Canadian Journal of Health Technologies

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

November 2024 Volume 4 Issue 11

Drugs Health Technologies Health Systems

Reimbursement Recommendation

Danicopan (Voydeya)

Indication: As an add-on to ravulizumab or eculizumab for the treatment of adult patients with paroxysmal nocturnal hemoglobinuria who have residual hemolytic anemia due to extravascular hemolysis

Sponsor: Alexion Pharma GmbH

Final recommendation: Reimburse with conditions

Summary

What Is the Reimbursement Recommendation for Voydeya?

Canada's Drug Agency (CDA-AMC) recommends that Voydeya be reimbursed by public drug plans as an add-on to ravulizumab or eculizumab for the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH) who have residual hemolytic anemia due to extravascular hemolysis (EVH) if certain conditions are met.

Which Patients Are Eligible for Coverage?

Voydeya should only be covered to treat adult patients with a diagnosis of PNH, who have met the public drug plan reimbursement criteria for initiating complement 5 inhibitor (C5i) treatments (ravulizumab or eculizumab) before receiving C5i treatment, and who have been on a stable dose of C5i treatment for 6 months or more, in addition, patients should also have persistent anemia caused by EVH, and an absolute reticulocyte count of 120×10^9/L or greater.

What Are the Conditions for Reimbursement?

Voydeya should only be reimbursed if prescribed by a hematologist with experience managing PNH. The cost of Voydeya should be negotiated so that Voydeya plus a C5i as a regimen does not exceed the drug program cost of treatment with pegcetacoplan for the treatment of adult patients with PNH who have residual hemolytic anemia due to EVH.

Why Did CDA-AMC Make This Recommendation?

- Evidence from a clinical trial showed that Voydeya likely improves hemoglobin levels and decreases markers of transfusion burden. It may also bring hemoglobin levels back to the normal range.
- Voydeya has the potential to address several unmet needs of patients, such as addressing intravascular hemolysis (IVH) and EVH comprehensively and reducing or eliminating transfusion dependence.
- Based on CDA-AMC assessment of the health economic evidence, Voydeya does not 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 Voydeya plus a C5i compared with treatment with pegcetacoplan, reimbursed for adult patients with PNH who have residual hemolytic anemia due to EVH.
- Based on public list prices, Voydeya is estimated to cost the public drug plans approximately $1.8 million over the next 3 years. However, the actual budget impact is uncertain.

Summary

Additional Information

What Is PNH?

PNH is a rare, chronic, and potentially life-threatening blood condition caused by an acquired genetic defect which leads to hemolysis of red blood cells (RBCs). Ravulizumab or eculizumab are used first-line to treat PNH. However, some patients may still have anemia and need blood transfusions due to EVH. Around 20% of patients with PNH who were stable on C5i treatment develop clinically important EVH. The prevalence of PNH in Canada is unknown, but it's estimated to affect 1.2 to 1.3 per 100,000 people in the US.

Unmet Needs in PNH

There is an unmet need for effective therapies that reduce treatment burden, decrease dependency on blood transfusions, and improve health-related quality of life (HRQoL) in patients who have residual hemolytic anemia due to EVH.

How Much Does Voydeya Cost?

Treatment with Voydeya is expected to cost approximately $75,525 to $100,699 per patient annually. When used in combination with a C5i, the regimen is expected to cost approximately $590,542 to $721,633 per patient in the first year, and approximately $550,490 to $670,658 per patient annually, in subsequent years (depending on dosing and choice of C5i).

Recommendation

Our Canadian Drug Expert Committee (CDEC) recommends that danicopan be reimbursed as an add-on to ravulizumab or eculizumab for the treatment of adult patients with PNH who have residual hemolytic anemia due to EVH only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

PNH is a rare disease with significant mortality and morbidity, and around 20% of patients with PNH who were clinically stable on C5i treatment develop clinically significant EVH. Although a treatment is currently available for patients with insufficient response to the current standard of care treatments, CDEC noted that the current standard of therapy with C5i monotherapy may not provide complete symptom control for all patients with PNH, and substantial morbidity still exists for patient with PNH and residual hemolytic anemia due to EVH. This highlights an important unmet need for these patients.

One randomized controlled trials (RCT) (ALPHA; 12-week placebo-controlled period [TP1] plus a 12-week single-arm, open-label period [TP2] and an additional 52-week long-term extension [LTE]) compared danicopan to placebo in patients on a C5i experiencing clinically significant EVH. The results at TP1 demonstrated improvements in the change in hemoglobin from baseline, the proportion of patients with hemoglobin increase of 2g/dL or more in the absence of transfusion, the proportion of patients attaining hemoglobin normalization and the proportion of patients with transfusion avoidance, as well as decreased markers of transfusion burden and absolute reticulocyte counts. Evidence for the impact on HRQoL from the trial demonstrated improvement in fatigue (Functional Assessment of Chronic Illness Therapy [FACIT]-Fatigue) scores and little to no difference in 2 other measures of HRQoL, EQ-5D-3L, and European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 [EORTC QLQ-C30]) at 12 weeks. Results from TP2 demonstrated that the impact on hematologic outcomes was maintained, and the impact on HRQoL suggested a trend toward maintained scores. Results from the full analysis demonstrated that in the LTE the reported trends from TP2 were maintained for several hematologic outcomes (proportion of patients with hemoglobin normalization, proportion of patients with hemoglobin increase of 2g/dL or greater, change in hemoglobin from baseline).

Patient input noted that EVH is a significant contributor to the symptoms and complications of PNH that they experience. They identified a need for treatment options which further reduce hemolysis symptoms such as fatigue, pain and shortness of breath, address IVH and EVH comprehensively, reduce or eliminate dependence on transfusions, avoid iron overload, reduce mortality and enhance HRQoL. Despite limitations in the comparative evidence, CDEC concluded that the patient population specified in the reimbursement criteria represented a group of patients who could benefit from additional therapeutic options for their disease, and that danicopan add-on therapy may meet some of the needs such as transfusion needs, addressing EVH, and fatigue.

At the sponsor submitted price for danicopan and publicly listed prices for all other drug costs (ravulizumab, eculizumab or pegcetacoplan), danicopan plus a C5i (ravulizumab or eculizumab) was more costly than

pegcetacoplan. As there is insufficient evidence to suggest that danicopan plus a C5i is more effective or safer than pegcetacoplan, the total drug cost of the regimen of danicopan plus a C5i should not exceed the total drug cost of treatment with pegcetacoplan.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Adult patients who are ≥ 18 years of age or older with a diagnosis of PNH with both of the following: 1.1. patients must have met the public drug plan reimbursement criteria for initiating C5i treatment (e.g., eculizumab or ravulizumab) before receiving C5i treatment. 1.2. patients must have been on a stable dose (i.e., no change in either the prescribed dose or interval) of either ravulizumab or eculizumab for ≥ 6 months.	The ALPHA trial enrolled adults with PNH aged 18 years or older with a diagnosis of PNH. The ALPHA trial enrolled patients who had been on stable doses (i.e., no change in either the prescribed dose or the interval) of a C5i, either ravulizumab or eculizumab, for a period of 6 months or longer with no change in the prescribed dose or interval.	—
2. patients should have persistent anemia, defined as hemoglobin levels ≤ 9.5 g/dL (95 g/L), caused by EVH, and an absolute reticulocyte count ≥ 120 × 10^9/L.	The ALPHA trial defined clinically significant EVH as hemoglobin levels ≤ 9.5 g/dL (95 g/L) and absolute reticulocyte count ≥ 120 × 10^9/L.	The clinical experts noted to CDEC that a clinical diagnosis for EVH is typically anemia along with normal or minimally elevated LDH, as well as elevated bilirubin and reticulocyte counts. Investigations to rule out other causes of anemia in patients with PNH should be undertaken.
3. The maximum duration of initial authorization should be 24 weeks.	The primary outcome of the ALPHA trial was measured at Weeks 12 and 24.	—
Renewal		
4. For renewal after initial authorization, the physician must provide proof of beneficial clinical effect when requesting continuation of reimbursement, defined as either of the following: 4.1. reduction in transfusion needs from baseline before initiating danicopan 4.2. normalization of hemoglobin levels to above the lower limit of the normal reference range.	Results from ALPHA demonstrated that treatment with danicopan plus C5i likely resulted in an increase in the proportion of patients with transfusion avoidance (defined as transfusion free and not requiring a transfusion) and may result in an increase in the proportion of patients with hemoglobin normalization when compared to placebo plus C5i. hemoglobin normalization in ALPHA was defined as hemoglobin values above the lower limit of the normal reference range.	The clinical experts noted to CDEC that any improvement from a patient's baseline in hemoglobin levels or transfusion needs could be considered a response to therapy.

Reimbursement condition	Reason	Implementation guidance
5. Subsequent renewals should be assessed annually to ensure clinical benefit, as defined in condition 4, is maintained.	This is to ensure the treatment is used for those benefiting from the therapy and would reduce the risk of unnecessary treatment.	—
Discontinuation		
6. Danicopan should be discontinued if the C5i (ravulizumab or eculizumab) that the patient is receiving is discontinued, or if the patient switches treatment to pegcetacoplan.	There is neither evidence supporting the use of danicopan as monotherapy, nor concomitant use of danicopan and pegcetacoplan.	—
Prescribing		
7. Danicopan must be prescribed by a hematologist with experience managing PNH.	This is meant to ensure that danicopan is prescribed only for appropriate patients. In addition, the clinical experts noted to CDEC that danicopan must be prescribed by a hematologist with experience managing PNH.	—
8. Danicopan should only be prescribed in combination with the C5is ravulizumab or eculizumab.	The only evidence available is when danicopan is prescribed an add-on to ravulizumab or eculizumab.	—
9. Danicopan should not be prescribed in combination with pegcetacoplan.	There is no evidence supporting concomitant use of danicopan and pegcetacoplan.	
Pricing		
10. Danicopan should be negotiated so that danicopan plus a C5i as a regimen does not exceed the drug program cost of treatment with pegcetacoplan for the treatment of adult patients with PNH who have residual hemolytic anemia due to EVH.	The indirect evidence submitted by the sponsor was subject to considerable limitations which challenged interpretation of the evidence, and the committee was unable to reach firm conclusions regarding the comparative efficacy and safety of danicopan relative to pegcetacoplan. As such, there is insufficient evidence to justify a cost premium for danicopan plus a C5i over pegcetacoplan, reimbursed for adult patients with PNH who have residual hemolytic anemia due to EVH.	—
Feasibility of adoption		
11. The feasibility of adoption of danicopan plus a C5i must be addressed.	At the submitted price, the magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of adoption, given the difference between the sponsor's estimate and our estimate(s).	—

C5i = complement 5 inhibitor; EVH = extravascular hemolysis; LDH = lactate dehydrogenase; PNH = paroxysmal nocturnal hemoglobinuria.

