CADTH REIMBURSEMENT REVIEW

Patient and Clinician Group Input

crovalimab (TBC)

(Hoffmann-La Roche Limited)

Indication: Crovalimab is indicated for the treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH).

October 15, 2024

This document compiles the input submitted by patient groups and clinician groups for the file under review. The information is used by CADTH in all phases of the review, including the appraisal of evidence and interpretation of the results. The input submitted for each review is also included in the briefing materials that are sent to expert committee members prior to committee meetings.

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CADTH Reimbursement Review
Patient Input Template

Patient Input Template for CADTH Reimbursement Reviews

Name of Drug: crovalimab
Indication: Paroxysmal Nocturnal Hemoglobinuria
Name of Patient Group: The Canadian Association of PNH Patients & Aplastic Anemia

Author of Submission: Barry Katsof & Cindy Anthony

1. About Your Patient Group

The Canadian Association of PNH Patients

Established in 2009, this patient advocacy group is a non-profit Canadian organization dedicated to serving individuals affected by Paroxysmal Nocturnal Hemoglobinuria (PNH). Its mission is twofold: to connect Canadians impacted by PNH and to advocate for optimal patient care, ensuring access to the latest tools and information for managing the condition effectively. Additionally, the organization offers support to caregivers and endeavors to raise awareness and understanding of PNH.

The Canadian Association of PNH Patients was initiated by Barry Katsof, a PNH patient, driven by his recognition of the inadequate support available to individuals in need of life-sustaining medications. Barry's own journey, characterized by successful self-advocacy in accessing the first biologic treatment, inspired him to extend his knowledge and support to all Canadians affected by PNH. Today, he channels his experiences to assist every Canadian PNH patient facing similar challenges to those he encountered back in 2007. The website is: http://www.pnhca.org

Aplastic Anemia & Myelodysplasia Association of Canada (AAMAC)

AAMAC was established in 1987 by a parent deeply affected by their child's aplastic anemia diagnosis. Among its primary objectives was advocating for the creation of a national bone marrow donor registry in Canada. Today, AAMAC stands as a federally incorporated and registered national charity with a bold

mission: to offer comprehensive support to every Canadian affected by aplastic anemia, myelodysplasia, or PNH, including patients, family members, friends, and healthcare providers. The website: https://aamac.ca/

About PNH

PNH is a rare, chronic, and serious blood disorder caused by complement-mediated destruction of red blood cells (RBCs). Individuals with PNH have an acquired mutation in some of their hematopoietic stem cells, located in the bone marrow, which develop into RBCs, white blood cells, and platelets. This mutation results in the production of RBCs that are vulnerable to premature destruction by the complement system, leading to both intravascular hemolysis (within blood vessels) and extravascular hemolysis (primarily in the spleen and liver). These processes cause anemia, thrombosis (blood clots), fatigue, and other debilitating symptoms that significantly impact quality of life.

Anemia, resulting from the destruction of RBCs, leads to a deficiency in the oxygen-carrying capacity of the blood. This can cause severe fatigue, weakness, and shortness of breath, making it difficult for individuals to engage in everyday activities. The ongoing need for blood transfusions to manage anemia can be both physically exhausting and emotionally challenging, as it requires frequent hospital visits and constant medical supervision.

Thrombosis, or the formation of blood clots, is a serious complication of PNH and can occur in unusual sites such as the veins in the abdomen, liver, brain, and skin. These clots can lead to life-threatening conditions such as stroke, pulmonary embolism, or Budd-Chiari syndrome, significantly increasing morbidity and mortality in PNH patients. Managing thrombosis often requires anticoagulant therapy, which carries its own risks and complications.

Extravascular hemolysis (EVH), primarily occurring in the spleen and liver, contributes to further complications. The breakdown of RBCs in these organs can lead to jaundice (yellowing of the skin and eyes), dark urine, and abdominal pain. Chronic hemolysis also results in the release of free hemoglobin into the bloodstream, which can damage the kidneys and other organs over time.

Intravascular hemolysis, the destruction of red blood cells within blood vessels, significantly impacts patients by causing severe anemia, which leads to fatigue, weakness, and shortness of breath due to reduced oxygen delivery to tissues. This process releases hemoglobin into the bloodstream, resulting in dark urine (hemoglobinuria) and potential kidney damage from the toxic effects of free hemoglobin. Additionally, patients may develop jaundice due to increased bilirubin levels, experience pain and discomfort, and face a heightened risk of thrombosis, which can lead to serious complications such as deep vein thrombosis or stroke. The condition also weakens the immune system, increasing susceptibility to infections, and imposes substantial psychological burdens, including anxiety and depression, due to its chronic nature and the complexity of its treatment regimen. Effective management is essential to alleviate these impacts and improve the quality of life for patients.

