Awareness Group of Ontario

Date: April 26th, 2024

CADTH

Clinician Group Input

CADTH Project Number: SG0831-000

Generic Drug Name (Brand Name): exagamglogene autotemcel

Indication: Sickle cell disease

Name of Clinician Group: Canadian Hemoglobinopathy Association (CanHaem)

Author of Submission: Catherine Corriveau-Bourque

1. About Your Clinician Group

The Canadian Hemoglobinopathy Association/ L'Association canadienne d'hémoglobinopathie (CanHaem) is a not for profit organization that was established in 2013 and is composed of healthcare providers dedicated to the care of individuals in Canada with hemoglobinopathies. CanHaem aims to provide multidisciplinary expertise and advance the quality of care to patients across the country through education, research, and advocacy in collaboration with key partners.

https://www.canhaem.org/

2. Information Gathering

The proposed submission was drafted by a CanHaem physician member and then shared amongst other members (including the CanHaem chair) for review. In addition, patient views on access were solicited within the clinic environment. The topic was also discussed with allied health professionals (other CanHaem members). Additional information sources include guidelines, standards of practice, and published research.

3. Current Treatments and Treatment Goals

Sickle cell disease (SCD) is the most common monogenic disease, and is estimated to be the most common "rare" disease in Canada (currently affects > 5000 Canadians). The population affected by the disease is rising swiftly due to immigration from Sub-Saharan Africa, the Middle East, India and the Caribbean. An estimated 70,000-100,000 Americans suffer from Sickle Cell Disease.

Sickle cell disease causes the production of abnormal hemoglobin which alters the structure and function of the red blood cell. This leads to blood vessel occlusion, rapid cell turnover, inflammation and cell death. Patients suffer from chronic anemia, severe acute debilitating pain (vaso-occlusive crisis), risk of serious infection (compromised immune system), acute respiratory failure (acute chest syndrome), chronic pain, ischemic and hemorrhagic stroke, liver disease, nephropathy and neurovascular disease. Every organ in the body is affected including their bones (osteoporosis, avascular necrosis of femoral/humeral heads), skin (retractable ulcers), heart (pulmonary hypertension, right heart failure), lungs (restrictive and obstructive lung defects), gastrointestinal system (chronic severe constipation, liver dysfunction), vision (retinopathy), brain (potential progressive cognitive decline, ischemic and hemorrhagic stroke) and more. Despite best available therapy, currently the median survival for patients with sickle cell disease is 48-52 years. Currently, iron chelation therapy options include oral agents deferasirox and deferiprone as well as subcutaneous or intravenous deferoxamine, either used as single agents or employed as dual chelation therapy in patients with dose limiting toxicities or severe iron overload.

Current treatments:

Treatment in sickle cell disease can be divided into preventative and disease modifying therapies.

Prevention:

Prevention entails screening with regular full system reviews and intervention with penicillin prophylaxis for functional asplenia, and extended vaccinations. Some patients also require primary or secondary prevention with transfusion therapy (see below).

Disease modifying therapies:

Proven effective treatments include hydroxyurea (10.1016/S0140-6736(11)60355-3; https://doi.org/10.1182/blood-2014-08-435768); the medication increases Hemoglobin F, decreases inflammation, decreases anemia and leads to less damage of the endothelium. It has been shown to reduce pain and acute chest syndrome in sickle cell disease. Hydroxyurea is not approved for use for patients with sickle cell disease but, due to overwhelming evidence, it is offered as standard practice, and its use is supported in national and international guidelines.

Blood Transfusion - patients with sickle cell disease can require transfusions in both acute and chronic situations. Transfusions decrease the amount of sickle hemoglobin and either dilute or replace with normal hemoglobin. High rates of rare blood types and increased risk of red cell alloimmunization result in routine transfusion therapy not being an option for a subset of patients.

There are additional disease modifying therapies approved in the US with variable efficacy such as L-glutamine, crizanlizumab and voxelotor. These are not approved for use in Canada and are not accessible to Canadians.

