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Reimbursement Recommendation

Crovalimab (Piasky)

Indication: For the treatment of paroxysmal nocturnal hemoglobinuria (PNH) in adults and adolescents 13 years of age and older with a body weight of at least 40 kg

Sponsor: Hoffmann-La Roche Limited

Final recommendation: Reimburse with conditions

Summary

What Is the Reimbursement Recommendation for Piasky?

Canada's Drug Agency (CDA-AMC) recommends that Piasky be reimbursed by public drug plans for the treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH) in adults and adolescents aged 13 years and older with a body weight of at least 40 kg, if certain conditions are met.

Which Patients Are Eligible for Coverage?

Piasky should only be covered to treat adults and adolescents (aged 13 years and older, weighing at least 40 kg) diagnosed with PNH, according to the reimbursement criteria used for other C5 inhibitors currently reimbursed for the treatment of PNH. Patients who are not responding as expected or the treatment failed with eculizumab or ravulizumab at the Health Canada–recommended dosage are not eligible for reimbursement of Piasky.

What Are the Conditions for Reimbursement?

Piasky should only be prescribed at the Health Canada–recommended dosage and the cost of Piasky should not exceed the drug program cost of treatment with the least costly C5 inhibitor reimbursed for the treatment of PNH. Piasky must be prescribed by, or in consultation with, a hematologist with experience managing PNH.

Why Did CDA-AMC Make This Recommendation?

- Evidence from 1 clinical trial demonstrated that Piasky works the same as eculizumab in terms of sustained effects in stopping or slowing down the destruction of red blood cells (RBCs), reducing the need for blood transfusion, and improving hemoglobin levels.
- Piasky helps meet patient needs by offering a convenient at-home injection and providing similar benefits to existing treatments for PNH.
- Based on the CDA-AMC assessment of the health economic evidence, Piasky may represent good value to the health care system at the public list price. The committee determined that there is not enough evidence to justify a greater cost for Piasky compared with eculizumab and ravulizumab.
- Based on public list prices, Piasky is estimated to lead to approximately $3 million dollars in cost savings for the public drug plans over the 3 next years. However, potential cost savings are uncertain.

Summary

Additional Information

What Is PNH?

PNH is an extremely rare disease in which the bone marrow produces abnormal RBCs that are prematurely destroyed by the immune system, leading to a wide range of symptoms and complications, including life-threatening blood clots. It is estimated that there are approximately 1.3 new cases per 1 million people per year.

Unmet Needs in PNH

Some patients treated with eculizumab or ravulizumab do not have a good response to treatment. Some patients and clinicians prefer treatments that are effective, easy to use at home, and reduce disruptions, and Piasky, given as a monthly injection under the skin, may meet those needs.

How Much Does Piasky Cost?

Treatment with Piasky is expected to cost the public drug plans between $496,807 and $721,240 in year 1 and between $416,907 and $625,360 in subsequent years, depending on patient weight.

Recommendation

The Canadian Drug Expert Committee (CDEC) recommends that crovalimab be reimbursed for the treatment of PNH in adults and adolescents aged 13 years and older with a body weight of at least 40 kg, only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One phase III, open-label, randomized, active-controlled trial (COMMODORE 2) demonstrated that, compared with eculizumab, treatment with crovalimab resulted in similar clinical benefit in patients with PNH who are naive to C5 inhibitors. The COMMODORE 2 trial showed statistically significant noninferiority in both primary outcomes — transfusion avoidance and hemolysis control — after 25 weeks of treatment. The weighted between-group difference for the proportion of patients with transfusion avoidance (crovalimab versus eculizumab) was −2.8% (95% confidence interval [CI], −15.7% to 11.1%; noninferiority margin of −20% for the lower bound of the 95% CI was met). The odds ratio for hemolysis control was 1.02 (95% CI, 0.57 to 1.82; noninferiority margin of 0.2 for the lower bound of the 95% CI was met). Crovalimab also demonstrated statistically significant noninferiority to eculizumab for secondary outcomes — breakthrough hemolysis and stabilized hemoglobin — after 25 weeks of treatment. In addition, results for patient-reported fatigue and health-related quality of life (HRQoL) suggested little to no difference between the study groups, based on the Functional Assessment of Chronic Illness Therapy – Fatigue Scale (FACIT-Fatigue) and European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) instruments; however, there was uncertainty due to the open-label design, short-term analyses, and small sample sizes. The results observed in the COMMODORE 2 trial were supported by exploratory efficacy analyses in the open-label, randomized COMMODORE 1 trial, suggesting maintenance in transfusion avoidance, hemolysis control, breakthrough hemolysis, and the FACIT-Fatigue score after 24 weeks of treatment with crovalimab in patients with PNH who switched from eculizumab. Findings from a descriptive open-label extension study, COMPOSER, appeared consistent with the randomized controlled periods in the COMMODORE 1 and 2 trials and suggested ongoing benefit with crovalimab treatment (median treatment duration = 3.4 years).

The results from 1 sponsor-submitted network meta-analysis (NMA) suggested that there may be little to no difference between crovalimab and ravulizumab; however, CDEC was unable to draw definitive conclusions from the analyses due to methodological limitations. The clinical experts indicated that the NMA results seemed plausible given that ravulizumab belongs to the same group of drugs as eculizumab and has shown similar efficacy and safety as eculizumab in head-to-head randomized controlled trials (RCTs).

Patients expressed a need for treatments that can effectively control intravascular hemolysis, improve anemia and fatigue, reduce the need for transfusion requirements, and provide a more convenient route of administration. Based on the evidence reviewed, CDEC concluded that crovalimab does not meet the unmet needs identified by patients when compared to existing treatment; however, the evidence is supportive of crovalimab as an additional treatment option with a subcutaneous (SC) mode of administration, that can be

administered in a patient's home. CDEC noted that there was no evidence assessing the impact of the SC route of administration on patients' HRQoL.

At the sponsor-submitted price for crovalimab and publicly listed prices for eculizumab and ravulizumab, crovalimab was less costly than eculizumab and ravulizumab. Given that there is insufficient evidence to suggest crovalimab is more effective than eculizumab or ravulizumab, the total drug cost of crovalimab should not exceed the total drug cost of the lowest cost C5 inhibitor.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation, renewal, discontinuation, and prescribing		
1. Reimbursement of first-line crovalimab should be based on the criteria used by each of the public drug plans for initiation, renewal, discontinuation, and prescribing of C5 inhibitors for the treatment of PNH with the addition of condition 2 for initiation and conditions 3 and 4 for prescribing.	Based on the results of the COMMODORE 1 and 2 trials, first-line treatment with crovalimab results in little to no difference compared to eculizumab in transfusion avoidance, hemolysis control, breakthrough hemolysis, stabilized hemoglobin, and FACIT-Fatigue score (COMMODORE 2 trial) and transfusion avoidance, hemolysis control, breakthrough hemolysis, and the FACIT-Fatigue score (COMMODORE 1 trial). Therefore, there is insufficient evidence to suggest that crovalimab should be held to a different standard than other first-line treatment options currently reimbursed for the treatment of PNH.	Patients already receiving first-line eculizumab or ravulizumab treatment with adequate treatment response should be eligible to directly switch to first-line crovalimab treatment without having to meet the initiation criteria. Patients who have intolerance to first-line eculizumab or ravulizumab treatment were not specifically studied in the COMMODORE 1 and 2 trials; however, CDEC considered it reasonable to reimburse first-line crovalimab treatment in these cases.
Initiation		
2. Patients with insufficient response or who have failed treatment with eculizumab or ravulizumab at the Health Canada–recommended dosage are not eligible for reimbursement of crovalimab.	There is insufficient evidence to demonstrate that patients who do not respond or lose response to treatment with eculizumab or ravulizumab will benefit from crovalimab.	—
Prescribing		
3. Crovalimab should only be prescribed at the Health Canada–recommended dosage.	Patients treated with crovalimab in COMMODORE 1 and 2 trials received the labelled dosage of crovalimab with no allowance for an increase in dose or frequency. Currently, there is no evidence to inform the usage of crovalimab beyond the labelled dosage.	—
4. Crovalimab should be prescribed by, or in consultation with, a hematologist with experience managing PNH.	This is meant to ensure that crovalimab is prescribed only for appropriate patients.	—

Reimbursement condition	Reason	Implementation guidance
Pricing		
5. Crovalimab should be negotiated so that it does not exceed the drug program cost of treatment with the least costly C5 inhibitor reimbursed for the treatment of PNH.	Crovalimab demonstrated comparable efficacy to eculizumab; however, conclusions in the C5 inhibitor experienced population were uncertain. An NMA was conducted to assess the relative efficacy and safety between crovalimab and ravulizumab. The NMA evidence was insufficient to suggest crovalimab is more effective than ravulizumab. As such, there is insufficient evidence to justify a cost premium for crovalimab compared with the least expensive C5 inhibitor reimbursed for PNH.	—

CDEC = Canadian Drug Expert Committee; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy – Fatigue Scale; NMA = network meta-analysis; PNH = paroxysmal nocturnal hemoglobinuria.

Discussion Points

- **Unmet need:** CDEC discussed the rarity of PNH and noted that despite its low incidence, effective first-line treatment options are available for patients (e.g., eculizumab and ravulizumab). However, CDEC acknowledged that not all treatment options may be available to every patient in all jurisdictions and available treatments are administered by IV infusions. CDEC acknowledged input from patients and clinicians expressing the preference for effective treatments that can be administered at home, reduce travel time, minimize work disruptions, improve access in remote areas, avoid challenges with venous access, and allow patients a sense of independence. The committee agreed that crovalimab, which is SC administered every 4 weeks, may address that need. CDEC noted that some patients and their clinicians may prefer IV over SC administration out of concerns about treatment adherence and managing or monitoring adverse side effects. CDEC concluded that there was no evidence assessing the impact of the SC route of administration on patients' HRQoL.
- **Efficacy**: The Grading of Recommendations Assessment, Development and Evaluation (GRADE) certainty of evidence assessment results in a rating of "high" or "moderate" for all efficacy outcomes in the COMMODORE 2 trial, except for the EORTC QLQ-C30 global health status scale and quality of life scale score which is rated as "low" certainty. Overall, the committee concluded that the evidence is supportive of crovalimab as an alternative first-line treatment option with efficacy that is noninferior to eculizumab in patients who have not previously received treatment with a C5 inhibitor. For the COMMODORE 1 trial, the GRADE assessment results in a rating of "low" for all efficacy outcomes, except for the EORTC QLQ-C30 global health status scale and quality of life scale score which is rated as "very low" certainty. The committee discussed that despite the uncertain evidence, the consistent effect of crovalimab in the COMMODORE 1 trial, compared to the COMMODORE 2 trial, across relevant efficacy outcomes, suggested that crovalimab may maintain disease control in patients with PNH who switch from other C5 inhibitors. Patients with rare genetic polymorphism which leads to an inadequate response to eculizumab or ravulizumab were studied in the nonrandomized

arm C (6 patients) of COMMODORE 1 with limited evidence; however, CDEC considered it reasonable to reimburse crovalimab treatment in these rare cases.