Approximately 10-20 people per million worldwide live with PNH. While it can develop at any age, it is most commonly diagnosed in individuals between the ages of 30 and 40. The diagnosis of PNH often follows a period of unexplained symptoms and significant health deterioration, as the condition can be challenging to identify due to its rarity and the variability of its presentation.

The chronic nature of PNH means that patients must manage their condition over a lifetime, dealing with the physical, emotional, and financial burdens associated with the disease. The impact on quality of life is profound, as patients must cope with the unpredictability of symptoms, the side effects of treatments, and the constant threat of serious complications. Regular monitoring and supportive care are essential to managing the disease and improving patient outcomes.

In summary, PNH is a complex and multifaceted disorder that requires comprehensive management to address the various aspects of the disease and improve the quality of life for those affected. Advances in understanding the pathophysiology of PNH and the development of new therapeutic options hold promise for better management and potential future cures.

2. Information Gathering

Due to the limited size of the clinical trial for crovalimab, we were able to gather personal experiences from only one Canadian patient who received this treatment. While the small sample size limits the breadth of

personal experiences from Canadian patients, this submission aims to highlight the trial's findings and demonstrate the potential efficacy of crovalimab in meeting a critical need for effective therapies that control the C5 pathway in adult patients living with PNH.

These combined perspectives help to underscore the importance of crovalimab as a promising treatment option. Notably, crovalimab's subcutaneous administration route—which offers the convenience of less frequent, low-volume injections—has the potential to significantly improve patients' quality of life by reducing the burden of regular IV infusions and hospital visits. This shift from invasive, time-consuming treatments to a more manageable, home-administered solution is especially meaningful for PNH patients, whose daily lives are often disrupted by the demands of ongoing therapy.

While the clinical trial involved a small cohort and had a relatively short duration, the insights gained from the sole Canadian patient provide valuable firsthand information that highlights the potential benefits of crovalimab. It will help illustrate how this therapy could fill a vital gap in the current treatment landscape for PNH patients in Canada, offering an innovative and patient-friendly approach.

3. Disease Experience

PNH is a rare, chronic, and serious blood disorder caused by complement-mediated destruction of red blood cells (RBCs). Individuals with PNH have an acquired mutation in some of their hematopoietic stem cells, located in the bone marrow, which develop into RBCs, white blood cells, and platelets. This mutation results in the production of RBCs that are vulnerable to premature destruction by the complement system, leading to both intravascular hemolysis and extravascular hemolysis (primarily in the spleen and liver). These processes cause anemia, thrombosis (blood clots), fatigue, and other debilitating symptoms that significantly impact quality of life.

Approximately 10-20 people per million worldwide live with PNH. While it can develop at any age, it is most diagnosed in individuals between the ages of 30 and 40.

C5 Pathway

The C5 pathway is part of the body's immune system, specifically a part called the complement system, which helps defend against infections. In a healthy person, this system works to attack and destroy harmful bacteria or viruses. However, in some conditions, like PNH, the complement system mistakenly attacks the body's own red blood cells.

The C5 protein is a key player in this process. When activated, it triggers a chain reaction that leads to the destruction of red blood cells, which can cause serious symptoms like fatigue, anemia, and blood clots.

Medications that target the C5 pathway, such as eculizumab, ravulizumab, and crovalimab, block the C5 protein. This prevents it from damaging red blood cells and helps control the symptoms of diseases like PNH. By stopping this harmful activity, these treatments protect your red blood cells and improve your overall health and quality of life.

When there’s an issue with the C5 pathway, it can cause the immune system to go into overdrive, mistakenly attacking healthy cells instead of just fighting infections. This happens in certain rare conditions like PNH, where the C5 protein becomes overactive. In these conditions, the C5 protein is part of a cascade of events within the complement system that leads to the formation of something called the membrane attack complex (MAC). The MAC punches holes in the membranes of cells, causing them to break apart. Normally, this helps destroy harmful bacteria, but when the C5 pathway is overactive or uncontrolled, it starts attacking the body's own cells—especially red blood cells in PNH, leading to their destruction (a process called hemolysis).

This destruction of red blood cells can cause several serious problems:

1. Anemia: When red blood cells are destroyed faster than they can be replaced, it leads to low hemoglobin levels, making you feel tired, weak, and short of breath.
2. Fatigue: Lack of healthy red blood cells can reduce the oxygen supply to your muscles and organs, leading to extreme tiredness.
3. Blood Clots: In PNH, the breakdown of red blood cells can increase the risk of dangerous blood clots, which can block blood flow to vital organs like the lungs, brain, or heart.

4. Dark Urine: When red blood cells are destroyed, hemoglobin is released into the bloodstream and eventually passed out in the urine, making it dark in color.