Discussion Points

- Given the uncertainty in the clinical evidence, CDEC deliberated on danicopan considering the criteria for significant unmet need described in section 9.3.1 of the *Procedures for CADTH Reimbursement Reviews*. Considering the rarity and severity of PNH and the medical need for additional effective and safe treatment options, CDEC concluded that the available evidence reasonably suggests that danicopan as an add-on to a C5i has the potential to reduce morbidity associated in patients with residual hemolytic anemia due to EVH.
- The GRADE certainty of evidence assessment resulted in a rating of moderate for most hematologic outcomes, indicating likely improvement in these measures relative to placebo plus a C5i. A GRADE rating of low was given for the HRQoL outcomes suggesting greater uncertainty in the evidence. Both hematologic outcomes and HRQoL were identified as important to patients and clinicians, and the results from the RCT demonstrated that danicopan added on to a C5i met several unmet needs important to patients. Considering the rarity of the disease and the notable morbidity ascribed to EVH by patients and clinicians, CDEC concluded that the uncertainty in the HRQoL measures was balanced by the unmet need and demonstrated improvements in hematologic outcomes.
- The clinical experts noted that response to therapy would typically be an improvement in hemoglobin and a reduction in transfusion requirements relative to the baseline for a given patient. Ongoing anemia or transfusion needs may not be considered a treatment failure, however a lack of improvement in hemoglobin and/or transfusion needs could be considered as such. Given the rarity and morbidity of the disease, CDEC concluded that improvement in hemoglobin and /or transfusion measures relative to a patients' baseline would be sufficient to demonstrate treatment response.
- In the absence of head-to-head comparisons with danicopan matching-adjusted indirect comparisons for danicopan plus a C5i compared to pegcetacoplan monotherapy were submitted to CDEC. CDEC concluded that the indirect evidence submitted was subject to considerable limitations which did not allow for firm conclusions on the comparative safety and efficacy of danicopan relative to pegcetacoplan. CDEC also noted that there is no evidence supporting concomitant use of danicopan and pegcetacoplan.
- The clinical experts consulted by CDEC noted that patients with clinically significant anemia, with optimized control of other causes of anemia, would be candidates for danicopan. Inherent to the implementation would be the need to accurately identify the patient population by diagnosing EVH as conclusively as possible. Clinical experts consulted by CDEC noted there is no standard definition of EVH but the diagnosis of EVH involves ruling out other potential causes of anemia. Potential alternate causes for anemia in PNH patients noted by the clinical experts included bone marrow suppression, hematinic deficiencies (such as vitamin B12 or iron), renal insufficiency or blood loss.
- CDEC acknowledged that the recommended criteria for starting danicopan could potentially overlap with the criteria currently implemented in some jurisdictions for discontinuing C5is (ravulizumab and eculizumab) for treating PNH. CDEC discussed the need to potentially modify the criteria for discontinuing C5is in those jurisdictions to allow patients with PNH who have residual hemolytic anemia due to EVH to continue receiving C5is, even if they meet the discontinuation criteria. This

adjustment would enable these patients to benefit from the treatment combination of danicopan with C5is (ravulizumab or eculizumab). CDEC also noted that because danicopan is indicated as add-on therapy to a C5i (ravulizumab or eculizumab), the criteria discussed within this document apply to concomitant C5i (ravulizumab or eculizumab) and danicopan use. The previously published recommendations regarding ravulizumab and eculizumab apply to their use as monotherapy and not in combination with danicopan. With the introduction of danicopan, reaching the discontinuation criteria for ravulizumab or eculizumab monotherapy could result in addition of danicopan to the current C5i therapy, or discontinuation of the C5i without initiation of danicopan, or prompt a switch from current C5i therapy to pegcetacoplan, without initiation of danicopan. In other words, *failure* or *meet the discontinuation criteria* on a C5i alone (ravulizumab or eculizumab) does not necessarily preclude further use with danicopan as this combination is considered a unique therapeutic option. CDEC also added that, in practice, jurisdictions may benefit from concurrently reviewing concomitant C5i (ravulizumab or eculizumab) and danicopan use. For example, jurisdictions may wish to synchronize the special authority approval dates for both drugs so that they are reviewed concurrently. If after adding danicopan to a C5i (ravulizumab or eculizumab), response to treatment as defined in condition 4 of Table 1 is not achieved, treatment with danicopan should be discontinued. Continuation of the C5i (ravulizumab or eculizumab) despite failure from combination C5i (ravulizumab or eculizumab) and danicopan use is out of the scope of this review.

Background

PNH is a rare, chronic, and potentially life-threatening blood condition. Because of the rarity of the disease, published prevalence and incidence estimates of PNH and EVH are not available for the population of people living in Canada; a study in the US estimated the prevalence of PNH at 1.2 to 1.3 per 100,000 persons between 2016 and 2017. PNH is caused by an acquired genetic defect in hematopoietic stem cells. This defect leads to the production of blood cells that lack 2 glycosylphosphatidylinositol-anchored complement regulatory proteins, CD55 and CD59, at their surface, causing the complement system to recognize RBCs as damaged. The uncontrolled activation of the complement cascade prematurely attacks these cells resulting in hemolysis. IVH occurs in both terminal and proximal pathways when RBCs are directly lysed due to the activation of the alternative complement pathway. Patients with PNH are susceptible to an increased risk of thrombosis, pain, organ damage (e.g., impaired renal function), underlying bone marrow dysfunction, and increased risk of morbidity and mortality. In Canada, ravulizumab or eculizumab are complement 5 inhibitors (C5i) used as first-line therapy to treat hemolytic PNH. However, some patients receiving C5i treatment remain anemic and transfusion dependent. Possible causes of this include breakthrough hemolysis (BTH), extravascular hemolysis (EVH), nutritional deficiencies and bone marrow failure. EVH is a mechanistic consequence believed to be caused by ongoing complement 3 (C3) deposition on surviving yet defective RBCs; while symptoms of EVH are not life-threatening, some patients with EVH remain asymptomatic while others may develop severe clinical symptoms and may require blood transfusions to manage ongoing anemia. Clinical trial and real-world data show that around 20% of patients with PNH who were clinically stable on C5i treatment develop clinically significant EVH.

The historical approach to managing anemia due to EVH in patients living in Canada with PNH has been supportive care (e.g., RBC transfusions, corticosteroids, splenectomy, danazol, and epoetin alfa) and continuing C5i treatment to prevent the life-threatening consequences of IVH. Pegcetacoplan, a subcutaneous (SC) proximal complement component complement 3 inhibitor (C3i) is indicated for patients with inadequate response to, or intolerant of, a C5i, and currently offered as a second-line pharmacologic option to patients with EVH. Danicopan has been approved by Health Canada as an add-on to ravulizumab or eculizumab for the treatment of adult patients with PNH who have residual hemolytic anemia due to EVH. Danicopan selectively inhibits complement alternative pathway (AP) factor D (FD) and is thought to mediate the deposition of C3 fragments on PNH blood cells, which is a key cause of EVH in patients receiving ravulizumab or eculizumab for PNH. Inhibition of FD activity targets the control point of the complement cascade amplification loop, blocking C3 convertase formation and thereby reducing the production of C3 fragments and downstream membrane attack complex formation. Although danicopan blocks the AP-mediated amplification of the complement classical pathway and lectin pathway, these 2 pathways remain active to provide residual complement-dependent protection against infectious pathogens. Danicopan is available as an oral tablet and the starting dosage recommended in the product monograph is 150 mg 3 times a day administered orally, approximately 8 hours apart (± 2 hours). The dose can be increased to 200 mg 3 times a day if a patient's hemoglobin level has not increased by at least 2g/dL after 4 weeks of therapy, if a patient required transfusion within the previous 4 weeks, or to achieve an appropriate hemoglobin response based on clinical judgment.

Sources of Information Used by the Committee

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

- a review of 1 phase III randomized, double-blind, placebo- controlled study with 1 LTE in adult patients with PNH receiving treatment with a C5i with clinically significant EVH (defined as hemoglobin of 9.5g/dL or less, and absolute reticulocyte count of 120 × 10^9/L or more); and 1 indirect treatment comparison
- patients' perspectives gathered by 1 joint input from 2 patient groups, the Canadian Association of PNH Patients and the Aplastic Anemia & Myelodysplasia Association of Canada
- input from public drug plans that participate in our review process
- 2 clinical specialist(s) 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

The Canadian Association of PNH Patients and the Aplastic Anemia & Myelodysplasia Association of Canada submitted a joint input for this review. A clinical summary of PNH was provided and information was gathered through the personal experiences of 1 patient living in Canada who received danicopan.

The patient group input expressed that PNH significantly impacts the quality of life for both patients and their caregivers. Beyond the persistent fatigue and weakness caused by chronic anemia from hemolysis, patients deal with other symptoms such as abdominal pain and dysphagia which influence their dietary habits and social interactions. Managing symptoms requires ongoing medical interventions, medication adjustments, and lifestyle changes. The input noted that even though currently available treatments for PNH, such as C5i (ravulizumab and eculizumab) and C3i (pegcetacoplan), effectively inhibit IVH, thrombosis and EVH, approximately 20% of patients continue to experience EVH and persistent anemia and require frequent blood transfusions. The financial costs associated with treatment exacerbate stress, creating a significant economic strain on patients and families. This wide-ranging impact underscores the importance of holistic management approaches to effectively support both patients and their caregivers in managing PNH.

The input stated that patients, caregivers, and families affected by PNH desire tolerable treatment options that reduce treatment burden, decrease hemolysis symptoms, decrease dependency on blood transfusions, slow disease progression, and improve long-term outcomes and quality of life. The input indicated that the 1 patient with experience with danicopan noticed a remarkable improvement in their symptoms.

Clinician Input

Input From Clinical Experts We Consulted

We consulted 2 clinical experts with experience treating PNH for this review. Per the clinical experts, PNH is a complicated disease, and the initial goals of therapy are to reduce mortality, reduce complications and morbidities associated with IVH, as well as reduce transfusion needs and improve HRQoL with better hemoglobin support, avoidance of iron overload, helping patients to attain better functional status and return to prediagnosis activities and employment. The initial treatment of choice for PNH is a C5i, which controls IVH and thus the major mortality and morbidity of the disease, as most deaths in PNH are due to thrombotic complications.

C5i can provide incomplete control of PNH in some circumstances: possible causes include rare genetic mutations (in people of Japanese ethnicity), inadequate dosing of C5i, response to vaccination, or infections leading to BTH or symptomatic EVH related to C5 inhibition. The experts estimated that approximately 40% of patients with PNH will continue to have low hemoglobin despite therapy, approximately 30% will require transfusions, and in 20% to 30% of patients EVH will contribute to their poor HRQoL.