- **Pediatric patients:** The COMMODORE 1 and 2 trials, respectively, enrolled 1 patient (aged [redacted] years) and 6 patients (aged between 13 and 17 years) into nonrandomized study arms of the trials. CDEC agreed with the clinical experts that it would be reasonable to generalize the trials' results to adolescents aged 13 years and older with a body weight of at least 40 kg, since it is unlikely that there will be trials specifically designed for this small group of patients and there is no biological rationale to assume that outcomes of crovalimab would be different between adults and adolescents. The treatment effect and safety profile of crovalimab in these patients appeared consistent with the randomized controlled periods in the COMMODORE 1 and 2 trials.
- **Adverse effects:** CDEC discussed the safety profile observed with crovalimab in the COMMODORE 2 trial and noted that it was consistent with that expected for a C5 inhibitor. Overall treatment-emerging adverse events (TEAEs) occurred with similar frequency in patients treated with crovalimab compared to those receiving C5 inhibitor therapy. Infusion-related reactions, hypokalemia, and upper respiratory tract infections were among the most commonly reported TEAEs in patients receiving crovalimab. While more patients experienced serious adverse events (SAEs) while receiving crovalimab therapy, treatment discontinuation due to adverse events (AEs) was rare across both study groups. While safety results for crovalimab in the COMMODORE 1 trial were largely consistent with the COMMODORE 2 trial, CDEC highlighted a newly identified risk of type III immune complex reactions (type III hypersensitivity reactions) which only occurred in patients who switched to crovalimab from another C5 inhibitor. CDEC noted that the majority of the type III immune complex reactions were grades 1 to 2 and resolved with no change in crovalimab treatment; however, the committee agreed with the clinical experts that adequate monitoring, potential dose adjustments, and education would be required to manage these events in clinical practice.
- **Indirect evidence:** CDEC considered 1 sponsor-submitted NMA assessing crovalimab relative to ravulizumab. The committee noted several limitations with the submitted comparative analysis, notably limited number of included studies, heterogeneity in patient characteristics across trials, and credible intervals that crossed the null. CDEC concluded that the comparative evidence was insufficient to draw definitive conclusions on the relative efficacy (i.e., transfusion avoidance, breakthrough hemolysis, hemoglobin stabilization, number of packed RBC [pRBC] transfusions, and FACIT-Fatigue score) and safety (i.e., any AEs) of crovalimab versus ravulizumab. The clinical experts indicated that the NMA results seemed plausible given that ravulizumab belongs to the same group of drugs as eculizumab and has shown similar efficacy and safety as eculizumab in head-to-head RCTs.
- **Higher dose of eculizumab:** CDEC heard from the clinical experts that approximately 20% of patients treated with eculizumab for PNH require a higher dose of eculizumab (1,200 mg dose) to achieve complete complement blockade. No evidence was available for these patients in the COMMODORE 1 and 2 trials as eculizumab was administered at the Health Canada–recommended dose of 900 mg with no dose modifications permitted. Therefore, the comparative efficacy and

safety of crovalimab versus eculizumab at a dose higher than recommended by Health Canada, in patients who have not previously received treatment with a C5 inhibitor or those who switched from eculizumab, is unknown.

- **Anticipated patent expiration of eculizumab:** The patent for eculizumab is expected to expire on March 15, 2027. If eculizumab biosimilars become available, it is uncertain whether crovalimab will be less costly than eculizumab biosimilars. Consequently, the cost of crovalimab at the submitted price may be less attractive to drug plans.

Background

PNH is a rare, life-threatening, complement-mediated hematological disorder. PNH is the primary manifestation of chronic intravascular hemolysis, associated with bone marrow failure and thrombophilia. Key clinical signs and symptoms of PNH include anemia, fatigue, thrombosis, esophageal spasms, erectile dysfunction, hemoglobinuria, abdominal pain, and dyspnea. Patients with PNH and their caregivers may experience impaired HRQoL and may struggle to complete normal everyday activities. Thromboembolic events were the leading cause of death in patients with PNH (40% to 67% of deaths with known cause). In Canada, patients with PNH receive C5 inhibitors as standard first-line therapy to reduce uncontrolled complement activation in the terminal complement cascade, and the primary C5 inhibitor therapies are ravulizumab and eculizumab, both administered through IV infusion.

The sponsor's reimbursement request is for the treatment of PNH in adults and adolescents aged 13 years and older with a body weight of at least 40 kg, which is aligned with the Health Canada indication.

Crovalimab is a recombinant humanized immunoglobulin G1-based monoclonal antibody that binds to a different C5 epitope compared to other C5 inhibitors (ravulizumab and eculizumab). It is available as 340 mg/2 mL for injection and the maintenance dosage recommended in the product monograph is 680 mg (body weight of 40 kg or greater to less than 100 kg) or 1,020 mg (body weight of 100 kg or greater) by SC injection once every 4 weeks, after 1 loading dose of 1,000 mg (body weight of 40 kg or greater to less than 100 kg) or 1,500 mg (body weight of 100 kg or greater) by IV infusion and 4 additional weekly doses of 340 mg by SC injection.

Sources of Information Used by the Committee

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

- a review of 2 phase III, open-label, RCTs in patients with PNH; 1 phase I/II long-term extension study; 1 indirect treatment comparison
- patients' perspectives gathered by 1 joint submission of 2 patient inputs, the Canadian Association of PNH Patients, and the Aplastic Anemia & Myelodysplasia Association of Canada (AAMAC)
- input from public drug plans that participate in the reimbursement review process

- 2 clinical specialists with expertise diagnosing and treating patients with PNH
- input from 1 clinician group, the Canadian PNH Network
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Perspectives of Patients, Clinicians, and Drug Programs

Patient Input

CDA-AMC received 1 joint input from the Canadian Association of PNH Patients and the AAMAC. The patient groups gathered personal experiences from 1 patient in Canada who received crovalimab and provided information from the crovalimab clinical trial to highlight the trial's findings and demonstrate the potential efficacy of crovalimab. The patient group input stated that 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. 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. According to the patient group input, 1 patient with PNH in Canada reported that the disease started with feeling constantly exhausted, followed by dark urine in the morning and chest pain. The patient explained feeling terrified of the risk of blood clots, not knowing the effect of the disease on life, job, and family, along with accepting that this is a lifelong condition. Based on the patient group input, 1 significant challenge with current treatments is that they require regular clinic visits every 2 to 8 weeks for IV infusions, which can be time-consuming and disruptive. The patient group stated that crovalimab has the potential to greatly improve patients' quality of life. 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. Fewer clinic visits and less travel for IV injections mean lower health care costs and less financial burden for patients. 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.

Clinician Input

Input From Clinical Experts Consulted for This Review

The clinical experts consulted for this review noted that crovalimab may meet an unmet need for some patients with a preference for an SC route of drug administration, particularly for those with poor venous access and who are apposed to a port-a-cath insertion. The clinical experts noted that crovalimab may be a safer alternative for patients living in isolated geographic locations that preclude guaranteed delivery of eculizumab, and some patients may be more comfortable with self-administration than having to travel to a clinic for IV therapy (which is associated with transportation costs and exposure to potential infections at a clinic). The clinical experts noted that where ravulizumab is funded, most patients with PNH would choose

to start ravulizumab as the first-line therapy compared to eculizumab or crovalimab (of note, ravulizumab is unfunded in some jurisdictions such as British Columbia). However, eculizumab would be preferred for patients who are pregnant. Furthermore, the clinical experts pointed out that patients who prefer to be more independent in receiving therapy, have significant needle phobia, or find it difficult to visit a clinic due to geographic locations, may choose crovalimab as first-line therapy. The clinical experts noted that switching from ravulizumab or eculizumab to crovalimab could be uncommon as there is a risk of type III immune complex reactions that only occur in patients switching to or from other C5 inhibitors. The clinical experts further pointed out that in children, due to the high association with aplastic or hypoplastic anemia, the management would be driven by treating aplastic or hypoplastic anemia. The clinical experts noted that the rare cases of isolated PNH would be treated along the same lines as adults, except that PNH clone size is smaller in children and only clones of greater than 10% would be eligible for C5 inhibition therapy. The clinical experts noted that patients who are fully motivated to self-administer the SC injections and those known to have genetic polymorphism that obviates efficacy with eculizumab or ravulizumab, would be best suited for treatment with crovalimab. The clinical experts pointed out that the outcomes used to assess the treatment response would be the same as for eculizumab or ravulizumab, including improvements in hemoglobin levels, transfusion avoidance, and renal function, along with reductions in smooth muscle spasm, less fatigue, normalization of lactate dehydrogenase (LDH) levels, and avoidance of breakthrough hemolysis. The clinical experts noted that frequent laboratory and patient assessments are required during the early stages of crovalimab, followed by standard assessments once the laboratory results stabilize. The clinical experts noted that if patients treated with crovalimab are not showing any clinical responses by 3 to 4 weeks, transition back to ravulizumab or eculizumab monitoring for the immune responses should be considered. The clinical experts pointed out that crovalimab should be discontinued when thrombosis occurs, or there is ongoing LDH elevation or ongoing symptoms of PNH.