One of the most dangerous complications of PNH is the formation of blood clots, which can block blood flow to essential organs such as the lungs, heart, and brain. These clots can lead to life-threatening events like heart attacks, strokes, or pulmonary embolism.

Blood clots in PNH are directly linked to the destruction of red blood cells by the complement system. When red blood cells break down, substances are released that make the blood "stickier," increasing the risk of clots. By targeting and blocking the C5 pathway, treatments prevent this destruction and dramatically lower the risk of clot formation. Why this matters: Studies show that patients on C5 inhibitors have a much lower rate of blood clots compared to untreated patients, and this significantly improves survival rates.

Certain patients have mutations that make them less responsive to other treatments. For example, some individuals (particularly in the Japanese population) have a specific mutation in the C5 gene that makes them resistant to eculizumab. In such cases, newer treatments like crovalimab, which target a different part of the C5 protein, can still be effective. This provides an important alternative for patients who don’t respond to standard therapies.

Because of these serious risks, inhibiting the C5 pathway is crucial for controlling these diseases. Drugs like eculizumab, ravulizumab, and crovalimab block the action of the C5 protein, preventing the destruction of red blood cells and other tissues. These treatments help to:

- Reduce or stop hemolysis (the destruction of red blood cells),
- Prevent blood clots,
- Improve anemia and fatigue,
- Protect organs like the kidneys and liver from damage.

In summary, when the C5 pathway malfunctions, it leads to the body's immune system attacking its own cells. Treatments that target this pathway are designed to block the harmful effects and protect your cells, improving symptoms and helping prevent complications.

Impact of Anemia

Anemia occurs when your body doesn't have enough healthy red blood cells to carry oxygen throughout your system. In PNH, the immune system mistakenly destroys red blood cells faster than your body can replace them. Since hemoglobin, found inside red blood cells, is responsible for transporting oxygen, this rapid destruction leads to low hemoglobin levels. As a result, patients may feel:

- Tired: Even after rest, there's a lingering sense of exhaustion.
- Weak: Tasks that used to be easy, like climbing stairs or lifting objects, become harder.
- Short of Breath: Because your muscles and organs aren't getting enough oxygen, activities that require more effort can leave you gasping for air.

Over time, severe anemia can impact your ability to carry out daily activities, and may require treatments like blood transfusions or medications to boost red blood cell production.

Impact of fatigue

Fatigue in PNH is more than just feeling tired. It's a deep, persistent sense of exhaustion caused by a lack of healthy red blood cells and oxygen in your body. When your muscles and organs don't get enough oxygen, they can't function properly, leaving you feeling drained, even after minimal effort. This type of fatigue can affect many areas of life, including:

- Physical activity: Simple tasks like walking, shopping, or doing household chores may become overwhelming.
- Mental clarity: Fatigue can make it hard to focus, concentrate, or stay engaged in conversations or work.
- Emotional well-being: Constant tiredness can lead to frustration, irritability, or feelings of hopelessness.

Since fatigue in PNH is linked to red blood cell destruction, addressing the root cause—hemolysis—through treatments like C5 inhibitors can help improve energy levels and quality of life.

Impact of blood clots

One of the most dangerous complications of PNH is the formation of blood clots, a condition known as thrombosis. When red blood cells are destroyed, substances are released into the bloodstream that make the blood more likely to clot. These clots can block blood flow in major blood vessels, leading to serious and potentially life-threatening problems such as:

- Pulmonary embolism: A blood clot in the lungs, which can cause difficulty breathing, chest pain, and in severe cases, be fatal.
- Stroke: A clot that blocks blood flow to the brain can cause sudden weakness, confusion, vision problems, and difficulty speaking or walking.
- Heart attack: A clot in the arteries that supply the heart can cause intense chest pain, shortness of breath, and may lead to heart damage or death.

Thrombosis is a leading cause of death in PNH patients, which makes preventing blood clots a key goal of treatments like C5 inhibitors. These treatments reduce the breakdown of red blood cells and lower the risk of clot formation, making them crucial in managing PNH.

Impact of dark urine

In PNH, when red blood cells are destroyed, hemoglobin—the protein that carries oxygen in the blood—is released into the bloodstream. This free hemoglobin is filtered by the kidneys and passed out in the urine, giving it a dark or reddish-brown color, a condition known as hemoglobinuria. Dark urine is often most noticeable in the morning, as more red blood cells are destroyed during the night.

Hemoglobinuria can cause additional problems:

- Kidney damage: Repeated filtering of large amounts of hemoglobin can stress the kidneys, potentially leading to kidney damage or failure over time.
- Dehydration: Dark urine is sometimes a sign that your body is losing fluids, which can worsen symptoms like fatigue and weakness.

