

Reimbursement Review

Iptacopan (Fabhalta)

Sponsor: Novartis Pharmaceuticals Canada Inc.

Therapeutic area: Complement 3 glomerulopathy

Summary

What Is Complement 3 Glomerulopathy?

Complement 3 glomerulopathy (C3G) is a rare, progressive kidney disease characterized by complement system dysregulation. The deposition of the complement protein C3 in the kidneys leads to progressive damage to glomeruli and impairs kidney function. This damage can lead to kidney failure in approximately 50% of patients within 10 years, a condition that requires dialysis or kidney transplantation. C3G is typically diagnosed in children and young adults. Based on data from 1992 to 2012, approximately 542 adults have a diagnosis of C3G in Canada (excluding Quebec).

What Are the Treatment Goals and Current Treatment Options for C3G?

- The primary treatment goals for C3G are to preserve kidney function, prevent progression to end-stage kidney disease, and improve health-related quality of life. Additional goals include minimizing medication-related side effects, managing physical symptoms, and addressing emotional well-being.
- Important outcomes for treatment for C3G include the following: reduction in proteinuria, stabilization of estimated glomerular filtration rate (eGFR), reduction in C3 deposits, and improvement in health-related quality of life. Other important outcomes include symptom relief (e.g., fatigue).
- Current treatment approaches are limited to supportive care: angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), and sodium-glucose cotransporter-2 (SGLT2) inhibitors to reduce proteinuria and slow eGFR decline. Immunosuppressive therapies are used in moderate to severe cases but have inconsistent efficacy and significant adverse effects. None of the currently available treatments target the underlying disease mechanism.

What Is Fabhalta and Why Did Canada's Drug Agency Conduct This Review?

- Fabhalta is a complement factor B inhibitor (i.e., a drug that affects the immune system) that is available as an oral capsule. Health Canada has approved Fabhalta for adult patients with C3G to reduce proteinuria.
- Canada's Drug Agency (CDA-AMC) reviewed Fabhalta to inform a recommendation to the participating public drug programs on whether it should be reimbursed for adult patients with C3G.

Summary

How Did CDA-AMC Evaluate Fabhalta?

- CDA-AMC reviewed the clinical evidence on the beneficial and harmful effects, as well as the economic evidence, of Fabhalta versus other treatments used in Canada for adults with C3G. Supportive treatment options were considered relevant treatments to compare with Fabhalta when reviewing the clinical evidence. These included ACE inhibitors, ARBs, and SGLT2 inhibitors, as well as immunosuppressants including mycophenolate mofetil and corticosteroids.
- CDA-AMC identified equity and ethical considerations relevant to Fabhalta and the treatment of adults with C3G.
- The review was informed by materials submitted by the sponsor, which included clinical and economic evidence.
- The review was also informed by 1 patient group submission, 1 clinician group submission, and 1 industry submission in response to our call for input, and by input from the participating public drug programs around issues that may impact their ability to implement a recommendation.
- Two clinical experts with expertise in the diagnosis and management of C3G were consulted as part of the review process.

What Were the Findings?

Clinical Evidence

- CDA-AMC reviewed the following clinical evidence:
 - one phase III, double-blind, placebo-controlled trial (APPEAR-C3G) comparing Fabhalta with placebo in 74 adults with C3G; patients in both groups received background supportive therapies
 - two extension studies, including the 6-month open-label period of the APPEAR-C3G study (N = 74) evaluating the long-term efficacy and safety of Fabhalta and a phase III rollover extension study (B12001B; N = 26) evaluating the long-term efficacy and safety of Fabhalta in eligible patients who completed the C3G phase II study (X2202)
 - one phase II, single-arm study (X2202; N = 27) evaluating the efficacy and safety of Fabhalta in 2 patient populations: Cohort A included patients with C3G and reduced C3 serum levels who had not had a kidney transplant and cohort B included patients who had a kidney transplant and had a C3G recurrence.
- For the comparison of Fabhalta versus placebo at 6 months based on the APPEAR-C3G trial:
 - Fabhalta likely results in a clinically meaningful reduction in

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- proteinuria (35.1% reduction; 95% confidence interval [CI] 13.8% to 51.1%) when assessed using a 25% improvement threshold suggested by clinician input. However, Fabhalta likely resulted in little to no clinically important difference when results were assessed using a more stringent threshold of 50% improvement, based on observations from the literature and also supported by clinicians.
- Fabhalta may result in little to no clinically important difference in eGFR (increase = 2.156 mL/min/1.73 m²; 95% CI, -2.749 mL/min/1.73 m² to 7.061 mL/min/1.73 m²).
 - Fabhalta likely results in a clinically important increase in the proportion of patients achieving the composite renal end point, which measures both kidney function and proteinuria (24.2% increase; 95% CI, 6% to 39.7%).
 - Fabhalta may result in a clinically important decrease in the glomerular C3 deposit score (1.875 decrease; 95% CI, -3.298 to -0.452).
 - Fabhalta may result in little to no clinically important difference in fatigue symptoms (2.598 decrease in fatigue score; 95% CI, -6.032 to 0.835).
 - No notable safety concerns for Fabhalta were identified during the double-blind period. Because the sample size was small and the event rates were relatively low, the findings were unlikely to adequately capture rare harms. The evidence is very uncertain about the effect of Fabhalta on the incidence of serious adverse events and infections by encapsulated bacteria.
 - Two open-label, noncomparative extension studies partially addressed an evidence gap by providing data on the efficacy and safety of Fabhalta beyond 6 months. Based on the additional 6-month, open-label treatment period of the APPEAR-C3G trial and on the B12001B long-term extension study:
 - Findings suggested potential sustained efficacy of Fabhalta, with continued reductions in proteinuria and stabilization of kidney function as measured by eGFR after 12 months. Findings beyond 12 months are highly uncertain because of the small sample size, risk of selection bias, and missing data. Causal interpretations about the effect of Fabhalta are not possible due to the single-arm design.
 - The safety profile of Fabhalta at 12 months was consistent with the previously reported data from the APPEAR-C3G study's double-blind, randomized treatment period. No new safety concerns for Fabhalta were identified with the additional follow-up; however, the limited

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sample size means that only common harms are likely to be detected.

- Study X2202 addressed another evidence gap from the APPEAR-C3G trial by providing supportive evidence of potential efficacy of Fabhalta in patients with posttransplant recurrence of C3G. Based on Study X2202:
 - Fabhalta was associated with reduction in C3 deposit score on kidney biopsy after 12 weeks in 7 patients with posttransplant recurrence of C3G. No new safety concerns were identified. However, findings are highly uncertain because of the small sample size.

Economic Evidence

- Fabhalta is available as a 200 mg oral capsule. At the submitted price of \$719.94 per 200 mg oral capsule, the annual cost of Fabhalta is expected to be \$525,916 per patient, based on the Health Canada–recommended dosage.
- Key clinical efficacy data (the change in eGFR) used to inform the economic model were derived from the APPEAR-C3G trial, which compared Fabhalta in combination with standard of care (SOC) with placebo in combination with SOC. Evidence submitted by the sponsor indicates that Fabhalta in combination with SOC may result in little to no difference in the decline in eGFR compared with placebo in combination with SOC among patients with C3G.
- The results of the CDA-AMC base case suggest:
 - Fabhalta in combination with SOC is predicted to be associated with higher costs to the health care system than SOC (incremental costs = \$15,833,147), primarily driven by increased costs associated with drug acquisition.
 - Fabhalta in combination with SOC is predicted to be associated with a gain of 3.49 life-years compared to SOC and may result in a gain of 5.73 quality-adjusted life-years (QALYs) compared to SOC.
 - The incremental cost-effectiveness ratio (ICER) of Fabhalta in combination with SOC compared to SOC was \$2,762,300 per QALY gained in the CDA-AMC base case. The estimated ICER was highly sensitive to the source of clinical efficacy. Approximately 99.9% of QALYs predicted were to be accrued after the observation period of the APPEAR-C3G study and Study B12001B.
 - The cost-effectiveness of Fabhalta in combination with SOC in the CDA-AMC base case is uncertain due to uncertainty around the treatment effect. The CDA-AMC base case is based on a post hoc analysis of randomized data from the APPEAR-C3G trial. However, this treatment effect estimate is imprecise and there are concerns

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that eGFR decline for a patient with C3G is underestimated relative to real-world clinical practice. Multiple scenario analyses were conducted to explore other potential treatment effects. In these scenarios, QALY gains varied from 1.76 to 7.93. QALY gains are largely determined by the extent to which iptacopan delays end-stage kidney disease with 1 scenario analysis predicting a delay of more than 20 years, in essence assuming a cure for C3G. In all scenarios, treatment costs remained greater than \$7 million. This means the ICER remains greater than \$1.7 million per QALY gained.

- CDA-AMC estimates that the budget impact of reimbursing Fabhalta for use in combination with SOC for the treatment of C3G will be approximately \$250.5 million over the first 3 years of reimbursement compared to the amount currently spent on comparators. The expenditure on Fabhalta over this period is predicted to be \$250.7 million (Fabhalta in combination with SOC = \$250.9 million). The actual budget impact of reimbursing Fabhalta will depend on the number of patients eligible for treatment, and the market uptake of Fabhalta. The economic feasibility must be addressed, given that the predicted incremental budget impact of reimbursing Fabhalta is predicted to be greater than \$40 million in year 1, year 2, and year 3, and due to the magnitude of uncertainty in the estimated budget impact.

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Abbreviations

ACE	angiotensin-converting enzyme
AE	adverse event
ARB	angiotensin receptor blocker
C3G	complement 3 glomerulopathy
CDA-AMC	Canada's Drug Agency
CI	confidence interval
CKD	chronic kidney disease
eGFR	estimated glomerular filtration rate
ESKD	end-stage kidney disease
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy – Fatigue Scale
GRADE	Grading of Recommendations Assessment, Development and Evaluation
ICE	intercurrent event
ICER	incremental cost-effectiveness ratio
IC-MPGN	immune-complex membranoproliferative glomerulonephritis
ITC	indirect treatment comparison
LTE	long-term extension
LY	life-year
MID	minimal important difference
MMF	mycophenolate mofetil
QALY	quality-adjusted life-year
RCT	randomized controlled trial
SAE	serious adverse event
SD	standard deviation
SGLT2	sodium-glucose cotransporter-2
SOC	standard of care
UACR	urine albumin-to-creatinine ratio
UPCR	urine protein-to-creatinine ratio

Background

Introduction

The objectives of this report are as follows:

- Review and critically appraise the evidence submitted by the sponsor on the beneficial and harmful effects of iptacopan (200 mg per capsule, oral) in the treatment of adult patients with complement 3 glomerulopathy (C3G). The focus will be placed on comparing iptacopan to relevant comparators in clinical practice in Canada in [Table 1](#).
- Review and critically appraise the economic information submitted by the sponsor, including a cost-effectiveness analysis and budget impact analysis. The focus of the Economic Review is aligned with the scope of the Clinical Review, unless otherwise stated. For most reviews, a base case for Canada's Drug Agency (CDA-AMC) is developed, informed by the available clinical evidence, clinical expert input, and the best interpretation of the economic evidence based on the information provided by the sponsor.

The application was submitted by the sponsor before receiving a Notice of Compliance from Health Canada. This report reflects the anticipated indication and recommended dosage for iptacopan during the initial CDA-AMC review period.

Table 1: Information on the Application Submitted for Review and on the CDA-AMC Review

Item	Description
Information on the application submitted for review	
Drug	Iptacopan (Fabhalta), 200 mg, hard capsules, oral
Sponsor	Novartis Pharmaceuticals Canada Inc.
Health Canada indication	For the treatment of adult patients with C3G to reduce proteinuria
Health Canada approval status	NOC
Health Canada review pathway	Standard review
NOC date	April 30, 2026
Mechanism of action	Factor B inhibitor
Recommended dosage	The recommended dosage is 200 mg orally twice daily
Submission type	Initial submission
Sponsor's reimbursement request	As per indication
Submitted price	\$719.94 per 200 mg capsule
Information on the CDA-AMC review	
Review type	Complex
Clinical review focus^a	Population: As defined in the Health Canada indication Intervention: Per recommended dosage Comparators: Supportive treatment options, including off-label use of ACE inhibitors, ARBs, and SGLT2 inhibitors, as well as immunosuppressants including corticosteroids

Item	Description
	and MMF Outcomes: Proteinuria (log-transformed UPCr or UACr), kidney function (eGFR), composite renal end point, histology total activity score, HRQoL, safety (AEs, SAEs, WDAEs, deaths)

ACE = angiotensin-converting enzyme; AE = adverse event; ARB = angiotensin receptor blocker; C3G = complement 3 glomerulopathy; CDA-AMC = Canada's Drug Agency; eGFR = estimated glomerular filtration rate; HRQoL = health-related quality of life; MMF = mycophenolate mofetil; NOC = Notice of Compliance; SAE = serious adverse event; SGLT2 = sodium-glucose cotransporter-2; UACr = urine albumin-to-creatinine ratio; UPCr = urine protein-to-creatinine ratio; WDAE = withdrawal due to adverse event.

^aThe Economic Review aligns with the scope of the Clinical Review, unless otherwise stated.

Submission History for the Drug Under Review

CDA-AMC has not previously reviewed iptacopan through the Reimbursement Review process.

Sources of Information

The contents of the Reimbursement Review report are informed by materials submitted by the sponsor, input received from interested parties (patient groups, clinician groups, and drug programs), and input from clinical experts consulted for this review.

Calls for patient group and clinician group input are issued for each Reimbursement Review. CDA-AMC received 1 patient group submission from The Kidney Foundation of Canada and 1 clinician group submission from the Canadian C3G and IC-MPGN Physician Network. The patient input was collected in September and October 2025 in both official languages via a self-administered online questionnaire across Canada. The survey was directed at individuals living with C3G or immune-complex membranoproliferative glomerulonephritis (IC-MPGN) and their caregivers and inquired about their lived experiences with C3G or IC-MPGN, their experiences with medications, and their expectations for new drug therapies in Canada. Both C3G and primary IC-MPGN are managed using similar therapeutic approaches despite some histological distinctions, as they share similar clinical features (kidney and nonkidney manifestations), progression patterns, and treatment responses. A total of 49 people responded to the survey, with 38 complete and 11 partial responses. Among those who provided demographic information, the majority (70%) were people living with C3G or IC-MPGN, while more than 30% were caregivers. The clinician input was gathered from the clinical experience of 17 clinician members and from relevant scientific or medical literature. The full submissions received are available on the [project landing page](#) in the consolidated input document.

Input from patient and clinician groups is considered throughout the review, including in the selection of outcomes to include in the Clinical Review and in the interpretation of the clinical and economic evidence. Relevant patient and clinician group input is summarized in the Disease Background, Current Management, and Unmet Needs and Existing Challenges sections.

The drug programs provide input on each drug being reviewed through the Reimbursement Review process by identifying issues that may impact their ability to implement a recommendation. The implementation questions from the public drug programs and corresponding responses from the clinical experts consulted for this review are summarized in the [Supplemental Material document](#), Appendix 1, Table 3.

