Canadian Journal of Health Technologies

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

September 2025 Volume 5 Issue 9

Drugs Health Technologies Health Systems

Reimbursement Recommendation

Mirikizumab (Omvoh)

Indication: For the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response, loss of response, or were intolerant to either conventional therapy or a biologic treatment

Sponsor: Eli Lilly Canada Inc.

Recommendation: Reimburse with conditions

Summary

What Is the Reimbursement Recommendation for Omvoh?

Canada's Drug Agency (CDA-AMC) recommends that Omvoh be reimbursed by public drug plans for the treatment of moderately to severely active Crohn disease (CD) in cases in which conventional treatment or biologic therapies have led to an inadequate response, a loss of response, or intolerable side effects, if certain conditions are met.

Which Patients Are Eligible for Coverage?

Omvoh should only be covered according to reimbursement eligibility criteria used by each of the public drug plans for other advanced therapies for the treatment of adults with moderately to severely active CD who have had an inadequate response, a loss of response, or intolerance to either conventional therapy or a biologic treatment.

What Are the Conditions for Reimbursement?

Omvoh should only be reimbursed if it is prescribed according to the criteria used by each of the public drug plans for other advanced therapies and if the cost of Omvoh is reduced so it does not cost the drug programs more than the least costly available advanced therapy reimbursed for the treatment of adult patients with moderately to severely active CD.

Why Did CDA-AMC Make This Recommendation?

- Evidence from a clinical trial demonstrated that patients treated with Omvoh felt better than those who took a placebo. They had fewer symptoms, less gut inflammation, and better health-related quality of life. The study also found that Omvoh works just as well as Stelara in improving symptoms and reducing inflammation.
- Based on the CDA-AMC assessment of the health economic evidence, Omvoh does not represent good value to the health care system at the public list price. The committee determined there is not enough evidence to justify a greater cost for Omvoh compared with other treatments reimbursed for treating moderately to severely active CD in adults.
- Compared with existing treatments for moderately to severely active CD, Omvoh does not meet the unmet needs identified by patients. However, the evidence is supportive of Omvoh as an additional treatment option for the indicated patient population.
- Based on public list prices, Omvoh is estimated to cost the public drug plans approximately $50.3 million over the next 3 years.

Summary

Additional Information

What Is CD?

CD is a chronic condition that causes swelling and irritation in the digestive system, which commonly affects the end of the small intestine and the beginning of the colon. Symptoms of CD include abdominal pain, diarrhea, fatigue, rectal bleeding, and weight loss. Symptoms come and go and differ across individual patients and may worsen over time if left untreated. In 2023, it was estimated that 410 of every 100,000 individuals in Canada were living with CD.

Unmet Needs in CD

There is currently no cure for CD. Available treatments focus on managing the condition; however, for many patients, the currently available treatments do not work well, stop working over time, or lead to side effects that are not tolerable. Patients and clinicians expressed a need for effective treatments that reduce symptoms and dependence on steroids, keep the disease under control over time, improve health-related quality of life, have fewer side effects, and are convenient to administer.

How Much Does Omvoh Cost?

Treatment with Omvoh is expected to cost approximately $50,773 per patient in the first year and $33,083 per patient in subsequent years.

Recommendation

The Canadian Drug Expert Committee (CDEC) recommends that mirikizumab (Omvoh) be reimbursed for the treatment of adult patients with moderately to severely active Crohn disease (CD) who have had an inadequate response, a loss of response, or intolerance to either conventional therapy or a biologic treatment only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One phase III, double-blind, placebo- and active-controlled (versus ustekinumab) trial (VIVID-1; N = 1,152) demonstrated that treatment with mirikizumab, administered over a 12-week induction and a 40-week maintenance period, results in added clinical benefit compared to placebo and similar benefit compared to ustekinumab in patients with moderately to severely active CD and prior inadequate response, loss of response, or intolerance to 1 or more biologic or conventional therapies. The VIVID-1 trial showed statistically significant and clinically meaningful improvements compared to placebo in the coprimary composite end points of clinical response at week 12 and endoscopic response at week 52 (between-group difference = 28.7%; 95% confidence interval [CI], 20.6% to 36.8%) and clinical response at week 12 and clinical remission at week 52 (between-group difference = 25.8%; 95% CI, 15.9% to 35.6%). The results observed in the primary analyses were supported by statistically significant and clinically important improvements in all major secondary outcomes compared with placebo, including the health-related quality of life (HRQoL) end point, measured by the Inflammatory Bowel Disease Questionnaire (IBDQ) total score. Mirikizumab showed little to no difference compared to ustekinumab across both major secondary end points: clinical remission at week 52 (the noninferiority margin of 10% was met) and endoscopic response at week 52 (superiority was not demonstrated). Comparative results versus ustekinumab across other secondary end points, including IBDQ total score, aligned with the findings for the 2 major secondary end points.