Allogeneic hematopoietic stem cell transplantation (HSCT) is the only available potentially curative option. Worldwide over 2000 patients with sickle cell disease have undergone transplant. Ideally, a HSCT donor is from an ABO-compatible HLA matched sibling. The outcomes from matched sibling donors (MSD) have been encouraging; however, results are variable. Alternative donor sources have historically had unacceptable rates of morbidity and mortality although recent reports are promising with lower complication rates. Pediatric transplant is restricted to 6 Canadian programs and there is a high burden placed on families to relocate for therapy. For adults with SCD, allogeneic transplant is offered at a limited number of sites and there is escalating risk with HSCT due to disease burden with age. In addition, access to HSCT is restricted due to resource limitation, with resulting in triage priorities; oncology, immunology, other hematological diseases, and metabolic patients requiring transplant for immediate life-sustaining reasons are triaged as higher priority, limiting access to HSCT for people with SCD.

What are the most important goals that an ideal treatment would address?
An ideal treatment is not yet available but would be curative, extend longevity, decrease cumulative disease burden, and increase quality of life. Obviously it would also have a low side effect profile and be easy to deliver.

4. Treatment Gaps (unmet needs)

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

- Available treatments do not stop disease progression and ongoing organ damage. Transplant may be curative but carries the potential risk of graft-vs-host disease, infertility and malignancy, and is not available to all patients due to lack of a suitable donor.
- Hydroxyurea - Not all patients respond or have intolerable side effects, It requires regular (~every 2-6 week) blood work monitoring to ensure safe use (which can present a barrier for patients esp. children).
- Transfusions - antibody formation can limit use, patient survival and interrupt appropriate care. There are major disadvantages to transfusion including a mismatch between the donor and recipient population. Other known risks can be found on the CBS website (https://professionaleducation.blood.ca/en/transfusion/clinical-guide-transfusion). This can limit the availability of blood and can be life limiting/threatening. Chronic transfusions (known from thalassemia data) hinders quality of life given the ongoing monthly infusions, need for iron chelation to manage transfusional iron overload, and additional monitoring.
- Hematopoietic stem cell transplantation - is curative dependent on the donor source. Unfortunately, only <15% of patients are eligible for a sibling donor transplant (some centers do not offer this therapy, donors may not be eligible for medical or social reasons, side effect profile may be unacceptable to the patient). Other transplant options (haplo transplant, unrelated donor transplant) increase the risk of graft-vs-host disease and other morbidities (essentially trading one disease for another). There is a risk of infertility and malignancy post-HSCT.

5. Place in Therapy

5.1. How would the drug under review fit into the current treatment paradigm?

Exagamglogene autotemcel involves genetic manipulation of stem cells by essentially inhibiting a gene that decreases hemoglobin F production. Elevated levels of HbF in people with SCD decreases morbidity and mortality as shown with the use of hydroxyurea.

The mechanism of action is novel within the Canadian treatment landscape. Whether other treatment will be additive is unknown at this time.

The product was shown to decrease pain and other complications.

This therapy could be considered a first-line treatment for patients 12 years of age and older with severe SCD phenotypes despite best supportive care measures who do not have an available HLA-matched sibling donor.

Side effects were consistent with high dose busulfan, are well known and include: myelosuppression, mucositis, fever with neutropenia, nausea/vomiting, myalgias and headache. Infertility is a major risk but the follow-up of this study did not allow for this outcome to be assessed.

The treatment is ideally a curative approach but long term data is unavailable at this time.

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

Severe sickle cell disease phenotype and

- History of at least two severe vaso-occlusive crisis events per year for the previous two years prior
- OR one severe VOC (defined by duration (>10 days requiring opioid or NSAID infusion therapy), ICU admission, resultant morbidity (i.e. bone malformations, surgical intervention etc).
- Red cell antibodies (deemed clinically significant)
- Suitable to receive myeloablative busulfan
- Splenic/hepatic sequestration (requiring transfusion therapy)
- Progressive silent cerebral infarcts (without the presence of neurovascular stenosis or overt infarct)
- Evidence of organ (hepatic, renal, lung, cardiac, GI) damage (where pt is still able to tolerate the proposed therapy)

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

Outcomes: Freedom from pain crises for at least 12 months post therapy. Hemoglobin F levels and continued monitoring for disease manifestations.

Monitoring is best overseen by a hemoglobinopathy specialist given a depth of knowledge regarding the effect of hemoglobin F and S in patients is required.