Each review team includes at least 1 clinical expert with expertise regarding the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process. Two clinical experts with expertise in the diagnosis and management of C3G participated as part of the review team.

Disease Background

C3G is a rare, progressive kidney disease driven by dysregulation of the complement system. This dysregulation leads to excessive deposition of C3 activation products (i.e., C3 deposits) in the glomeruli, triggering inflammation.¹⁻⁵ The accumulation of C3 deposits in the glomeruli causes structural damage and leakage into the urine of protein (proteinuria) and red blood cells (hematuria).⁶ Progressive glomerular inflammation ultimately leads to the development of chronic kidney disease (CKD). Continuous decline in kidney function culminates in kidney failure in approximately 50% of patients within 10 years, a condition which requires dialysis or kidney transplantation.⁷⁻¹⁰ However, kidney transplantation does not address the underlying mechanism of disease, leading to high rates of recurrence and kidney allograft loss.^{8,11-15} A retrospective cohort study of adult patients who had a first kidney transplant in the United States between 1996 and 2011 revealed that patients with C3G or primary IC-MPGN have a 76% greater relative hazard of mortality after transplant than patients with IgA nephropathy after a median follow-up of 5.5 years.^{16,17}

Disease onset for most patients occurs in childhood or young adulthood. Data from the UK and Ireland ranging from 1992 to 2012 suggested that the annual incidence of biopsy-proven C3G was 2 cases per million population.¹ This led to an estimated prevalence of 20 cases per million people, assuming renal survival of 10 years.⁸ The sponsor projected that approximately 542 adults have a diagnosis of C3G in Canada (excluding Quebec).¹⁸ None of the available inputs identified whether any equity-deserving groups experience a higher prevalence of C3G.

Patients with C3G typically present to their health care provider with nonspecific symptoms of kidney dysfunction,¹⁹ which substantially impair individuals' quality of life, daily functioning, and productivity.²⁰⁻²² Initial evaluation includes assessment of a urine analysis for proteinuria and hematuria, quantification of proteinuria, and measurement of estimated glomerular filtration rate (eGFR) to assess the degree of kidney impairment.²³⁻²⁵ However, a definitive diagnosis of C3G requires a kidney biopsy with histopathology analysis through light microscopy and immunofluorescence staining³ and ideally, electron microscopy, because the disease presentation often overlaps with other glomerular diseases. The clinical experts consulted for this review indicated that kidney biopsy procedures are generally available across Canada, although access may be limited in remote regions, requiring referrals to larger centres.²⁶

Patient group input: Input from the patient group indicated that C3G has a negative impact on quality of life, largely due to fatigue, low energy, and lethargy, but also due to a range of additional physical symptoms. Most participants described multiple symptoms and signs such as protein in the urine (95%); high blood pressure (83%); swelling in the legs, ankles, or feet (75%); blood in the urine (43%); and joint pain or swelling (43%). Patients described disruptions to their daily routines and social life due to the burden of complex medication schedules and frequent medical appointments. Likewise, caregivers noted the emotional

toll and stress of managing treatments and symptoms daily. Patients also emphasized the financial burden stemming from out-of-pocket medical expenses and loss of employment.

Current Management

Treatment Goals

Patient group input: Input from The Kidney Foundation of Canada, which included patients with C3G and their caregivers, identified the key treatment goals as follows: improvement in both physical and psychological symptoms related to the disease (e.g., fatigue, sleep interference, mood changes), slowing down disease progression, as well as minimizing side effects and costs from the treatments. The patient group emphasized that an ideal treatment for patients with C3G should be effective, affordable, tolerable, compatible with patients' daily lives, and delivered to patients in a timely manner.

Clinician input: According to the clinical experts consulted by CDA-AMC, the long-term goal of treatment is to prevent disease progression, preserve kidney function, and reduce the lifetime risk of end-stage kidney disease (ESKD). Clinician input from the Canadian C3G and IC-MPGN Physician Network was consistent with that of the clinical experts, indicating that to preserve kidney function, treatment should lead to reduction in proteinuria, stabilization of eGFR, and reduction in C3 deposits on histology if a repeat kidney biopsy is performed. Input from the clinician group also emphasized improvement of patients' symptoms as an important goal.

The clinical experts and clinician group input agreed that reducing proteinuria is the most relevant surrogate outcome, which is considered prognostic of long-term clinical outcomes based on observational evidence.^{27,28} Proteinuria less than 1 g/day or greater than 50% reduction would be deemed a clinically meaningful response.

Current Treatment Options

According to the clinical experts consulted by CDA-AMC, there are currently no approved therapies in Canada that address the pathophysiologic mechanism for C3G. The current management primarily involves supportive care, including the use of angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and increasingly sodium-glucose cotransporter-2 (SGLT2) inhibitors, to help reduce proteinuria and slow the decline in eGFR. However, these treatments do not address the underlying complement pathway dysregulation that drives disease progression.^{3,7,10,25} In the absence of Canadian-specific clinical guidelines, the clinical experts indicated that the treatment of C3G is largely guided by international expert consensus, due to the absence of disease-specific therapies and randomized controlled trials (RCTs) informing the use of these supportive care treatment options. Clinicians may also refer to clinical practice guidelines developed internationally by Kidney Disease: Improving Global Outcomes (KDIGO).²⁵ For patients with proteinuria more than 1 g/day and hematuria, or declining kidney function for at least 6 months, immunosuppressive therapies, primarily mycophenolate mofetil (MMF) and corticosteroids, have shown inconsistent results in individuals with C3G,^{25,29} and are associated with significant adverse events (AEs). Other rescue therapies like rituximab, cyclophosphamide, calcineurin inhibitors, eculizumab, and avacopan are being used off label in Canada. These treatments are generally considered rescue options

rather than relevant comparators because they have shown limited benefit and are associated with poor accessibility.

Due to the lack of effective treatment options, nearly half of patients progress to kidney failure within 10 years of diagnosis.^{8,11-15} Dialysis and kidney transplantation remain options for patients with kidney failure. However, dialysis is associated with substantial physical side effects, emotional distress, and financial burden, further contributing to the overall treatment burden for patients, families, and their caregivers.^{21,30-35} Kidney transplantation does not address C3 overactivation, and recurrence of kidney disease occurs in 55% to 85% of patients within 14 to 28 months after transplant, and leads to graft loss in more than 50% of patients within 4 to 6 years.^{3,8,11-15,36}

Key characteristics of iptacopan are summarized with other treatments available for C3G in the Supplemental Material document (available on the [project landing page](#)), Appendix 1, Table 1.

Unmet Needs and Existing Challenges

Patient group input: Input from the patient group highlighted the need for treatments that are effective, affordable, tolerable, and compatible with patients' daily lives. Respondents to the survey indicated that the disease has led to chronic fatigue, physical discomfort, and emotional strain, significantly reducing their overall quality of life. The input noted significant financial challenges due to decreased income because of limited working hours and various out-of-pocket expenses. The input further noted inequities due to variations in government coverage and financial support across jurisdictions.

Clinician input: The clinical experts highlighted significant unmet needs in the treatment of C3G in Canada, particularly the need for therapies that are both effective and tolerable, and that have meaningful impacts on long-term kidney function and overall patient well-being. C3G mainly affects young people whose lives become altered by this relentless disease, through considerable productivity loss and high mortality rates. There are currently no approved therapies in Canada that target the underlying pathophysiology of complement dysregulation and that have a meaningful impact on preventing progression to ESKD or recurrence after transplant. Many patients remain on dialysis for most of their lives; kidney transplantation does not offer long-term wellness as it does in other renal diseases.

In addition, the harms profiles of available immunosuppressive therapies pose significant challenges including teratogenicity, gastrointestinal symptoms, bone marrow suppression, hyperglycemia, increased infection risk, hypertension, metabolic complications, and osteoporosis, all of which have substantial negative impact on patients' quality of life. Input from the clinician group was consistent with that of the clinical experts consulted for this review. The clinician group also noted that patients face uncertainty, frequent medication changes, and emotional distress due to lack of effective treatments.

Considerations for Using the Drug Under Review

Contents within this section have been informed by input from the clinical experts consulted for the purpose of this review and from clinician groups, as well as the reimbursement conditions proposed by the sponsor (refer to the Supplemental Material document [available on the [project landing page](#)], Appendix 1, Table 2).

The implementation questions from the public drug programs and corresponding responses from the clinical experts consulted for this review are summarized in the Supplemental Material document, Appendix 1, Table 3. The following has been summarized by the review team.

Place in Therapy

C3G is a rare disease associated with the devastating outcomes of kidney failure, and dialysis or kidney transplantation. The clinical experts anticipate iptacopan to cause a paradigm shift in the management of C3G because it would be the first available treatment that directly targets the pathogenesis of the disease, which is supported by clinical trial data. The clinical experts agreed that it should be considered a first-line therapy and potentially a new standard of care (SOC), especially for patients at high risk of disease progression. The experts also indicated that while iptacopan may be used as monotherapy, combination with short-term courses of concurrent immunosuppressants, such as MMF with or without glucocorticoids, could be considered in patients with aggressive presentations. Adjunctive use of ACE inhibitors, ARBs, and SGLT2 inhibitors is expected to continue, because these may be helpful for patients with hypertension or renal scarring.

Patient Population

The clinical experts indicated that patients with C3G who are at high risk of disease progression are most in need of intervention and would be best suited for treatment with iptacopan. High-risk features typically include proteinuria of 0.5 g/day to 1 g/day or more, rapid or progressive decline in eGFR, high-risk biopsy findings (such as severe inflammation), high-risk genetic or autoantibody profiles, and recurrence in kidney transplant recipients.

The sponsor's proposed initiation criteria are adult patients who have a confirmed diagnosis of C3G based on renal biopsy, and who have proteinuria of at least 1 g/day and an eGFR of 30 mL/min/1.73 m² or higher. According to the clinical experts, these criteria were appropriate, feasible for implementation, and aligned well with the patient population that is most in need in clinical practice. Diagnosis of C3G can be complex, and involvement of a specialist with expertise in the management of the condition is important. Kidney biopsy is essential for diagnosing C3G and is routinely performed in clinical practice; therefore, this would not constitute a barrier to implementation.

However, the clinical experts emphasized that patients with lower levels of proteinuria (e.g., between 0.5 g/day and 1 g/day) or a lower eGFR (e.g., > 15 mL/min/1.73 m² but < 30 mL/min/1.73 m²) may also be at a high risk of disease progression, particularly when additional risk factors are present. Early intervention, especially in younger patients with confirmed diagnosis, may offer the greatest potential for preserving kidney function. Conversely, patients with advanced CKD, defined as an eGFR of less than 15 mL/min/1.73 m², or minimal disease activity (e.g., proteinuria < 0.15 g/day), would be considered less likely to benefit from iptacopan. Patients with secondary causes of C3G, including lymphoproliferative disorders, monoclonal gammopathy of renal significance, infection, connective tissue diseases, and relevant cancers, would not be suitable for treatment with iptacopan.

The clinical experts supported a flexible, clinician-driven approach to identifying high-risk patients, noting that rigid thresholds may exclude individuals who could benefit from early intervention. The experts noted that there is no established method to predict which patients will experience a response to iptacopan.

Input from the clinician group was consistent with that of the clinical experts, including in terms of high-risk features and characteristics of patients who may not benefit from treatment with iptacopan.

Assessing the Response to Treatment

The clinical experts agreed that treatment response in C3G is primarily assessed using objective measures such as reduction in proteinuria, and stabilization or improvement of eGFR. The clinical experts suggested that a clinically meaningful response generally includes proteinuria less than 1 g/day, a 25% to 50% reduction in proteinuria over 6 to 12 months, and slowing or stabilization of eGFR decline, although thresholds and interpretation may vary among physicians.³⁷⁻³⁹ The clinical experts stated that response assessment typically occurs every 3 to 6 months, but meaningful changes often require at least 6 to 12 months. The experts noted that eGFR stabilization, although relevant, is challenging to measure in clinical practice based on eGFR slope. They also noted that eGFR is a lagging marker of disease improvement, so that eGFR may not accurately reflect short-term response to treatment.

Input from the clinician group noted that formal remission criteria for C3G have not yet been established. Clinicians suggested a somewhat lower threshold for clinically meaningful response, which would include a 20% to 30% reduction in proteinuria within 6 months, stabilization or a mild eGFR increase from baseline, or a positive change in eGFR slope over 1 to 2 years, with assessments occurring every 3 to 6 months in clinical practice.

Discontinuing Treatment

The clinical experts stated that discontinuation of iptacopan should be considered in cases of recurrent or severe AEs, allergy to the drug, progression to ESKD without an imminent plan for kidney transplantation, or clear lack of meaningful response after an adequate treatment period (typically up to 12 months). For patients who receive a kidney transplant, iptacopan should continue due to the high risk of disease recurrence and graft loss. The experts indicated that defining *nonresponse* is challenging and requires specialist judgment, often based on failure to reduce proteinuria and stabilize eGFR. Overall, the clinical experts stated that discontinuation decisions should balance clinical benefit against risks and feasibility of long-term therapy, recognizing that C3G is a chronic and progressive condition that is likely to require long-term treatment.

Input from the clinician group agreed with the clinical experts on the definition of nonresponse, while indicating that the optimal duration of iptacopan therapy remains undetermined and that discontinuation may increase the risk of disease relapse. They also mentioned that treatment discontinuation decisions may be guided by patient preference and pregnancy planning.

Prescribing Considerations

The clinical experts indicated that experienced specialists are needed for an accurate diagnosis of C3G and appropriate treatment plan. The clinical experts suggested that iptacopan should be prescribed by

or in consultation with a nephrologist with experience in diagnosing and managing patients with C3G, to ensure that iptacopan is prescribed only for appropriate patients, and to facilitate equitable access to care for patients in different geographic regions. Unavailability of experienced nephrologists may result in a risk of misdiagnosis and overtreatment or undertreatment if iptacopan is prescribed by all nephrologists. Input from the clinician group echoed the importance of expert nephrologist in disease diagnosis, treatment, and monitoring.

Clinical Review

Methods

The CDA-AMC review considers the following for inclusion: studies in the sponsor's systematic review (pivotal studies and RCTs), sponsor-submitted long-term extension (LTE) studies, indirect treatment comparisons (ITCs), and studies addressing gaps in the evidence. Eligible studies in the sponsor-submitted systematic review included published and unpublished pivotal studies and phase III RCTs. Relevant patients and interventions were defined by the indication or reimbursement request and the recommended dosage in the product monograph.

Relevant comparators for iptacopan were treatments used as SOC (i.e., supportive therapies) in clinical practice in Canada to treat patients described in the indication under review. These included ACE inhibitors, ARBs, SGLT2 inhibitors, MMF, and corticosteroids. Other rescue therapies like rituximab, cyclophosphamide, calcineurin inhibitors, eculizumab, and avacopan are being used off label in Canada. These treatments are generally considered rescue options rather than relevant comparators because they have shown limited benefit and are associated with poor accessibility.