CDEC considered the results from 1 sponsor-submitted network meta-analysis (NMA) comparing the efficacy and safety of mirikizumab to currently available therapies (adalimumab, infliximab, risankizumab, upadacitinib, ustekinumab, and vedolizumab). CDEC was unable to draw definitive conclusions from the NMA results due to methodological limitations in the analyses. Thus, the comparative efficacy and safety of mirikizumab versus other relevant comparators remains uncertain.

Patients expressed a need for effective treatments that reduce side effects, improve symptom control, achieve sustained remission or response, reduce corticosteroid use, improve HRQoL, and offer a convenient route of administration. Based on the evidence reviewed, CDEC concluded that mirikizumab does not meet the unmet needs identified by patients compared to existing treatments; however, the evidence supports mirikizumab as an additional treatment option. Mirikizumab is given intravenously during the induction phase and has a subcutaneous maintenance option that can be administered at home. CDEC noted there was no evidence assessing the effect of mirikizumab's route and frequency of administration on HRQoL outcomes.

CDEC noted that no new safety signals were identified and that the safety profile of mirikizumab appeared consistent with that of the drug class.

At the sponsor-submitted price for mirikizumab and publicly listed prices for comparators, mirikizumab was more costly than other reimbursed advanced therapies for adult patients with moderately to severely active CD who have had an inadequate response, a loss of response, or intolerance to either conventional therapy or a biologic treatment. Because no definitive conclusions can be drawn regarding the relative efficacy of mirikizumab compared to other advanced therapies, the total drug cost of mirikizumab should not exceed the total drug cost of the least costly relevant advanced therapy reimbursed for this patient population.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation, renewal, discontinuation, and prescribing		
1. Eligibility for reimbursement of mirikizumab should be based on the criteria used by each of the public drug plans for initiation, renewal, discontinuation, and prescribing of other advanced therapies for the treatment of adults with moderately to severely active CD who have had an inadequate response, a loss of response, or intolerance to either conventional therapy or a biologic treatment.	CDEC considered it appropriate to align the reimbursement conditions for mirikizumab with the reimbursement criteria used by public drug plans for the treatment of adults with moderately to severely active CD who have had an inadequate response, a loss of response, or intolerance to either conventional therapy or a biologic treatment.	—
Pricing		
2. Mirikizumab should be negotiated so that it does not exceed the drug program cost of treatment with the least costly available relevant advanced therapy reimbursed for the treatment of adult patients with moderately to severely active CD.	Evidence from the sponsor-submitted network meta-analysis was insufficient to show a difference in efficacy of mirikizumab compared with other currently available treatments for moderately to severely active CD. As such, there is insufficient evidence to justify a cost premium for mirikizumab over the least costly relevant advanced therapy reimbursed for adult patients with moderately to severely active CD.	—

CD = Crohn disease; CDEC = Canadian Drug Expert Committee.

Discussion Points

- **Unmet need:** Patients and clinicians identified a need for additional effective advanced therapy options for CD. CDEC heard from the clinical experts that, in clinical practice, some patients have inadequate response or loss of response to currently available advanced therapies and require alternative treatments. The committee noted there are several approved advanced therapies currently available for CD. Based on the submitted evidence, CDEC concluded that mirikizumab does not meet the unmet needs identified by patients compared with other advanced therapies. However,

the evidence is supportive of mirikizumab as an additional treatment option in the indicated patient population, which is consistent with the VIVID-1 trial population.