Per the experts, there is no standard definition for EVH and a diagnosis of EVH generally requires ruling out other possible causes of anemia, which may be challenging as patients often have other comorbidities and it may not be evident that anemia is due to 1 cause. Clinical diagnosis for EVH typically requires anemia along

with normal or minimally elevated lactate dehydrogenase (LDH), as well as elevated bilirubin and reticulocyte counts. Alternative explanations for anemia which the experts noted would have to be ruled out include bone marrow failure, hematinic deficiencies (such as vitamin B12 or ferritin), renal insufficiency or blood loss.

Treatment goals for patients with PNH and EVH remain to reduce mortality, inhibit IVH and improve HRQoL with better hemoglobin support that does not require transfusion, avoids iron overload, and leads to better functional status for patients. The main nonpharmacologic treatment for EVH and persistent anemia in PNH while on C5 treatment is transfusion support, which is associated with several drawbacks such as lengthy hospital visits and risks with transfusion including infection, antibody development, or iron overload. In addition, most patients on transfusion will have significantly reduced HRQoL and be unable to maintain regular employment.

Pegcetacoplan is the primary pharmacologic option offered for patients with clinically significant EVH. Pegcetacoplan is a SC infusion with twice-weekly dosing and specific transportation requirements. If BTH occurs the experts noted that the frequency of pegcetacoplan will usually be increased to 3 times weekly.

The experts noted that danicopan would be an alternative to pegcetacoplan, as a second-line drug, and would be used as an add-on therapy for patients already on C5i. Some patients already on pegcetacoplan may wish to switch to danicopan plus a C5i if they were having ongoing BTH or issues with SC infusions.

Response to therapy would typically be an improvement in hemoglobin and a reduction in transfusion requirements relative to the baseline for a given patient. The experts noted that ongoing anemia and transfusion needs may or may not be a treatment failure, as it is possible that other concurrent diseases such as bone marrow failure, aplastic anemia, other cancers or comorbidities could be contributing factors. Intolerance or allergy to danicopan would be reason to discontinue therapy, as would a lack of improvement in hemoglobin levels and transfusion needs. The experts noted that an episode of BTH or transfusion requirement in another setting would not be considered a treatment failure, nor would a required stoppage of therapy due to pregnancy or breastfeeding. Stopping danicopan therapy should be considered independent of the C5i as that treatment controls IVH.

Clinician Group Input

One clinician group, the Canadian PNH Network, submitted input for this review based on contributions from 9 clinicians. Information was gathered through publicly available documents, congress abstracts, and published literature.

The clinician group agreed with the clinical experts that the current standard of care for PNH is C5i (i.e., eculizumab and ravulizumab), which act via terminal complement blockade, and that there are still some unmet therapeutic needs within the available PNH treatment regimen. The clinician group input agreed with the clinical experts that some patients remain anemic due to EVH, and some remain transfusion dependent with C5i.

The clinician group agreed with the experts that a subset of patients would benefit from proximal complement inhibition given the development of clinically significant EVH, but for whom pegcetacoplan is less than ideal.

Dual complement blockade (i.e., C5i plus danicopan) would provide these patients with the same benefits of improved hemoglobin but with a lower risk of complications.

The clinician group and the clinical experts were also aligned on the patients most likely to benefit from danicopan being those who have persistent anemia despite stable-dose C5i, in whom EVH is suspected. Patients who may receive proximal inhibition monotherapy (e.g., pegcetacoplan) who may not tolerate it or have repeated BTH, or other concerns could also benefit from the therapy. The input further noted that treatment is least suitable for those who are not anemic, or who meet exclusion criteria in clinical trials, such as pregnancy.

The clinician input noted that clinically meaningful response to treatment would be sustained control of LDH but with further hemoglobin increases and improvement in anemia-related symptoms. A lack of improvement in the first few months of therapy would be a prompt to dose-increase. Danicopan discontinuation should be considered in patients who develop adverse events that preclude ongoing therapy, including poor treatment compliance and intolerable side effects. The most important feature to watch for would be evidence of BTH.

The clinical experts and clinician group input agreed that patients with PNH should be followed by clinicians who specialize in the area.

Drug Program Input

Input was obtained from the drug programs that participate in our reimbursement review process. The following were identified as key factors that could potentially impact the implementation of our recommendation for danicopan:

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

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

Table 2: Responses to Questions From the Drug Programs

Implementation issues	Response
Relevant comparators	
The comparator in the ALPHA trial was placebo, which is appropriate for an add-in therapy, however pegcetacoplan is approved for patients who have had an inadequate response to C5i therapy. Could danicopan be used as an add-on therapy to pegcetacoplan as well?	CDEC agreed with the clinical experts that as there are no studies on the use of danicopan in combination with pegcetacoplan, and that such combination would not be used for the time being.

Implementation issues	Response
Considerations for initiation of therapy	
The specific requirements in the ALPHA trial for a definition of clinically significant EVH were: • anemia: hemoglobin ≤ 9.5 g/dL • absolute reticulocyte count ≥ 120 × 10^9/L. Patients also need to have C5i treatment for at least 6 months and a platelet count ≥ 30 000/μL. Are these measurements typical or standard to define EVH? Do these criteria represent a typical patient? Are these criteria readily measurable?	The clinical experts noted to CDEC that there are no specific definitions or standards to define EVH. The experts noted that broadly speaking it consists of signs of hemolysis that are not intravascular, plus suggestive changes in laboratory markers including reticulocytes, bilirubin, or coomb's test. Patients do have to have anemia; however, the cut-off of 9.5 g/dL (95 g/L) did not pertain to a specific standard. The experts commented that at 9.5 g/dL (95 g/L) they would likely not consider transfusion unless other patient factors suggested it should be done. CDED agreed with the clinical experts that the criteria defined in the ALPHA trial represent a typical patient; however, the experts also noted that the platelet count threshold does not represent an indication or contraindication to therapy. It may be a criterion in the trial to ensure that there are not too many patients with bone marrow failure, which they noted this is standard for research practice. CDEC recommended that patients should have persistent anemia, defined as hemoglobin levels ≤ 9.5 g/dL (95 g/L), caused by EVH, and an absolute reticulocyte count ≥ 120 × 109/L to be eligible to danicopan. The clinical experts also noted to CDEC that all criteria would be measurable with standard laboratory testing.
Could clinically significant EVH be seen with pegcetacoplan, the current second-line therapy? Could danicopan be added on to pegcetacoplan therapy?	The clinical experts noted to CDEC that clinically significant EVH could be observed with pegcetacoplan, bearing in mind the caveats about the lack of a specific clinical definition for EVH. The clinical experts also noted that, due to a lack of studies combining pegcetacoplan and danicopan they would not use the combination at this time. CDEC recommended that danicopan must not be used in combination with pegcetacoplan.
Considerations for continuation or renewal of therapy	
Frequent monitoring of bloodwork is required, can this be defined as to what is needed and when to assess response?	The clinical experts noted to CDEC that their patients are frequently complex and so the type and frequency of bloodwork or transfusions was patient-dependent; they may treat patients at frequencies varying from weekly to every 6 months, although their baseline visit frequency was usually every 3 months. They highlighted that those measures for blood count, creatinine, electrolytes, bilirubin, lactate dehydrogenase and haptoglobin were regular laboratory tests, with the possibility of adding on measures such as reticulocyte counts, vitamin levels, or other biomarkers to identify the source of patient concerns or symptoms. CDEC recommended that for renewal after initial authorization, the physician must provide proof of beneficial clinical effect when requesting continuation of reimbursement, defined as either of the following reduction in transfusion needs from baseline before initiating danicopan, or normalization of hemoglobin levels to above the lower limit of the normal reference range. CDEC also recommended that subsequent renewals should be assessed annually to ensure clinical benefit observed at the previous assessment, is maintained.

Implementation issues	Response
Considerations for discontinuation of therapy	
Can loss of response or a lack of response to danicopan therapy be defined?	The clinical experts noted to CDEC that an important concern in PNH therapy was defining whether a patient was experiencing a loss of response due to poor adherence or inadequate dosing, which would be considered a loss of response, as opposed to a treatment failure. The clinical experts also indicated that if a patient were to become anemic and transfusion dependent again, they would consider that a loss of response. However, if a patient did not improve in any measures after starting a new therapy, the clinical experts considered it a lack of response.
Is danicopan therapy intended to be indefinite?	The clinical experts noted to CDEC that danicopan would be considered indefinite, apart from specific situations such as palliative care or bone marrow grafts.
Considerations for prescribing of therapy	
Are there concerns about combining danicopan as an add-on to pegcetacoplan?	CDEC agreed with the clinical experts that as there are no studies on this combination, it is not 1 they would envision using at this time. CDEC recommended that danicopan should not be prescribed in combination with pegcetacoplan.
Generalizability	
Should patients have to be on a C5i for at least 6 months before adding on danicopan? It may be desired to add-on sooner, and in our previous review of pegcetacoplan, 3 months was needed before initiating.	The clinical experts noted to CDEC that the 3-month duration was a requirement for the clinical trial in pegcetacoplan, but in clinical practice they noted that changes to therapy are rarely made before the patient has been on a medication for 6 months. The clinical experts also noted that these changes exclude dose adjustments. CDEC recommended that patients must have been on a stable dose (i.e., no change in either the prescribed dose or interval) of either ravulizumab or eculizumab for ≥ 6 months to be eligible for danicopan.
Could patients currently on pegcetacoplan want to be switched back to a C5i with danicopan add-on?	The clinical experts noted to CDEC that there would likely be some patients who are either suboptimally controlled with pegcetacoplan or who prefer not to use it due to the requirement for infusions, or whose quality of life was otherwise impacted by the medication administration. The clinical experts also noted it would likely not be most patients as in their experience, patients are often hesitant to switch medications.
Care provision issues	
Will *N. meningitidis* vaccinations and/or antibiotic drugs be required before initiation?	The clinical experts noted to CDEC that all patients are usually vaccinated for meningitis group B, C and D strains every 3 to 5 years but there is inconsistent access for other vaccines which might be required such as pneumococcus vaccines. They noted that access and required vaccines per province is unequal. They did not have issues with vaccine access specifically. CDEC noted that the updated product monograph for danicopan should be consulted.

C5i = complement 5 inhibitor; EVH = extravascular hemolysis; IVH = intravascular hemolysis; PNH = paroxysmal nocturnal hemoglobinuria.