Clinician Group Input

CDA-AMC received 1 clinician group input from the Canadian PNH Network. Information for this submission was obtained via publicly available documents, congress abstracts, and published literature. The members of the Canadian PNH Network were invited to contribute to various sections. Three clinicians contributed to this submission. According to the clinician group input, the current standard of care for patients with hemolytic PNH is terminal complement inhibition with C5 blockade; eculizumab and ravulizumab remain the only first-line therapies across Canada. The only curative treatment for PNH is allogeneic hematopoietic stem cell transplant, which 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.

The Canadian PNH Network highlighted that crovalimab is expected to address important treatment goals unmet by current therapies, including offering a C5 inhibitory strategy that does not require IV access, enabling self-administration by patients or caregivers, and providing an option for rare cases of resistance to eculizumab or ravulizumab due to a C5 polymorphism. Additionally, the clinician group expected that crovalimab would be another first-line option for patients with PNH, either switching from IV C5 inhibitor or starting from being treatment naive. Patients who favour the freedom and reduced treatment burden of SC administration would very likely select this therapy. On the other hand, patients with PNH least suitable would

be those who are not accepting SC drug delivery, or those who develop clinically significant extravascular hemolysis which necessitates proximal complement inhibition strategies.

The Canadian PNH Network stated that response to treatment focuses on LDH reduction which reduces hemolysis and risk of thrombosis and may improve hemoglobin and transfusion-dependence in patients with PNH. Clinical outcomes related to the response included decreased fatigue and transfusion requirements as well as, improved quality of life and overall survival. Efficacy outcomes would typically be assessed every 2 to 4 weeks initially after starting a new therapy or switching, but follow-up would be required less often (e.g., every 3 to 6 months) as a patient becomes established on the drug and does not show evidence of side effects or other concerns.

Based on the input, some of the factors that should be considered to discontinue the treatment include AEs, type III hypersensitivity, poor compliance, and pregnancy. The clinician group added that treatment with crovalimab will most likely be done either entirely at the patient's home or (in the case of loading doses) at a local infusion clinic.

Drug Program Input

The clinical experts consulted for the review provided advice on the potential implementation issues raised by the drug programs.

Table 2: Responses to Questions From the Drug Programs

Drug program implementation questions	Clinical expert response
Relevant comparators	
Issues with the choice of comparator in the submitted trials Soliris (eculizumab): 6 provinces and territories (British Columbia, Alberta, Manitoba, Ontario, New Brunswick, and NIHB) provide coverage. There is no coverage information for 8 other provinces and territories. Ultomiris (ravulizumab): 8 provinces and territories (Alberta, Saskatchewan, Manitoba, Ontario, Nova Scotia, Northwest Territories, NIHB, and VAC) provide coverage. There is no coverage information for 6 other provinces and territories. It is anticipated that crovalimab will be positioned as a first-line drug alongside eculizumab and ravulizumab. In the pivotal trials (COMMODORE 2 and COMMODORE 1), crovalimab was only compared with Soliris (eculizumab).	This is a comment from the drug plans to inform CDEC deliberations.
Considerations for initiation of therapy	
Prior therapies required for eligibility First-line options, such as Soliris (eculizumab) and Ultomiris (ravulizumab) **Question for the clinical experts:** Should patients having experienced a drug of the same class (C5 inhibitors), such as first-line Soliris (eculizumab) or Ultomiris (ravulizumab), be eligible for crovalimab?	The clinical experts consulted for this review noted that patients who have experienced a drug of the same class, i.e., a C5 inhibitor (e.g., eculizumab and ravulizumab) are eligible for crovalimab. The clinical experts noted that patients who switch between different C5 inhibitors are at risk of developing DTDC-associated type III immune complex reactions (in the COMMODORE and COMPOSER studies, approximately 18% of the patients who switched from eculizumab to crovalimab

Drug program implementation questions	Clinical expert response
Consider alignment with prescribing criteria for Soliris (eculizumab) and Ultomiris (ravulizumab).	over an observation period of 44 weeks), which are generally self-limiting, or manageable with appropriate treatment. CDEC agreed with the clinical experts that patients who had a clinical beneficial experience with a drug of the same class, i.e., C5 inhibitor, would be eligible for crovalimab. CDEC agreed to align prescribing criteria for crovalimab with eculizumab and ravulizumab.
Soliris (eculizumab) is covered in 6 provinces and territories (British Columbia, Alberta, Manitoba, Ontario, New Brunswick, and NIHB). For consistency, consider alignment with initiation criteria for Soliris and Ultomiris (initial approval of 6 months) **Question for the clinical experts:** To reduce the risk for meningococcal disease,[a] should there be a consideration for antimicrobial prophylaxis with oral antibiotics for the duration of therapy?	The clinical experts consulted for this review recommended that patients must be fully vaccinated against meningococcal infections (per the guidelines, the vaccinations for meningitis are given every 3 years). Regarding antimicrobial prophylaxis with oral antibiotics for the duration of therapy with crovalimab, the clinical experts were concerned about the adverse effects associated with long-term antimicrobial prophylaxis and recommended against universal use of oral antibiotics as routine prophylaxis among the patient target population. However, the clinical experts noted that the treating physician should assess the risk of infections, especially meningitis, based on the patients' characteristics, comorbidities, and testing results, and decide whether an antimicrobial prophylaxis is required during the therapy. CDEC acknowledged the input from the clinical experts.
Considerations for continuation or renewal of therapy	
For consistency, consider alignment with prescribing criteria for Soliris and Ultomiris.	This is a comment from the drug plans to inform CDEC deliberations.
Considerations for discontinuation of therapy	
For consistency, consider alignment with prescribing criteria for Soliris and Ultomiris.	This is a comment from the drug plans to inform CDEC deliberations.
Considerations for prescribing of therapy	
With the weight-based loading dose of day 1 being IV administered, other loading doses are days 2, 8, 15, and 22. **Question for the clinical experts:** Are there any recommendations if post-day 1 loading doses are missed?	The clinical experts consulted for this review suggested that patients should strictly follow the schedule of crovalimab administration; and if any post-day 1 loading doses are missed, the patients should take the missed dose as soon as possible before the day of the next scheduled dose. The clinical experts noted that if it is almost time for the next dose, the patient should skip the missed dose and continue their regular dosing schedule without taking a double dose on the same day to make up for a missed one. The clinical experts' recommended criteria for missed doses are in line with the criteria about missing a dose of crovalimab in the COMMODORE 2 and COMMODORE 1 studies. CDEC acknowledged the input from the clinical experts.
System and economic issues	
The BIA seems to be underestimating the number of clients starting or switched to crovalimab. Given the subcutaneous administration, it is believed that there would be higher utilization of crovalimab due to patient and prescriber	This is a comment from the drug plans to inform CDEC deliberations.

Drug program implementation questions	Clinical expert response
preference. Patent expiry for Soliris is 2027 and for Ultomiris is 2035. If patients transition to the new, more convenient C5 inhibitor, then savings that could be obtained by the entry of biosimilars will be lost.	
Confidential price agreements exist for Ultomiris and Soliris in PNH.	This is a comment from the drug plans to inform CDEC deliberations.

BIA = budget impact analysis; CDEC = Canadian Drug Expert Committee; DTDC = drug-target-drug-complex; NA = not applicable; NIHB = noninsured health benefits program; NR = not reported; PNH = paroxysmal nocturnal hemoglobinuria; VAC = Veterans Affairs Canada.

[a]McNamara LA, Topaz N, Wang X, Hariri S, Fox L, MacNeil JR. High risk for invasive meningococcal disease among patients receiving eculizumab (Soliris) despite receipt of meningococcal vaccine. *MMWR Morb Mortal Wkly Rep*. 2017;66(27):734-737. doi:10.15585/mmwr.mm6627e1 [PubMed 28704351]

Clinical Evidence

Systematic Review

Description of Studies

Two multicentre, phase III, randomized, open-label, active-controlled trials submitted by the sponsor were included comparing crovalimab (maintenance dose: 680 mg [body weight ≥ 40 kg to < 100 kg] or 1,020 mg [≥ 100 kg] by SC injection once every 4 weeks) with eculizumab (maintenance dose: 900 mg by IV infusion once every 2 weeks) in adult patients with PNH who had not been previously treated with a complement inhibitor (COMMODORE 2 trial, randomized N = 204) and patients with documented treatment with complement inhibitors (COMMODORE 1 trial, randomized N = 89), respectively. Patients were randomized to receive either crovalimab (arm A) or eculizumab (arm B) in a 2:1 ratio in the COMMODORE 2 study, and in a 1:1 ratio in the COMMODORE 1 study. In addition, both trials enrolled a nonrandomized, descriptive arm (arm C) who only received crovalimab (6 patients with PNH aged younger than 18 years in the COMMODORE 2 trial, and 38 patients on a complement inhibitor treatment, including 1 patient with PNH aged younger than 18 years in the COMMODORE 1 trial, at the clinical cut-off date of November 16, 2022). In both trials, the primary treatment period was 24 weeks for all arms. After 24 weeks, all patients had the opportunity to continue or switch to crovalimab in a 46-week safety follow-up period. In the COMMODORE 2 trial, transfusion avoidance and hemolysis control (measured by LDH ≤ 1.5 × upper limit of normal [ULN] at central laboratory) were coprimary outcomes. Secondary outcomes were breakthrough hemolysis (BTH), stabilized hemoglobin, and FACIT-Fatigue score. Mean percent change in LDH levels, maintenance of a minimum hemoglobin level, and pRBC units transfused, among the others, were also reported as exploratory outcomes. HRQoL assessed with EORTC QLQ-C30, and selected symptoms of the EORTC Item Library 40 were evaluated. Patient preference for crovalimab or eculizumab and harms were also reported. In the COMMODORE 1 trial, due to the introduction of ravulizumab into the treatment landscape, and a reduced pool of patients treated with eculizumab over time, randomization was stopped in November 2022 per the amended protocol, which was earlier than the initial plan of study. As a result, the evaluation of safety

became the primary objective, and all efficacy objectives became exploratory end points. The specific safety and efficacy outcomes in the COMMODORE 1 trial were similar to those in the COMMODORE 2 trial.