LTEs of included pivotal studies and RCTs were included in the review, regardless of whether there was a comparison group. Studies addressing gaps submitted by the sponsor were included when they filled an identified gap in the systematic review evidence (e.g., longer follow-up time). No ITCs were included in the review.

The review team selected outcomes (and follow-up times) for review considering the sponsor's Summary of Clinical Evidence, clinical expert input, and patient and clinician group input. Included outcomes are those considered relevant to expert committee deliberations, and they were selected in consultation with committee members. Evidence from the systematic review for the most important outcomes at 6 months was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. These outcomes address important treatment goals for C3G, are considered relevant to patients and clinicians according to patient group and clinician input, and may provide the source for a key input in the sponsor's pharmacoeconomic model:

- urine protein-to-creatinine ratio (UPCR)
- change from baseline in eGFR

- proportion of patients who achieved the composite renal end point (based on UPCR criteria and eGFR criteria)
- change from baseline in glomerular C3 deposit from a renal biopsy
- change in symptoms as measured by Functional Assessment of Chronic Illness Therapy – Fatigue scale (FACIT-Fatigue).

Methods for data extraction, risk of bias appraisal, and certainty of evidence assessment are in the Supplemental Material document, Appendix 2.

Outcomes not assessed using GRADE but pertinent to the review and appearing in the report include urine albumin-to-creatinine ratio (UACR) and change from baseline in histology total activity score at 6 months. Results for these outcomes were considered less critical to decision-making but were nevertheless included as supportive outcomes for contextual interpretation and/or pharmacoeconomic modelling. Detailed results of these outcomes can be found in the Supplemental Material document, Appendix 4.

Clinical Evidence

In this report, the following sources of evidence submitted by the sponsor are reviewed and appraised:

- one phase III, double-blind, placebo-controlled pivotal RCT included in the systematic review (APPEAR-C3G)⁴⁰
- two LTE studies (APPEAR-C3G extension⁴⁰ and B12001B)⁴¹
- one phase II study addressing gaps in the evidence (X2202).⁴²

Systematic Review

Description of Studies

Study Characteristics

Characteristics of the APPEAR-C3G trial are summarized in [Table 2](#). Details pertaining to the eligibility criteria, interventions and comparators, and relevant outcome measures are in the Supplemental Material document, Appendix 3.

Table 2: Characteristics of Studies Included in the Systematic Review

Study name, design, and sample size	Key inclusion criteria	Key exclusion criteria	Intervention and comparator	Relevant end points
APPEAR-C3G Multicentre, phase III, double-blind, parallel group, placebo-controlled RCT Total N = 74	• Patients aged ≥ 18 and ≤ 60 years • Diagnosis of C3G as confirmed by kidney biopsy within 12 months • Maximally recommended or tolerated dose of an ACE inhibitor or	• Any cell or solid organ transplantation, including kidney transplantation • RPGN (i.e., 50% decline in eGFR within 3 months with kidney biopsy findings of glomerular crescent formation in $\geq 50\%$ of glomeruli) • Kidney biopsy showing	Intervention: iptacopan orally 200 mg b.i.d. for 6 months (double blind) Comparator: Placebo orally (matching capsule) b.i.d. for 6 months (double blind)	Primary: Log-transformed ratio to baseline in UPCR (sampled from a 24-hour urine collection) at 6 months Secondary: • Change from baseline in eGFR • Percent of patients

Study name, design, and sample size	Key inclusion criteria	Key exclusion criteria	Intervention and comparator	Relevant end points
	- ARB for ≥ 90 days - Other antiproteinuric medications (MPA, corticosteroids, SGLT2 inhibitors, and MRAs) allowed if dose was stable for ≥ 90 days - Reduced serum C3 (< 77 mg/dL) - UPCR ≥ 1.0 g/g (first morning void urine sample at day -75 and day -15) - eGFR ≥ 30 mL/min/1.73 m² at screening and day -15 - Vaccination against <i>Neisseria meningitidis</i> and <i>Streptococcus pneumoniae</i>	- interstitial fibrosis or tubular atrophy of $> 50\%$ - Confirmed MGUS - Acute postinfectious glomerulonephritis - Active systemic bacterial, viral, or fungal infection within 14 days or presence of fever $\geq 38^{\circ}\text{C}$ within 7 days before study treatment - Recurrent invasive infections caused by encapsulated organisms - Use of inhibitors of complement factors within 6 months (e.g., factor B, factor D, C3 inhibitors, anti-C5 antibodies, C5a receptor antagonists) - Immunosuppressants or cyclophosphamide within 90 days (except prednisone ≤ 7.5 mg/day or equivalent and MPA) - Use of MPA within 90 days in India	All patients received concomitant treatment as follows: stable, supportive care regimen for C3G Double-blind treatment was followed by open-label iptacopan 200 mg b.i.d. for all patients for an additional 6 months	achieving composite renal end point^a - Change from baseline in histology total activity score - Change from baseline in the FACIT-Fatigue score - Occurrence of AEs, AESIs, and study drug discontinuation due to an AE Exploratory: - Change from baseline in glomerular C3 deposit in renal biopsy - Log-transformed ratio to baseline in UACR All relevant end points assessed at 6 months

ACE = angiotensin-converting enzyme; AE = adverse event; AESI = adverse event of special interest; ARB = angiotensin receptor blocker; b.i.d. = twice a day; C3G = complement 3 glomerulopathy; eGFR = estimated glomerular filtration rate; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy – Fatigue scale; MGUS = monoclonal gammopathy of undetermined significance; MPA = mycophenolic acid; MRA = mineralocorticoid receptor antagonist; RCT = randomized controlled study; RPGN = rapidly progressive crescentic glomerulonephritis; SGLT2 = sodium-glucose cotransporter-2; UACR = urine albumin-to-creatinine ratio; UPCR = urine protein-to-creatinine ratio.

^aComposite renal end point: a participant meets the requirements if the following criteria are met at the 6-month time point: a stable or improved eGFR compared to the baseline visit ($\leq 15\%$ reduction in eGFR) and $\geq 50\%$ reduction in UPCR compared to the baseline visit.

Source: Clinical Study Report for the APPEAR-C3G study.⁴⁰ Details included in the table are from the sponsor's Summary of Clinical Evidence.⁴⁴

The APPEAR-C3G study was a phase III, double-blind, placebo-controlled RCT that evaluated the efficacy and safety of iptacopan compared to placebo in adults with confirmed C3G. The study was conducted at 82 sites in 19 countries in North America (including 3 sites in Canada), South America, Europe, and Asia.⁴³ Patients were randomized at a 1:1 ratio to receive either iptacopan ($n = 38$) or placebo ($n = 36$). Randomization was conducted using an interactive response technology and stratified by concomitant use of corticosteroids and/or mycophenolic acid treatment (yes versus no). Patients were required to be on supportive treatments with a maximally recommended or tolerated dose of an ACE inhibitor or ARB for at least 90 days as per inclusion criteria and remained on these treatments throughout the trial.

The APPEAR-C3G study comprised 4 periods: screening and run-in (up to 90 days), 6-month blinded treatment, 6-month open-label treatment, and 30-day safety follow-up, or optionally, patients transitioned to

a C3G rollover extension study to continue open-label treatment with iptacopan (Study B12001B; refer to Long-Term Extension Studies section). Patients received iptacopan or placebo according to their assigned groups during the double-blind period, and all patients received iptacopan during open-label treatment, for a total of 12 months. The primary efficacy end point was based on proteinuria results and was assessed at 6 months (cut-off date: November 7, 2023, when the last patient completed the 6-month double-blind, randomized treatment period).

Statistical Testing and Analysis Populations

Assuming a reduction in UPCR of 50% in the iptacopan group versus 20% in the placebo group (i.e., a relative reduction versus placebo in UPCR of 37.5%), a sample size of 68 participants provided at least 80% power at the 1-sided 0.025 significance level. For change from baseline to 6 months in eGFR, the planned sample size of 68 adult participants provides at least 82% power assuming a true treatment difference of 5.6 mL/min/1.73 m² and a standard deviation (SD) of 8 mL/min/1.73 m² based on the interim analysis of the C3G phase II trial (X2202).

The trial-wise type I error rate for the primary, key secondary, and additional secondary end points was controlled at a 0.025 significance level (1-sided). The multiple test procedures controlled the familywise error rate of the secondary end points at a 1-sided 0.05 significance level given the rare nature of the disease. If the null hypothesis associated with the primary end point was rejected, the hypotheses associated with 4 secondary end points would be sequentially tested. Testing stopped once a null hypothesis was not rejected. Secondary end points were tested in the following order:

1. change from baseline to 6 months in eGFR
2. proportion of patients who achieved composite renal end point
3. change from baseline to 6 months in the histology total activity score
4. change from baseline to 6 months in the FACIT-Fatigue total score.

Post hoc analyses of annualized eGFR slope change were performed. Historical eGFR data (for treatment before iptacopan) as well as eGFR data in the APPEAR-C3G trial (screening and run-in, double-blind, and open-label periods) from all 74 patients were considered in the overall eGFR slope analyses.

Efficacy analyses were performed primarily using the full analysis set, which included all randomized patients, analyzed according to their assigned treatment groups. Safety analyses were performed on the safety set, which included all patients who received at least 1 dose of iptacopan or placebo, grouped according to the actual treatment received.

Details pertaining to detailed statistical analysis methods, missing data handling strategies, and sensitivity analyses are described in the Supplemental Material document, Appendix 3, Table 6.

Patient Disposition

A total of 132 patients with C3G were screened, of which 74 patients (56.1%) completed the screening and run-in period and were randomized. The most common reasons for screening failure included [REDACTED]. All 74 patients randomized completed the 6-month

double-blind treatment period; of these, 2 patients in the iptacopan group discontinued their treatment, 1 due to participant decision and 1 due to inadvertent unblinding at day 90. Per protocol, these 2 patients remained in the study and transitioned to the open-label treatment period.

Details of patient disposition for the APPEAR-C3G trial are summarized in the Supplemental Material, Appendix 4.

Baseline Characteristics

Detailed baseline characteristics for patients in the APPEAR-C3G trial are available in the Supplemental Material document. Of 74 patients, 27 were female (36.5%) and 47 were male (63.5%). The mean age of all patients was 27.9 years (SD = 10.68 years). Close to half of patients in the trial were taking corticosteroid and/or mycophenolic acid.

There were some notable imbalances between the 2 groups in proteinuria, eGFR, and C3G subtype. More specifically, the geometric mean 24-hour UPCR was numerically higher in the iptacopan group (mean = 3.33 g/g; 95% confidence interval [CI], 2.79 g/g to 3.97 g/g) than in the placebo group (mean = 2.58 g/g; 95% CI, 2.18 g/g to 3.05 g/g), and so was the proportion of patients with nephrotic range proteinuria, with 21 patients (55.3%) in the iptacopan group versus 11 patients (30.6%) in the placebo group. The mean eGFR was numerically lower in the iptacopan group (mean = 89.3 mL/min/1.73 m²; SD = 35.20 mL/min/1.73 m²) than in the placebo group (mean = 99.2 mL/min/1.73 m²; SD = 26.88 mL/min/1.73 m²). Nineteen patients (50.0%) in the iptacopan group had a baseline eGFR less than 90 mL/min/1.73 m² compared to 12 (33.3%) in the placebo group. In terms of C3G subtypes, there was imbalance in the proportion of patients who were diagnosed with C3 glomerulonephritis and the dense deposit disease subtypes.

Table 3: Summary of Baseline Characteristics From the APPEAR-C3G Study (FAS)

Characteristic	APPEAR-C3G	
	Iptacopan (n = 38)	Placebo (n = 36)
Age (years)		
Mean (SD)	26.1 (10.39)	29.8 (10.79)
Median		
Sex, n (%)		
Female	11 (28.9)	16 (44.4)
Male	27 (71.1)	20 (55.6)
Baseline 24-hour UPCR (g/g)		
Mean (SD)	3.85 (2.288)	2.93 (1.710)
Geometric mean (95% CI)	3.33 (2.793 to 3.968)	2.58 (2.178 to 3.051)
Median (range)		
≥ 339 g/mol (3 g/g), n (%)	21 (55.3)	11 (30.6)
Baseline eGFR (mL/min/1.73 m²)		

Characteristic	APPEAR-C3G	
	Iptacopan (n = 38)	Placebo (n = 36)
Mean (SD)	89.30 (35.198)	99.22 (26.880)
Median (range)		
< 90 mL/min/1.73 m ² , n (%)	19 (50.0)	12 (33.3)
Corticosteroid and/or MPA at randomization, n (%)		
Yes	16 (42.1)	17 (47.2)
No	22 (57.9)	19 (52.8)
Years since C3G diagnosis		
Mean (SD)	4.60 (4.443)	4.82 (6.046)
Median (range)		
C3G subtype at diagnosis, n (%)		
C3GN	26 (68.4)	32 (88.9)
DDD	9 (23.7)	1 (2.8)
Mixed C3GN and DDD	2 (5.3)	2 (5.6)
Unknown	1 (2.6)	1 (2.8)

C3G = complement 3 glomerulopathy; C3GN = C3 glomerulonephritis; CI = confidence interval; DDD = dense deposit disease; eGFR = estimated glomerular filtration rate; FAS = full analysis set; MPA = mycophenolic acid; SD = standard deviation; UPCR = urine protein-to-creatinine ratio.

Source: Clinical Study Report for the APPEAR-C3G study.⁴⁰ Details included in the table are from the sponsor's Summary of Clinical Evidence.⁴⁴

Treatment Exposure and Concomitant Medications

Details of patients' treatment exposure, and use of concomitant medications, subsequent treatments, and/or rescue therapies in the APPEAR-C3G trial are provided in the Supplemental Material document, Appendix 4.

In the double-blind period, the median duration of treatment was

Overall, 37 patients (97.4%) in the iptacopan group and 36 patients (100%) in the placebo group received at least 1 concomitant medication affecting proteinuria. The most frequently used concomitant medications were ACE inhibitors, ARBs, and/or renin angiotensin aldosterone system inhibitors, which were reported for 37 patients (97.4%) in the iptacopan group and 36 patients (100%) in the placebo group. Other common concomitant therapies included selective immunosuppressants such as MPA for 14 patients (36.8%) in the iptacopan group and 13 patients (36.1%) in the placebo group; glucocorticoids for 11 patients (28.9%) and 13 patients (36.1%), respectively; and SGLT2 inhibitors for 2 patients in each group (5.3% and 5.6%, respectively).

Critical Appraisal

Internal Validity

In the APPEAR-C3G trial, the methods of randomization and blinding were considered appropriate; however, randomization seems to have failed to balance the measured and unmeasured confounders between the 2 treatment groups. The imbalances may be due to sampling variability, which was related to the small

sample size, within which there is an increased risk that prognostic balance between groups was not achieved. There were some imbalances between the 2 treatment groups in patients' baseline characteristics. Compared to the patients in the placebo group, those in the iptacopan group had longer time since diagnosis, higher urinary protein levels, lower eGFR, and were more likely to have hypertension at baseline. The clinical experts consulted by the review team suggested that these particular imbalances could introduce bias against the treatment effect of iptacopan. Indeed, a higher proportion of patients in the iptacopan group had characteristics that were consistent with a more advanced disease at baseline, which may indicate that those patients are expected to have a poorer response to treatment with iptacopan. In addition, the clinical experts noted that the magnitude of treatment effect observed in the placebo group was not consistent with natural disease progression; patients who received placebo experienced a UPCR improvement at 6 months versus baseline that is unlikely to be observed in clinical practice with the use of supportive therapies only. This further suggests that patients who were randomized to placebo may have had less severe disease than patients randomized to iptacopan, as well as a less severe disease than most patients seen in clinical practice.