While dark urine may seem like a minor issue, it's an important warning sign that red blood cells are being destroyed, and it often indicates that more aggressive treatment is needed to stop the hemolysis.

By addressing these serious problems—anemia, fatigue, blood clots, and dark urine—PNH treatments can significantly improve a patient's quality of life. Targeting the underlying cause of red blood cell destruction, such as through C5 inhibitors, can reduce these symptoms, prevent complications, and help patients live more comfortably with their condition.

"Living with PNH has been a journey that I never expected. I was in my early thirties when I started to feel constantly exhausted, and it wasn't the kind of tiredness you can shake off with a nap. Simple things like walking up a flight of stairs or playing with my kids would leave me completely drained. At first, I thought it was just stress or something minor, but then I started noticing other symptoms—like dark urine in the morning and strange bouts of chest pain. After a lot of tests and a lot of confusion, I was finally diagnosed with PNH.

At first, it was terrifying. The idea that my own immune system was attacking my red blood cells and that I was at risk for blood clots was overwhelming. I didn't know how this was going to affect my life, my job, or my family. The fatigue was one of the hardest things to deal with. It's not just feeling tired; it's this deep, bone-level exhaustion that makes it hard to do anything. Even talking sometimes felt like too much effort. On top of that, knowing that I could develop a life-threatening blood clot at any time was always in the back of my mind.

The hardest part is accepting that this is a lifelong condition, and there will always be ups and downs. I've learned to manage it, but PNH is always there, affecting how I plan my day, my work, and even my social life. It's something I have to think about all the time.

What I would say to others going through this is that you're not alone. It can feel isolating because it's such a rare disease, but there are others out there who understand what you're going through. The treatments available now can make a huge difference, and it's possible to live a full life with PNH. It's a tough road, but it's not impossible." – Canadian patient

4. Experiences with Currently Available Treatments

In Canada, several treatments are approved for PNH. The treatment primarily focuses on inhibiting the complement system, especially the C5 & C3 proteins, to reduce hemolysis and associated symptoms. Here are the currently approved treatments for PNH in Canada: eculizumab, ravulizumab, pegcetacoplan & iptacopan (soon to be approved).

Crovalimab, eculizumab, and ravulizumab are all monoclonal antibodies used to inhibit the complement system, specifically targeting the C5 protein in the complement cascade. These medications are typically used to treat complement-mediated diseases like PNH. However, they differ in their structure, dosing schedules, and potential effects. Crovalimab has a longer half-life and has been engineered for subcutaneous use; it potentially offers easier administration (via subcutaneous injections), fewer hospital visits, and improved quality of life for patients.

Both eculizumab and ravulizumab work by reducing the breakdown of red blood cells in the bloodstream, which helps improve symptoms, overall quality of life, and may even extend life expectancy. However, some studies have shown that eculizumab, when given at the standard dose of 900 mg every two weeks, may not be effective for everyone. In fact, nearly half of the patients still showed signs of ongoing red blood cell destruction (hemolysis), which increases the chance of symptoms coming back because of low drug levels in the body. As a result, between 20% to 40% of patients may need a higher dose than the standard to manage their symptoms. Additionally, there is no current data on how patients who need higher doses of eculizumab respond if they switch to ravulizumab, since these patients were not included in the main clinical trials. Currently, both eculizumab and ravulizumab are only available as intravenous (IV) treatments. For some patients, particularly about 3% of the Japanese population, a specific genetic mutation can make eculizumab less effective, and likely ravulizumab as well since both medications work in a similar way. One significant challenge with these treatments is that they require regular clinic visits for IV infusions, which can be time-consuming and disruptive. This can make it difficult for some patients to start or continue treatment long-term.

5. Improved Outcomes

Crovalimab is part of a special type of therapy called SMART antibody technology, designed to work more efficiently in the body. This advanced technology allows crovalimab to bind tightly to the C5 protein, which plays a key role in the destruction of red blood cells in PNH.

One of crovalimab's unique features is its ability to be recycled within the body, meaning it stays active for longer periods, allowing for fewer doses. Additionally, because it is highly soluble, it can be given as a small

subcutaneous injection, making it more convenient for patients than intravenous treatments. Crovalimab works by blocking the activity of the C5 protein, preventing the formation of harmful complexes that cause tissue damage, which is a major concern in PNH.

Studies in animals suggest that crovalimab may be just as effective, or even better, than current treatments while requiring smaller amounts of the drug. However, during a switch from eculizumab to crovalimab, some interactions between the two drugs could potentially affect how they work or their safety, so this transition needs to be monitored carefully. In earlier parts of the COMPOSER study, crovalimab was found to be safe and well-tolerated by both healthy volunteers and PNH patients.