At baseline, the median age of the randomized population in the crovalimab and eculizumab arms was 36 years (range, 18 to 76 years) and 38 years (range, 17 to 78 years) in the COMMODORE 2 trial, and 42 years (range, 21 to 81 years) and 49 years (range, 22 to 85 years) in the COMMODORE 1 trial. The proportions of males and females were similar between the 2 arms in both studies (51% to 57% were males and 43% to 49% were females in the COMMODORE 2 trial; 47% to 50% were males and 50% to 53% were females in the COMMODORE 1 trial). Most patients were of Asian ethnicity (64% in the crovalimab arm and 74% in the eculizumab arm) or white (33% versus 23%), followed by other or unknown (3%) in the COMMODORE 2 trial; in the COMMODORE 1 trial, most patients were white (76% versus 73%), followed by of Asian ethnicity (20% versus 16%), and other or unknown (4% versus 11%). In the COMMODORE 2 trial, the baseline mean LDH level was 7.6 multiplied by ULN (standard deviation [SD] = 3.4 x ULN) and 7.8 multiplied by ULN (SD = 3.5 x ULN) in the crovalimab and eculizumab arms, respectively. In the COMMODORE 2 trial, a total of 77% of patients in the crovalimab arm had received pRBC transfusion in 12 months or less before screening, with a mean transfused pRBC of 6.5 units (SD = 8.3); 74% of patients in the eculizumab arm had received pRBC transfusion with a mean of 6.6 units (SD = 8.7) (one-half of patients received > 0 to ≤ 6 units of pRBC transfusion in the prior 6 months in both arms). In the COMMODORE 1 trial, 23% of the patients in the crovalimab arm (mean pRBC transfused = 1.6 units [SD = 3.7]) and 25% of the patients in the eculizumab arm (mean = 2.3 units [SD = 5.4]) had received pRBC transfusion. In both studies, the median of PNH clone size was smaller in the crovalimab arm than the eculizumab arm for erythrocytes (crovalimab: 25% versus eculizumab: 45% in the COMMODORE 2 trial; 45% versus 47% in the COMMODORE 1 trial), for granulocytes (60% versus 75% in the COMMODORE 2 trial; 67% versus 68% in the COMMODORE 1 trial), and for monocytes (91% versus 95% in the COMMODORE 2 trial; 89% versus 96% in the COMMODORE 1 trial). The main history PNH-relevant conditions were aplastic anemia (39% versus 38% in the COMMODORE 2 trial; 33% versus 36% in the COMMODORE 1 trial), and major vascular events (16% versus 15% in the COMMODORE 2 trial; 22% versus 23% in the COMMODORE 1 trial).

Efficacy Results

The key efficacy results from the COMMODORE 2 and COMMODORE 1 trials are summarized in Table 3 and Table 4, respectively, ordered by importance and categories suggested by the clinical experts consulted for this review. In the COMMODORE 1 trial, all efficacy outcomes are exploratory as randomization was stopped early, and there was no sufficient power for formal statistical noninferiority or superiority testing.

Hemolysis Outcomes

Hemolysis Control

In the COMMODORE 2 trial, crovalimab demonstrated noninferiority compared with eculizumab for hemolysis control as measured by central LDH of 1.5 or less multiplied by ULN (odds ratio [OR] = 1.02; 95% CI, 0.57 to 1.82; P = [redacted]) based on a predefined noninferiority margin (NIM) of 0.2 for the lower limit of the 95% CI. The mean proportion of patients with hemolysis control from week 5 through week 25

was 79.3% (95% CI, 72.9% to 84.5%) in the crovalimab group and 79.0% (95% CI, 69.7% to 86.0%) in the eculizumab group.

In the COMMODORE 1 trial, the proportion of patients with central LDH of 1.5 or less multiplied by ULN at baseline was 93.2% for crovalimab and 95.2% for eculizumab. The mean proportion of patients who achieved hemolysis control (central LDH ≤ 1.5 × ULN) during the primary treatment period (i.e., from baseline through week 25) was 92.9% (95% CI, 86.6% to 96.4%) in the crovalimab group and 93.7% (95% CI, 87.3% to 97.0%) in the eculizumab group.

Breakthrough Hemolysis

In the COMMODORE 2 trial, crovalimab showed noninferiority efficacy compared with eculizumab in the proportion of patients with a BTH event from baseline through week 25 (crovalimab: 10.4%; 95% CI, 6.0% to 17.2% versus eculizumab: 14.5%; 95% CI, 7.5% to 25.5%) with a weighted difference of −3.9% (95% CI, −14.8% to 5.3%; P = [redacted]) based on a predefined NIM of 20% for the upper limit of the 95% CI.

In the COMMODORE 1 trial, the proportion of patients with BTH from baseline through week 25 was 10.3% (95% CI, 3.3% to 25.2%) for the crovalimab arm and13.5% (95% CI, 5.1% to 29.6%) in the eculizumab arm.

Mean Percent Change in LDH Levels

In the COMMODORE 2 trial, the mean percent reduction in LDH levels from baseline to week 25 was −73.6% (95% CI, −78.95% to −68.2%) in the crovalimab group and −64.1% (95% CI, −71.4% to −56.8%) in the eculizumab group.

In the COMMODORE 1 trial, the mean percent change in central LDH from baseline to the average over weeks 21, 23, and 25 was 16.6% (95% CI, [redacted]) in the crovalimab group and 4.5% (95% CI, [redacted]) in the eculizumab group.

Hemoglobin Outcomes

Stabilized Hemoglobin

In the COMMODORE 2 trial, crovalimab showed noninferiority efficacy compared with eculizumab in the proportion of patients reaching hemoglobin stabilization (avoidance of a ≥ 2 g/dL decrease in hemoglobin level from baseline, in the absence of transfusion) from baseline through week 25 (crovalimab: 63.4%; 95% CI, 54.6% to 71.5% versus eculizumab: 60.9%; 95% CI, 48.4% to 72.2%) with a weighted difference of 2.2% (95% CI, −11.4% to 16.3%; P = [redacted]) based on a predefined NIM of −20% for the lower limit of the 95% CI.

In the COMMODORE 1 trial, the proportion of patients with stabilized hemoglobin from baseline through week 25 was 59.0% (95% CI, 42.2% to 74.0%) in the crovalimab arm versus 70.3% (95% CI, 52.8% to 83.6%) in the eculizumab arm.

Patients Who Reached and Maintained a Minimum Hemoglobin Level (Hemoglobin ≥ 10 g/dL Without Subsequent Decrease < 9 g/dL)

The proportion of patients who reached and maintained a minimum hemoglobin level from baseline through week 25 was [redacted]) in the crovalimab arm and [redacted]

[redacted] in the eculizumab arm in the COMMODORE 2 trial; in the COMMODORE 1 trial, the proportion was [redacted] in the crovalimab arm and [redacted] in the eculizumab arm.

Transfusion Outcomes

Transfusion Avoidance

In the COMMODORE 2 trial, crovalimab demonstrated noninferiority compared with eculizumab for transfusion avoidance from baseline through week 25 with the weighted difference in the proportion of patients with transfusion avoidance of −2.8% (95% CI, −15.7% to 11.1%, P = [redacted]) based on the predefined NIM of −20% for the lower limit of the 95% CI. In the crovalimab arm, 65.7% (95% CI, 56.9% to 73.5%) of patients were transfusion free from baseline through week 25 compared with 68.1% (95% CI, 55.7% to 78.5%) of patients in the eculizumab arm.

In the COMMODORE 1 trial, the proportion of patients who achieved transfusion avoidance from baseline through week 25 was 79.5% (95% CI, 63.1% to 90.1%) for the crovalimab group and 78.4% (95% CI, 61.3% to 89.6%) for the eculizumab group.

RBC Transfusions (pRBC Units Transfused)

In the COMMODORE 2 trial, during the 24-week randomization, primary treatment period, 45 patients (33.6%) in the crovalimab arm and 22 patients (31.9%) in the eculizumab arm had at least 1 transfusion. The mean number of units of pRBCs transfused were 2.3 units (95% CI, 1.3 to 3.4) and 2.2 units (95% CI, 1.0 to 3.4) in the crovalimab and eculizumab groups, respectively.

In the COMMODORE 1 trial, 8 patients (20.5%) in the crovalimab arm and 7 patients (18.9%) in the eculizumab arm had at least 1 transfusion, and the mean number of pRBC units transfused from baseline to week 25 in all patients who were randomized was 0.97 unit (95% CI, 0.2 to 1.7) in the crovalimab arm and 1.9 units (95% CI, 0.5 to 3.3) in the eculizumab arm.

Patient-Reported Outcomes

FACIT-Fatigue

In both COMMODORE 2 and COMMODORE 1 studies, FACIT-Fatigue (range, 0 to 52, with a higher score indicative of less fatigue) was assessed in adult patients (≥ 18 years) only.

In the COMMODORE 2 trial, FACIT-Fatigue data were evaluable in 95.5% of adult patients in the crovalimab arm and 95.7% of adult patients in the eculizumab arm at each visit from baseline through week 25. The adjusted mean change (improvement) from baseline at week 25 in FACIT-Fatigue was 7.8 points (95% CI, 6.5 to 9.1) in the crovalimab arm compared to 5.2 points (95% CI, 3.4 to 6.9) in the eculizumab arm, with a between-group difference of 2.6 points (95% CI, 0.7 to 4.6). By week 25, 58.6% of patients in the crovalimab arm and 54.5% of patients in the eculizumab arm had an improvement in fatigue severity of at least 5 points.

In the COMMODORE 1 trial, FACIT-Fatigue data were evaluable in 86.4% of adult patients in the crovalimab arm and 76.2% of adult patients in the eculizumab arm at each visit from baseline through week 25. The adjusted mean change in FACIT-Fatigue scores from baseline to week 25 was 1.1 points (95% CI, −1.5

to 3.7) in the crovalimab arm and −2.6 (95% CI, −5.4 to 0.1) in the eculizumab arm, with a between-group difference of 3.7 points (95% CI, 0.05 to 7.4). The proportion of patients with a 5-point or more improvement from baseline in FACIT-Fatigue was not reported for the COMMODORE 1 trial.

EORTC QLQ-C30 Global Health Status Scale and Quality of Life Scale

In the COMMODORE 2 trial, the mean change in EORTC QLQ-C30 global health status scale and quality of life scale score from baseline to week 25 was 13.4 points (95% CI, 10.1 to 16.7) for the crovalimab arm and 9.9 points (95% CI, 4.8 to 14.9) for the eculizumab arm. Mean values at week 25 were similar to normative populations values.