Clinical Evidence

Systematic Review

Description of Studies

The ALPHA trial is an ongoing phase III, double-blind, randomized placebo-controlled trial which enrolled a total of 86 patients with PNH who had clinically significant EVH and receiving treatment with ravulizumab or eculizumab. The study used a 45-day screening period and randomization was stratified by transfusion history (more than 2 transfusions or 2 or less transfusions in the 6 months before screening), hemoglobin at screening (less than 8.5g/dL or 8.5g/dL or more), and Japanese patient (yes or no). Stochastic dynamic allocation rules were used to randomize patients 2:1 through an interactive response technology to either receive danicopan 3 times a day added onto their C5i or a placebo 3 times a day added onto their C5i monotherapy, respectively. The study design consisted of a 12-week treatment period 1 (TP1) which was randomized, double-blind and placebo-controlled, followed by a 12-week treatment period 2 (TP2) where patients initially randomized to placebo switched to receive danicopan and patients initially randomized to danicopan continued to receive danicopan. Patients completing TP2 were eligible to continue onto to a total of 2 long-term extensions (LTE1 or LTE2); results from patients who have completed LTE1 to date were included in the submission.

The prespecified interim analysis submitted for this reimbursement review was planned for when approximately 75% (N = 63 patients) of the total planned sample had been randomized and completed the TP1; the purpose of this analysis, per the submission, was to assess stopping early for efficacy. The data cut-off for the TP1 interim analysis was conducted on June 28, 2022, and a second interim data analysis for TP2 results was conducted with a data cut-off of September 20, 2022. A total of 63 patients formed the interim efficacy analysis set and a total of 86 patients (the entire randomized study sample) formed the interim safety analysis set.

Patients eligible to participate in the study were required to be 18 years of age or older, have a diagnosis of PNH and have clinically significant EVH defined as patients presenting with anemia (hemoglobin less than or equal to 9.5 g/dL) and increased reticulocyte count (greater than or equal to 120 × 10^9/L), with or without the need for transfusion, had to be receiving an approved C5i (ravulizumab or eculizumab) with no change in dose or interval for at least 6 months, as well as meet a platelet count threshold of 30 000 or more per µL and a neutrophil count of 500 or more per µL. Patients were eligible regardless of transfusion status. Patients were excluded if they had a history or presence of any clinically significant medical condition or comorbidity, including any conditions leading to anemia that are not primarily due to PNH; if they had any procedures and/or laboratory anomalies that would put them at undue risk to receive danicopan; or patients who were, or who had partners who were pregnant, nursing, or planning to become pregnant during the study or within 90 days of study intervention.

All patients received either danicopan or placebo in the form of 50 mg or 100 mg film-coated oral tablets. To assess adherence, adherence was calculated as a percentage of danicopan doses taken divided by the

doses scheduled to be taken. The dosage administered started at 150 mg 3 times a day; dosing could be escalated up to a maximum of 200 mg at specific time points and specific clinical circumstances in the study.

The primary outcome was change in hemoglobin levels from baseline to week 12. Key secondary outcomes were the proportion of patients with hemoglobin increase of 2 g/dL or greater in the absence of transfusion at week 12; transfusion avoidance (transfusion free and not requiring transfusion) at week 12; change in absolute reticulocyte count from baseline to week 12; and change in Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scores from baseline to week 12. The primary and key secondary outcomes were controlled for multiple comparisons and an alpha-spending procedure was applied to account for the fact that a smaller sample size than was required by the power calculations was used for this analysis. The alpha-spending procedure and hierarchical testing structure controlled the family-wise type I error rate for these end points. Secondary outcomes were the proportion of patients with hemoglobin normalization (defined as patients with hemoglobin values above the lower limit of the normal reference range (110 g/L for female patients, 125 g/L for male patients); transfusion burden, defined as the number of RBC units transfused and the number of transfusion instances; and change in LDH from baseline. Exploratory outcomes were change from baseline in the EQ-5D-3L visual analogue scale (VAS) scores and EORTC QLQ-C30 Global Health Status/Quality of Life (QoL) Score. All primary, key secondary, secondary and exploratory outcomes were measured at weeks 12 and 24; hemoglobin, absolute reticulocyte count, LDH, FACIT-Fatigue, EQ-5D-3L and EORTC QLQ-C30 were also measured at week 72 among patients with data at that time point and reported as LTE1 results.

Most baseline characteristics were broadly similar between study arms. There was a numeric difference in the proportion of female patients (66.7% in the placebo + C5i arm, 54.8% in the danicopan + C5i arm), and the proportion of Asian patients (33.3% in the placebo + C5i arm, 42.9% in the danicopan + C5i arm). There were also numeric differences in the proportion of patients treated with each C5i (64.3% of patients in the danicopan + C5i arm and 47.6% of patients in the placebo + C5i arm were treated with ravulizumab). There was a numerically higher LDH in the danicopan + C5i arm (298.73 U/L) relative to the placebo + C5i arm (278.25 U/L), and a numerically higher proportion of patients in the danicopan + C5i arm had received a transfusion within 24 weeks of receiving the study drug (90.5% in the danicopan + C5i arm, 81.0% in the placebo + C5i arm).

Efficacy Results

Change in Hemoglobin Levels

The least squares (LS) mean change from baseline in hemoglobin level to 12 weeks was the primary outcome. At TP1, the LS mean difference for the change in hemoglobin from baseline between the danicopan + C5i and the placebo + C5i arms was 24.44 g/L (98.2% confidence interval [CI], 15.25 to 33.63; P ≤ 0.0001). At TP2, the LS mean change from baseline to week 24 in the danicopan-emergent arm (patients who received danicopan + C5i from weeks 0 to 12 and continued to receive danicopan + C5i from weeks 12 to 24) was 31.67 g/L (95% CI, 25.61 to 27.74). In the placebo-emergent arm (patients who received placebo + C5i from weeks 0 to 12 and who subsequently switched to receive danicopan + C5i from weeks 12 to 24), the LS mean change from baseline to week 24 was 22.58 g/L (95% CI, 15.72 to 29.44). At LTE1, the

observed mean change from baseline in hemoglobin levels was 32.00 g/L (standard deviation [SD] = 11.81 g/L) in the danicopan-emergent arm and 31.50 (SD = 10.61) in the placebo-emergent arm.

Proportion of Patients With Hemoglobin Level Increase of 2g/dL or Greater in the Absence of Transfusion

The proportion of patients with hemoglobin level increases of 2g/dL or greater was a key secondary outcome in the analysis. At TP1, the LS mean difference for the proportion of patients with hemoglobin level increase of 2g/dL or greater between the danicopan + C5i and the placebo + C5i arms was 45.90% (95.8% CI, 27.40 to 64.42%; P ≤ 0.0001). At TP2, the proportion of patients with this outcome in the danicopan-emergent arm was 46.3% (95% CI, 30.66 to 62.58%); results were not reported for the placebo-emergent arm. This outcome was not reported at LTE1 in either arm.

Proportion of Patients With Hemoglobin Normalization

The proportion of patients with hemoglobin normalization was a secondary outcome. At TP1, the LS mean difference for the change in the proportion of patients with hemoglobin normalization between the danicopan + C5i and the placebo + C5i arms was 18.40% (95% CI, –0.84 to 37.71%; P = 0.0080). At TP2, the proportion of patients with this outcome in the danicopan-emergent arm was 19.50% (95% CI, 8.82 to 34.87%). This outcome was not reported for the placebo-emergent arm at TP2 and was not reported at LTE1 for either arm.

Transfusion Avoidance

Transfusion avoidance at TP1 was a key secondary outcome in the analysis. At TP1, the LS mean treatment difference for the proportion of patients with transfusion avoidance between the danicopan + C5i and the placebo + C5i arms was 40.80% (95.8% CI, 21.08 to 60.58%; P = 0.0004). At TP2, the proportion of patients with this outcome in the danicopan-emergent arm was 78.00% (95% CI, 62.39 to 89.44%), and was 90.00% (95% CI, 68.30 to 98.77%) in the placebo-emergent arm. This outcome was not reported at LTE1 in either arm.

Transfusion Burden

Transfusion burden was measured by the number of RBC units transfused and the number of transfusion instances; both were secondary outcomes. At TP1, the LS mean treatment difference between the danicopan + C5i arm and the placebo + C5i arm for the change in the number of RBC units transfused between the 12 weeks before study drug initiation and the 12 weeks after study drug initiation was –1.31 (95.8% CI, –2.24 to –0.37; P = 0.0072). At TP2, the change in the number of RBC units transfused in the 24 weeks after treatment initiation relative to the 24 weeks before treatment initiation in the danicopan-emergent arm was –2.80 (95% CI, –4.55 to –1.11). This outcome was not reported in the placebo-emergent arm or at LTE1 in either arm.

At TP1, the LS mean treatment difference between the danicopan + C5i arm and the placebo + C5i arm for the change in the number of transfusion instances between the 12 weeks before study drug initiation and the 12 weeks after study drug initiation was –0.72 (95% CI, –1.32 to –0.11; P = 0.0207). At TP2, the change in the number of transfusion instances between the 24 weeks before study drug initiation and the 24 weeks

after study drug initiation in the danicopan-emergent arm was –1.50 (95% CI, –2.36 to –0.67). This outcome was not reported in the placebo-emergent arm or at LTE1 in either arm.

Absolute Reticulocyte Count

Change in absolute reticulocyte count from baseline to week 12 was a key secondary outcome. At TP1, the LS mean treatment difference between the danicopan + C5i arm and the placebo + C5i arm for the change in absolute reticulocyte count from baseline was –0.087 x10^{12}/L (95.8% CI, –0.119 to –0.056 × 10^{12}/L; P ≤ 0.0001). At TP2, the change from baseline in absolute reticulocyte counts in the danicopan-emergent arm was –0.080 × 10^{12}/L (SD = 0.073 × 10^{12}/L), and in the placebo-emergent arm was –0.084 × 10^{12}/L (SD = 0.110 × 10^{12}/L). At LTE1, the observed mean change from baseline in absolute reticulocyte counts in the danicopan-emergent arm was –0.041 × 10^{12}/L (SD = 0.029 × 10^{12}/L), and in the placebo-emergent arm was –0.106 × 10^{12}/L (SD = not applicable [NA]; N = 1 patient).

Lactate Dehydrogenase

Change in LDH from baseline was a secondary outcome. At TP1, the LS mean treatment difference between the danicopan + C5i arm and the placebo + C5i arm for the change in LDH from baseline was –20.57 U/L (95% CI, –49.28 U/L to 8.15 U/L; P = 0.1569). At TP2, the mean change from baseline in LDH in the danicopan-emergent arm was –23.46 U/L (SD = 105.40 U/L), and in the placebo-emergent arm was 0.21 U/L (SD = 84.89 U/L). At LTE1, the mean change from baseline in LDH in the danicopan-emergent arm was –20.83 U/L (SD = 67.00 U/L), and in the placebo-emergent arm was 5.00 U/L (SD = 111.89 U/L).