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

Not applicable as this therapy is only performed once

5.5 What settings are appropriate for treatment with drug under review? Is a specialist required to diagnose, treat, and monitor patients who might receive drug under review?

Therapy must be delivered in the inpatient setting, (with an available ICU), and speciality services include hematology and a multidisciplinary team. Ideally this center has experience with myeloablative therapy and or cellular therapy. Patients would stay admitted until neutrophil engraftment.

6. Additional Information

Patients with sickle cell disease face numerous challenges including lack of effective therapy for their disease (especially if hydroxyurea is ineffective), resulting in significant morbidity and early mortality. As a result, additional therapeutic options are urgently needed. This product has the potential to improve quality of life, and extend life expectancy (if the patient has antibodies to blood products). Currently, access to certain therapies is inequitable for SCD patients, one example being people unable to afford relocating for HSCT if they live some distance away from a treatment center. In order to avoid further resource based discrimination, CanHaem would like to highlight the need for equitable access for this therapy to eligible patients, so that patients, regardless of their geographic distance from treatment centers are able to access this therapy. In addition, CanHaem recognizes that this treatment is associated with a high risk of infertility and that the cost of fertility preservation should be included in price negotiations.

7. Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

5. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

   No

6. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

   No

7. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for each clinician who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

CanHaem – the following companies provided sponsorship of our annual meeting in 2022 and 2023

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Vertex				x
Chiesi				x
BMS				x
Pfizer		x		
Alexion		x		

Declaration for Clinician 1

Name: Aisha Bruce

Position: Pediatric Hematologist, previous CanHaem chair
Date: 10/05/2024

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 1

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Vertex	x			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 2

Name: Catherine Corriveau-Bourque

Position: Pediatric Hematologist, current CanHaem chair

Date: 12/05/2024

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 1

Company	**Check appropriate dollar range***

	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Vertex	x			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 3

Name: Lauren Bolster
Position: Adult Hematologist, Northern Alberta Hemoglobinopathy Clinic Director
Date: 13/05/2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 2: Conflict of Interest Declaration for Clinician 2

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Vertex Pharmaceuticals	x			

* Place an X in the appropriate dollar range cells for each company.

CADTH Project Number: SG0830-000

Generic Drug Name (Brand Name): exagamglogene autotemcel (CASGEVY)

Indication: Sickle cell disease in patients 12 and older with recurrent vaso-occlusive crises (VOCs)

Name of Clinician Group: Cell Therapy Transplant Canada (CTTC)

Author of Submission: CTTC Physician member

1. About Your Clinician Group

Cell Therapy Transplant Canada (CTTC; www.cttcanada.org) is a member-led, national, multidisciplinary organization providing leadership and promoting excellence in patient care, research and education in the field of hematopoietic stem cell transplant and cell therapy.

We are the professional society representing the stem cell transplant community in Canada, including physician, nursing, laboratory, and allied health professionals, along with an active family and caregiver group.

2. Information Gathering

The proposed submission was drafted by a CTTC physician member and then shared with two committees – our Board of Directors, and our standing committee of program directors, representing the cell therapy and stem cell transplant programs across Canada. These two committees were provided an opportunity to review this report and provide input.

3. Current Treatments and Treatment Goals

Sickle cell disease (SCD) is the most common monogenetic disease in the world and affects hemoglobin production while also causing systemic vasculopathy. This disease affects over 5000 Canadians and millions worldwide, with growing numbers in Canada due to immigration from Sub-Saharan Africa, the Middle East, India and the Caribbean.[1]

SCD not only causes anemia, but patients can have severe acute vaso-occlusive crises, chronic pain, stroke, nephropathy and neurovascular disease. With age, right sided heart failure, respiratory decline, progressive renal insufficiency, hyposplenism and chronic pain lead to early death and significant morbidity. Current treatments include penicillin prophylaxis, vaccinations, screening for neurovascular disease and hydroxyurea. There are additional disease modifying therapies approved in the US with variable efficacy such as L-glutamine, voxelotor and crizanlizumab. Mechanisms of action are variable, including increase in HbF production, reduced inflammation and cell adhesion, reduced sickling of red blood cells, reduction of oxidative stress and increased nitric oxide production.[2] While these disease-modifying and preventative interventions have improved survival by age 18 years to over 95%, life expectancy for those with SCD is still around 50 years of age, with significant impact on quality of life prior to death. Goals of therapy include preventing fatal infections, stroke and acute chest crises, minimizing painful crises and chronic pain, and limiting end-organ damage. In short, disease modifying treatments are given to improve quality of life and maximize life expectancy.