In the COMMODORE 1 trial, the mean change in EORTC QLQ-C30 global health status scale and quality of life scale score from baseline to week 25 was 5.7 points (95% CI, −2.4 to 13.8) in the crovalimab arm and −1.0 (95% CI, −6.9 to 4.9) in the eculizumab arm.

Harms Results

in the COMMODORE 2 trial during the 24-week primary safety period, there were similar proportions of patients in the 2 treatment arms who reported at least 1 AE with 78% in the crovalimab arm and 80% in the eculizumab arm. A total of 10% of patients in the crovalimab arm and 13% in the eculizumab arm reported at least 1 SAE. The most common AEs were any infections (24% in the crovalimab arm and 36% in the eculizumab arm), infusion-related reactions (16% versus 13%), hypokalemia (11% versus 13%), hypersensitivity other than type III hypersensitivity reactions ([redacted]), and injection-related reactions (5% versus not applicable). The most common SAEs were infections and infestations (3% versus 7%).

In the COMMODORE 1 trial, a higher proportion of patients in the crovalimab arm compared with the eculizumab arm reported at least 1 AE (77% versus 67%) or at least 1 SAE (14% versus 2%). The most common AEs were any infections (41% versus 36%), infusion-related reactions (14% versus 0), hypersensitivity other than type III hypersensitivity reactions ([redacted]), and injection-related reactions (7% versus not applicable). The most common SAEs were infections and infestations (7% versus 2%).

In both trials, no cases of infection with *Neisseria meningitidis*, including meningococcal meningitis, were reported in either arm.

One patient each from the crovalimab (0.7%) and eculizumab (1.4%) arms in the COMMODORE 2 trial, and no patients in the COMMODORE 1 trial experienced AEs leading to withdrawal from treatment with crovalimab or eculizumab.

In the COMMODORE 2 trial, no AEs of special interest of type III hypersensitivity reactions related to drug-target-drug complexes were reported in either arm during the primary treatment period as the patients were treatment naive. In the COMMODORE 1 trial, 7 patients (15.9%) in the crovalimab arm versus no patients in the eculizumab arm experienced a type III hypersensitivity reaction, as these AEs were expected only in patients that switched from eculizumab to crovalimab who were at risk of developing drug-target-drug complexes associated type III hypersensitivity reactions. In both trials, there were no AEs of special interest

reported for abnormal liver function tests and suspected transmission of an infectious agent by the study drug in either arm.

In the COMMODORE 2 trial, death was reported in 2 patients (1.5%; 1 patient died of respiratory tract hemorrhage, and the other patient died of myocardial infarction) in the crovalimab arm and 1 patient (1.4%; 1 patient died of ischemic stroke) in the eculizumab arm. In the COMMODORE 1 trial, no deaths were reported during the primary safety period.

Critical Appraisal

Methods for randomization and allocation concealment were appropriate in both COMMODORE 2 and COMMODORE 1 trials. In both trials, most baseline characteristics were similar between the randomized crovalimab and eculizumab arms, except for numeric differences in a few of the characteristics, such as the following: in the COMMODORE 2 trial, race (crovalimab: Asian = 64%, white = 33%; eculizumab: Asian = 74%, white = 23%), the median PNH clone size for erythrocytes (crovalimab: 25%, eculizumab: 45%), and for granulocytes (60% versus 75%), as well as the history of myelodysplastic syndrome before enrolment (4% versus 9%), and in the COMMODORE 1 trial, the median PNH clone size for monocytes (89% versus 96%). Nevertheless, the clinical expert did not consider that the between-group imbalance in these characteristics would impact the efficacy and safety results in both studies. In the COMMODORE 2 trial, the predefined NIMs for the efficacy outcomes were considered appropriate. In the COMMODORE 1 trial, the randomization was stopped early (in November 2022 per-protocol amendment version 6) due to the introduction of ravulizumab into the treatment landscape, and a reduced pool of patients treated with eculizumab over time. The initially targeted sample size for the randomized arms of approximately 200 patients could not be reached, providing insufficient statistical power for efficacy analyses. The results of the exploratory efficacy analyses were reported descriptively, with no formal statistical noninferiority or superiority testing, limiting the interpretation and certainty of efficacy results of the COMMODORE 1 trial.

The clinical experts consulted for this review noted that the maintenance dose of eculizumab (900 mg maintenance every 2 weeks for IV infusion) in both pivotal studies aligned with its product monograph. In clinical practice, when breakthrough hemolysis occurs repetitively, increasing of eculizumab dose may be considered according to the clinical experts. For the COMMODORE 2 trial, the lack of permitted dosage adjustments may have biased the efficacy results in favour of crovalimab relative to how eculizumab is dosed in clinical practice; however, the magnitude of this potential bias is unclear. In the pivotal trials, there is no randomized comparative evidence of crovalimab versus eculizumab at a higher dose than Health Canada recommended in patients who are C5 inhibitor naive and in patients who switched from eculizumab given at higher doses than Health Canada recommended.

Fatigue and HRQoL results were evaluable in most patients in the COMMODORE 2 trial (96%) and in 76% to 86% of the patients in the COMMODORE 1 trial. For these outcomes, the impact of missing outcome data in the COMMODORE 2 trial is minimal and the impact of missing outcome data (14% in the crovalimab arm and 24% in the eculizumab arm) in the COMMODORE 1 trial is unclear. The open-label design of both trials may impact reporting of subjective patient-reported outcomes, including FACIT-Fatigue, EORTC QLQ-C30

global health status scale and quality of life scale, EORTC Item Library 40 symptoms, and patient treatment preference.

The interpretation of results of arm C in both trials is limited due to the lack of comparator, the limited number of patients and events, and the descriptive summary of data. Similarly, the lack of a comparator arm does not allow for a conclusion to be drawn on the effect of crovalimab versus any comparator during the extension periods beyond week 25 in both the COMMODORE 2 and COMMODORE 1 trials.

The clinical experts noted that overall, the eligibility criteria of patients in both trials aligned with the diagnosis standard and treatment indication for PNH in clinical settings, and the demographic and disease characteristics (including LDH levels and history of transfusion) of the patients were mostly aligned with the patients seen in clinical practice in Canada. The clinical experts consulted for this review noted that the patients excluded from the COMMODORE 2 and COMMODORE 1 trials due to failure of meeting 1 of the patient inclusion criteria (granulocyte or monocyte clone size ≥ 10%) are typically asymptomatic and would less likely be considered for treatment. If these patients were showing other disease manifestations indicating a therapy, crovalimab could also be used with anticipated similar efficacy and safety results as seen in the 2 trials as per the clinical experts.

The sample size of pediatric patients was small in the COMMODORE 2 (n = 6) and COMMODORE 1 (n = 1) trials, and only descriptive results were available. The clinical experts expected that pediatric patients would have similar efficacy results as in the main trial arms; however, there is a need for enhanced safety consideration regarding risk of infections including meningitis in pediatric patients. The recommended body weight-based doses of crovalimab once every 4 weeks via SC injection was considered as adequate and reasonable in clinical practice in Canada by the clinical experts. The clinical experts pointed out the importance of monitoring patients for any occurrence of kidney issues or infections (particularly meningitis) during the treatment of crovalimab. According to the clinical expert and clinician group, given compliance may impact treatment effects, longer-term comparative evidence on the durability of effectiveness of crovalimab would be informative. Likewise, the occurrence of some AEs, especially rare ones (e.g., meningitis), may take longer time than 24 weeks to be identified. Comparative longer-term follow-up to assess safety between crovalimab to other complement inhibitors would be preferred.

GRADE Summary of Findings and Certainty of the Evidence

Methods for Assessing the Certainty of the Evidence

For pivotal studies and RCTs identified in the sponsor's systematic review, the GRADE framework was used to assess the certainty of the evidence for outcomes considered most relevant to inform the expert committee deliberations, and a final certainty rating was determined as outlined by the GRADE Working Group. Following the GRADE approach, evidence from RCTs started as high-certainty evidence and could be rated down for concerns related to study limitations (which refers to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias.

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

- Clinical outcomes: hemolysis control, breakthrough hemolysis, mean percent change in LDH levels, stabilized hemoglobin, reached and maintained minimum hemoglobin level, transfusion avoidance, and pRBC units transfused.
- HRQoL outcomes: FACIT-Fatigue score and EORTC QLQ-C30 global health status scale and quality of life scale score.
- Harms outcomes: infections and deaths.

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

For the COMMODORE 2 trial, the target of certainty of evidence assessment was the presence or absence of a predefined NIM per study protocol for hemolysis control, breakthrough hemolysis, stabilized hemoglobin, reached and maintained minimum hemoglobin level, and transfusion avoidance. Due to the lack of a formal minimal important difference estimate or NIM value, the target of certainty of evidence assessment was the presence or absence of any (non-null) effect for mean percent change in LDH levels, pRBC units transfused, EORTC QLQ-C30 global health status scale and quality of life scale score, infections, and deaths.

For the COMMODORE 1 trial, due to the lack of a formal minimal important difference estimate or NIM (after amendment of the COMMODORE 1 trial, all the efficacy end points became exploratory and descriptive, thus NIM values were not applicable), the target of certainty of evidence assessment was the presence or absence of any (non-null) effect for hemolysis control, breakthrough hemolysis, mean percent change in LDH levels, stabilized hemoglobin, reached and maintained minimum hemoglobin level, transfusion avoidance, pRBC units transfused, EORTC QLQ-C30 global health status scale and quality of life scale score, infections, and deaths.

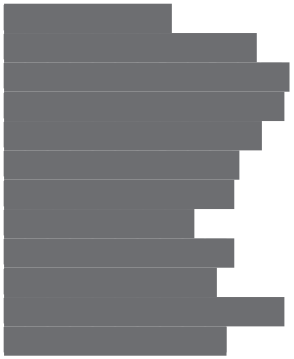
For the GRADE assessments, the COMMODORE 2 and COMMODORE 1 studies were assessed individually because the COMMODORE 2 trial included patients who were naive to complement inhibition and the COMMODORE 1 trial included patients who had experienced complement inhibition.