In the APPEAR-C3G trial, concomitant use of SOC treatment options was permitted, which can independently reduce proteinuria and potentially bias results. As the concomitant therapies used in the trial were balanced between the 2 groups, it is unlikely that the concomitant use of SOC in the trial would bias the study findings. In addition, the risk of bias was mitigated by mandating stable doses of concomitant C3G therapies.

Evidence for iptacopan based on the APPEAR-C3G trial relies on surrogate outcomes, such as proteinuria and eGFR. According to the clinical experts consulted for this review, the 24-hour urine collection method used in the trial allows a more accurate assessment of change in protein levels compared with a random sample. This is generally preferred in clinical practice. Previous research has demonstrated that reduction in proteinuria and stabilization of eGFR may be associated with longer-term clinical outcomes such as preservation of kidney function, which means reduction in the risk of kidney failure and the need for dialysis or kidney transplant.^{37,45-47} The reliance on surrogate outcomes likely reflects feasibility constraints; however, collecting data on outcomes such as progression to ESKD would require long-term follow-up and a substantially larger sample size, which is challenging given the rarity of the condition. Nevertheless, this represents an evidence gap that introduces some level of uncertainty regarding the true clinical impact of treatment on the hard clinical outcomes mentioned.

The randomized controlled period in the APPEAR-C3G trial was 6 months. The trial duration was considered sufficient to detect a clinically meaningful difference in proteinuria according to the literature and the clinical experts. However, treatment effect in clinical practice is generally assessed after 12 months. More specifically, as eGFR is a lagging marker of disease improvement, short-term response to treatment observed via a reduction in proteinuria may not necessarily be accompanied with stabilization of eGFR after only 6 months of treatment. According to the clinical experts, the relatively short trial duration may potentially underestimate the true treatment effect of iptacopan.

The sample size of the APPEAR-C3G trial was adequate for the primary analysis according to sample size assumptions stated in the statistical analysis plan. Subgroup analyses were prespecified and performed to evaluate the consistency of treatment effects across different subgroups. The clinical experts noted that none of the prespecified subgroups are considered effect modifiers; therefore, none were considered relevant to the focus of this review.

In the APPEAR-C3G study, several strategies were applied to handle intercurrent events (ICEs). For example, the “jump-reference” imputation approach was used to impute values after the occurrence of the ICEs for participants in the iptacopan group. By using the jump-reference method, after the occurrence of an ICE for patients in the iptacopan group, the patients’ future outcomes will be imputed as if they had switched to the reference group and behaved like the reference group from that point onward. Values for the placebo group were imputed under the missing-at-random assumption. For the primary estimates, the ICEs included the following: the initiation or intensification of antiproteinuric therapies, the initiation of renal replacement therapies (e.g., hemodialysis or kidney transplantation), and discontinuation of study drug for any other reasons (other than the antiproteinuric therapies or renal replacement therapy). Although the assumptions used for handling ICEs cannot be verified, they arguably may be considered reasonable given that the ICEs likely indicate treatment failure. The proportion of patients with ICEs was small, suggesting limited impact of these assumptions on the results. For missing data that were not related to ICEs, they were imputed under a missing-at-random assumption, which may not be plausible, as patients who received placebo may be more likely to drop out due to a lack of treatment effect. Again, because proportions of missing data for the primary end point and eGFR were small, it is unlikely that this assumption had an important impact on the results.

The FACIT-Fatigue is a 13-item questionnaire that assesses self-reported fatigue and its impact on daily activities and function. The use of the FACIT-Fatigue in patients with CKD has been reported in several publications and is sensitive to changes in disease status, allowing demonstration of statistically and clinically significant results.^{4,48} In FACIT-Fatigue, higher score indicates less severe fatigue symptoms or better quality of life. Meaningful differences on the questionnaire between iptacopan and placebo may however not have been detectable according to the clinical experts; indeed, the experts indicated that fatigue is not always a noticeable symptom that they observe in clinical practice in patients who are in the early stage of C3G. There was however a difference between groups in the completion rate at 6 months (■ in the iptacopan group and ■ in the placebo group). Missing data, as well as short duration and small sample size of the study, may therefore introduce uncertainty in the symptom assessment and interpretation of the results.

Multiplicity was adequately controlled across the primary and key secondary end points using a prespecified hierarchical testing procedure. However, the statistical hierarchy failed after the first key secondary end point (change in eGFR). As a result, no formal statistical testing was conducted for subsequent end points, including proportion of patients achieving composite renal end point, change in histologic activity score, and change in FACIT-Fatigue total score. Therefore, findings for these end points should be interpreted as supportive evidence rather than confirmatory.

External Validity

Outcome measures in the APPEAR-C3G trial were appropriate and aligned with the protocol objectives. Most outcomes are commonly used in clinical practice; however, these were assessed as surrogate end points in the context of the trial. For the primary end point of proteinuria reduction, the use of log-transformed UPCR helped normalize skewed data and minimized the influence of extreme values. Clinical experts noted that this approach is standard across clinical trials, but the values may not be readily interpretable for clinicians. The trial also reported geometric means for UPCR comparisons, offering a more clinically meaningful representation of treatment effect.

The APPEAR-C3G trial required patients to be on a stable regimen of supportive care (e.g., ACE inhibitor or ARB) for at least 90 days before randomization. The clinical experts indicated that this criterion does not reflect real-world practice, as prior or current use of these agents should not determine eligibility for iptacopan. In routine care, sequencing and combination of supportive therapies are individualized based on patient characteristics and clinician judgment and the rationale for requiring a stable dose of prior background therapies is to avoid adjustments during the trial. The treatment goal for C3G is to intervene as soon as possible to prevent irreversible damage to the kidney.

According to clinical experts, the eligibility criteria of the APPEAR-C3G trial were generally reflective of clinical practice for C3G, but were more restrictive in several aspects, which may limit external validity. For example, the trial excluded adolescents and children aged younger than 18 years, patients with posttransplant C3G recurrence, and patients with rapidly progressive disease who could not maintain a stable background regimen, even though these groups receive treatment in real-world settings and may benefit most from early intervention according to the clinical experts. Additionally, patients with proteinuria between 0.5 g/day and less than 1 g/day were not studied (15.2% of the screened patients were excluded from the trial due to not meeting the criteria of UPCR $\geq$ 1.0 g/g); however, evidence from registries and observational studies indicate that this range is also associated with a risk of progression.^{22,49-51} The requirement for eGFR of at least 30 mL/min/1.73 m² also does not align with clinical practice, as experts emphasized that patients with more advanced disease may still benefit from treatment. In addition, baseline characteristics indicate that participants were predominantly white, with limited or no representation of other racial or ethnic groups (e.g., Black or African American, American Indian or Alaskan Native [categories are as reported in study]). Given the small overall sample size, there may be some limitations in the generalizability to diverse populations of patients with C3G. The CDA-AMC review team however acknowledges that larger trials may not be feasible due to the rarity of the condition.

The follow-up duration in the APPEAR-C3G study may be acceptable to assess short-term response based on proteinuria; however, study duration may not have been long enough to detect a difference between groups in outcomes such as eGFR. Because patients are expected to remain on treatment for a longer period, extended follow-up is needed to fully characterize long-term efficacy and safety.

Results

The key efficacy and harms results and findings from the GRADE assessment are presented in this section. Detailed efficacy and harms results can be found in the Supplemental Material document, Appendix 4.

Efficacy

In addition to study treatment, all patients also received optimized background therapy including ACE inhibitors or ARBs, with or without corticosteroids and/or mycophenolic acid. Key results follow.

Log-transformed ratio to baseline in UPCR at 6 months: The adjusted geometric mean ratio to baseline of 24-hour UPCR was 0.698 g/g (95% CI, 0.572 g/g to 0.852 g/g) in the iptacopan group and 1.076 g/g (95% CI, 0.881 g/g to 1.313 g/g) in the placebo group. The between-group difference was [REDACTED], corresponding to a relative reduction of 35.1% (95% CI, 13.8% to 51.1%; $P = 0.0014$) with iptacopan compared to placebo. Consistent results for the primary end point were demonstrated across several sensitivity, supplementary, and post hoc sensitivity analyses.

Change from baseline in eGFR at 6 months: The adjusted mean change from baseline in eGFR was 1.295 mL/min/1.73 m² (95% CI, -2.136 mL/min/1.73 m² to 4.726 mL/min/1.73 m²) in the iptacopan group and -0.861 mL/min/1.73 m² (95% CI, -4.357 mL/min/1.73 m² to 2.635 mL/min/1.73 m²) in the placebo group. The adjusted mean difference between the iptacopan and placebo groups was 2.156 mL/min/1.73 m² (95% CI, -2.749 mL/min/1.73 m² to 7.061 mL/min/1.73 m²; 1-sided $P = 0.1945$; multiplicity adjusted 1-sided $P = 0.3241$). Consistent results were demonstrated across sensitivity analyses performed.

A slope change analysis was performed based on the prior 2-year historical data. Results did not reach statistical significance, although tended to a halting of the eGFR decline leading to stabilization of eGFR after iptacopan treatment. The mean annualized eGFR slope in the placebo group continued to decline, but at a slower rate than previously observed. The difference between groups in the change in slopes per year was 6.166 in favour of iptacopan (95% CI, -4.410 to 16.742).

Proportion of patients who achieved composite renal end point at 6 months: A total of 29.0% of patients (95% CI, 14.9% to 43.1%) in the iptacopan group and 5.7% (95% CI, -1.9% to 13.4%) in the placebo group achieved the composite renal end point. The between-group difference was [REDACTED] in favour of iptacopan versus placebo. This end point was not formally tested due to earlier failure of the statistical hierarchy.

- The proportion of patients with stable or improved eGFR compared to baseline was 89.5% with iptacopan and 88.9% with placebo.
- The proportion of patients with at least a 50% reduction in proteinuria compared to baseline was 29.7% with iptacopan and 5.6% with placebo.

Change from baseline in glomerular C3 deposit score at 6 months: The mean change from baseline in C3 deposit score was -0.781 (95% CI, -1.811 to 0.250) in the iptacopan group and 1.094 (95% CI, 0.111 to 2.078) in the placebo group. The mean difference between the iptacopan and placebo groups was -1.875 (95% CI, -3.298 to -0.452).

Change from baseline to 6 months in FACIT-Fatigue total score: The mean FACIT-Fatigue scores at baseline were 42.4 (SD = 10.08) in the iptacopan group and 41.9 (SD = 8.91) in the placebo group. The adjusted mean change from baseline in the FACIT-Fatigue total score was -0.410 points (95% CI, -2.755 to 1.935) in the iptacopan group and 2.188 points (95% CI, -0.334 to 4.711) in the placebo group. The

between-group difference was -2.598 (95% CI, -6.032 to 0.835) in favour of iptacopan versus placebo. This end point was not formally tested due to earlier failure of the statistical hierarchy.

Supportive outcomes: Results for the following supportive outcomes are in the Supplementary Material document, Appendix 4: Change from baseline to 6 months in histology total activity score and in log-transformed ratio of UACR.

Harms

Key results include the following:

- At least 1 AE was reported for 30 of 38 patients (78.9%) in the iptacopan group and for 24 of 36 patients (66.7%) in the placebo group. The most common AEs ($\geq 10\%$) in the iptacopan group, compared with the placebo group, were COVID-19 infection (21.1% versus 16.7%), increased blood creatine phosphokinase (13.2% versus 2.8%), and nasopharyngitis (10.5% versus 2.8%).
- At least 1 serious AE (SAE) was reported for 7.9% (3 of 38) of patients in the iptacopan group and 2.8% (1 of 36) in the placebo group. The between-group difference for the incidence of SAEs was [REDACTED]. Positive blood culture, chest discomfort, and infected bite were reported in 3 separate patients in the iptacopan group, while acute kidney injury and ascites were reported in the same patient in the placebo group.
- There were no treatment discontinuations due to treatment-emergent AEs reported in the double-blind period.
- Deaths were not reported during the double-blind period of the study.
- The clinical experts identified infections caused by encapsulated bacteria as AEs of special interest for treatment with iptacopan, and these were reported in 5.3% (2 of 38) of patients in the iptacopan group versus 2.8% (1 of 36) in the placebo group. The between-group difference for the incidence of this AE of special interest was [REDACTED].
- Details of the results can be found in the Supplemental Material document, Appendix 4.

Summary of Findings and Certainty of the Evidence

In the absence of literature-based minimal important difference (MID) estimates, thresholds based on expert opinion were used for between-group differences at 6 months in proteinuria (threshold of at least 25%, ideally 50% reduction), proportion of patients who met the composite renal end point (threshold of 20% difference), and FACIT-Fatigue total score (threshold of 5-point improvement).

The clinical experts were unable to suggest a specific threshold for a clinically important effect for other outcomes. Therefore, change from baseline in eGFR and in glomerular C3 deposit score, as well as harms, were evaluated in the presence of a non-null effect.

Details of the summary of outcome measures can be found in the Supplemental Material document, Appendix 3.