Functional Assessment of Chronic Illness Therapy – Fatigue

The change in FACIT-Fatigue (ranging from zero [extreme fatigue] to 52 [no fatigue] with higher scores indicating less fatigue)[33] scores from baseline was a key secondary outcome. At TP1, the LS mean treatment difference between the danicopan + C5i arm and the placebo + C5i arm for the change in FACIT-Fatigue scores from baseline was 6.12 (95.8% CI, 2.18 to 10.06; P = 0.0021). At TP2, the LS mean change from baseline in FACIT-Fatigue scores in the danicopan-emergent arm was 6.12 (95% CI, 3.41 to 8.82), and in the placebo-emergent arm was 6.44 (95% CI, 1.23 to 11.64). At LTE1, the mean change from baseline in the danicopan-emergent arm was 3.86 (SD = 7.15) and –4.33 (SD = 9.07) in the placebo-emergent arm.

EQ-5D Visual Analogue Scale

The change in EQ-5D-3L VAS (health rating on a scale from 0 to 100, with 0 representing the worst imaginable health state and 100 the best)[34,35] scores from baseline was an exploratory outcome. At TP1, the LS mean treatment difference between the danicopan + C5i arm and the placebo + C5i arm for the change from baseline in EQ-5D-3L VAS scores was 6.27 (95% CI, –2.85 to 15.40; P = 0.1738). At TP2, the mean change from baseline in EQ-5D-3L VAS scores was 13.70 (SD = 20.12) in the danicopan-emergent arm and 9.70 (SD = 21.93) in the placebo-emergent arm. At LTE1, the mean change from baseline in the danicopan-emergent arm was 12.30 (SD = 18.70) and –11.00 (SD = 12.73) in the placebo-emergent arm.

European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 Scale

The change in EORTC QLQ-C30 Global Health (standardized score ranging from 0 to 100, higher score represents higher HRQoL) scores from baseline was an exploratory outcome. At TP1, the LS mean treatment difference between the danicopan + C5i arm and the placebo + C5i arm for the change from baseline in EORTC QLQ-C30 Global Health scores was 6.62 (95% CI, –1.17 to 14.41; P = 0.0941). At TP2, the mean change from baseline in EORTC QLQ-C30 Global Health scores was 8.56 (SD = 16.96) in the danicopan-emergent arm and 10.53 (SD = 14.92) in the placebo-emergent arm. At LTE1, the mean change from baseline in the danicopan-emergent arm was 1.19 (SD = 26.97) and 8.33 (SD = 22.05) in the placebo-emergent arm.

Results From Full Analysis

The patient disposition reported that a total of 70 (81.4%) patients (46; 80.7%) patients initially randomized to danicopan plus C5i and 24 (82.8%) patients initially randomized to placebo + C5i) completed the study, including years 1 and 2 of the LTE phase. Results at TP1 were either numerically similar for the full analysis (FA) compared to the interim analysis (IA), or the numeric changes observed did not materially impact the interpretation of the evidence, with some exceptions. A numeric increase in the LS mean treatment difference for the proportion of patients with transfusion avoidance was reported in the FA relative to the IA (IA result = 40.80; 95% CI, 21.08 to 60.58 and FA result = 48.40; 95% CI, 31.79 to 64.94). A slight numeric increase, sufficient to attain statistical significance, was reported for the treatment difference in the proportion of patients with hemoglobin normalization (IA result = 18.40; 95% CI, –0.84 to 37.71; P = 0.008 and FA result = 19.20; 95% CI, 3.34 to 35.10; P = 0.0023). Results for the proportion of patient with hemoglobin normalization and the proportion of patients with hemoglobin increase of 2g/dL or greater were numerically similar between TP2 and LTE, suggesting a maintained effect. There was slight numeric reduction in the observed change in hemoglobin from baseline between TP2 and LTE in the placebo-emergent arm (FA observed mean change from baseline at TP2 = 25.00; SD = 14.46 and FA observed mean change from baseline at LTE = 22.70; SD = 18.27 in the placebo-emergent arm), which was not observed in the danicopan-emergent arm. There was a notable reduction in the proportion of patients with transfusion avoidance at LTE in the danicopan-emergent arm relative to the result at TP2 (FA result at TP2 = 69.10; 95% CI, 55.19 to 80.86 and FA result at LTE = 59.30; 95% CI, 45.03 to 72.43). Both results at TP2 and LTE represented a numeric decrease from TP1 in the danicopan-emergent arm. Results for this outcome were not reported from TP2 to LTE for the placebo-emergent arm. LTE results were not reported for the FA for LDH. In terms of the measures of HRQoL, there were observed numeric decreases in both treatment arms between TP2 and LTE for EQ-5D-3L and EORTC QLQ-C30 scores. Overall, the efficacy results are still subject to the limitations (except for those inherent to interim analyses) which were highlighted in the critical appraisal. The clinical experts noted that any improvement to hematologic outcomes would be clinically meaningful to them and on this basis, the additional data from FA demonstrate that the results from most outcomes still meet this criterion, although decreases in some hemoglobin markers and the patient-reported outcomes are reported in the longer term and remain important to note.

Harms Results

Harms were reported separately for TP1, TP2 and LTE1 cutoffs, as well as overall during the entire time patients were exposed to danicopan (total danicopan treatment). Overall, a total of 93.0% of patients in the danicopan-emergent arm and 82.6% of patients in the placebo-emergent arm experienced treatment-emergent adverse events (TEAEs) during treatment with danicopan.

During TP1, there were numeric differences in the proportion of patients experiencing TEAEs for anemia (1.8% danicopan + C5i, 13.8% placebo + C5i), vomiting (5.3% danicopan + C5i, 0 placebo + C5i), upper abdominal pain (1.8% danicopan + C5i, 6.9% placebo + C5i), pyrexia (5.3% danicopan + C5i, 0 placebo + C5i), asthenia (0 danicopan + C5i, 13.8% placebo + C5i), ear infection (0 danicopan + C5i, 6.9% placebo + C5i), contusion (1.8% danicopan + C5i, 10.3% placebo + C5i), increased aspartate aminotransferase (AST; 3.5% danicopan + C5i, 10.3% placebo + C5i), pain in extremity (5.3% danicopan + C5i, 0 placebo + C5i), dizziness (1.8% danicopan + C5i, 6.9% placebo + C5i), and insomnia (1.8% danicopan + C5i, 10.3% placebo + C5i). A total of 57 patients in the danicopan + C5i arm and 29 patients in the placebo + C5i arm contributed data. There were numeric differences in the proportion of patients experiencing TEAEs for nausea (2.1% danicopan-emergent, 13.0% placebo-emergent), and pyrexia (10.4% danicopan-emergent, 0 placebo-emergent). A total of 48 patients in the danicopan-emergent arm and 23 patients in the placebo-emergent arm contributed data. During LTE there were numeric differences in the proportion of patients experiencing TEAEs for diarrhea (2.5% danicopan-emergent, 10.0% placebo-emergent), asthenia (2.5% danicopan-emergent, 15.0% placebo-emergent), and back pain (2.5% danicopan-emergent, 10.0% placebo-emergent). A total of 40 patients in the danicopan-emergent arm and 20 patients in the placebo-emergent arm contributed data.

Overall, a total of 12.3% of patients in the danicopan-emergent arm and 26.1% of patients in the placebo-emergent arm experienced any serious adverse event (SAE) while being treated with danicopan. During TP1, 5.3% of patients in the danicopan + C5i arm experienced any SAE; the SAEs were pancreatitis, cholecystitis, COVID-19, and blood bilirubin increase (1 report of each). A total of 6.9% of patients in the placebo + C5i arm experienced any SAE; the SAEs were anemia, abdominal pain, and headache (1 report of each). During TP2, 6.3% of patients in the danicopan-emergent arm experienced any SAE; the SAEs were Dieulafoy's vascular malformation, pyrexia, COVID-19 pneumonia, and staphylococcus sepsis (1 report of each). In the placebo-emergent arm, 13.0% of patients experienced any SAE; the SAEs were hemolysis, vertigo, and headache (1 report of each). During LTE, 7.5% of patients in the danicopan-emergent arm experienced any SAE; the SAEs were stent-graft endoleak, decreased hemoglobin, invasive ductal breast carcinoma, pulmonary embolism, and pulmonary hemorrhage (1 report of each). In the placebo-emergent arm, 20.0% of patients experienced any SAE; the SAEs were pericardial effusion, diarrhea, disease progression, COVID-19, and body temperature increased (1 report of each).

During TP1, TEAEs led to withdrawal of the study drug for 5.3% of patients in the danicopan + C5i arm and 3.4% of patients in the placebo + C5i arm. SAEs led to withdrawal of the study drug for 1.8% of patients in the danicopan + C5i arm, and 0 patients in the placebo + C5i arm. During TP2, there were no TEAEs or SAEs leading to withdrawal of the study drug in either treatment arm. During LTE, TEAEs led to withdrawal of the study drug in 5.0% of patients in the placebo-emergent arm; there were no TEAEs leading to withdrawal

of the study drug in the danicopan-emergent arm. There were no SAEs leading to withdrawal of the study drug in either treatment arm. There were no deaths reported in either study arm, at any time point during the trial to date.

Meningococcal infections and liver enzyme elevations were prespecified adverse events (AEs) of special interest during the ALPHA study. Throughout TP1, TP2, and LTE, there were no reported AEs of meningococcal infections in either study arm. During TP1, liver enzyme elevations occurred in 14.0% of patients in the danicopan + C5i arm and 10.3% of patients in the placebo + C5i arm. During TP2, liver enzyme elevations occurred in 6.3% of patients in the danicopan-emergent arm and 13.0% of patients in the placebo-emergent arm. During LTE, liver enzyme elevations occurred in 2.5% of patients in the danicopan-emergent arm and 5.0% of patients in the placebo-emergent arm. There was a total of 8 TEAEs of hemolysis reported in 7 patients during the study to date. Four of them were related to hemolysis and 4 of which were BTH based on investigator judgment. All patients were stable on their C5i. No case-specific details were provided in the submission on the management of the hemolysis or BTH events. Per the submission, no events led to treatment discontinuation, and none were associated with an LDH level above 2.2 × upper limit of normal.