- **Efficacy outcomes**: The Grading of Recommendations Assessment, Development and Evaluation (GRADE) certainty of evidence versus placebo was rated as high to moderate for the coprimary and major secondary outcomes, indicating improvements in the signs and symptoms of CD, underlying mucosal inflammation, and HRQoL. For the comparison with ustekinumab, the certainty of evidence for the 2 major secondary end points was rated as moderate using the GRADE approach, indicating that clinical remission and endoscopic response at week 52 likely showed little to no difference between treatment groups. Comparative results versus ustekinumab across other secondary end points, including HRQoL, aligned with findings for the 2 major secondary end points. The GRADE certainty of evidence for these outcomes rated as high to moderate, except for endoscopic remission at week 52 and the composite end point of clinical response at week 12 and endoscopic response at week 52, which were both rated as low. Overall, CDEC noted the consistency in the direction of results across outcomes and concluded that mirikizumab likely results in little to no difference compared to ustekinumab.
- **Adverse events:** CDEC discussed patients' desire for treatments with fewer adverse effects. CDEC noted that within the VIVID-1 trial, treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and adverse events (AEs) leading to study treatment discontinuation occurred more frequently in patients in the placebo group compared with those in the mirikizumab group. In the VIVID-1 trial, the most common AEs in the mirikizumab group were COVID-19, anemia, arthralgia, headache, upper respiratory tract infection, nasopharyngitis, and diarrhea; however, all of these were reported more commonly in patients who received placebo. Treatment with mirikizumab was associated with rates of TEAEs, SAEs, and treatment discontinuations due to AEs similar to those with ustekinumab. In terms of AEs of special interest, injection site reactions and nonimmediate hypersensitivity reactions occurred slightly more frequently in patients receiving mirikizumab than those receiving placebo or ustekinumab. CDEC heard from the clinical experts that the safety profile of mirikizumab in the VIVID-1 trial appeared generally consistent with other anti–interleukin-23 (anti-IL-23) therapies used to treat CD, with no new safety concerns identified.
- **Indirect treatment comparison:** CDEC considered 1 sponsor-submitted NMA assessing mirikizumab relative to the following currently available therapies: adalimumab, infliximab, risankizumab, upadacitinib, ustekinumab, and vedolizumab. CDEC noted several limitations with the submitted comparative analysis, notably the limited number of included studies, risk of bias, clinical and methodological heterogeneity, and imprecision. CDEC concluded that the comparative evidence was insufficient to draw definitive conclusions on the relative efficacy (i.e., enhanced clinical response, clinical remission, endoscopic response, and endoscopic remission) and safety (i.e., all-cause discontinuations and SAEs) of mirikizumab versus comparator treatments.
- **Long-term extension study:** CDEC considered the data from the noncomparative long-term extension study of the VIVID-1 trial (VIVID-2), which suggested sustained benefits of mirikizumab up to 104 weeks, and a safety profile of mirikizumab that was consistent with the randomized

controlled period of the VIVID-1 trial. However, interpretation of the long-term results was limited by missing data, the open-label design, and the descriptive nature of the analyses. Therefore, this was considered supportive evidence by CDEC.

- **Administration method:** CDEC discussed the administration method and dosage schedule of mirikizumab and relevant comparators. According to the clinical experts, risankizumab and upadacitinib are currently used more commonly than ustekinumab in the indicated patient population. CDEC noted that, compared with risankizumab, the administration of mirikizumab requires longer infusion times (at least 90 minutes versus at least 60 minutes) during induction treatment and more frequent injections during maintenance (2 consecutive injections every 4 weeks versus 1 injection every 8 weeks). CDEC heard from the clinical experts that a more frequent injection schedule may reduce tolerability related to administration (e.g., injection site reaction) and negatively impact treatment adherence. Upadacitinib is administered as a once daily oral tablet. According to the clinical experts, the choice between therapies is guided by multiple factors, such as availability, route and frequency of administration, patient preference, disease characteristics, and contraindications. CDEC concluded there was no evidence assessing the effect of the route of administration and/or the length of intervals between doses on patients' HRQoL.

Background

CD is an idiopathic form of inflammatory bowel disease (IBD) characterized by chronic, relapsing, and remitting transmural inflammation that is usually segmental and asymmetric. Signs and symptoms associated with CD vary from patient to patient, but the hallmark symptoms include abdominal pain, persistent diarrhea, and fatigue. Individuals also experience rectal bleeding, fever, bowel urgency, a sensation of incomplete bowel evacuation, constipation, loss of appetite, weight loss, anemia, and low energy. Repeated cycles of intestinal inflammation persist even in periods of quiescence and may lead to the development of strictures and complications of penetrating disease (e.g., fistulas and abscess formation) that frequently require surgery. The chronic and progressive nature of the disease can have a debilitating effect on an individual's social, educational, professional, and family activities. In 2023, the prevalence of CD was estimated to be 410 per 100,000 individuals in Canada and the incidence of CD was estimated to be 12.2 per 100,000 individuals.

Currently, there are no curative treatments for CD. Treatment management of CD consists of an induction and a maintenance phase to achieve and maintain control of symptoms arising from the overly active intestinal immune system. Treatment goals have evolved toward achieving endoscopic and mucosal healing. The treatment of CD is individualized based on disease location, extent, phenotype, and severity. Major categories of pharmacotherapies used to treat CD include conventional therapies (corticosteroids, 5-aminosalicylic acid, and immunomodulators), biologic therapies (tumour necrosis factor [TNF]-alpha antagonists, integrin inhibitors, IL-12 and IL-23 inhibitors), and oral small molecule drugs (upadacitinib). Although typically used as first-line treatment for mild to moderate CD, these conventional therapies are not recommended in CD treatment guidelines due to their limited efficacy. The clinical experts consulted by

CDA-AMC noted that biologic therapies are increasingly used as first, second, or later lines of therapy for moderately to severely active CD. The small molecule therapy (upadacitinib) was the first oral therapy to be approved for the treatment of CD in patients who have had an inadequate response to, a loss of response to, or intolerance to conventional therapies or biologics.