Table 4: Summary of Findings for Iptacopan vs. Placebo for Patients With C3G

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo	Iptacopan	Difference		
Proteinuria							
Ratio of UPCR (g/g) at 6 months	74 (1 RCT)	Log-transformed ratio of UPCR, 6 months to baseline, geometric-adjusted mean: - Iptacopan = 0.698 (95% CI, 0.572 to 0.852) - Placebo = 1.076 (95% CI, 0.881 to 1.313) - Between-group difference =  Geometric mean ratio of UPCR, iptacopan vs. placebo (relative change): - Iptacopan vs. placebo = 0.649 (95% CI, 0.489 to 0.862) - Relative difference = 35.1% reduction (95% CI, 13.8% to 51.1%)				Moderate ^a (serious imprecision)	Iptacopan likely results in little to no clinically important difference in proteinuria at 6 months when compared with placebo based on an MID of 50% reduction.
						Moderate ^b (serious imprecision)	Iptacopan likely results in a clinically important relative reduction in proteinuria at 6 months when compared with placebo based on an MID of 25% reduction.
eGFR							
Change from baseline in eGFR at 6 months (mL/min/1.73 m ²)	74 (1 RCT)	NR	-0.861 (-4.357 to 2.635)	1.295 (-2.136 to 4.726)	2.156 (-2.749 to 7.061)	Low ^c (serious imprecision)	Iptacopan may result in little to no clinically important difference in eGFR at 6 months when compared with placebo.
Composite renal end point							
Proportion of patients achieving the composite renal end point at 6 months	74 (1 RCT)	OR = 7.145 (1.429 to 35.723)				Moderate ^d (serious imprecision)	Iptacopan likely results in a clinically important increase in the proportion of patients achieving the composite renal end point at 6 months when compared with placebo.
C3							
Change from baseline in glomerular C3	71 (1 RCT)	NR	1.094 (0.111 to 2.078)	-0.781 (-1.811 to 0.250)	-1.875 (-3.298 to -0.452)	Low ^e (serious risk of bias and imprecision)	Iptacopan may result in a decrease in the glomerular C3 deposit score on kidney

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo	Iptacopan	Difference		
deposit score at 6 months							biopsy at 6 months when compared with placebo.
Symptoms							
Change from baseline in the FACIT-Fatigue total score Follow-up: 6 months	74 (1 RCT)	NR	2.188 (-0.334 to 4.711)	-0.410 (-2.755 to 1.935)	-2.598 (-6.032 to 0.835)	Low ^f (serious risk of bias and imprecision)	Iptacopan may result in little to no clinically important difference in FACIT-Fatigue total score at 6 months when compared with placebo.
Harms							
Incidence of SAEs Follow-up: 6 months	74 (1 RCT)	NR				Very low ^g (extremely serious imprecision)	The evidence is very uncertain about the effect of iptacopan on the incidence of SAEs at 6 months when compared with placebo.
Incidence of infection by encapsulated bacteria Follow-up: 6 months	74 (1 RCT)	NR				Very low ^g (extremely serious imprecision)	The evidence is very uncertain about the effect of iptacopan on the incidence of infection by encapsulated bacteria at 6 months when compared with placebo.

C3G = complement 3 glomerulopathy; CDA-AMC = Canada's Drug Agency; CI = confidence interval; eGFR = estimated glomerular filtration rate; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy – Fatigue scale; MID = minimal important difference; NR = not reported; OR = odds ratio; RCT = randomized controlled trial; SAE = serious adverse event; UPCR = urine protein-to-creatinine ratio; vs. = versus.

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.

^aRated down 1 level for serious imprecision. There is no established between-group MID for log-transformed UPCR or geometric mean ratio. The clinical experts consulted by CDA-AMC suggested that a 50% reduction in proteinuria over 6 months would be considered an ideal MID, based on observations from the literature. The point estimate and lower bound of the 95% CI for the difference between groups suggested little to no clinically important difference and the upper bound of the 95% CI (51.1%) was barely crossing the 50% threshold. Regardless of the MID threshold, given the small sample size (N = 74), the effect estimate is likely unstable.

^bRated down 1 level for serious imprecision. There is no established between-group MID log-transformed UPCR or geometric mean ratio. The clinical experts consulted by CDA-AMC suggested that a 50% reduction in proteinuria over 6 months would be considered an ideal MID for proteinuria, based on observations from the literature. However, the experts noted that thresholds and interpretation may vary among physicians, and that physicians in clinical practice could consider a 25% reduction in proteinuria over 6 months as an appropriate MID. Of note, this was consistent with the clinician group input received. In this case, the point estimates and upper bound of the 95% CIs for the difference between groups suggested a difference exceeding this threshold; however, the 95% CI also includes the possibility of no difference based on the lower bound (13.8%). Regardless of the MID threshold, given the small sample size (N = 74), the effect estimate is likely unstable.

^cRated down 2 levels for serious imprecision. There is no established between-group MID for the change from baseline in eGFR at 6 months. The clinical experts consulted by CDA-AMC could not suggest a threshold of importance but considered the point estimate for the between-group difference clinically meaningful. However, the 95% CI spans the null and extends from improved eGFR to worsened eGFR. Given the small sample size (N = 74), the effect estimate is likely unstable. Further uncertainty was brought by the baseline imbalance in eGFR, as well as by the follow-up time of 6 months, which may have been too short to detect a difference according to the clinical experts.

⁴⁰Rated down 1 level for serious imprecision. There is no established between-group MID for the proportion of patients achieving the composite renal end point at 6 months. The clinical experts suggested that a 20% difference between groups could be considered clinically meaningful. The point estimates and upper bound of the 95% CIs for the difference between groups suggested a difference exceeding this threshold; however, the 95% CI also includes the possibility of no difference based on the lower bound (7.2%). Given the small sample size (N = 74), the effect estimate is likely unstable.

⁴¹Rated down 1 level for serious imprecision and 1 level for serious risk of bias. There is no established between-group MID for the change in C3 deposit score at 6 months. The clinical experts consulted by CDA-AMC could not suggest a threshold of importance; therefore, the clinical importance was assessed against the null. According to the experts, C3 deposit is not correlated to clinical outcomes; therefore, the clinical importance of this decrease cannot be judged. In fact, the experts noted that this outcome reflects the underlying pathophysiology of the disease. The C3c staining outcome was assessed only in patients with available biopsy samples. Given the small sample size (number of patients included in the analysis = 71), the effect estimate is likely unstable. Additionally, this was an exploratory outcome in the APPEAR-C3G study. No statistical analysis was reported and results were summarized descriptively.

⁴²Rated down 1 level for serious risk of bias and 1 level for serious imprecision. There is no established between-group MID for the FACIT-Fatigue total score at 6 months. The clinical experts consulted by CDA-AMC agreed with the sponsor-suggested threshold of a 5-point improvement for patients who responded to the study drug. Certainty was rated down 1 level given the 95% CI for the difference between groups included the possibility of no difference. In addition, certainty was rated down 1 level for risk of bias. There was a difference between groups in the completion rate at 6 months (95% in the iptacopan group and 86% in the placebo group). Given the small sample size (N = 74), the effect estimate is likely unstable.

⁴³Rated down 3 levels for very serious imprecision. There is no established between-group MID for incidence of SAEs or infection by encapsulated bacteria. The clinical experts consulted by CDA-AMC could not suggest a threshold of importance. The certainty of evidence assessment focused on whether there was any effect relative to the null. The 95% CI for the difference between groups included benefit, harm, and no difference. For these harm outcomes, given that only very few cases of event were reported for either iptacopan or placebo, the harm may be rare, and the sample size was insufficient to reliably estimate the risk. Due to the extremely sparse data, imprecision was further rated down. The evidence available to support a definitive conclusion is very limited for SAEs or infection by encapsulated bacteria.

Sources: Clinical Study Report for the APPEAR-C3G study⁴⁰ and sponsor-provided additional data (January 30, 2026).⁵² Details included in the table are from the sponsor's Summary of Clinical Evidence.⁴⁴

Long-Term Extension Studies

This section summarizes the 6-month, open-label treatment period of the APPEAR-C3G trial, and the phase III rollover extension Study B12001B, which was an ongoing open-label, nonrandomized extension study.

Open-Label Treatment Period of the APPEAR-C3G Trial

The objective of the open-label treatment period of the APPEAR-C3G study was to evaluate the long-term efficacy and safety of iptacopan for up to 12 months based on the same outcomes as reported in the double-blind, randomized treatment period of the trial. Patients who received iptacopan 200 mg twice a day in the double-blind period continued iptacopan for an additional 6 months, while patients who received placebo switched to iptacopan 200 mg twice a day for 6 months on day 180 of the study (6 months). Upon completion of study treatment at 12 months, participants had the option to discontinue iptacopan treatment and enter a safety follow-up period or continue open-label iptacopan treatment by transitioning to the C3G rollover open-label extension Study B12001B.

For analysis of change from 6 to 12 months in the placebo arm, the visit remapping rule was followed. This rule aligns time point visits in the placebo arm during the open-label period with corresponding time points in the iptacopan arm. For example, day 360 in the placebo arm was considered equivalent to day 180 in the iptacopan arm, as both treatment arms received iptacopan for 6 months at those respective time points.

All participants randomized to the iptacopan arm and all participants randomized to the placebo arm who were then treated with iptacopan in the open-label period were defined as the combined full analysis set. This set was used to analyze iptacopan efficacy data, and the analysis considered all data collected after the first administration of iptacopan.

The open-label final analysis data cut-off date was May 6, 2024. Additional study details are summarized in the Supplemental Material document, Appendix 5.

Of the 74 participants who completed the 6-month double-blind treatment period, 73 participants completed the 6-month open-label period (12-month study). One participant originally randomized to the placebo arm discontinued treatment during the open-label period due to participant decision, subsequently discontinued from the study, and was lost to follow-up.

Total exposure in the combined full analysis set population was [REDACTED] (i.e., including those randomized to placebo and switched to iptacopan in the open-label period).

Concomitant medications were defined in the same manner in the open-label period and the double-blind period. The use of concomitant medication during the 12-month study period was similar to that of the double-blind period.

Critical Appraisal

Internal Validity

The single-arm design of the open-label treatment period of the APPEAR-C3G trial does not support causal interpretations about the effect of iptacopan and may influence the perception of improvement by patients and clinicians, particularly for outcomes that are subjective in measurement and interpretation (e.g.,

subjective AEs, FACIT-Fatigue score). The measurement of objective key study end points would not be affected. A total of 73 of the 74 randomized participants completed the 12-month study. The overall statistical analyses of the outcomes and the handling of missing data were done adequately. Assumptions applied to handle ICEs cannot be verified, but they arguably may be considered reasonable given that the ICEs are likely to indicate treatment failure. The proportion of patients with ICEs was small, suggesting limited impact of these assumptions on the results.

Similar to the double-blind period, concomitant use of SOC treatment options was permitted, and unlikely to bias the findings during the open-label phase. According to the clinical experts consulted by CDA-AMC, effect of the study drugs on the improvement in proteinuria and eGFR are generally assessed at 1 year in clinical practice. Therefore, the open-label treatment period of the APPEAR-C3G trial may offer sufficient follow-up duration to detect a clinically meaningful difference in eGFR; however, it is not possible to draw a causal relation due to the open-label nature of the extended period.

External Validity

Because the patients who took part in the open-label LTE phase were originally from the double-blind trial and the eligibility criteria remained the same, it is reasonable to expect that the same limitations to generalizability are relevant to the open-label phase as well.

Results

Efficacy

Detailed results for outcomes relevant to this review are in the Supplemental Material document, Appendix 5.

Key results include the following.

- **Primary outcome**
 - **Log-transformed ratio to baseline in UPCR at 12 months:** At 12 months, the adjusted geometric mean ratio to baseline of 24-hour UPCR was [REDACTED] in the iptacopan-to-iptacopan group and [REDACTED] in the placebo-to-iptacopan crossover group. Participants in the iptacopan-to-iptacopan group had a sustained reduction of 40% (95% CI, 0.45% to 0.80%) in 24-hour UPCR at day 360 compared to baseline. Participants in the placebo-to-iptacopan crossover group had a 27% (95% CI, 0.58% to 0.92%) reduction in 24-hour UPCR at day 360 compared to baseline.
- **Secondary outcomes**
 - **Proportion of participants who achieved composite renal end point at 12 months:** The proportion of participants who achieved the composite renal end point in the iptacopan-to-iptacopan group was 44.7% (17 of 38) at day 360. In the placebo-to-iptacopan crossover group, the proportion of participants who achieved the composite renal end point was 23.5% (8 of 34) at day 360 (after receiving iptacopan for 6 months).

- **Stable eGFR at 12 months:** At 12 months, 84.2% patients achieved a stable eGFR ($\leq 15\%$ reduction) in the iptacopan-to-iptacopan group and 88.2% achieved a stable eGFR in the placebo-to-iptacopan crossover group.
- **Change in histology total activity score at 12 months:** Only 6 participants, 2 from the iptacopan-to-iptacopan group and 4 from the placebo-to-iptacopan crossover group, had evaluable renal biopsies at the end of the open-label period. In the iptacopan-to-iptacopan group, the mean change from baseline (day 1) in histology total activity score was -2.0 (SD = 2.83) at day 360 (n = 2). In the placebo-to-iptacopan crossover group, the mean change from day 180 was -1.5 (SD = 1.91) at day 360 (n = 4).
- **Change in FACIT-Fatigue total score at 12 months:** The adjusted mean changes from baseline in the FACIT-Fatigue total score in the iptacopan-to-iptacopan group was -0.78 (95% CI, -3.180 to 1.625) and in the placebo-to-iptacopan crossover group was 2.723 (95% CI, 0.074 to 5.371) at day 360. In the placebo-to-iptacopan crossover group, the mean change in FACIT-Fatigue total score from day 180 to day 360 was 0.2 (SD = 3.54).
- **Exploratory outcome**
 - **Change in eGFR at 12 months:** At day 360, the adjusted mean changes from baseline in eGFR were 0.439 mL/min/ 1.73 m² (95% CI, -3.762 mL/min/ 1.73 m² to 4.641 mL/min/ 1.73 m²) in the iptacopan-to-iptacopan group and 1.152 mL/min/ 1.73 m² (95% CI, -3.222 mL/min/ 1.73 m² to 5.526 mL/min/ 1.73 m²) in the placebo-to-iptacopan crossover group.

The results of the prespecified eGFR slope analyses at 12 months were similar to the results of the 6-month post hoc analysis of eGFR slope.

Harms

Detailed results for harms are presented in the Supplemental Material document, Appendix 5. Key results at 12 months include the following.

- At least 1 AE was reported by 84.2% (32 out of 38) participants in the iptacopan-to-iptacopan group and 75.7% (56 out of 74) in the overall study participants. The most common ($\geq 10\%$) AEs in the iptacopan-to-iptacopan group were [REDACTED]
- At least 1 SAE was reported for 10.5% (4 out of 38) participants in the iptacopan-to-iptacopan group. Overall, 8.1% (56 out of 74) participants experienced SAEs in the overall study population; 4 participants in the iptacopan-to-iptacopan group and 2 participants in the placebo-to-iptacopan crossover group.
- There were no treatment discontinuations due to treatment-emergent AEs reported in the open-label period.
- Deaths were not reported during the study.
- The clinical experts consulted by CDA-AMC identified the following AEs of special interest for the treatment with iptacopan:
 - infections caused by encapsulated bacteria: [REDACTED] in the iptacopan-to-iptacopan group at 12 months

- serious or severe infections: 5.3% in the iptacopan-to-iptacopan group at 12 months.

Open-Label Extension Study B12001B

Study B12001B is an ongoing open-label extension study.⁴¹ The primary objective was to collect long-term efficacy, safety, and tolerability data in eligible participants who completed either the C3G phase II study (X2202⁴²) or the pivotal C3G phase III study (APPEAR-C3G). Study X2202 evaluated the efficacy and safety of iptacopan in 2 patient populations: patients in cohort A had C3G, had not received a kidney transplant, and had reduced C3 serum levels ($< 0.90 \times$ lower limit of the laboratory normal range); and patients in cohort B had undergone kidney transplant and had C3G recurrence.

However, at the time of data cut-off on May 6, 2024, the duration of follow-up in Study B12001B for the participants rolling over from the APPEAR-C3G study was limited, so that long-term efficacy and safety data submitted to CDA-AMC focus only on participants who rolled over from Study X2202, with up to 39 months of iptacopan treatment (3 months in Study X2202 and 36 months in the extension Study B12001B). The study design for Study B12001B for participants transitioning from Study X2202 is summarized in the Supplemental Material document, Appendix 5.