Harms From the FA

The FA of ALPHA contained updated harms information. Briefly, the most common AEs during the entire study as per the FA were similar to the IA, with the most common being COVID-19 (26.3% patients in the danicopan-emergent arm, 40.7% patients in the placebo-emergent arm), pyrexia (33.3% patients in the danicopan-emergent arm, 11.%% patients in the placebo-emergent arm), headache (26.3% patients in the danicopan-emergent arm, 11.1% in the placebo-emergent arm), nausea (17.5% in the danicopan-emergent arm, 11.1% in the placebo-emergent arm), and asthenia (10.5% patients in the danicopan-emergent arm, 18.5% patients in the placebo-emergent arm). The proportion of patients with TEAEs during TP1 did not change notably; during TP1 there was 1 additional SAE reported (cholelithiasis) in the danicopan arm. The proportion of patients with any TEAE during TP2 increased from 64.6% to 74.5% of patients in the danicopan-emergent arm and from 56.5% to 66.7% of patients in the placebo-emergent arm; there were additional SAEs reported of hemolysis, cholecystitis and femur fracture (1 report of each, placebo-emergent arm). The proportion of patients with any TEAE during LTE (entire study) increased from 62.5% to 88.9% in the danicopan-emergent arm and from 80.0% to 92.3% in the placebo-emergent arm. There were additional SAE reports in the danicopan-emergent arm of anemia, abdominal pain, nausea, vomiting, noncardiac chest pain, pyrexia, COVID-19, and decreased platelet count (1 report of each). There were additional SAE reports in the placebo-emergent arm of hemorrhagic diathesis, upper abdominal pain, COVID-19, pneumonia, cystitis, neutropenic sepsis, arthralgia, and PNH (1 report of each). Relative to the IA, there were additional increases in the proportion of patients who withdrew the study drug due to AEs or SAEs during all treatment periods; information in the FA was split into withdrawal due to AE and SAE instead of due to specific events. During TP1, in the danicopan + C5i arm 3 (5.3%) patients discontinued due to AEs and 1 (1.8%) discontinued due to SAEs (overall increase of 1 patient who withdrew the study drug relative to IA); 1 (3.4%) patient withdrew the study drug due to AEs in the placebo-emergent arm (unchanged from IA). During TP2, 1 (3.7%) patient withdrew the study drug due to AEs in the placebo-emergent arm (overall increase of 1 patient

relative to the IA). During LTE, 1 (1.9%) patient in the danicopan-emergent arm withdrew the study drug due to AEs, and 1 (3.8%) patient in the placebo-emergent arm withdrew due to AEs (increase of 1 patient in the danicopan-emergent arm relative to IA). There was 1 death reported in the placebo-emergent arm during the study in the FA, which took place in the LTE; the patient had an SAE of pneumonia. (increase of 1 patient relative to the IA). The FA did not report any additional AEs of meningococcal infections but reported 1 additional patient in the danicopan-emergent arm with liver enzyme elevations in the LTE. Overall, the safety results from the FA provided additional safety signals including 1 death, however the overall proportion of patients with SAEs and the proportion of patients who withdrew the study drug due to AEs or SAEs remained numerically low and broadly similar between study arms, similar to results from the IA.

Critical Appraisal

There are some limitations pertaining to patient disposition and patient characteristics to note. A total of 18.9% of patients failed to meet the inclusion or exclusion criteria, but it isn't specified which inclusion/exclusion criteria were not met during screening, therefore it is not known whether excluded patients were systematically different from included ones. In addition, while baseline characteristics were broadly balanced between study arms, the differences in the proportion of patients treated with each C5i (64.3% of patients in the danicopan + C5i arm and 47.6% of patients in the placebo + C5i arm were treated with ravulizumab) may bias the harms results as according to the clinical experts and literature, ravulizumab is the preferred C5i drug.[37] In addition, TP1 and TP2 time points had numerically low patient dropout, however the small number of patients who have completed LTE1 to date make long-term results for efficacy and safety highly uncertain. There are also some potential limitations associated with the study design. The ALPHA trial IA used a prespecified interim stopping criteria at 75% of patients, as well as an alpha-spending procedure for the primary and key secondary end points. However, given the IA was conducted based on 75% of the originally targeted sample size, there is an increased risk that the true effect of danicopan on these end points is over-estimated by the IA. In addition, while the primary and key secondary end points were controlled for multiple comparisons, the secondary and exploratory outcomes were not controlled for this or for the smaller sample size, and there is a risk of inflated type I error when interpreting results from these comparisons. Furthermore, there are possible limitations pertaining to the numbers of complete cases in the danicopan + C5i and subsequent danicopan-emergent arm; without further information on the patients who were missing, the degree to which the missingness may be informative to the results is not known. In addition, there was no placebo comparator after the end of TP1 therefore observed results in TP2 and LTE may not all be attributable to treatment. Lastly, there are some potential limitations associated with outcome ascertainment. While laboratory outcomes such as hemoglobin or LDH are likely at low risk of bias due to being centrally measured, the open-label design of TP2 and LTE mean that knowledge of the treatment being received may impact reporting of subjective QoL outcomes at those time points (impacting FACIT-Fatigue, EORTC QLQ-C30, and EQ-5D-3L outcomes). Similarly, while a measure of treatment adherence was reported in the study, this was based on tablet counts and there is a possibility of reporting bias.

There are some limitations regarding the study population to note. Per the clinical experts, most of the inclusion criteria were reasonable for PNH patients in the context of Canada, however the minimum thresholds for platelet and neutrophil counts, as well as the exclusion criteria ruling out patients with other

causes of anemia or other clinical comorbidities may exclude patients who could be candidates for treatment in a real-world setting. The clinical experts also noted that while there are certain clinical characteristics alongside persistent anemia whose presence indicate that EVH is the likely cause, there is no standard diagnostic definition of the condition. The cut-off used in ALPHA to define anemia was a level at which the clinical experts speculated patients would likely feel symptoms and could require intervention but was not based on a known standard. In addition, the clinical experts noted that transfusion practices vary greatly and are partially dependent on patient factors such as lifestyle or comorbidities. Therefore, the study population included in ALPHA may not represent all PNH patients with EVH. There are also some limitations regarding the generalizability of the results to clinical situations. The frequency of visits used in the trial setting may not exactly reflect daily clinical practice in Canada and therefore the efficacy and safety profile during the trial may not be extrapolatable to the general patient population. During the trial, the approved C5i dose was neither permitted to be increased, nor the interval shortened, which also may not reflect clinical practice. FACIT-Fatigue and EORTC QLQ-C30 are validated tools in PNH patients, but the EQ-5D-3L is not validated in PNH specifically, therefore changes in health status reflected in that score may not translate perfectly to changes in health status in PNH. Furthermore, there were no minimally important differences (MIDs) provided by the sponsor or the clinical experts for all but 1 of the outcomes in PNH patients, therefore information on clinically meaningful change for most outcomes remain lacking.

GRADE Summary of Findings and Certainty of the Evidence

For pivotal studies and RCTs identified in the sponsor's systematic review, GRADE was used to assess the certainty of the evidence for outcomes considered most relevant to inform CADTH's 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.

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). The target of the certainty of evidence assessment was based on thresholds informed by the sponsor submission, input from the clinical experts, and/or thresholds identified in the literature. 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 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 — change from baseline to week 12 in the following:
  - hemoglobin levels
  - proportion of patients with hemoglobin increase of at least 2g/dL in the absence of transfusion

    - transfusion avoidance
    - absolute reticulocyte count
    - transfusion burden (number of RBC units transfused, number of transfusion instances)
    - LDH
    - proportion of patients with hemoglobin normalization
- Fatigue and HRQoL outcomes — change from baseline to week 12 in the following:
    - FACIT-Fatigue
    - EQ-5D-3L
    - EORTC QLQ-C30
- Mortality: proportion of patients who died
- Harms: proportion of patients with meningococcal infections, proportion of patients with liver enzyme elevation

Table 3: Summary of Findings for Danicopan Plus C5i Versus Placebo Plus C5i for Patients With PNH Experiencing EVH[a]

Outcome and follow-up	Patients (studies), N[b]	Absolute effects (98.2%, 95.8%, or 95% CI)[c]			Certainty	What happens
		Placebo + C5i	Danicopan + C5i	Difference		
Hematologic Outcomes						
LS mean change in hemoglobin from baseline (g/L) Follow-up: 12 weeks	63 (1 RCT)	4.96 (–2.70 to 12.61)	29.40 (24.23 to 34.57)	24.44 (15.25 to 33.63)	Moderate[d]	Treatment with danicopan plus C5i therapy likely results in an increase in hemoglobin levels when compared to placebo plus C5i therapy.
Proportion of patients with hemoglobin increase of ≥ 2g/dL (20 g/L) in the absence of transfusion Follow-up: 12 weeks	63 (1 RCT)	0 (0.00 to 16.80)	59.50 (42.73 to 74.84)	45.90 (27.40 to 64.42)	Moderate[d]	Treatment with danicopan plus C5i therapy likely results in an increase in the proportion of patients with a hemoglobin increase of ≥ 2g/dL (20 g/L) in the absence of transfusion when compared to placebo plus C5i therapy. The clinical importance of the increase is unclear.
Proportion of patients achieving transfusion avoidance (transfusion free and do not require a transfusion) Follow-up: 12 weeks	63 (1 RCT)	38.10 (17.56 to 62.32)	83.30 (68.08 to 93.27)	40.80 (21.08 to 60.58)	Moderate[d]	Treatment with danicopan plus C5i therapy likely results in an increase in the proportion of patients achieving transfusion avoidance (i.e., transfusion free and do not require a transfusion) when compared to placebo plus C5i therapy. The clinical importance of the increase is unclear.
LS mean change from baseline in absolute reticulocyte counts (10^{12}/L) Follow-up: 12 weeks	63 (1 RCT)	0.004 (–0.023 to 0.030)	–0.084 (–0.102 to –0.065)	–0.087 (–0.119 to –0.056)	Moderate[d]	Treatment with danicopan plus C5i therapy likely results in an increase in the LS mean change from baseline in absolute reticulocyte counts when compared to placebo plus C5i therapy. The clinical importance of the increase is unclear.
LS mean change from baseline in transfusion burden						
Number of RBC units transfused[e] Follow-up: 12 weeks pretrial to 12 weeks posttreatment	63 (1 RCT)	–0.18 (–0.94 to 0.59)	–1.48 (–2.02 to –0.94)	–1.31 (–2.24 to –0.37)	Moderate[d]	Treatment with danicopan plus C5i therapy likely results in a decrease in the number of RBC units transfused when compared to placebo plus C5i therapy. The clinical importance of the decrease is unclear.