Results of GRADE Assessments

Table 3 and Table 4 present the GRADE summary of findings for crovalimab versus eculizumab for patients with PNH who were naive to and had experienced complement inhibitors, respectively.

Table 3: Summary of Findings for Crovalimab Versus Eculizumab for Patients With PNH and Naive to Complement Inhibition

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Eculizumab	Crovalimab	Difference		
Hemolysis outcomes							
Mean proportion of patients with hemolysis control (measured by LDH ≤ 1.5 x ULN) from week 5 through week 25 Follow-up: 24 weeks	203 (1 RCT)	OR = 1.02 (0.57 to 1.82)	790 per 1,000	793 per 1,000 (729 to 845 per 1,000)	NR	High[a,b]	Crovalimab results in little to no difference (i.e., a noninferior effect) in the proportion of patients with hemolysis control compared with eculizumab.
Proportion of patients with breakthrough hemolysis from baseline to week 25 Follow-up: 24 weeks	203 (1 RCT)	NR	145 per 1,000	104 per 1,000 (60 to 172 per 1,000)	39 fewer per 1,000 (from 148 fewer to 53 more per 1,000)	High[a,c]	Crovalimab results in little to no difference (i.e., a noninferior effect) in the proportion of patients with breakthrough hemolysis when compared with eculizumab.
Mean percent change in LDH levels from baseline through week 25 Follow-up: 24 weeks	203 (1 RCT)	NA	−64.1%	−73.6% (−79.0% to −68.2%)	−9.5% (−18.4% to −0.6%)	Moderate[d]	Crovalimab likely results in a reduction in the mean percent in LDH levels when compared with eculizumab; the clinical importance of the reduction is uncertain.
Hemoglobin outcomes							
Proportion of patients with stabilized hemoglobin from baseline through week 25 Follow-up: 24 weeks	203 (1 RCT)	NR	609 per 1,000	634 per 1,000 (546 to 715 per 1,000)	22 more per 1,000 (114 fewer to 163 more per 1,000)	High[a,e]	Crovalimab results in little to no difference (i.e., a noninferior effect) in the proportion of patients with stabilized hemoglobin when compared with eculizumab.
Proportion of patients who reached and maintained a minimum hemoglobin level from	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Eculizumab	Crovalimab	Difference		
baseline through week 25 Follow-up: 24 weeks							
Transfusion outcomes							
Proportion of patients who achieved transfusion avoidance from baseline through week 25 Follow-up: 24 weeks	203 (1 RCT)	NR	681 per 1,000	657 per 1,000 (569 to 735 per 1,000)	28 fewer per 1,000 (157 fewer to 111 more per 1,000)	High[a,g]	Crovalimab results in little to no difference (i.e., a noninferior effect) in the proportion of patients who achieved transfusion avoidance when compared with eculizumab.
Mean units of pRBC transfused from baseline through week 25 Follow-up: 24 weeks	203 (1 RCT)	NA	2.2	2.3 (1.3 to 3.4)	NR	Moderate[h,i]	Crovalimab likely results in little to no difference in mean units of pRBC transfused when compared with eculizumab.
Patient-reported outcomes							
Adjusted mean change from baseline in FACIT-Fatigue (0 [worst] to 52 [best]) Follow-up: 24 weeks	194 (1 RCT)	NA	5.2	7.8 (6.5 to 9.1)	2.6 (0.7 to 4.6)	Moderate[j,k]	Crovalimab likely results in little to no clinically important difference in FACIT-Fatigue when compared with eculizumab.

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Eculizumab	Crovalimab	Difference		
Absolute change in EORTC QLQ-C30 global health status scale and quality of life scale score from baseline (0 [worst] to 100 [best]) Follow-up: 24 weeks	194 (1 RCT)	NA	9.9	13.4 (10.1 to 16.7)	NR	Low[h,j]	Crovalimab may result in little to no difference in the EORTC QLQ-C30 global health status scale and quality of life scale compared with eculizumab.
Harms							
Proportion of patients with infections (including *Neisseria meningitidis*) Follow-up: 24 weeks	204 (1 RCT)	NR	362 per 1,000	237 per 1,000 (NR)	125 fewer per 1,000 (from 259 fewer to 9 more per 1,000)[l]	Low[m]	Crovalimab may result in a reduction in the proportion of patients with infections compared with eculizumab.
Deaths							
Proportion of patients who died Follow-up: 24 weeks	204 (1 RCT)	NR	14 per 1,000	15 per 1,000 (NR)	NR	Low[n]	Crovalimab may result in little to no difference in the proportion of patients who died when compared with eculizumab.

CDA-AMC = Canada's Drug Agency; CI = confidence interval; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 ; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy – Fatigue Scale; LDH = lactate dehydrogenase; MID = minimal important difference; NA = not applicable; NIM = noninferiority margin; NR = not reported; OR = odds ratio; PNH = paroxysmal nocturnal hemoglobinuria; pRBC = packed red blood cell; RCT = randomized controlled trial; ULN = upper limit of normal.

Note: Study limitations (which refer to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias were considered when assessing the certainty of the evidence. All serious concerns in these domains that led to the rating down of the level of certainty are documented in the table footnotes. Data presented in this table were based on analyses at clinical cut-off date of November 16, 2022. The outcomes of patients who reached and maintained a minimum hemoglobin level, mean percent change in LDH levels, mean units of pRBC transfused, and EORTC QLQ-C30 global health status scale and quality of life scale score were not adjusted for multiplicity and should be considered as supportive evidence.

[a]Imprecision did not result in the level of certainty being rated down. The point estimate and both the lower and upper boundaries of the 95% CI of the between-group comparison indicate trivial or no clinically meaningful difference according to the clinical experts consulted for this review. The 95% CI of the effect excludes the predefined NIM.

[b]For hemolysis control, the NIM for the lower 95% CI limit of the OR was 0.2. In the absence of available data for the between-group difference in mean proportion of patients with hemolysis control, the judgment of imprecision is based on the 95% CI for the OR of crovalimab versus eculizumab using the predefined NIM of 0.2 as threshold (the lower limit of the 95% CI was higher than 0.2, declaring noninferiority of eculizumab).

[c]Breakthrough hemolysis was defined as at least 1 new or worsening symptom or sign of intravascular hemolysis (fatigue, hemoglobinuria, abdominal pain, shortness of breath [dyspnea], anemia [hemoglobin < 10 g/dL], a major adverse vascular event [including thrombosis], dysphagia, or erectile dysfunction) in the presence of elevated LDH ≥ 2 x ULN after prior reduction of LDH to ≤ 1.5 x ULN on treatment. For breakthrough hemolysis, the NIM for the upper 95% CI limit for the weighted difference in proportions was 20%.

[d]The level of evidence was rated down 1 level for serious imprecision. There were no known MID and clinical experts consulted by CDA-AMC could not provide a threshold of important difference. The CDA-AMC review team judged that the upper bound of the 95% CI was close to the null and unlikely to include an important effect.

[e]Stabilized hemoglobin was defined as avoidance of a ≥ 2 g/dL decrease in hemoglobin level from baseline, in the absence of transfusion. For stabilized hemoglobin, the NIM for the lower 95% CI limit of the weighted difference in proportions was −20%.

[f]Patients who reached and maintained a minimum hemoglobin level was defined as patients who reached a hemoglobin level of at least 10 g/dL, without subsequent decrease below 9 g/dL, in absence of transfusion. For this outcome, the NIM was −20%.

[g]Transfusion avoidance was defined as patients who were pRBC transfusion free and did not require transfusion per-protocol specified guidelines. For transfusion avoidance, the NIM for lower 95% CI limit of the weighted difference in proportions was −20%.

[h]The level of evidence was rated down 1 level for serious imprecision. The level of evidence was rated down 1 level for serious imprecision as unable to conclusively determine whether the between-group difference included the null threshold of 0, which would have been used to assess certainty as the review team was unable to identify the MID to assess a between-group difference from the literature or the clinical expert consulted for this review. The within-group CIs overlapped, and the overall sample size was small.

[i]This outcome presents the total number of pRBC units transfused among the full population.

[j]The level of evidence was rated down 1 level for serious risk of bias in favour of crovalimab (maintenance dose based on body weight every 4 weeks, SC injections) compared with eculizumab (maintenance dose of 900 mg every 2 weeks, IV infusion) arising from the open-label nature of the study and the subjective nature of the outcome.

[k]FACIT-Fatigue was assessed in adult patients (≥ 18 years) only. Imprecision did not result in the level of certainty being rated down. Based on the MID identified in the literature (5 points), which the clinical experts consulted for this review regarded as reasonable, the point estimate and both the lower and upper boundaries of the 95% CI of the between-group comparison suggested little to no difference.

[l]This analysis was not part of the sponsor's statistical analysis plan and was requested by CDA-AMC to facilitate a certainty of evidence appraisal.

[m]This outcome refers to the proportion of patients with at least 1 infection. No patients in either group had *Neisseria meningitidis*. The level of evidence was rated down 2 levels for very serious imprecision. The review team was unable to identify the MID to assess a between-group difference from literature or the clinical experts consulted for this review; therefore, the null was used to assess certainty. The 95% CI of the absolute effect included the null threshold of 0.

[n]The level of evidence was rated down 2 levels for very serious imprecision. There were a very small number of events captured.