Participants in Study B12001B received iptacopan 200 mg twice daily. Visits were planned every 3 months for the first year, and every 6 months thereafter. A kidney biopsy was requested within 6 to 9 months after enrolment. Data collection was separated into 2 distinct periods:

- primary data collection period: up to 9 months (i.e., 12 months of continuous treatment, 3 of which occurred during in Study X2202)
- longer-term data collection period: starting at the 9-month visit and continuing until the end of the study.

Participants who had severe concurrent comorbidities, severe pulmonary arterial hypertension (WHO class IV), or any illness or medical condition that in the opinion of the investigator and sponsor was likely to prevent the participants from safely tolerating iptacopan or complying with the requirements of the study were excluded. Participants with an active systemic bacterial, viral, or fungal infection within 14 days before screening or the presence of fever of 38°C (100.4°F) or more within 7 days before screening; history of HIV or any other immunodeficiency disease; or history or current diagnosis of electrocardiogram abnormalities indicating significant risk of safety for participants were excluded.

The screened analysis set was defined as all participants who signed the informed consent for participation in Study B12001B. The safety analysis set was defined as all participants who received any study drug and had at least 1 postextension day 1 safety assessment in Study B12001B. All primary, secondary, and exploratory end point analyses were carried out on the safety analysis set. Statistical analyses are summarized in the Supplemental Material document, Appendix 5.

Patient Disposition

Patient disposition for Study B12001B is summarized in the Supplemental Material document, Appendix 5, Table 19. A total of 26 participants entered Study B12001B, including 16 participants with reduced C3 serum levels (cohort A) and 10 participants with C3G recurrence after transplant (cohort B). Twenty-one participants

(80.8%; 13 from cohort A and 8 from cohort B) completed the 39-month follow-up. At the time of data cut-off, 69.2% of participants (11 from cohort A and 7 from cohort B) continued study treatment with iptacopan [REDACTED] discontinued from the study. The main reasons of study discontinuation were [REDACTED].

Baseline Characteristics

Baseline characteristics of participants from Study X2202 who rolled over into Study B12001B are presented in the Supplemental Material document, Appendix 5. The median age was 22.0 years in cohort A, with most participants being male (female: 38%; male: 63%); all participants were white. The median age at C3G diagnosis was [REDACTED] years, and the median time from C3G diagnosis until the first dose of iptacopan was [REDACTED] years. In cohort B, the median age was 32.5 years with most participants being male (female: 27%; male: 73%) and white (American Indian or Alaska: 9%; Black or African: 9%; white: 82%). The median age at recurrence of C3G diagnosis was [REDACTED] years. The median time from recurrence of C3G diagnosis until the first dose of iptacopan was [REDACTED] years (after the most recent kidney transplantation). The median time from kidney transplantation until the first study dose was [REDACTED] years, indicating the rapid onset of C3G recurrence despite all patients receiving routine posttransplant immunosuppressive therapy.

Exposure to Study Treatments

In cohort A, the total treatment duration was 60.37 participant years, with individual treatment duration ranging from [REDACTED]. In cohort B, the total treatment duration was 33.24 participant years, with individual treatment duration ranging from [REDACTED].

All 26 participants were taking at least 1 concomitant medication. In cohort A, the most frequently reported concomitant medications were [REDACTED]. In cohort B, all participants were receiving routine posttransplant immunosuppressive therapy for the prevention of allograft rejection. This included the use of calcineurin inhibitors in all participants, and [REDACTED] of participants. Almost all [REDACTED] participants were also receiving ACE inhibitors or ARBs. Details of patients' use of concomitant medications in Study B12001B are in the Supplemental Material document, Appendix 5.

Critical Appraisal

Internal Validity

The single-arm design of Study B12001B does not support causal interpretations about the effect of iptacopan and may influence the perception of improvement by patients and clinicians, particularly for outcomes that are subjective in measurement and interpretation (e.g., subjective AEs). The measurement of objective end points would not be affected. No data were included in the interim Clinical Study Report for participants rolling over from the APPEAR-C3G trial; at the time of data cut-off, data were only reported for participants who completed the 3-month phase II X2202 study. The very small sample size increases the likelihood of chance findings attributable to random variation rather than the true treatment effects. Discontinuation was high, and reasons for discontinuation suggested that patients in the more severe end of the disease spectrum were lost. As a result, the long-term performance of iptacopan may appear more favourable. The limited sample size also means that only common harms are likely to be detected.

External Validity

Because the patients who took part in the open-label LTE Study B12001B were originally from Study X2202 and the eligibility criteria remained the same, it is reasonable to expect that the same limitations to generalizability are relevant to the open-label extension study as well.

Results

Efficacy

Detailed results for outcomes relevant to this review are in the Supplemental Material document, Appendix 5.

Key results include the following.

- **Change from baseline in log-transformed UPCR:** The adjusted geometric mean ratio from 36 months to baseline was [REDACTED] in cohort A (n = 12) and [REDACTED] in cohort B (n = 7).
- **Change from baseline in eGFR:** The adjusted mean change from baseline was [REDACTED] in cohort A (n = 13) and [REDACTED] in cohort B (n = 8).

Harms

Detailed results for harms are presented in the Supplemental Material document, Appendix 5. Key results include the following:

- At least 1 AE was reported by all participants in both cohort A and cohort B.
- The most commonly reported treatment-emergent AEs (10% or more) in cohort A [REDACTED]
[REDACTED]
[REDACTED].
- The most commonly reported (10% or more) treatment-emergent AEs in cohort B [REDACTED]
[REDACTED]
[REDACTED].
- At least 1 SAE was reported for 4 of 16 (25%) patients in cohort A and 6 of 10 (60%) patients in cohort B.
- There were no treatment discontinuations due to treatment-emergent AEs in cohort A. In total, 20% of patients stopped treatment due to AEs in cohort B.
- One death was reported in cohort A due to cardiac arrhythmia. No deaths were reported in cohort B.
- The AEs of special interest were infections caused by encapsulated bacteria: [REDACTED]
[REDACTED].

Indirect Evidence

There were no ITCs included in the sponsor's submission.

The sponsor conducted a feasibility assessment to evaluate the feasibility of an ITC with iptacopan and relevant comparators in the treatment of adult patients with native kidney C3G. The patient population was

adults with a diagnosis of native kidney C3G. Comparators included rituximab, eculizumab, ravulizumab, pegcetacoplan, and best supportive care (e.g., corticosteroids, MMF, SGLT2 inhibitors). The outcomes of interest were UPCR, eGFR, composite renal end point, total activity score, C3 levels, UACR, AEs, discontinuations, and symptom relief (measured with the FACIT-Fatigue). Cross-trial heterogeneity was examined based on study designs, populations, patient characteristics at baseline, and the outcomes of interest among potentially relevant trials. In this analysis, there was no published evidence eligible for the comparisons between iptacopan and any best supportive care, biologic agents (e.g., eculizumab, ravulizumab, rituximab), or pegcetacoplan. Therefore, the sponsor concluded that no ITCs can be made currently to assess the efficacy of iptacopan relative to other active treatments for C3G.

Studies Addressing Gaps in the Systematic Review Evidence

This section summarizes 1 phase II study (X2202),⁴² which was a nonconfirmatory, open-label, 2 cohort, single-arm, nonrandomized study evaluating the efficacy and safety of iptacopan in 2 adult patient populations: cohort A included patients with C3G who had not undergone kidney transplant and had reduced C3 serum levels ($< 0.90 \times$ lower limit of the lab normal range) and cohort B included patients who had undergone kidney transplant and had C3G recurrence. The study addresses a gap in the evidence by providing evidence on the use of iptacopan in patients who have C3G recurrence after kidney transplant.

Characteristics of the patients included Study X2202 are summarized in the Supplemental Material document, Appendix 7. The study design was overall similar between the 2 cohorts. All patients had a C3G diagnosis confirmed by renal biopsy within 12 months before enrolment. Participants in cohort A had C3G with reduced C3 serum levels and participants in cohort B had C3G recurrence after transplantation. Patients were required to have an eGFR of 30 mL/min/1.73 m² or greater. In cohort A, patients needed to have a UPCR of 100 mg/mmol or greater and antiproteinuric medication at a stable dose for at least 30 days. In cohort B, patients needed to have normal or elevated urinary protein excretion, transplantation of a kidney allograft, and stable dose of immunosuppressive regimen for at least 90 days, as well as no signs of allorejection and no other prior transplant (solid organ or bone marrow). Previous vaccinations against *Neisseria meningitidis*, *Streptococcus pneumoniae*, and *Haemophilus influenzae* were required at least 4 weeks before receiving iptacopan. Antibiotic prophylaxis was mandatory during the study for patients enrolled in cohort B.

The primary outcomes of Study X2202 were the ratio to baseline of UPCR in cohort A and change from baseline in C3 deposit score in cohort B, both measured at week 12.

During the 30-day baseline period, patients received stable doses of supportive therapy (e.g., ACE inhibitor or ARB or other antihypertensive therapy, MMF, systemic corticosteroids with or without diuretics, and statins) and remained on their supportive therapy for the duration of the trial. The study included 2 treatment periods: a 4-week dose-escalation phase followed by an additional 8 weeks of treatment with iptacopan 200 mg twice daily, and a 12-week nonmandatory treatment extension. Upon completion of the study, patients had the option to discontinue iptacopan treatment and enter a safety follow-up period or continue open-label iptacopan treatment by transitioning to the C3G single-arm rollover extension Study B12001B.

Statistical analyses are summarized in Appendix 7.

Patient disposition: A total of 27 patients, 16 patients in cohort A and 11 patients in cohort B, were enrolled and treated in treatment period 1. All 27 patients completed the study. Twenty-six patients rolled over into the extension study to continue long-term treatment. One patient in cohort B did not rollover and completed the tapering down and follow-up period.

Baseline characteristics: Demographics and other baseline characteristics are summarized in the Supplemental Material document, Appendix 7, Table 25. The median age of all patients in cohort A was [REDACTED] patients were white and [REDACTED] of them were males ([REDACTED]). The median age of all patients in cohort B was [REDACTED] patients were white ([REDACTED]) and males ([REDACTED]). For cohort B, the median C3 deposit score was [REDACTED].

Exposure to study treatments: All 27 patients received iptacopan according to the trial protocol during treatment period 1 (i.e., 4-week dose escalation and 8 weeks of treatment). One patient interrupted treatment temporarily due to infection with COVID-19. Dosing errors were reported in 3 patients. Only 1 patient, from cohort B, entered the optional treatment period 2 and received iptacopan per protocol for 12 weeks.

Overall, 26 patients received at least 1 concomitant medication. The most common ($\geq 40\%$) concomitant medications were ACE inhibitor (12 patients [75%] in cohort A and 4 patients [36.4%] in cohort B), selective immunosuppressant (5 patients [31.3%] in cohort A and 9 patients [81.8%] in cohort B), glucocorticoids (3 patients [18.8%] in cohort A and 9 patients [81.8%] in cohort B), and calcineurin inhibitors (11 patients [100%] in cohort B). Details of patients' use of concomitant medications in Study X2202 are in the Supplemental Material document, Appendix 7.

Critical Appraisal

Internal Validity

Study X2202 was single arm and nonrandomized in design, which did not allow any comparisons for efficacy and safety, and may influence the perception of improvement by patients and clinicians for subjective outcomes (e.g., subjective AEs). The measurement of objective end points would not be affected. The very small sample size increases the likelihood of chance findings attributable to random variation rather than the true treatment effects. The limited sample size also means that only common harms are likely to be detected.

External Validity

Because participants who had severe concurrent comorbidities were excluded from Study B12001B, the restrictive criteria and limited diversity may limit generalizability to broader patient groups encountered in practice in Canada. Additionally, almost all patients were white, potentially limiting the generalizability of findings to other racial or ethnic populations.

Results

Efficacy

The detailed efficacy outcomes are presented in the Supplemental Material document, Appendix 7.

In cohort A, the adjusted geometric mean ratio to baseline of 24-hour UPCR was 0.55 (80% CI, 0.46 to 0.65) at week 12.

In cohort B, biopsies were available for 7 patients at week 12. In these patients, the median change from baseline in C3 deposit score was -2.50 (80% CI, -3.75 to -0.75).

Harms

- At least 1 AE was reported by 14 of 16 (87.5%) participants in cohort A and 8 of 11 (72.7%) participants in cohort B. The most commonly reported AEs ($\geq 10\%$) in cohort A, reported in 2 of 16 (12.5%) participants each, were blood creatine phosphokinase increased, nausea, upper respiratory tract infection, anemia, and upper abdominal pain. The most common AEs ($\geq 10\%$) in cohort B were headache and hyperkalemia in 2 of 11 (18.2%) participants.
- At least 1 SAE was reported for 1 of 16 (6.3%) patients in cohort A and 3 of 11 (27.3%) patients in cohort B.
- No patients stopped treatment due to AEs.
- No deaths were reported in this study.

Discussion

Efficacy

With an estimated prevalence of 2 per 100,000 people,⁸ C3G is a rare disease associated with a poor prognosis, a high disease burden, as well as a high risk of recurrence among patients after kidney transplant.^{5,7-10} Overall, the unmet needs within the current SOC supportive treatments include a lack of disease-specific, effective, and well-tolerated therapies that can meaningfully reduce the burden of the disease and improve quality of life. Patients' expectations of important outcomes include slowing disease progression, preserving kidney function, and improving quality of life.

The APPEAR-C3G trial evaluated the effects of iptacopan on proteinuria (UPCR), kidney function (eGFR), composite renal end point, and patient symptoms (measured by the FACIT-Fatigue). The reported end points are surrogate end points that are indicative of disease progression rather than direct clinical outcomes (e.g., progression to ESKD, need for dialysis or kidney transplantation, cardiovascular events, and mortality). Observational evidence from the literature suggests that reductions in UPCR and stabilization of eGFR may each be associated with longer-term patient-important clinical outcomes, such as delayed progression to ESKD and reduced mortality.^{14,28,37,45} Surrogate measures are commonly used in rare renal disease trials due to feasibility constraints in generating RCT evidence on long-term clinical outcomes. Because C3G is rare, it would not be feasible to recruit the number of patients required to power the trial for these outcomes, and long follow-up would be required. Regardless, surrogate outcomes do not reflect how patients feel, function, or survive.