Outcome and follow-up	Patients (studies), N[b]	Absolute effects (98.2%, 95.8%, or 95% CI)[c]			Certainty	What happens
		Placebo + C5i	Danicopan + C5i	Difference		
Number of transfusion instances[e] Follow-up: 12 weeks pretrial to 12 weeks posttreatment	63 (1 RCT)	–0.21 (–0.70 to 0.29)	–0.92 (–1.27 to –0.57)	–0.72 (–1.32 to –0.11)	Moderate[d]	Treatment with danicopan plus C5i therapy likely results in a decrease in the number of transfusion instances when compared to placebo plus C5i therapy. The clinical importance of the decrease is unclear.
Proportion of patients with hemoglobin normalization (hemoglobin above the LLN for reference range)[e] Follow-up: 12 weeks	63 (1 RCT)	0 (0.00 to 16.11)	28.6 (15.72 to 44.58)	18.40 (–0.84 to 37.71)	Low[d,f]	Treatment with danicopan plus C5i therapy may result in an increase in the proportion of patients with hemoglobin normalization when compared to placebo plus C5i therapy.
LS mean change from baseline in LDH[e] Follow-up: 12 weeks	63 (1 RCT)	–2.92 (–26.76 to 20.93)	–23.49 (–40.08 to –6.90)	–20.57 (–49.28 to 8.15)	Low[d,g]	Treatment with danicopan plus C5i therapy may result in a decrease in LDH when compared to placebo plus C5i therapy. The clinical importance of the decrease is unclear.
Fatigue and HRQoL						
LS mean change from baseline in FACIT-Fatigue scores Follow-up: 12 weeks	63 (1 RCT)	1.85 (–1.31 to 5.02)	7.97 (5.72 to 10.23)	6.12 (2.33 to 9.91)	Low[d,h]	Treatment with danicopan plus C5i therapy may result in an increase in FACIT-Fatigue scores when compared to placebo plus C5i therapy.
LS mean change from baseline in EQ–5D–3L VAS scores[c] Follow-up: 12 weeks	63 (1 RCT)	5.25 (–2.46 to 12.96)	11.53 (6.25 to 16.81)	6.27 (–2.85 to 15.40)	Low[d,g]	Treatment with danicopan plus C5i therapy may result in little to no change in EQ–5D–3L VAS scores when compared to placebo plus C5i therapy.
LS mean change from baseline in EORTC QLQ–C30 Global Health Status/ QoL scores[c] Follow-up: 12 weeks	63 (1 RCT)	3.80 (–2.78 to 10.38)	10.42 (5.87 to 14.97)	6.62 (–1.17 to 14.41)	Low[d,g]	Treatment with danicopan plus C5i therapy may result in little to no change in EORTC QLQ–C30 Global Health Status /QoL scores when compared to placebo plus C5i therapy.
Harms						
Number of patients with meningococcal infections Follow-up: 72 weeks	63 (1 RCT)	0 (NR)	0 (NR)	NR (NR)	Very Low[d,i,j]	The evidence is very uncertain about the effect of danicopan plus C5i therapy on the number

Outcome and follow-up	Patients (studies), N[b]	Absolute effects (98.2%, 95.8%, or 95% CI)[c]			Certainty	What happens
		Placebo + C5i	Danicopan + C5i	Difference		
						of patients with meningococcal infections when compared to placebo plus C5i therapy.
Number of patients with liver enzyme elevations Follow-up: 72 weeks	63 (1 RCT)	10 (NR)	4 (NR)	NR (NR)	Very low[d,i,j]	The evidence is very uncertain about the effect of danicopan plus C5i therapy on the number of patients with liver enzyme elevations when compared to placebo plus C5i therapy.
Mortality						
Proportion of patients who died Follow-up: 72 weeks	63 (1 RCT)	0 (NR)	0 (NR)	NR (NR)	Very low[d,i,j]	The evidence is very uncertain about the effect of danicopan plus C5i therapy on the number of patients who died when compared to placebo plus C5i therapy.

C5i = complement 5 inhibitor; CI = confidence interval; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 Scale; FACIT = Functional Assessment of Chronic Illness Therapy; HRQoL = health-related quality of life; LDH = lactate dehydrogenase; LLN = lower limit of normal; LS = least squares; MID = minimal important difference; RBC = red blood cell; RCT = randomized controlled trial.

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.

[a]Clinically significant EVH was defined in ALPHA as anemia: hemoglobin ≤ 9.5 g/dL, and as absolute reticulocyte count ≥ 120 × 10^9/L.

[b]Results are from the interim efficacy analysis of ALPHA (N = 63 patients; 42 patients randomized to receive danicopan add-on therapy and 21 patients randomized to receive placebo add-on therapy).

[c]Confidence intervals for the primary outcome (change in hemoglobin from baseline) are 98.2% and for the key secondary outcomes (proportion of patients with hemoglobin increase of ≥ 2g/dL in the absence of transfusion; proportion of patients achieving transfusion avoidance; change from baseline in absolute reticulocyte counts; change from baseline in FACIT-Fatigue scores) confidence intervals are 95.8%, per the IA alpha-spending procedure. For all other outcomes, confidence intervals are 95%.

[d]Rated down 1 for serious indirectness. Per the clinical experts, there is no standard definition for EVH, the exclusion criteria do not provide a specific list of comorbidities or laboratory values used in screening, and the minimum requirements for platelet and neutrophil counts may exclude patients with comorbidities who could be considered for treatment with danicopan.

[e]Statistical testing for this outcome was not adjusted for multiple comparisons in the trial.

[f]Rated down1 for serious imprecision. The clinical experts specified that the target for the certainty of evidence would be the presence of a non-null effect. The confidence interval includes the possibility of a decrease in the outcome, no effect on the outcome, and an increase in the outcome.

[g]Rated down 1 for serious imprecision. The target of the certainty assessment is the presence of a non-null effect. The confidence interval includes the possibility of potential benefit as well as potential harm.

[h]Rated down 1 for serious imprecision. The MID provided in the submission was a change in scores from baseline of 5 points. The confidence interval includes the possibility of clinically meaningful benefit as well as the possibility of benefit that is not clinically meaningful.

[i]Rated down 1 for serious study limitations. The evidence submitted for ALPHA was an interim analysis, and as the study is still ongoing the reporting of harms information is incomplete and may bias the reported results.

[j]Rated down 2 for very serious imprecision. There are a very small number of events captured.

Source: Details included in the table are from the sponsor's Summary of Clinical Evidence, the ALPHA CSR and additional information provided by the sponsor.

LTE Studies

Results of the LTE of ALPHA are summarized in the Systematic Review section.

Indirect Comparisons

Description of Studies

Indirect evidence was required to be considered as part of the submission because the ALPHA trial compared danicopan + C5i therapy with placebo + C5i therapy, however comparative data against pegcetacoplan, the other second-line therapeutic option for PNH, remains lacking. The submission included a systematic literature review (SLR) and feasibility assessment to undertake a matching-adjusted indirect comparison (MAIC) with the PEGASUS trial, which compared pegcetacoplan with eculizumab in adult patients with PNH. A naive comparison of these 2 trials was also submitted but was not appraised due to considerable methodological limitations with this method.

The feasibility assessment consisted of a comparison of the between-trial heterogeneity in trial design, trial end points, patient eligibility criteria and baseline patient characteristics.

The MAIC analysis compared a subset of the ALPHA population which was trimmed to meet the additional inclusion criteria which were a part of PEGASUS but not ALPHA:

- body mass index less than 40 kg/m^2
- platelet count greater than 50 000/µL.

The MAIC used a weighting approach per the methodology reported by Signorovitch et al. and qualitatively reported on the 2 methods in terms of balancing characteristics. The weight model included baseline hemoglobin and baseline reticulocyte count. Efficacy results were reported in the anchored MAICs as differences of treatment differences (TD) for each trial (danicopan and C5i, placebo, and C5i or pegcetacoplan, eculizumab). The unanchored MAICs reported efficacy results as TDs between the danicopan plus C5i arm and the pegcetacoplan alone arm.

The distribution of calculated weights from both methods was reported, as well as the baseline characteristics after adjustment by both methods. After weighting, anchored and unanchored MAICs were undertaken for the following efficacy outcomes: change in hemoglobin from baseline, change in absolute reticulocyte count from baseline, change in LDH from baseline, change in FACIT-Fatigue scores from baseline, and transfusion avoidance. The following safety outcomes were also reported from the MAICs: time to hemolysis AE, and probability of BTH during extended follow-up (48 weeks for pegcetacoplan and 34.5 weeks for ALPHA). Time to discontinuation due to BTH was also reported, but in an unweighted population and therefore was not appraised. All analyses compared results from ALPHA at 12 weeks to results from PEGASUS at 20 weeks (the study design consisted of a 4-week run-in with C5i monotherapy coadministration, followed by a 16-week randomized period).

Efficacy Results

In the feasibility assessment, the sponsor detailed differences in trial design, inclusion criteria, baseline characteristics, and treatment duration between the ALPHA trial and the PEGASUS trial. Differences in the

mean baseline hemoglobin were also highlighted by the sponsor in the baseline characteristics between the trimmed ALPHA population (7.7g/dL in the danicopan + C5i arm, 7.8g/dL in the placebo + C5i arm) and the PEGASUS population (8.69 g/dL in the pegcetacoplan arm, 8.68 g/dL in the eculizumab arm). In addition, there were numeric differences between the trimmed ALPHA population and the PEGASUS population in the proportion of Asian patients (47.4% danicopan + C5i arm, 31.6% placebo + C5i arm of ALPHA versus 12% in the pegcetacoplan arm, 18% in the eculizumab arm of PEGASUS), proportion of white patients (42.1% danicopan + C5i, 47.4% placebo + C5i in ALPHA versus 59% pegcetacoplan and 64% eculizumab in PEGASUS), absolute reticulocyte count (238.8 × 10^9 danicopan + C5i, 242.9 × 10^9 placebo + C5i in ALPHA versus 217.5 × 10^9 pegcetacoplan, 216.2 × 10^9 eculizumab in PEGASUS), and total bilirubin (33.2 µmol/L danicopan + C5i, 34.8 µmol/L placebo + C5i in ALPHA, 42.5 µmol/L pegcetacoplan, 40.5 µmol/L eculizumab in PEGASUS). There was no information on the potential clinical importance of these differences in the submission.

The conclusions for the anchored and unanchored MAICs were numerically similar for most efficacy outcomes, with 2 exceptions: transfusion avoidance, where the unanchored MAIC showed that danicopan was favoured for transfusion avoidance, but the anchored MAIC did not (anchored TD = –0.32; 95% CI, –2.70 to 2.06; unanchored TD = 1.64; 95% CI, 0.06 to 3.22), and absolute reticulocyte count, where the reduction reported favoured pegcetacoplan with a greater reduction than danicopan + C5i (anchored TD = 53.70; 95% CI, 16.90 to 90.50; unanchored TD = 32.80; 95% CI, 13.60 to 51.90). Neither danicopan plus C5i nor pegcetacoplan were favoured for the outcomes of hemoglobin change from baseline, LDH change from baseline, change in FACIT-Fatigue scores from baseline, or transfusion avoidance (anchored MAIC only).

Harms Results

Based on a time-to-event analysis of BTH, there was no significant difference between the time to BTH AE for patients in the trimmed ALPHA sample or in PEGASUS. Based on the extended follow-up from PEGASUS (48 weeks) and a median follow-up of 34.6 weeks from patients in the danicopan-emergent arm of ALPHA, the results from the weighted, unanchored MAIC found that there was no difference in the probability of BTH between the 2 trials.