Allogeneic hematopoietic cell transplantation (HCT) is a potentially curative option.[4] Over the last 40 years, over 2000 patients have been transplanted worldwide and most recipients have been cured of their disease.[5] The number of transplants per year increases annually as HCT approaches become safer and less toxic. “Cure” has typically been defined as sufficient donor engraftment to maintain an HbS < 50% and the absence of new sickling crises.[5] Ideally patients will have no evidence of hemolysis. Typically end-organ damage does not improve or worsen, although there are reports of both improvement and worsening.[reference] In the absence of graft-versus-host disease (GVHD), quality of life is typically reported as better post-HCT.[6] Lack of deterioration of end-organ function and neurocognitive decline are seen as successes, in contrast to what would be expected with the natural history of the disease- including with many disease modifying agents. Data do not exist as to whether HCT prolongs life expectancy. Monitoring for treatment-related neoplasms remains important.

About ~90% of HCTs performed to date have been with a matched sibling donor (MSD).[5] The reason for this practice has historically been due to unacceptable rates of mortality and GVHD with alternative donors. Unfortunately, only 15-20% of those with SCD have a fully human leukocyte antigen-matched sibling donor who is unaffected by SCD. Trait donors are acceptable. Fortunately, in recent years outcomes with matched unrelated donors and haploidentical donors using novel GVHD prevention strategies have reduced rates of GVHD and improved safety.[7-8] Increasingly, centres with experience with HCT for SCD are offering alternative donor HCT for patients with severe phenotypes outside of clinical trials.[8]

In Canada, all six pediatric HCT programs offer HCT for SCD with an MSD. For patients with an MSD, HCT is considered reasonable with even non-severe phenotypes, although practice is variable internationally as to what disease severity should be required for eligibility.[4, 10] Fewer programs will offer alternative donor HCT due to historic risks while awaiting more data to support alternative donor HCT as a standard of care option for those with severe SCD. Some adult HCT programs in Canada offer allogeneic HCT, but due to increasing risks of HCT with age, nonmyeloablative regimens and more stringent eligibility are used.[10-12] Most adults with SCD are not offered HCT.

4. Treatment Gaps (unmet needs)

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

In Canada, current unmet needs are:

- Most patients do not have an MSD, therefore are not offered HCT
- Alternative donor HCT has not been established as a standard of care for severe SCD outside of clinical trials (although alternative donor HCTs are increasingly performed outside of clinical trials due to lack of available trials and increasing data supporting safety and efficacy)
- Graft rejection is a particular challenge for younger patients who undergo haploidentical donor HCT (i.e. under 18 years of age)
- GVHD remains a cause of morbidity and mortality, especially for patients over 13 years of age
- Treatment-related mortality is higher in adults with intensive conditioning regimens (even with an MSD)

5. Place in Therapy

5.1. How would the drug under review fit into the current treatment paradigm?

The proposed therapy involves genetic manipulation of autologous hematopoietic stem cells (HSCs) using the clustered regularly interspaced short palindromic repeats (CRISPR)-Cas9 nuclease system.[13] Autologous HSCs are collected after mobilization with AMD-3100 during an apheresis procedure. CRISPR-Cas9 technology is used to inactivate the BCL11A erythroid-specific enhancer gene. This gene inhibits HbF production, so its disruption results in higher levels of HbF. Elevated levels of HbF have been well established to ameliorate morbidity and mortality through studies of hydroxyurea, which also increases HbF production.[2] Patients with inherently higher levels of HbF are known to have milder phenotypes of SCD, although they still can have crises and morbidity.[14]

Once the product has been manufactured, high dose busulfan (myeloablative dosing) is given followed by infused of the autologous gene therapy product. Risks of high dose busulfan are well established.