Based on results of the APPEAR-C3G trial, iptacopan reduced the primary end point of proteinuria at 6 months compared with placebo; however, uncertainty surrounds the clinical interpretation and importance of these findings. There is no established between-group MID for log-transformed ratio or geometric mean ratio of UPCR. The clinical experts consulted by CDA-AMC suggested that a 50% reduction in proteinuria over 6 months would be considered an ideal MID for proteinuria, based on observations from the literature. However, the experts noted that thresholds and interpretation may vary among physicians,

and that physicians in clinical practice could consider a 25% reduction in proteinuria over 6 months as an appropriate MID. This lower MID threshold was favoured by the clinical experts and consistent with the clinician group input received. In the APPEAR-C3G study, iptacopan achieved a statistically significant 35.1% reduction (95% CI, 13.8% to 51.1%) in 24-hour UPCR from baseline after 6 months of treatment compared to placebo. Therefore, the effect of iptacopan could extend from a clinically important relative reduction in proteinuria, based on a 25% reduction of MID, to little to no clinically important difference, if a 50% threshold was selected. The imbalance in patient baseline characteristics in favour of placebo introduced additional uncertainty regarding the true magnitude of effect. The clinical experts noted that patients who received placebo also experienced a level of improvement in proteinuria that is unlikely to be observed in clinical practice with the use of supportive therapies only, based on the natural disease progression. The relatively small sample size adds further uncertainty, as small studies usually yield unstable estimates.⁵³

In the APPEAR-C3G study, there is uncertainty as to whether findings of the key secondary end points may be supportive of the primary end point of proteinuria reductions. Iptacopan may result in little to no clinically important increase in eGFR at 6 months when compared with placebo, as the associated 95% CI crossed the null and included both the possibility of improved and worsened eGFR. Therefore, the clinical importance of any eGFR improvement based on the point estimate is highly uncertain. The clinical experts indicated that the study duration in the APPEAR-C3G study is likely insufficient to observe a meaningful change for this outcome, as eGFR is a lagging marker of disease improvement and may not accurately reflect short-term response to treatment. Iptacopan likely resulted in a clinically important increase in the proportion of patients achieving the composite renal end point at 6 months when compared with placebo. According to the clinical experts, the composite renal end point primarily served to support that proteinuria lowering was not achieved at the expense of kidney function (i.e., eGFR), addressing the concern that some interventions (e.g., nonsteroidal anti-inflammatory drugs) can reduce proteinuria while harming kidney function. This end point was not formally tested, however, due to earlier failure of the statistical hierarchy. Iptacopan may result in a decrease in C3 deposit on kidney biopsy at 6 months when compared with placebo. The clinical experts noted that this does not necessarily correlate with the clinical disease presentation; however, it may be considered impactful because it demonstrates tissue-level improvement that is typically not observed over 6 months in the natural disease trajectory of C3G. Of note, the effect estimate was likely unstable for all secondary outcomes given the small sample size.

Findings from the APPEAR-C3G trial showed that iptacopan may result in little to no clinically important difference in FACIT-Fatigue total score at 6 months when compared with placebo, as the between-group difference was not clinically important. This was anticipated by the clinical experts given that the enrolled patients, although considered high risk, were in relatively early stages of kidney disease that are typically asymptomatic and primarily monitored through laboratory parameters. Although patients indicated that they desire improvement in symptoms and overall quality of life, the clinical experts considered the absence of deterioration reassuring, as the primary concern in this context is to avoid any negative impact of the treatment or disease progression.

The randomized controlled phase of the APPEAR-C3G trial did not provide data on the long-term efficacy and safety of iptacopan beyond 6 months. This evidence gap was partially addressed by the open-label

treatment period of the APPEAR-C3G trial. Findings suggested potential sustained efficacy of iptacopan, with continued reductions in proteinuria and stabilization of kidney function at 12 months. Evidence beyond 12 months is from the ongoing open-label extension Study B12001B, with results reported for patients who rolled over from Study X2202. The small sample size and substantial missing data, however, limit the validity of the findings regarding longer-term outcomes, thus reducing the overall strength of evidence. Causal interpretations about the effect of iptacopan are not possible due to the single-arm design.

Study X2202 was an open-label, single-arm study that aimed to address an important evidence gap related to the efficacy and safety of iptacopan in patients with recurrent C3G following kidney transplantation. Findings may be suggestive of the potential efficacy of iptacopan in this high-risk subgroup; however, this evidence is highly uncertain due to the very small sample size of 7 patients with available biopsy results, within which it is not possible to confidently separate true treatment effects from chance findings. Causal interpretation of the findings is further limited by a lack of comparison groups.

Harms

In the APPEAR-C3G trial, patients in the iptacopan group reported higher incidence of overall AEs, SAEs, and notable harms. However, SAEs and notable harm were reported by very few patients. The clinical experts noted that the safety profile is consistent with expectations for C3 inhibitors, with the primary concern being an increased risk of infections caused by encapsulated bacteria (e.g., meningococcal and pneumococcal). These risks can be mitigated through vaccination and antibiotic prophylaxis. Overall, clinical experts concluded that, with appropriate infection prevention measures, iptacopan is considered to have an acceptable and tolerable safety profile.

The safety profile of iptacopan in the 6-month open-label period of the APPEAR-C3G study (N = 74) and in the B12001B LTE study (N = 26) was consistent with the previously reported data from the APPEAR-C3G trial, and, as of the data cut-off date, no new safety concerns for iptacopan were identified with the additional follow-up period. The sample size means that uncommon harms were unlikely to be captured. The X2202 study, which included patients with posttransplant recurrence of C3G, was very small (n = 10 in cohort B) and therefore, could only capture very common harms.

Ethics and Equity Considerations

No information was available in any of the inputs (from patient group, clinician group, and clinical experts consulted by CDA-AMC) regarding whether any racial or ethnic groups experience a higher prevalence of C3G. In addition, there was limited representation of participants from diverse racial and ethnic groups in the APPEAR-C3G trial, its LTE study (B12001B), and the study addressing gaps in the evidence (X2202). Clinical experts consulted by CDA-AMC indicated that findings from these studies are expected to be generalizable to the overall population in clinical practice; however, CDA-AMC notes that the uncertainty regarding this lack of data on the safety and efficacy of iptacopan in diverse population groups should be accounted for in clinical decision-making when considering treatment with iptacopan in populations or groups not represented in the trials.

In addition, diagnostic inequities exist, including limited access to kidney biopsies for people in rural and remote regions and the lack of C3c-specific staining in some laboratories across Canada, which may delay diagnosis for some patients. People living far from major centres may not have the opportunity to access adequate health care. Iptacopan may address some of the access considerations due to its at-home, oral administration.

According to the clinical experts consulted for this review, the most important ethical issues and equity considerations, however, stem from the rarity of C3G. Evidence generation is inherently constrained, and it is neither feasible nor ethical to hold these conditions to evidentiary standards typical of common diseases (e.g., large hard-outcome trials). C3G can substantially compromise patients' autonomy and dignity by limiting their ability to maintain independence and control over daily activities. Persistent symptoms such as fatigue, edema, pain, and gastrointestinal issues, coupled with the demands of strict dietary restrictions, complex medication regimens, and frequent medical appointments, impose significant physical and emotional burdens. These factors often disrupt social engagement and routine responsibilities, diminishing quality of life and contributing to a loss of personal agency. Regional shortages of nephrologists may result in need for consultation-based, shared-care models to enable timely initiation and monitoring where local expertise is scarce. Allied health professionals can also facilitate ongoing monitoring, which further supports timely initiation and continuity of care where local expertise is limited.

Finally, the potentially high cost of iptacopan should be weighed against avoided downstream costs (dialysis, kidney transplantation) and the broader impacts on autonomy, dignity, and caregiver burden (time off work, income loss, stress). Funding policies that acknowledge constraints of rare diseases and support home-based care with adequate training and monitoring are essential to ensure appropriate use and equitable uptake across Canada.

Conclusion

C3G is a rare, progressive kidney disease associated with a poor prognosis and a high disease burden. One phase III, randomized, double-blind, placebo-controlled trial (APPEAR-C3G) provided evidence for the efficacy and safety of iptacopan in adults with C3G. Evidence from the APPEAR-C3G trial showed that iptacopan resulted, with moderate certainty, in a clinically important reduction in proteinuria at 6 months compared with placebo, based on the MID threshold of 25% improvement suggested by the clinical experts and clinician input. However, iptacopan likely resulted in little to no clinically important difference when results were assessed using a more stringent MID threshold of 50% improvement, which was also suggested by the clinical experts and based on observations from the literature. Proteinuria is considered prognostic of long-term clinical outcomes based on observational evidence and expert opinions. Despite this, it remains an evidence gap, and reliance on surrogate measures is common in rare kidney diseases and reflects feasibility challenges in generating evidence. Nevertheless, uncertainty surrounds the clinical interpretation and importance of the findings; with a small sample size of 74 patients, the effect estimate is likely unstable. Furthermore, baseline imbalances introduced a risk of bias against iptacopan. According to the clinical experts, patients in the placebo group had characteristics that were consistent with less advanced disease

and experienced a level of improvement in proteinuria that is unlikely to be observed in clinical practice based on the natural progression of the disease.

Iptacopan likely resulted in a clinically important increase in the proportion of patients achieving the composite renal end point and may also result in a clinically important decrease in the glomerular C3 deposit on kidney biopsy at 6 months compared with placebo. Iptacopan may result in little to no clinically important difference in eGFR; 6 months is likely insufficient to observe a meaningful change as eGFR is a lagging marker of disease improvement and may not accurately reflect short-term response to treatment. Iptacopan may have little to no clinically meaningful impact on patients' symptom relief compared to placebo. This was anticipated by the clinical experts given that patients in relatively early stages of kidney disease are typically asymptomatic despite being at high risk of progression. Patients in both groups received supportive therapies; however, none of the currently available treatments target the underlying disease pathophysiology of complement dysregulation. The study population was broadly representative of patients seen in clinical practice in Canada; however, certain patient groups who may stand to benefit from early intervention were excluded according to the clinical experts. The restrictive criteria and limited diversity of the APPEAR-C3G trial may limit generalizability of the study findings to broader patient groups encountered in practice in Canada. Results from the open-label treatment period of the APPEAR-C3G study and from the LTE B12001B study suggested potential for sustained efficacy beyond 6 months, but causal interpretations could not be made due to single-arm design and substantial reductions in sample size over time. Study X2202 provided limited evidence regarding the potential efficacy of iptacopan in patients with posttransplant recurrence of C3G.

The evidence in the APPEAR-C3G trial is very uncertain about the effect of iptacopan on the incidence of SAEs and infection by encapsulated bacteria at 6 months. The LTE study (B12001B) and study addressing evidence gaps (X2202) support a consistent safety profile for iptacopan during extended follow-up and in patients with posttransplant recurrence of C3G. These studies were small and unlikely to detect harms that are uncommon. Overall, no new safety signals were identified; according to the experts consulted by CDA-AMC and harms were considered manageable in clinical practice.

Economic Review

Methods

The review team appraised the pharmacoeconomic evidence submitted by the sponsor on the cost-effectiveness and budget impact of iptacopan in combination with SOC compared to other SOC for adult patients with C3G. Iptacopan is being reviewed by CDA-AMC through the complex review pathway (scenario 1); as such, CDA-AMC has appraised 2 cost-effectiveness analyses submitted by the sponsor, 1 adopting a publicly funded health care payer perspective and 1 adopting a societal perspective.

Summary of the Submitted Economic Evaluation

The sponsor submitted a cost-utility analysis to estimate the cost-effectiveness of iptacopan from the perspective of a public health care payer in Canada and from a societal perspective over a lifetime horizon (100 years). The modelled population comprised adult patients with C3G, which is aligned with the proposed Health Canada indication and was based on the participants in the APPEAR-C3G trial. The sponsor's base-case analysis included costs related to drug acquisition, health care resource use, vaccination, and AEs. The sponsor's societal base case included additional costs associated with patient and caregiver productivity loss and out-of-pocket expenses.

In the sponsor's base case, which adopted a health care payer perspective, iptacopan in combination with SOC was associated with incremental costs of \$5,095,575 and 2.77 incremental quality-adjusted life-years (QALYs) relative to SOC. This resulted in an incremental cost-effectiveness ratio (ICER) of \$1,899,006 per QALY gained. From a societal perspective, the ICER was \$1,841,235 per QALY gained. Of the incremental benefit compared to SOC (2.77 incremental QALYs), approximately 99% of benefit was predicted to be accrued after the observation period of the APPEAR-C3G trial and Study B12001B extension study (2 years). Additional information about the sponsor's submission is summarized in the Supplemental Material document, Appendix 11.

CDA-AMC identified several key issues with the sponsor's analysis (refer to [Table 5](#); full details are provided in Supplemental Material document, Appendix 12).

Table 5: Key Issues With the Sponsor's Economic Submission

Issue	What evidence is there to inform this issue?	How was this issue addressed by CDA-AMC?	Did CDA-AMC explore uncertainty in a scenario analysis?
The clinical benefit associated with iptacopan is uncertain.	The CDA-AMC Clinical Review report concluded that there may be little to no difference in eGFR for iptacopan in combination with SOC when compared to placebo in combination with SOC. In the model, for SOC eGFR decline, the sponsor pooled historic data before patients received iptacopan, including those who were assigned to placebo therapy in the 6-month double-blind period from the APPEAR-C3G trial. For iptacopan eGFR decline, the sponsor pooled data after patients received iptacopan, including data from patients originally randomized to the placebo arm of the APPEAR-C3G trial after switching to open-label iptacopan following the double-blinded	The treatment effect derived from the randomized controlled trial was used to derive the eGFR curve for iptacopan.	To explore uncertainty around this issue, CDA-AMC conducted 2 scenario analyses: 1 scenario maintained the sponsor's approach of using the historic pre-iptacopan approach for SOC and Study B12001B for iptacopan, and 1 scenario used the historic pre-iptacopan SOC slope with the trial-based iptacopan treatment effect applied.

Issue	What evidence is there to inform this issue?	How was this issue addressed by CDA-AMC?	Did CDA-AMC explore uncertainty in a scenario analysis?
	period. This means the evidence informing the economic analysis is nonrandomized and based mostly on a before and after comparison. The eGFR decline in the trial for patients on SOC was deemed below expectations by clinical experts consulted by CDA-AMC. Therefore, all available sources of evidence to inform iptacopan treatment effect is uncertain.		
The long-term benefits associated with iptacopan predicted by the model are uncertain.	The model assumed eGFR would decrease linearly over time; however, this was only informed by a limited amount of evidence. As the treatment effect is applied over a lifetime, this results in large improvements in dialysis-free years, fewer kidney transplants, and decreased mortality. ⁵⁴ While clinical experts and published literature support the use of eGFR as a surrogate end point as a predictor of these long-term outcomes, ⁵⁵ the magnitude of benefit associated with iptacopan remains uncertain.	CDA-AMC was unable to address this limitation due to a lack of long-term evidence. As there is no evidence that supports or disputes the assumed lifetime benefit of iptacopan, the economic model may overestimate the true clinical and economic impact of treatment as treatment benefit does not wane over time.	No scenario analysis was conducted.
The modelled population does not fully capture the patients treated in clinical practice.	As noted in the Clinical Review, the APPEAR-C3G trial excluded patients with posttransplant recurrence, and rapid progressive disease who could not maintain a stable background regimen. ⁴⁰ Clinical experts consulted by CDA-AMC indicated that the aforementioned patients, who are included in the proposed Health Canada indication, may be treated with iptacopan if available.	CDA-AMC was unable to address this limitation as there is a lack of evidence in these patient populations. The clinical effectiveness and cost-effectiveness of iptacopan in the full proposed Health Canada indication is therefore unknown.	No scenario analysis was conducted.
Iptacopan discontinuation was likely overestimated.	The sponsor's model assumed that patients treated with iptacopan would discontinue iptacopan therapy at an annual rate of 5.3% or upon progressing to CKD stage 5. ^{40-42,54} Clinical experts consulted by CDA-AMC indicated that patients would be unlikely to discontinue at a rate of 5.3% indefinitely due to adverse events. Further, it is unlikely that they would be clinically	In reanalysis, CDA-AMC assumed that patients would discontinue during the 2 years of iptacopan treatment and upon progression to CKD stage 5.	No scenario analysis was conducted.