Table 4: Summary of Findings for Crovalimab Versus Eculizumab for Patients With PNH and Experience With Complement Inhibitors

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Eculizumab	Crovalimab	Difference		
Hemolysis outcomes							
Mean proportion of patients with hemolysis control (measured by LDH ≤ 1.5 x ULN) from baseline through week 25 Follow-up: 24 weeks	76 (1 RCT)	OR = 0.88 (0.28 to 2.77)	937 per 1,000	929 per 1,000 (866 to 964 per 1,000)	NR	Low[a]	Crovalimab may result in little to no difference in the proportion of patients with hemolysis control when compared with eculizumab.
Proportion of patients with breakthrough hemolysis from	76 (1 RCT)	NR	135 per 1,000	103 per 1,000 (33 to 252 per 1,000)	35 fewer per 1,000 (from 192 fewer to 117 more per 1,000)	Low[b,c]	Crovalimab may result in little to no difference in the proportion of patients with breakthrough hemolysis

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Eculizumab	Crovalimab	Difference		
baseline to week 25 Follow-up: 24 weeks							when compared with eculizumab.
Mean percent change in LDH levels from baseline to average of weeks 21, 23, and 25 Follow-up: 24 weeks	76 (1 RCT)	NA	4.5%	16.6% [redacted]	12.1% [redacted]	Low[c]	Crovalimab may result in an increase in the mean percent change in LDH levels when compared with eculizumab.
Hemoglobin outcomes							
Proportion of patients with stabilized hemoglobin from baseline through week 25 Follow-up: 24 weeks	76 (1 RCT)	NR	703 per 1,000	590 per 1,000 (422 to 740 per 1,000)	108 fewer per 1,000 (308 fewer to 104 more per 1,000)	Low[c,d]	Crovalimab may result in a decrease in the proportion of patients with stabilized hemoglobin when compared with eculizumab.
Proportion of patients who reached or maintained a minimum hemoglobin level from baseline through week 25 Follow-up: 24 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Transfusion outcomes							
Proportion of patients with transfusion avoidance from baseline through week 25 Follow-up: 24 weeks	76 (1 RCT)	NR	784 per 1,000	795 per 1,000 (631 to 901 per 1,000)	18 more per 1,000 (167 fewer to 199 more per 1,000)	Low[c,f]	Crovalimab may result in little to no difference in the proportion of patients with transfusion avoidance when compared with eculizumab.

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Eculizumab	Crovalimab	Difference		
Mean units of pRBC transfused from baseline through week 25 Follow-up: 24 weeks	76 (1 RCT)	NA	1.9	1.0 (0.2 to 1.7)	NR	Low[g,h]	Crovalimab may result in little to no difference in the mean units of pRBC transfused when compared with eculizumab.
Patient-reported outcomes							
Adjusted mean change from baseline in FACIT-Fatigue (0 [worst] to 52 [best]) Follow-up: 24 weeks	70 (1 RCT)	NA	−2.6	1.1 (−1.5 to 3.7)	3.7 (0.05 to 7.4)	Low[i,j,k]	Crovalimab may result in little to no clinically important difference in FACIT-Fatigue scores when compared with eculizumab.
Absolute change in EORTC QLQ-C30 global health status scale and quality of life scale score from baseline (0 [worst] to 100 [best]) Follow-up: 24 weeks	70 (1 RCT)	NA	−1.0	5.7 (−2.4 to 13.8)	NR	Very low[h,i,k]	The evidence is very uncertain about the effect of crovalimab on the EORTC QLQ-C30 global health status scale and quality of life scale compared with eculizumab.
Harms							
Proportion of patients with infections (including *Neisseria meningitidis*) Follow-up: 24 weeks	86 (1 RCT)	NR	357 per 1,000	409 per 1,000 (NR)	52 more per 1,000 (from 153 fewer to 257 more per 1,000)[l]	Low[m]	Crovalimab may result in little to no difference in the proportion of patients with infections compared with eculizumab.
Deaths							
Number of deaths Follow-up: 24 weeks	86 (1 RCT)	NR	0	0	NA	Low[n]	Crovalimab may result in little to no difference in the proportion of patients who died when compared with eculizumab.

CDA-AMC = Canada's Drug Agency; CI = confidence interval; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy – Fatigue Scale; LDH = lactate dehydrogenase; MID = minimal important difference; NA = not applicable; NR = not reported; OR = odds ratio; PNH = paroxysmal nocturnal hemoglobinuria; pRBC = packed red blood cell; RCT = randomized controlled trial; ULN = upper limit of normal.

Note: Study limitations (which refer to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias were considered when assessing the certainty of the evidence. All serious concerns in these domains that led to the rating down of the level of certainty are documented in the table footnotes. Data presented in this table were based on analyses at clinical cut-off date of November 16, 2022. The COMMODORE 1 trial was originally planned to recruit 200 patients into the randomized arms to be sufficiently powered to assess the efficacy of crovalimab. However, due to the introduction of ravulizumab into the treatment landscape, and a reduced pool of patients treated with eculizumab over time, randomization into crovalimab and eculizumab arms was stopped in November 2022 per-protocol amendment 6. The evaluation of safety became the primary objective, and all efficacy objectives became exploratory. The results of the exploratory efficacy analyses were only reported descriptively, as there was not sufficient power for formal statistical noninferiority or superiority testing. All the outcomes in this table were not adjusted for multiplicity and should be considered as supportive evidence.

[a]The level of evidence was rated down 2 levels for very serious imprecision. The review team was unable to identify the MID to assess a between-group difference from literature or the clinical experts consulted for this review; therefore, the null was used to assess certainty. The 95% CI of the OR included the null threshold of 1.

[b]Breakthrough hemolysis was defined as at least 1 new or worsening symptom or sign of intravascular hemolysis (fatigue, hemoglobinuria, abdominal pain, shortness of breath [dyspnea], anemia [hemoglobin < 10 g/dL], a major adverse vascular event [including thrombosis], dysphagia, or erectile dysfunction) in the presence of elevated LDH ≥ 2 x ULN after prior reduction of LDH to ≤ 1.5 x ULN on treatment.

[c]The level of evidence was rated down 2 levels for very serious imprecision. The review team was unable to identify the MID to assess a between-group difference from literature or the clinical experts consulted for this review; therefore, the null was used to assess certainty. The 95% CI of the absolute effect included the null threshold of 0.

[d]Stabilized hemoglobin was defined as avoidance of a ≥ 2 g/dL decrease in hemoglobin level from baseline, in the absence of transfusion.

[e]Patients who reached or maintained a minimum hemoglobin level was defined as patients who reached or maintained a hemoglobin level of at least 10 g/dL, without subsequent decrease below 9 g/dL, in absence of transfusion.

[f]Transfusion avoidance was defined as patients who were pRBC transfusion free and did not require transfusion per-protocol specified guidelines.

[g]This outcome presents the total number of pRBC units transfused among the full population.

[h]The level of evidence was rated down 2 levels for very serious imprecision as the within-group CIs overlapped, the overall sample size was small, and as unable to conclusively determine whether the between-group difference included the null threshold of 0, which would have been used to assess certainty as the review team was unable to identify the MID to assess a between-group difference from the literature or the clinical expert consulted for this review.

[i]The level of evidence was rated down 1 level for serious risk of bias in favour of crovalimab (maintenance dose based on body weight every 4 weeks, SC injections) compared with eculizumab (900 mg every 2 weeks, IV infusion) arising from the open-label nature of the study and the subjective nature of the outcome.

[j]FACIT-Fatigue was assessed in adult patients (≥ 18 years) only. The level of evidence was rated down 1 level for serious impression. Based on the MID identified in the literature (5 points) that the clinical experts consulted for this review regarded as reasonable, the point estimate and the lower boundary of the 95% CI suggested little to no difference, and the 95% CI for the between-group difference crossed the MID threshold.

[k]The level of evidence was further rated down 1 level for potential risk of bias due to missing data (14% in the crovalimab arm and 24% in the eculizumab). The impact of these missing outcome data are unclear.

[l]This analysis was not part of the sponsor's statistical analysis plan and was requested by CDA-AMC to facilitate a certainty of evidence appraisal.

[m]This outcome refers to the proportion of patients with at least 1 infection. No patients in either group had *Neisseria meningitidis*. This analysis was not part of the sponsor's statistical analysis plan and was requested by CDA-AMC to facilitate a certainty of evidence appraisal. The level of evidence was rated down 2 levels for very serious imprecision. There were a very small number of events captured.

[n]The level of evidence was rated down 2 levels for very serious imprecision. There were a very small number of events captured.

Long-Term Extension Studies

Description of Studies

The phase I/II COMPOSER trial (NCT03157635) consisted of 4 sequential parts and an open-label extension (OLE). This section includes a summary of the OLE period that evaluated the safety and tolerability, pharmacokinetic, and pharmacodynamic of crovalimab in patients with PNH, aged 18 to 75 years, who were treatment naive, or switched from eculizumab. Participants were enrolled at 14 sites in 6 countries: France (1), Germany (3), Hungary (2), Italy (1), Japan (5), and South Korea (2). The study did not include sites in Canada.

Efficacy Results

Hemolysis Control

The proportion of patients reaching LDH of 1.5 or less multiplied by ULN per visit suggested there was little to no difference during the OLE, with 80% to 100% of the patients who were evaluated at each visit having LDH of 1.5 or less multiplied by ULN.

Mean normalized LDH was generally maintained at less than 1.5 multiplied by ULN during the OLE phase. The point estimate of the mean normalized LDH by visit ranged from 1.09 to 1.24 multiplied by ULN.

Transfusion Avoidance

The proportion of patients with transfusion avoidance remained relatively stable over time during the OLE, with 82.9% to 91.7% of all patients avoiding transfusion across the 24-week intervals. Seven of the 11 patients who received a blood transfusion during the OLE period reported a history of aplastic anemia and/or anemia.

Stabilized Hemoglobin

The proportion of patients reaching hemoglobin stabilization also remained relatively stable over time during the OLE, with 79.5% to 87.5% of all patients reaching hemoglobin stabilization across the 24-week intervals.

Breakthrough Hemolysis

The proportion of patients with BTH events was low during the OLE, with 0 to 4.9% of all patients reporting a BTH event across the 24-week intervals. One patient who had a BTH event discontinued the study before completing the full interval from week 20 to week 44 in which the BTH event occurred. Consequently, this BTH event was reported and included in the computation of the rate of BTH events adjusted for patient-years at risk but is not included in the calculation of the proportion of patients with BTH events per 24-week interval analyses.

Harms Results

[redacted] of the 44 patients that were enrolled in parts 2, 3, and 4 of the study entered the OLE, and [redacted] patients ([redacted] patients who were treatment naive and [redacted] patients who switched from eculizumab) were ongoing on crovalimab treatment at the time of the most recent clinical cut-off date (CCOD) (August 28, 2023). Overall, a total of [redacted] patients discontinued from the OLE ([redacted] patient originally enrolled to part 2 [treatment naive], [redacted] patients originally enrolled in part 3 [switch], [redacted] patients originally enrolled to part 4,

arm A [treatment naive], and [redacted] patient originally enrolled to part 4, arm B [switch]). No patients discontinued from the study due to an AE. The median treatment duration from baseline to the CCOD was [redacted] years.