6. Experience With Drug Under Review

Crovalimab has shown in the clinical trial to be well-tolerated and safe while effectively blocking the harmful activity of the complement system in patients with PNH.

Crovalimab works by targeting a different part of the C5 protein compared to other available treatments. This means it could be effective for a broader range of patients, especially those who may not respond well to current treatments. In one part of a study, patients who had more complex cases of PNH—such as those needing frequent blood transfusions, having high levels of LDH (a marker of red blood cell destruction), or requiring higher-than-normal doses of eculizumab—were included. These patients better reflect the general PNH population compared to earlier trials with ravulizumab, which focused on patients who were more stable.

For example, 11 of 19 patients in this study had been on higher doses of eculizumab, had elevated LDH levels, or still experienced symptoms despite treatment. Crovalimab was able to maintain or improve their condition, even for patients who were more difficult to manage.

In addition to better control of PNH, crovalimab treatment led to significant improvements in patients' fatigue, physical health, and overall quality of life. The ability to self-administer crovalimab at home with fast, low-

volume injections could make treatment more convenient, reducing the need for clinic visits. These encouraging results support continued development of crovalimab as a promising treatment for PNH.

"Being diagnosed with PNH was overwhelming. The symptoms were draining—constant fatigue, dark urine, and the fear of blood clots—it felt like my body was fighting against me. When I was first told I had PNH, the concept of my immune system attacking my own red blood cells was hard to grasp. Even harder was the idea that this rare disease was something I would live with for the rest of my life.

Before starting treatment, I was constantly fatigued. I'm not talking about being tired at the end of the day, but this all-consuming exhaustion where even getting out of bed felt like climbing a mountain. I also dealt with episodes of severe chest pain and unexplained dark urine in the mornings. The risk of blood clots was always hanging over me, which was terrifying, especially since PNH makes those clots so dangerous. There were days when it was hard to think about anything else.

When my doctor told me about crovalimab, I was cautiously hopeful. The idea that I could switch to a subcutaneous treatment that only needed to be taken once every four weeks sounded like a dream compared to my previous treatment, which required regular IV infusions. The convenience was a big deal to me. With crovalimab, I don't have to plan my life around hospital visits anymore. The injections are quick and easy, and I can do them at home.

But what's even more important is how much better I feel. The treatment has significantly reduced my hemolysis, which means fewer of my red blood cells are being destroyed. I noticed a change in my energy levels within the first few months. The overwhelming fatigue started to lift. Don't get me wrong—I still have some bad days—but they are fewer and farther between. I'm able to work full-time again, and I have the energy to be more present with my family. The fear of blood clots has also eased, which is a huge relief. I know I'm not completely out of the woods but knowing that crovalimab helps reduce that risk has taken a massive weight off my shoulders.

What surprised me most was how quickly my body adjusted. The side effects were minimal, and any concerns I had about the transition from my old treatment quickly disappeared. I feel more in control of my life now, which I hadn't felt in years. I no longer feel tethered to the hospital, and the ability to manage my condition with such an easy-to-use treatment has given me back a sense of independence.

Crovalimab has been a game changer for me. The fatigue, the constant doctor's visits, the anxiety over blood clots—so much of that has been dialed down since I started this treatment. I'm not just surviving with PNH anymore; I'm actually living my life again. For anyone facing PNH, I want to say that while the diagnosis can feel like the end of the world, there are treatments out there that can help. Crovalimab has been that for me—it gave me back my life, and for that, I'm incredibly grateful." – Canadian patient

7. Companion Diagnostic Test

N/A

8. Anything Else?

Crovalimab's subcutaneous administration route represents a significant advancement for patients with PNH. Traditionally, treatments for PNH, like eculizumab and ravulizumab, have required intravenous (IV) infusions, often administered in hospitals or specialized clinics. These IV infusions can be time-consuming, invasive, and burdensome, with patients needing frequent visits every 2-8 weeks depending on the treatment.

Impact on Quality of Life

The introduction of crovalimab, which can be administered via subcutaneous injections (small-volume injections under the skin), has the potential to greatly improve the quality of life for patients in several ways:

1. Convenience and Flexibility:
    - Instead of regular hospital or clinic visits, Crovalimab can be self-administered at home, offering greater convenience and flexibility. This means fewer interruptions in daily life, allowing patients to manage their condition on their own schedule without the hassle of frequent medical appointments. For people with busy personal or professional lives, this flexibility is a game-changer.
    - The subcutaneous injections are given every 4 weeks, compared to the bi-weekly IV infusions of some traditional treatments, further minimizing the frequency of interventions.
2. Reduced Physical and Emotional Burden:
    - IV infusions can be invasive and uncomfortable, often requiring placement of needles or catheters into veins for extended periods. This can cause pain or discomfort, particularly in patients who have difficult vein access. Crovalimab's subcutaneous injections, on the other hand, are less invasive, quicker, and generally easier to administer, leading to a more comfortable experience.
    - The emotional toll of frequent hospital visits can also be significant. The constant reminder of illness through repeated medical appointments can cause anxiety or emotional stress. By

reducing the number of clinic visits, patients may feel a greater sense of independence and normalcy in their lives.