Data submitted to the US Food and Drug Administration (FDA) included 44 patients treated on a single arm, multi-centre trial of children and adolescents with SCD.[13] Disease severity eligibility required that participants had at least two severe vaso-occlusive crises in each of the two years prior to enrollment. The primary endpoint of this study was freedom from severe vaso-occlusive crises for 12 or more consecutive months in the 24 months post-infusion. Transfusion requirements were also captured. All patients met the definition for engraftment with no patient sustaining graft rejection at the time of FDA submission.

Side effects were consistent with high dose busulfan, which are not insignificant. These include myelosuppression, mucositis, fever with neutropenia, nausea/vomiting, myalgias and headache. Infertility would be expected for most patients with high dose busulfan, but the follow-up of this study did not allow for this outcome to be assessed.

It is unclear if this treatment is “curative”- see section 5.2. While the study clearly demonstrated clinical benefit, high levels of HbF alone do not prevent all SCD-related complications, as evidenced by data for hydroxyurea and those patients with inherently higher HbF levels.[2, 14] Long-term follow-up and the outcomes of other possible SCD-related outcomes are awaited with ongoing surveillance, including for treatment-related neoplasms.

This therapy could be considered a first-line treatment for patients 12 years of age and older with severe SCD phenotypes despite best supportive care measures who lack an MSD. Patients should be offered penicillin prophylaxis (depending on age), vaccinations, hydroxyurea and chronic transfusions (if appropriate) and evaluated for disease severity prior to consideration of exagamglogene autotemcel. Newer disease modifying agents approved by the FDA might subsequently receive Health Canada approval. If a patient is eligible for such treatments, they should be considered prior to exagamglogene autotemcel as well, with the goal of ensuring that the patient has a severe phenotype despite best supportive care and disease-modifying therapy. These criteria typically also apply to alternative donor transplantation.

Exagamglogene autotemcel could be considered in the population with severe SCD identified above instead of alternative donor HCT. There is no risk of GVHD with the gene therapy product, an important cause of morbidity and mortality in older patients (although these rates are decreasing with newer haploidentical practices and GVHD preventing medications). Ongoing follow-up of outcomes with the new therapy must be considered as these data emerge, as well as compared to emerging data for alternative donor HCT.

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

The patients best suited for the therapy under review are patients with severe SCD who do not have an MSD. Some adults may not be considered candidates for allogeneic HCT even if they have an MSD due to risks of treatment-related mortality or GVHD, so gene therapy might be a better option for select older patients regardless of donor availability. Adolescents and young adults (ie over 12 years of age) would be most appropriate candidates.

Severe SCD has been defined as:

- βS/βS, βS/β0, βS/β+ genotypes (other SCD genotypes may be considered if severe phenotypes)
- Suitable to receive myeloablative busulfan
- History of at least two severe vaso-occlusive crisis events per year for the previous two years prior to gene therapy despite receipt of hydroxyurea or regular transfusion therapy OR
- Other severe manifestations which in the opinion of the referring hematologist justify therapy with curative intent (eg clinically significant alloimmunization, progressive silent cerebral infarcts with no overt stroke or neurovascular disease)

Patients with an MSD should be offered allogeneic HCT as first line curative therapy, especially those under 13 years of age. Rates of GVHD are particularly low in those under 13 years of age, and allogeneic HCT has a long track record of efficacy with more long-term follow-up data and reports of outcomes other than pain crises and transfusion requirements.[6, 10, 15] Patients who have received an HCT with graft failure are not suitable for exagamglogene autotemcel. Patients who cannot safely receive myeloablative busulfan should also not be given this therapy.

The studies of the therapy under review were also limited to patients 12 years of age and older, so the safety and efficacy in younger patients is unknown. However, a clinical trial with a lower age eligibility criterion is underway. In addition, patients with a history of stroke or severe neurovascular disease were excluded from the clinical trials for exagamglogene autotemcel.[13] There is no evidence that patients with a history of stroke can safely stop transfusional support if they have not undergone allogeneic HCT, and gene therapy trials have excluded patients with a history of stroke.[16] Therefore, patients under 12 year of age and those with a history of stroke or neurovascular disease requiring chronic transfusion may not appropriate candidates based on existing data.

However, with safety data forthcoming for patients under 12 years of age and collaborative discussion between hematologists and transplant physicians for those with a history of stroke- and consideration of chronic transfusion post-gene therapy- the role of this product for these and other unique patient subgroups should be re-visited continuously.