A total of [redacted] patients experienced at least 1 AE from baseline to CCOD. [redacted]. No AEs resulted in withdrawal of a patient from the study. A total of [redacted] patients experienced at least 1 SAE. SAEs were reported in [redacted] of patients in the treatment-naive group and in [redacted] of patients in the switched from eculizumab group. The most frequently reported AEs by System Organ Class (at least 50% incidence in the total population) were Infections and infestations ([redacted]), gastrointestinal disorders ([redacted] and musculoskeletal and connective tissue disorders ([redacted]).

The most frequently reported AEs with at least 15% incidence in the total population were nasopharyngitis ([redacted]), COVID-19 ([redacted]), upper respiratory tract infection ([redacted]), headache ([redacted]), back pain ([redacted]), pyrexia ([redacted]), arthralgia ([redacted]), cough ([redacted]), bronchitis ([redacted]), and dizziness ([redacted]).

A total of [redacted] patients experienced at least 1 infection up to the CCOD (which was an increase from 36 patients [81.8%] as reported in the Update Clinical Study Report).

Critical Appraisal

The OLE period of the COMPOSER study was conducted to evaluate the longer-term safety and exploratory efficacy outcomes in 44 patients with PNH, beyond the 20-week primary evaluation period. Patients were enrolled in the extension period if study investigators determined that the patient derived benefit from treatment with crovalimab in the 20-week primary study period. The open-label design may increase the risk of bias in patient selection and outcome ascertainment for end points that include more subjective assessments as the lack of blinding may impact investigators and patients' expectations of treatment. The direction and magnitude of potential bias remains unclear. Given the design, the long-term extension is noncomparative as all patients in parts 2, 3, and 4 received crovalimab. As a result, the comparative safety and efficacy of crovalimab to relevant comparators was not addressed and precludes conclusions about the comparative safety and efficacy of crovalimab. The small number of patients included in each study part, the single-arm setting, and the open-label design introduces significant uncertainty into study results and conclusions. There was variability in visit schedules across study parts, which may have introduced confounding into the study and limited the number of patients available at each follow-up time point.

The efficacy-evaluable population included all efficacy-evaluable patients who completed the primary treatment period in parts 2, 3, or 4 of the study and were enrolled into the OLE period (18 patients who were treatment naive and 25 patients who switched treatments). The study analysis included patients who were both treatment naive and treatment experienced, and populations that differed in disease characteristics, such as transfusion history and LDH level. The impact of including patients who were both treatment naive and treatment experienced in the same analysis on the results is unclear.

During the OLE period, patients who were not receiving dosing every 4 weeks were required to switch to receive either 680 mg SC every 4 weeks (body weight ≥ 40 kg to < 100 kg) or 1,020 mg SC every 4 weeks (body weight ≥ 100 kg), which is aligned with the product monograph recommendation.

No method for imputation of missing values was reported, and the attrition rate was 11.6%.

The study included diverse geographical representation and populations with varying demographics and health care systems, which may enhance the generalizability of the results. However, the patients who were included were mostly males (60% to 86%), with an ethnicity of "not Hispanic or Latino [from original source]," and included patients with median ages ranging from 44 to 56 years, therefore results may not be generalizable to a broader population. Patients with conditions such as psychiatric disorder; hereditary complement deficiency; history of meningococcal meningitis; active primary or secondary immunodeficiency; known history of HIV infection; chronic active hepatitis C; malignant disease; and alcohol, drug, or chemical abuse within 1 year before screening were excluded, and the results may not be generalizable to these groups of patients.

The dose-escalation approach which allowed for the inclusion of different dosing frequencies may enhance the generalizability across patient subgroups; however, frequent modifications and variations between groups increases intergroup variability and impacts the certainty and interpretation of study results.

Indirect Comparisons

Description of Studies

Due to the scarcity of direct evidence comparing crovalimab with other existing relevant therapies including ravulizumab, eculizumab biosimilar, and the standard of care without a C5 inhibitor for PNH, the sponsor conducted an NMA comparing crovalimab with ravulizumab, eculizumab biosimilar, and the standard of care without a C5 inhibitor for PNH.

Efficacy Results

The NMA suggested little to no difference between crovalimab and ravulizumab for the mean difference in the proportion of patients with transfusion avoidance, hemoglobin stabilization, and the number of pRBC transfusions; however, the 95% credible intervals were wide, and include the possibility that either treatment may be favoured. The NMA suggested little to no difference between crovalimab and ravulizumab for the change in FACIT-Fatigue score; however, the CIs were wide and included the possibility of a clinically important effect that favoured crovalimab.

Harms Results

[redacted].

Critical Appraisal

Overall, the NMA was conducted according to accepted methodological guidance. A key limitation of the NMA was the heterogeneity in effect modifiers and prognostic factors across the included studies. The base-case analysis included patients who were both treatment naive and treatment experienced, populations that differed in disease characteristics, such as transfusion history and LDH level. This heterogeneity suggests that the assumption of similarity across the included studies may not hold true for the NMA, increasing the uncertainty about the validity of the results for determining the comparative effectiveness of crovalimab compared to ravulizumab. In a subgroup analysis of patients who were treatment naive and treatment experienced the results were consistent overall with base-case results. Other limitations included that the evidence networks were sparse, the connections between treatment nodes were informed by 1 or 2 trials, and the total number of patients in the included studies were relatively small. The previously mentioned limitations may increase the potential for biased treatment effect estimates, and the results of NMA should be interpreted with consideration of the limitations.

Economic Evidence

Note that the sponsor's application was filed on a pre-Notice of Compliance basis and the pharmacoeconomic submission and budget impact analysis is reflective of the indication that was initially submitted to Health Canada and CDA-AMC. The sponsor's submission included a broader age range and weight range than the final indication.

Cost and Cost-Effectiveness

Table 5: Summary of Economic Evidence

Component	Description
Type of economic evaluation	Cost minimization analysis
Target population	Patients with PNH
Treatment	Crovalimab
Dose regimen	For patients weighing between 40 kg and 100 kg: One loading dose of 1,000 mg administered intravenously, followed by 4 weekly loading doses of 340 mg subcutaneously starting on day 2 of week 1. Maintenance dosing starts on day 29 and is 680 mg subcutaneously every 28 days. For patients weighing more than 100 kg: One loading dose of 1,500 mg administered intravenously, followed by 4 weekly doses of 340 mg subcutaneously starting on day 2 of week 1. Maintenance dosing starts on day 29 and is 1,020 mg subcutaneously every 28 days.
Submitted price	Crovalimab: $15,980.00 per 340 mg vial
Submitted treatment costs	Year 1: $544,247 per patient annually Year 2 and onward: $424,060 per patient annually
Comparators	• Eculizumab • Ravulizumab

Component	Description
Perspective	Canadian publicly funded health care payer
Time horizon	Lifetime (60 years)
Key data source	COMMODORE 1 and 2, phase III randomized controlled trials assessing crovalimab in comparison to eculizumab in patients who were treatment experienced and treatment naive, supplemented by an NMA to inform efficacy of crovalimab in comparison to ravulizumab
Costs considered	Drug acquisition, administration, blood transfusion and medical resource utilization costs (hospitalizations, dialysis treatments, and physician visits)
Key limitations	• The Clinical Review concluded that there is high to moderate certainty that crovalimab and eculizumab have similar efficacy in the patient population who are C5 inhibitor naive. In patients who are experienced with C5 inhibitors, results were suggestive of little to no difference between crovalimab and eculizumab. As well, while indirect evidence from the sponsor's NMA suggested that crovalimab may provide comparable efficacy and safety to ravulizumab, definitive conclusions could not be made due to limitations in the NMA (i.e., limited number of included studies, heterogeneity in patient characteristics across trials, and credible intervals that crossed the null). As such, there is some uncertainty regarding whether crovalimab is similar to eculizumab and ravulizumab. • The sponsor assumed that 20% of patients treated with eculizumab required continuous up-dosing. This is uncertain as clinical experts consulted by CDA-AMC highlighted that this rate could vary. Additionally, no evidence was available to inform the proportion of patients who required up-dosing as the dose for eculizumab was fixed in the COMMODORE 1 and 2 trials. As up-dosing increases eculizumab treatment acquisition costs, and if up-dosing is lower than assumed by the sponsor, cost savings associated with crovalimab compared with eculizumab would be less. • The modelled prices for eculizumab and ravulizumab reflect publicly available list prices and do not account for potential confidential discounts from negotiated agreements. If actual comparator prices are lower than list prices, crovalimab may require price reductions to achieve cost-effectiveness.
CDA-AMC reanalysis results	CDA-AMC did not conduct reanalyses for the base case. Based on public list prices, crovalimab is cost-saving compared with ravulizumab and eculizumab. The existence of cost savings associated with crovalimab are dependent on confidentially negotiated prices. If the actual prices paid for eculizumab and ravulizumab were 23% and 16% less than public list prices, reimbursing crovalimab at the sponsor-submitted price would become cost neutral.

CDA-AMC = Canada's Drug Agency; NMA = network meta-analysis; PNH = paroxysmal nocturnal hemoglobinuria.

Budget Impact

CDA-AMC identified the following key limitations from the sponsor's analysis: continuous up-dosing of eculizumab is uncertain and may add additional treatment acquisition costs for eculizumab, the rate of public drug coverage is uncertain, and the price of drugs paid by public drug plans is uncertain as confidential list pricing of comparators may be in place.

CDA-AMC did not conduct a base-case reanalysis. In the sponsor's analysis, the 3-year budget impact of reimbursing crovalimab for patients with PNH is -$2,738,865 (year 1: -$129,340; year 2: -$844,604; year 3: -$1,764,921).

The budget impact analysis results were sensitive to all scenarios undertaken by CDA-AMC (i.e., reduced cost savings when eculizumab up-dosing was removed, increased cost savings when the population size was increased by assuming 100% eligibility for public coverage and expanding the population to align with the Health Canada indication).

CDEC Information

Members of the Committee

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

Meeting date: February 26, 2025

Regrets: None

Conflicts of interest: None

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