3. Travel and Mobility:
    - For patients who live far from treatment centers, traveling for IV infusions can be time-consuming and costly. Crovalimab's subcutaneous route eliminates the need for these frequent trips, making life easier for those in remote areas or who have limited access to specialized care.
    - This allows patients more freedom to travel or engage in work or social activities without having to schedule around regular infusions.
4. Reduced Healthcare Costs:
    - Fewer clinic visits also mean lower healthcare costs, both for patients and the healthcare system. The ability to self-administer the drug at home can significantly reduce the overall cost of treatment, eliminating the need for clinic or hospital infrastructure and professional administration fees.
5. Improved Treatment Adherence:
    - The simplicity and convenience of subcutaneous injections may lead to better treatment adherence. Since patients don't have to take time off work or reorganize their lives to attend hospital appointments, they may be more consistent with their treatment schedule, leading to better long-term health outcomes.
6. Psychological Benefits:
    - Many patients with chronic illnesses, including PNH, report a sense of empowerment when they can take an active role in their treatment. With Crovalimab, patients have more control over their care, which can boost mental well-being. Feeling less dependent on the healthcare system can improve self-esteem and lower stress levels, helping patients feel more in control of their disease.

In summary, crovalimab's subcutaneous administration has the potential to transform the treatment experience for PNH patients. It reduces the physical, emotional, and logistical burdens associated with traditional IV therapies, allowing patients to regain a sense of freedom and control over their lives. This more

convenient and less invasive approach can significantly improve not only patients' quality of life but also their overall well-being and adherence to treatment, leading to better health outcomes.

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.

1. Did you receive help from outside your patient group to complete this submission? If yes, please detail the help 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.
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.
4. 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
Alexion			X (direct interest)	
Novartis			X	
Roche		X		
Sobi			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: Barry Katsof
Position: President & Founder
Patient Group: The Canadian Association of PNH Patients
Date: September 16th, 2024

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Abbvie		X		
Alexion				X
BMS			X	
Sobi			X	

Regenron			X	
Taiho		X		
Roche		X		
Novartis			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: Cindy Anthony
Position: Executive director
Patient Group: AAMAC
Date: September 16th, 2024

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CADTH Reimbursement Review

Clinician Group Input

CADTH Project Number: **SR0858-000**
Generic Drug Name (Brand Name): **CROVALIMAB ([redacted])**
Indication: **Treatment of patients with paroxysmal nocturnal hemoglobinuria**
Name of Clinician Group: **Canadian PNH Network**
Author of Submission: **Dr. C. Patriquin, on behalf of the Network, with direct contribution and editorial support by the cosignatories of this document**

1. About Your Clinician Group

The Canadian PNH Network is a group of Canadian hematologists with a special interest and expertise in the care of patients with paroxysmal nocturnal hemoglobinuria (PNH). Members represent centres of expertise from Newfoundland, Nova Scotia, Quebec, Ontario, Alberta, and British Columbia. The Canadian PNH Network sites follow the majority of PNH patients in Canada, either directly or as part of shared-care relationships with community physicians. We also set consensus for diagnosis and management of PNH in the country (Patriquin CJ et al. [2019] Eur J Haematol) and serve as sites for ongoing observational and interventional research activities, both nationally and internationally.

2. Information Gathering

Information for this submission was obtained via publicly available documents, congress abstracts, and the published literature (including the COMMODORE-1 [Scheiberg *et al.*] and COMMODORE-2 [Röth *et al.*], both published in American Journal of Hematology, 2024). Standard of care data were similarly obtained, and the members of the Canadian PNH Network were invited to contribute to the various sections.

3. Current Treatments and Treatment Goals

The current standard of care (SOC) for patients with hemolytic PNH is terminal complement inhibition with C5 blockade. Eculizumab and, more recently, ravulizumab remain the only first-line therapies across the country. To be approved for eculizumab or ravulizumab in Canada, patients must have evidence of a PNH clone (granulocytes or leukocytes) ≥ 10%, lactate dehydrogenase (LDH) > 1.5 x the upper limit of normal (ULN), and at least one significant clinical manifestation such as thrombosis, anemia, transfusion-dependence, advanced renal or respiratory failure without other explanation, and smooth muscle dystonic symptoms (e.g. abdominal pain, dysphagia) requiring either hospitalization or opioid analgesia. Both eculizumab and ravulizumab are administered intravenously, requiring the support of trained nursing staff, repeated venipuncture (fortnightly for eculizumab, every 8 weeks for ravulizumab), and either travel to an infusion centre or having someone come into the home.