Issue	What evidence is there to inform this issue?	How was this issue addressed by CDA-AMC?	Did CDA-AMC explore uncertainty in a scenario analysis?
	indicated to discontinue after the first years of treatment.		
The modelled mortality is associated with uncertainty.	SMRs within the model were informed by published literature. ^{56,57} The SMRs for CKD stages 1 to 4 were informed by a UK RaDaR study, and it is uncertain if the all-cause mortality from a collection of rare renal diseases may be generalizable to patients with C3G. ⁵⁷ The SMR for dialysis and posttransplant were similar; however, clinical experts consulted by CDA-AMC indicated that after the acute mortality risk associated with surgery, the mortality for a patient posttransplant would decrease to be similar to the general population.	CDA-AMC was unable to provide an alternative mortality for patients with a successful kidney transplant as the model structure did not allow for an acute mortality risk.	CDA-AMC conducted a scenario analysis where the SMR for the posttransplant state was assumed to be equal to the SMR for CKD stages 1 to 4.
The proportion of patients on each supportive therapy did not reflect the clinical evidence.	The proportion of patients who were treated with each supportive therapy was informed by a sponsor-conducted survey, not the proportions from APPEAR-C3G, meaning that SOC drug acquisition costs were not aligned with the SOC clinical efficacy from APPEAR-C3G. ^{18,40,54}	Given that the clinical efficacy is sourced from APPEAR-C3G, CDA-AMC adjusted the proportion of patients on each supportive therapy to match the APPEAR-C3G trial.	No scenario analysis was conducted.
The societal perspective is associated with uncertainty.	No robust evidence was provided to inform productivity loss and out-of-pocket costs. As well, the sponsor assumed that productivity losses persisted for the patients' entire lifetime (i.e., used a human capital approach) which overestimates productivity losses. ⁵⁴	This issue could not be addressed.	No scenario analysis was conducted.

C3G = complement 3 glomerulopathy; CDA-AMC = Canada's Drug Agency; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; RaDaR = Registry of Rare Kidney Diseases; SMR = standard mortality ratio; SOC = standard of care.

Note: Full details of the issues identified by CDA-AMC are provided in the Supplemental Material document, Appendix 12.

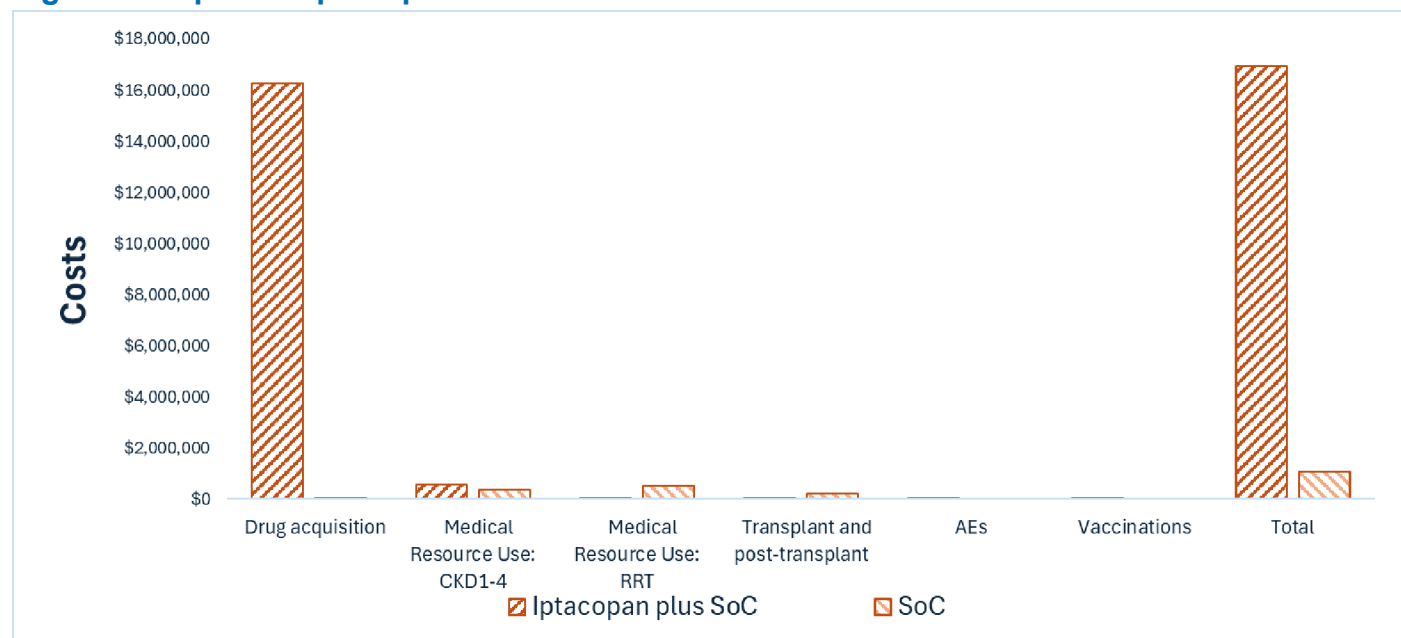
CDA-AMC Assessment of Cost-Effectiveness

The CDA-AMC base case was derived by making changes to model parameter values and assumptions (refer to Supplemental Material document, Appendix 12, Table 33), in consultation with clinical experts. Detailed information about the CDA-AMC base case is provided in Appendix 12.

Impact on Health Care Costs

Iptacopan in combination with SOC is predicted to be associated with additional health care costs compared to SOC (incremental costs = \$15,833,147). This increase in health care spending primarily results from drug acquisition costs associated with iptacopan (refer to [Figure 1](#)).

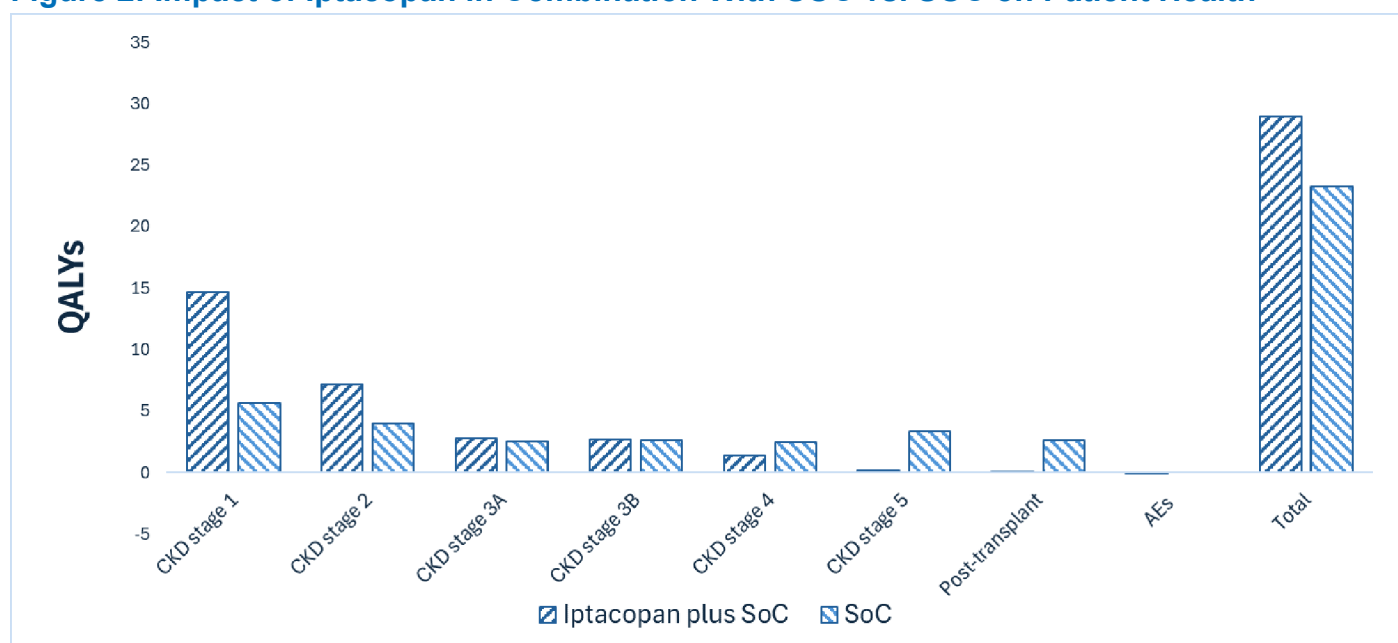
Figure 1: Impact of Iptacopan in Combination With SOC vs. SOC on Health Care Costs



AE = adverse event; CKD = chronic kidney disease; RRT = renal replacement therapy; SoC = standard of care; vs. = versus.

Impact on Health

Relative to SOC, iptacopan in combination with SOC is predicted to delay progression CKD stage 5 by 14.01 years (refer to [Figure 2](#)). As patients spend more time in the CKD stage 1 to 3 health states, patients treated with iptacopan in combination with SOC are predicted to gain 3.49 life-years (LYs) compared to SOC. Considering the impact of treatment on both quality and length of life, iptacopan in combination with SOC is predicted to result in 5.73 additional QALYs per patient compared to SOC. Approximately 99.9% of the predicted incremental benefit was accrued on the basis of extrapolation.

Figure 2: Impact of Iptacopan in Combination With SOC vs. SOC on Patient Health

AE = adverse event; CKD = chronic kidney disease; QALY = quality-adjusted life-year; SoC = standard of care; vs. = versus.

Overall Results

The results of the CDA-AMC base case suggest an ICER of \$2,762,300 per QALY gained for iptacopan in combination with SOC compared to SOC (refer to [Table 6](#)). Additional details on the CDA-AMC base case are available in the Supplemental Material document, Appendix 12.

Table 6: Summary of CDA-AMC Economic Evaluation Results

Drug	Total costs (\$)	Total QALYs	ICER vs. SOC (\$/QALY)
SOC	1,086,937	23.27	Reference
Iptacopan in combination with SOC	16,920,083	29.00	2,762,300

CDA-AMC = Canada's Drug Agency; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; SOC = standard of care; vs. = versus.

Note: Publicly available list prices were used for all comparators.

Uncertainty and Sensitivity

- The treatment effect for iptacopan versus SOC in relation to eGFR decline is uncertain. Although the base-case analysis is based on randomized data, the treatment effect benefit is imprecise and there are concerns with the slow rate of eGFR decline in the SOC arm relative to real-world practice. Alternative treatment effect scenarios were explored, although it should be noted some of these assume the impact on eGFR decline is so vast that iptacopan delays patients from experiencing stage 5 CKD or dialysis, which essentially cures the condition with eGFR decline matching the general population. In all scenarios the ICER remains greater than \$1.7 million per QALY gained as treatment costs remain greater than \$7 million.

- Scenario 1 selected for the data observed during the pre-iptacopan and double-blinded portion of the APPEAR-C3G trial for SOC, and the double-blinded portion of the APPEAR-C3G trial and the duration of the B12001B extension study for iptacopan in combination with SOC (ICER = \$1,797,767 per QALY gained).
- Scenario 2 adjusted the treatment efficacy by retaining the SOC eGFR slope observed from the pre-iptacopan historical data and applying the iptacopan treatment effect based on the double-blinded portion of the APPEAR-C3G study (ICER = \$4,158,041 per QALY gained).
- The assumption that posttransplant mortality was similar to that of mortality in CKD stages 1 to 4 was explored in a scenario analysis (ICER = \$3,050,237 per QALY gained).

Summary of the Budget Impact

The sponsor submitted a budget impact analysis to estimate the 3-year (2027 to 2029) budget impact of reimbursing iptacopan in combination with SOC for use in the Health Canada–indicated population.⁵⁸ The sponsor assumed that the payer would be CDA-AMC–participating public drug plans and derived the size of the eligible population using an epidemiological approach.^{1,18,58} The price of iptacopan was aligned with the price included in the sponsor’s economic evaluation,⁵⁹ while the prices of comparators were based on the publicly available list prices. Additional information pertaining to the sponsor’s submission is provided in the Supplemental Material document, Appendix 13.

CDA-AMC identified a number of issues with the sponsor’s estimated budget impact and made changes to model parameters and assumptions in consultation with clinical experts to derive the CDA-AMC base case (Supplemental Material document, Appendix 13). CDA-AMC estimated that by year 3 of reimbursement, 215 patients would be eligible for iptacopan in combination with SOC; of these, 183 patients are expected to receive iptacopan. The estimated incremental budget impact of reimbursing iptacopan is predicted to be approximately \$250.5 million over the first 3 years, with an expected expenditure of \$250.7 million on iptacopan. The actual budget impact will depend on the proportion of patients eligible based on proteinuria and eGFR levels, and the iptacopan uptake.

Conclusion

Based on the CDA-AMC base case, iptacopan for use in combination with SOC would be considered cost-effective at the submitted price if the public health care system was willing to pay at least \$2,762,300 for each additional QALY gained. If the public health care system is not willing to pay that amount, a price reduction should be considered (refer to [Figure 3](#); full details of the impact of price reductions on cost-effectiveness are presented in Supplemental Material document, Appendix 12, Table 36). The estimated cost-effectiveness of iptacopan in combination with SOC compared to SOC is uncertain due to uncertainty in the treatment effect of iptacopan and uncertainty of iptacopan on long-term renal outcomes.

The budget impact of reimbursing iptacopan to the public drug plans in the first 3 years is estimated to be approximately \$250.5 million. The 3-year expenditure on iptacopan (i.e., not accounting for current expenditure on comparators) is estimated to be \$250.7 million. The estimated budget impact is uncertain due

to the proportion of patients considered eligible for treatment based on proteinuria and eGFR levels and the market uptake of iptacopan.

Figure 3: Summary of the CDA-AMC Economic Analysis and Price Reduction

% price reduction	Annual cost of Iptacopan plus SoC		Expenditure on Iptacopan plus SoC in first 3 years	ICER — Cost per QALY gained versus SoC
No reduction (list price)	\$525,916		\$250.7 million	\$2,762,300
10% reduction	\$473,325		\$225.6 million	\$2,478,572
30% reduction	\$368,141		\$158 million	\$1,911,116
50% reduction	\$262,958		\$79 million	\$1,343,660
70% reduction	\$157,775		\$23.7 million	\$776,203
90% reduction	\$52,592		\$2.4 million	\$208,747

CDA-AMC = Canada's Drug Agency; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; SoC = standard of care.

Note: Expenditure includes only the drug cost of iptacopan.

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