Critical Appraisal

The indirect evidence assessment is subject to several major limitations that make drawing firm conclusions about the comparative results challenging. With regard to the SLR and feasibility assessment, the submission did not provide a preregistered protocol for their SLR and so it is not known whether the search criteria, study selection, or subgroups of interest were prespecified before the search. It is also not known whether statistical testing was undertaken during the feasibility assessment to determine differences in study population or whether there was a prespecified threshold to determine the meaningfulness of differences between populations. Per the clinical experts we consulted, the differences highlighted in the feasibility assessment for inclusion criteria and baseline characteristics did not represent clinically meaningful differences. They noted that the anemia and platelet cutoffs being different was not hugely meaningful from a clinical perspective as the mean values for both in the baseline characteristics were similar; they also noted that patient-specific factors such as lifestyle and important symptoms are often a driver of treatment choices.

As this information was not included in the submission, the impact of these factors on patient differences is unknown. Ravulizumab is the suggested C5i therapy over eculizumab when both are available, however the 2 therapies have similar efficacy results.[37] Therefore, there is enough overlap between the study populations to suggest that the reported characteristics do not represent enough of a source of heterogeneity to rule out a MAIC.

The MAICs themselves are also subject to considerable limitations. The anchored MAICs provided control on 2 treatment effect modifiers and the sponsor noted that these were the only effect modifiers able to be adjusted on; however, the clinical experts noted that the modifiers used in weighting were not a comprehensive list of possible modifiers or prognostic factors. Therefore, the anchored MAICs would not be able to account for all possible sources of heterogeneity between the study populations. In addition, key differences in the comparator arms for the ALPHA and PEGASUS trials were noted including which C5i therapies were used in the placebo arm and the duration of follow-up, which suggests that the comparators in these 2 trials may not be an appropriate anchor for the MAIC. This increases the uncertainty in the results, and thus, drawing firm conclusions based on these results about the comparative effectiveness of danicopan add-on and pegcetacoplan is not recommended. Unanchored MAICs were also undertaken for all efficacy and safety outcomes. This method requires the assumption that all prognostic factors and treatment effect modifiers are accounted for, which is a strong assumption largely considered impossible to meet — failure of this assumption leads to an unknown amount of bias in the effect estimate.

In addition, the ALPHA and PEGASUS trials differ in other ways which may impact the risk of bias in the results and the generalizability of the results. Patients in PEGASUS were exposed to pegcetacoplan monotherapy for 4 weeks longer than patients were exposed to danicopan in ALPHA, which may bias the efficacy results to favour pegcetacoplan. Furthermore, the trial design for pegcetacoplan was an open-label trial, which may bias the reporting of FACIT-Fatigue, a subjective outcome. The results from the MAICs are subject to the same concerns about generalizability to the PNH population as ALPHA, and without detailed information from PEGASUS the generalizability of that study population to the wider PNH population is unknown. In addition, results were only reported for efficacy outcomes at week 20 for PEGASUS and week 12 for ALPHA, and so any information on efficacy past this time is not known. For BTH events, these were reported only up to 48 weeks in PEGASUS and 34.6 weeks for ALPHA, therefore longer term data on safety and information on other harms is unknown.

Economic Evidence

Cost and Cost-Effectiveness

Table 4: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	Adult patients with PNH with signs or symptoms of EVH (i.e., clinically significant EVH; signs/symptoms of anemia that cannot be explained by other causes of anemia)
Treatment	Danicopan as an add-on to ravulizumab or eculizumab
Dose regimen	Recommended starting dose of danicopan is 150 mg t.i.d. (in addition to ravulizumab or eculizumab). Depending on clinical response[a], the danicopan dose can be increased to 200 mg t.i.d.
Submitted price	Danicopan 50 mg: $22.97 per tablet 100 mg: $45.95 per tablet
Submitted annual treatment cost	Danicopan as an add-on to C5i: $618,485 per patient per year Note, the danicopan treatment cost is $85,282 and the C5i treatment cost is $533,203
Comparator(s)	• C5i monotherapy (eculizumab or ravulizumab) • Pegcetacoplan (co-administered with C5i during the initial 4-week period)
Perspective	Canadian publicly funded health care payer
Outcome	QALYs
Time horizon	Lifetime (45.7 years)
Key data source	ALPHA trial informed efficacy and safety of danicopan + C5i and C5i monotherapy; and utility values for health states for all treatment arms PEGASUS trial (and its analysis by Hakimi 2022) informed efficacy and safety of pegcetacoplan
Key limitations	• Comparative clinical efficacy and safety vs. pegcetacoplan is uncertain as there are no head-to-head studies comparing the 2. The sponsor conducted a MAIC but due to feasibility concerns around the comparability of the 2 trials, relied on a naive comparison of danicopan + C5i (informed by the ALPHA trial) vs. pegcetacoplan (informed by the PEGASUS trial) as the basis for the pharmacoeconomic analysis. The naive comparison informed treatment efficacy (hemoglobin levels), probabilities of severe BTH events (i.e., pegcetacoplan was associated with a 10-fold probability of experiencing a BTH event), and probability of experiencing transfusion-related iron overload (i.e., pegcetacoplan associated with an approximately 40% higher probability). The evidence did not allow for firm conclusions on the relative effectiveness or safety of danicopan + C5i and pegcetacoplan due to the limitations associated with the MAICs, as well as those associated with a naive comparison. • The submitted model was not designed to reflect the different severity of BTH events and associated effects on transfusion requirements. The clinical experts we consulted noted that the risk of iron overload during transfusion is not inherently affected by the treatment, but instead, more closely related to the volume of the transfusions. The risk of iron overload should reasonably be the same between treatments unless the model accounted for the different volumes of transfusion between treatment arms, which is not included in the submitted model. • The method used to derive the health state transition probabilities has limited validity. It is unclear whether relevant variables were omitted from the risk equation, as the sponsor did not select

Component	Description
	covariates specific to the ALPHA trial. Consequently, the validity of the calculated transition probabilities for danicopan + C5i and C5i monotherapy remains uncertain and potentially inappropriate. • The submitted model does not align with the indicated population or capture all aspects of the condition and its management. Danicopan add-on may be used in third line after suboptimal response to pegcetacoplan as the proposed HC indication is line agnostic. The model did not explicitly account for cost and health-related quality of life associated with thrombosis (the most devastating consequence of PNH), up-dosing of danicopan due to continuous BTH events, or discontinuation of danicopan due to liver toxicity. Furthermore, the model structure does not allow revisions to the model to consider equal QALY estimates for danicopan and pegcetacoplan.
Our reanalysis results	• We conducted reanalyses to address some of the key limitations, which included: assuming equivalent efficacy and safety between danicopan + C5i and pegcetacoplan (i.e., equal health states transition probabilities; equal BTH event probabilities; and equal probability of experiencing iron overload) and all patients treated for iron overload receive chelation therapy with an increased proportion of patients receiving deferasirox. Our reanalysis attempts to preserve the comparison in efficacy between danicopan + C5i vs. C5i monotherapy by maintaining the data derived from the ALPHA trial data. • In our base case, all treatment options remained on the cost-effectiveness frontier. Pegcetacoplan was associated with an ICER of $113,166 per QALY compared to C5i monotherapy. The ICER of danicopan + C5i compared to pegcetacoplan was $7,056,575 per QALYs gained (incremental QALYs gain: 0.23; incremental cost: $1,606,562). A price reduction of 90.4% would be needed for danicopan when used in addition to a C5i be cost-effective compared to C5i monotherapy at a WTP threshold of $50,000 per QALY. However, our reanalysis was not able to fully address all identified limitations. There is no robust clinical evidence to justify a price premium for danicopan + C5i compared to pegcetacoplan. • Scenario analyses were conducted to explore the use of data from the MAICs to derive health state transition probabilities, and the effects of reverting pegcetacoplan's severe BTH probabilities and iron overload probabilities to the sponsor's original estimates (from the naive comparison). The use of data from the MAICs or higher iron overload (40% higher) assumptions resulted in similar results to our base case (i.e., pegcetacoplan is not dominated by danicopan + C5i and the ICERs of danicopan + C5i vs. pegcetacoplan ranged from $6.5 to 6.9 million per QALY gained). Reverting pegcetacoplan's severe BTH probability (10-fold higher) had the largest impact and resulted in pegcetacoplan being dominated by danicopan + C5i (similar to the sponsor's submitted base case). In this scenario, a price reduction of 90.1% would be necessary for danicopan + C5i to be cost-effective compared to C5i monotherapy at a WTP threshold of $50,000 per QALY gained.

BTH = breakthrough hemolysis; C5i = complement 5 inhibitor; EVH = extravascular hemolysis; ICER = incremental cost-effectiveness ratio; LY = life-year; MAIC = matching-adjusted indirect comparison; PNH = paroxysmal nocturnal hemoglobinuria; PSM = partitioned survival model; QALY = quality-adjusted life-year; t.i.d. = 3 times a day; WTP = willingness to pay.

[a]Clinical response to increase dose to 200 mg 3 times daily is defined as if a patient's hemoglobin level has not increased by at least 2 g/dL after 4 weeks of therapy, if a patient required a transfusion within the previous 4 weeks, or to achieve an appropriate hemoglobin response based on clinical judgment.

Budget Impact

We identified the following key limitations with the sponsor's analysis: drug acquisition costs were uncertain and misaligned with the pharmacoeconomic model, and the coverage rates and market share were uncertain. We conducted reanalyses of the budget impact analysis by estimating the annual drug acquisition cost with our base case cost-utility analysis. Based on our base case, the estimated budget impact associated with the reimbursement of danicopan for the treatment of adult patients with PNH who have signs or symptoms of EVH is expected to be $518,523 in year 1, $599,737 in year 2, $682,737 in year 3, for a cumulative 3-year total incremental cost of $1,800,996.

We conducted scenario analyses to address uncertainty in the coverage rates, market shares or assuming a higher BTH event probability while on pegcetacoplan. Our reanalyses indicated that the budgetary impact may range between half to a 3-fold increase from what the sponsor originally estimated.

CDEC Information

Members of the Committee

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunsky, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Trudy Huyghebaert, Dr. Peter Jamieson, Mr. Morris Joseph, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Dr. Danyaal Raza, Dr. Edward Xie, and Dr. Peter Zed.

Meeting date: August 28, 2024

Regrets: Two expert committee members did not attend.

Conflicts of interest: None

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

ISSN: 2563-6596

Canada's Drug Agency (CDA-AMC) is a pan-Canadian health organization. Created and funded by Canada's federal, provincial, and territorial governments, we're responsible for driving better coordination, alignment, and public value within Canada's drug and health technology landscape. We provide Canada's health system leaders with independent evidence and advice so they can make informed drug, health technology, and health system decisions, and we collaborate with national and international partners to enhance our collective impact.

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