The only curative treatment for PNH at this time is allogeneic hematopoietic stem cell transplant. It should be noted, however, that this is reserved for patients with predominant or progressive bone marrow failure (e.g. aplastic anemia), which can coincide with, precede, or follow a diagnosis of PNH. Transplant is not recommended for all patients given the increased risk of complications and transplant-related mortality compared to C5 inhibition. Though complement inhibition does not address the underlying marrow mutations which cause PNH, complement blockade and associated control of intravascular hemolysis (IVH) leads to significant improvement in quality of life, fatigue, transfusion-dependence, thrombosis, and overall survival. Supportive therapies for PNH patients, if needed, include hematinic support (folate, iron), analgesia, and anticoagulation, either to treat or protect against thromboembolic events. It should be noted, however, that anticoagulation alone does not protect against thrombosis in PNH, which is the leading cause of death in untreated patients (40-67%, in case series where causes of death are known).

C5 inhibition is highly effective at controlling intravascular hemolysis in PNH. This is measured by targeting an LDH <1.5 x ULN. Associated with this, we would watch for improvement in hemoglobin, reduced transfusion needs, and absence of other end-organ complications like thrombosis, renal failure, and pulmonary hypertension.

With C5 inhibition, PNH red cells are now able to survive and circulate where previously they would have been exquisitely sensitive to terminal complement-mediated IVH. Now that red cells survive, they can have more and more C3 split products (e.g. iC3b, C3dg) bind to their membranes. As cell-bound complement inhibitors are missing, the dense C3 deposits drive extravascular hemolysis, mostly via receptors in the liver. Because of this, about a third of PNH patients remain symptomatically anemic and possibly still transfusion-dependent (Debureaux P et al. [2021] Bone Marrow Transplant), with increasing rates of extravascular hemolysis coinciding with reduced levels of hematologic response. Due to the underlying disease phenotype, any C5 inhibitor can drive the extravascular hemolysis; however, not every patient has clinically significant EVH (csEVH).

For those with csEVH, two approved therapies are available in Canada. The first, pegcetacoplan, has been recently approved in Canada and is publicly available in most jurisdictions. This is a twice-weekly subcutaneous infusion indicated for patients with persistent anemia despite at least 3 months of C5 inhibitor-based therapy or should they be intolerant to C5 inhibitors. More recently, danicopan (a 3x daily oral Factor D inhibitor), has received a positive recommendation; it is used in combination with a continued C5 inhibitor, either eculizumab or ravulizumab.

A general therapeutic approach to patients with PNH with a Canadian focus can be found in our consensus guidelines (Patriquin CJ et al. [2019] Eur J Haematol) and a recent review (Oliver M & Patriquin CJ [2023] J Blood Medicine).

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.

Crovalimab, as a novel C5 inhibitor, will be expected to meet the same goals as our currently approved C5 inhibitors, eculizumab and ravulizumab. Like ravulizumab, it is a weight-based approach that reduces the burden of treatment for patients while showing non-inferiority in terms of efficacy and no significant new safety concerns (excluding the potential for drug-target-drug complexes, the occurrence of which would be monitored and managed as required). The important treatment goals that crovalimab would be expected to meet, where current therapeutics do not, include providing a C5 inhibitory strategy not requiring IV access, the opportunity for patients and/or caregivers to self-administer, and for those uncommon situations when a patient is found to be resistant to eculizumab or ravulizumab due to a C5 polymorphism.

5. Place in Therapy

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

Crovalimab is a novel C5 inhibitor which, after IV loading, is given subcutaneously every 4 weeks, with low volume of infusion. As a C5 inhibitor, we would expect that it would be another first-line option for patients with PNH (i.e. alongside ravulizumab). In patients who are complement inhibitor-experienced, as shown in COMMODORE-1, this would provide a therapeutic option with the same molecular target that does not require IV access or regular need to see an infusion nurse (for those who can self-administer or who have a caregiver who can support this). Crovalimab would also be a reasonable option to start for those still naïve to complement inhibition, as demonstrated in the COMMODORE-2 trial. Though the likelihood is low, crovalimab would also be the treatment of choice for patients who are found to a C5 polymorphism that makes eculizumab and ravulizumab ineffective (Nishimura et al. [2014] *NEJM*). Note that, until such time as there are more pregnancy-related data, our approach would be to convert any pregnant PNH patients back to eculizumab (or possibly ravulizumab, as data for safety in pregnancy are anticipated). As with ravulizumab or eculizumab, some patients may over time develop csEVH and require a transition to a proximal inhibitor. For those best suited to danicopan add-on therapy, current reimbursement recommendations would require a transition back to ravulizumab or eculizumab.