It is highly recommended that any candidate for a therapy with curative intent meet with hematologists and transplant physicians with expertise in sickle cell disease to discuss the benefits and risks of disease modifying therapies, allogeneic HCT and gene therapy for an informed and shared decision.

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

The primary endpoint of the single arm, multi-centre clinical trial was a 12 month period free of vaso-occlusive crises in the 24 months which followed infusion. Transfusion requirements post-infusion were also reported. While these are important endpoints in SCD, additional key endpoints are critical to consider when offering a therapy which includes high dose myeloablative chemotherapy and the associated financial costs with gene therapy products. Endpoints defining “cure” are critical in evaluating any potentially curative therapy, whether it be gene therapy or allogeneic HCT.[2, 17]

A clinically meaningful response to treatment would include absence of vaso-occlusive crises, improved self-reported quality of life, engraftment of engineered cells with persistence of genetically targeted stem cells, independence of transfusion, absence of hemolysis, absence of treatment-related neoplasms and stability of cardiovascular, renal and pulmonary function.

Consistent measures of successful outcomes across treatment centres and compared to best supportive care/disease modifying therapy and allogeneic HCT will be critical moving forward to truly understand the benefits of each therapeutic option. Registries and real-world evidence will help guide best practice recommendations moving forward.

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

This is a “one-time” therapy, and patients will have undergone and completed the therapy before the outcome of the therapy is known. Manufacturing failure would be another reason to abandon therapy prior to myeloablation.

5.5 What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

This therapy should be delivered at Health Canada and FACT (Foundation for the Accreditation of Cellular Therapy) institutions with expertise in SCD care for children, adolescents and adults. Centres should have access to busulfan pharmacokinetics. Eligibility decisions should be reviewed by a hematologist with expertise in SCD *and* a cellular therapy physician with experience in curative therapies for SCD.

6. Additional Information

Patients with SCD are at higher risk of myeloid malignancies, and busulfan has been associated with myeloid malignancies and solid tumours in patients who have undergone HCT for SCD.[18-19] Clonal hematopoiesis variant allele frequency increases with age in people with SCD, so particular caution must be exercised in older patients. There have been 2 cases of myeloid neoplasms with another gene therapy product (lentiviral), which are not believed to be due to the lentiviral vector but due to busulfan exposure. Ongoing post-market monitoring for treatment-related neoplasms is imperative.

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7. Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

8. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

   Review and feedback from two CanHaem leadership members, Drs. Aisha Bruce and Michael Leaker.

9. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

   N/A

10. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for each clinician who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Name: Gregory Guilcher

Position: Pediatric Hematologist/Oncologist, academic transplant physician, Alberta Children's Hospital, Calgary

Date: 25-04-2024

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 1

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
bluebirdbio				X

I received no direct remuneration from bluebirdbio. I am the Principal Investigator for Project Sickle Cure, a Sickle Cell Transplant Advocacy and Research Alliance study which is partially funded by bbb.

Declaration for Clinician 2

Name: Rajat Kumar

Position: Professor of Medicine, University of Toronto; Hematologist at Allogeneic Blood and Marrow Transplant program at Princess Margaret Cancer Centre, Toronto

Date: 29-04-2024

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 2: Conflict of Interest Declaration for Clinician 2

Company	Check appropriate dollar range*

	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Vertex	X			

Declaration for Clinician 3

Name: Imran Ahamd

Position: Hematologist, Cellular Therapy & Transplantation Program Director, HMR, Université de Montréal
Date: 08-05-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 3: Conflict of Interest Declaration for Clinician 3

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
None				

Declaration for Clinician 4

Name: Mona Shafey

Position: Clinical Associate Professor, Division of Hematology & Hematologic Malignancies, University of Calgary

Date: 09-05-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 4: Conflict of Interest Declaration for Clinician 4

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Vertex	X			

Declaration for Clinician 5

Name: Gizelle Popradi

Position: Director, Stem Cell Transplant Program, McGill University Health Center

Date: 09-05-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 5

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
None				

Declaration for Clinician 6

Name: Ashley Chopek

Position: MD, Director Pediatric Bone Marrow Transplant Program, Cancercare Manitoba

Date: 10-05-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 6: Conflict of Interest Declaration for Clinician 6

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
None				