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?

Patients suitable for treatment with crovalimab would first meet the general inclusion criteria of the COMMODORE-1 and the COMMODORE-2 trials. As this is a C5 inhibitor, it would be offered as first-line treatment to PNH patients, either switching from IV C5 inhibitor or starting from being treatment-naïve. Patients who favour the freedom and reduced treatment burden of subcutaneous administration would very likely select this therapy. For those transitioning from eculizumab or ravulizumab, patients would need to accept the potential risk of developing drug-target-drug immune complex (type-3) hypersensitivity, which has been documented in approximately 15% of "switch" patients (N.B. the majority of these have been short-lived, mild/moderate, and resolved without the need to stop crovalimab).

PNH patients least suitable would be those patients who are not accepting of subcutaneous drug delivery, who struggle with the delivery mechanism, or those who develop csEVH (necessitating proximal complement inhibition strategies). Lastly, until such time as safety data are available in pregnancy, those planning to get pregnant we would transition back to eculizumab (Kelly R et al. [2015] *NEJM*).

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?

Response to complement blockade in PNH patients first and foremost focuses on reduction in LDH, which is a consistent surrogate used to identify intravascular hemolysis activity. The goal is to have patients consistently fall below an LDH ratio of 1.5x ULN. This not only reduces hemolysis and may improve hemoglobin and transfusion-dependence, but it also reduces the risk of thrombosis in PNH. Clinical outcomes related to this, as seen in the landmark eculizumab and ravulizumab trials, are decreased fatigue, transfusion requirements, improved QoL and, given the maturity of eculizumab data available, also improved overall survival (see Kelly RJ *et al.* [2024] Blood). As document in the phase-3 crovalimab clinical trials, hemolysis control was maintained (COMMODORE-1) or improved (COMMODORE-2) similar to those receiving eculizumab. Importantly, there was no significant difference in terms of breakthrough hemolysis (BTH) or hemoglobin stabilization either. Efficacy outcomes would typically be followed every 2-4 weeks initially after starting a new therapy or switching, but follow-up would be required less often (e.g. every 3-6 months) as a patient becomes established on the drug and does not show evidence of side effects or other concerns.

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

Crovalimab discontinuation should be considered in patients who have adverse events that preclude ongoing therapy, though the likelihood of this appears low. As documented in COMMODORE-1, a minority of patients may experience type-3 hypersensitivity from drug-target-drug immune complex deposition, but would be an unlikely reason to stop; this reaction would be expected to resolve over time as the circulating levels of eculizumab or ravulizumab decline and crovalimab concentrations increase. As crovalimab is expected to be primarily a self-administered therapy, another reason to discontinue therapy would be poor compliance which could lead to breakthrough hemolysis and associated risks (e.g. thrombosis, renal insufficiency, pulmonary hypertension). Lastly, any patient who becomes pregnant and/or was breastfeeding would need to have their crovalimab stopped temporarily, at least for now, as there are no safety data in this context.

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

PNH is an ultrarare disease with nuances to diagnosis, treatment, and overall management. Patients likely benefit from being followed by clinicians who specialize in the area, particularly once we are considering patients for more recently approved and/or next-line therapeutic strategies. Members of the Canadian PNH Network would certainly be included in this categorization. Monitoring of patients can be done with standard laboratory investigations and clinical visits. However, specifically regarding treatment with crovalimab, this is most likely going to be done either entirely at the patient's home or at a local infusion clinic (it is uncommon for hospital-based administration though there can be variation based on local/provincial practices). Patients can even travel with their drug, especially with a switch from eculizumab or ravulizumab to a weight-based, self-administered C5 inhibitor (once the IV loading dose is complete).

6. Additional Information

We believe that the submission above addresses the various points, data, and clinical opinions we hope to convey; however, should there be points that we can clarify, please do not hesitate to contact us at your earliest convenience.

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.

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

   We did not.

2. 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.

   We did not.

3. 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: Dr. Christopher Patriquin
Position: Assistant Professor of Medicine (Hematology), Clinician Investigator, University Health Network / Chair, Canadian PNH Network
Date: 12 October 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**
Alexion			X	
Sobi			X	
Novartis		X		
Roche		X		
Amgen	X			

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

Declaration for Clinician 2

Name: Dr. Monika Oliver
Position: Hematologist, University of Alberta
Date: 12 October 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**
Alexion			X	
Novartis		X		
Roche	X			
Sobi	X			

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

Declaration for Clinician 3

Name: Dr. Marc Nicolas Bienz
Position: Hematologist, Jewish General Hospital, Montreal/Assistant professor, McGill University
Date: 13 October 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 7: Conflict of Interest Declaration for Clinician 7

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

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