Despite advancements in treatments for CD, the clinical experts consulted by CDA-AMC noted several unmet needs, such as failure to achieve or sustain clinical response and remission, as well as primary nonresponse or secondary loss of response. They also noted that treatment decisions and adherence are often affected by long-term safety concerns and tolerability issues related to administration. Other unmet needs that were highlighted by the clinical experts were the inadequacy of existing treatments for CD in addressing symptoms and a paucity of evidence for treatments for CD among certain populations (e.g., patients who are pregnant, pediatric patients, older adults, and patients with postoperative recurrence).

Mirikizumab has been approved by Health Canada for the treatment of adult patients with moderately to severely active CD who have had an inadequate response, a loss of response, or intolerance to either conventional therapy or a biologic treatment. Mirikizumab is an IL-23 inhibitor. It is available as 300 mg per 15 mL solution for infusion after dilution in a vial for IV infusion or as 100 mg per 1 mL solution or 200 mg per 2 mL solution in a prefilled pen or syringe for subcutaneous injection. The recommended induction dosing regimen in the product monograph is 900 mg infused intravenously for at least 90 minutes at week 0, week 4, and week 8. The recommended maintenance dosing regimen is 300 mg (given as 2 consecutive subcutaneous injections of 100 mg and 200 mg in any order) every 4 weeks starting at week 12 upon completion of induction dosing.

Sources of Information Used by the Committee

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

- a review of 1 phase III, multicentre, double-blind, placebo- and active-controlled, treat-through trial in patients with moderately to severely active CD; 1 long-term extension study; and 1 indirect treatment comparison
- patients' perspectives gathered by 3 patient groups, the Canadian Digestive Health Foundation (CDHF), Crohn's and Colitis Canada, and the GI Society
- input from public drug plans that participate in the reimbursement review process
- input from 2 clinical specialists with expertise in diagnosing and treating patients with CD
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Perspectives of Patients, Clinicians, and Drug Programs

Patient Input

Three patient groups, CDHF, Crohn's and Colitis Canada, and the GI Society, provided their input for this submission.

CDHF's mission is to "reduce suffering and improve quality of life by providing trusted, accessible, and accurate information about digestive health and disease" and empower individuals to manage their digestive health with confidence and optimism. Information was gathered from CDHF's experience with patients living with IBD, through feedback on surveys, and social media campaigns.

The GI Society is committed to improving the lives of people with GI and liver conditions, supporting research, advocating for appropriate patient access to health care, and promoting GI and liver health. Information for this submission was gathered primarily through interviews, including a round table with gastroenterologists, patients, and patient groups, and phone or email or social media interactions with patients living with IBD. Several surveys were conducted between 2015 and 2024, and information was collected regarding the unmet needs of individuals living with IBD, opinions on biologics and biosimilars, and patient journeys.

Crohn's and Colitis Canada is a national, volunteer-based health charity focused on finding cures for CD and ulcerative colitis, and is aimed at improving lives of children and adults affected by these diseases. Information for this submission was drawn from Crohn's and Colitis Canada's 2023 report on understanding the impact of IBD in Canada. An online survey was conducted in 2022 to better understand the unmet needs and priority concerns. The survey included responses from 1,706 participants living in Canada, from patients with CD and ulcerative colitis, caregivers, including patients with moderately to severely active CD (N = 687). None of the patients or respondents from either of the patient groups had experience with mirikizumab.

The GI Society highlighted how CD affects a person in every aspect of life — physically, emotionally, and socially — whether at home, in school, or in the workplace. This patient advocacy group also highlighted the unique challenges faced by children and young adults because the disease can influence their sense of self and identity. Patients noted several concerns, including unpredictable flares, feelings of hopelessness, lack of improvement with current treatments, mental health issues, risk of mortality, and bowel urgency.

CDHF noted that 60% to 74% of patients with CD experience bowel urgency and that 25% to 50% of patients experience bowel urgency at least once daily. This patient group highlighted that the burden of fecal urgency on patients' lives is underestimated, with ramifications including disruption in daily activities and social interactions and emotional distress, resulting in impairment of quality of life.

The patient groups noted that the treatment of CD includes a combination of medications. These include biosimilars, corticosteroids, aminosalicylates, biologics, antibiotics, Janus kinase inhibitors, and immunomodulators. CDHF and the GI Society further noted that symptom management includes lifestyle adjustments and, in some cases, surgical interventions (i.e., bowel resection). Some benefits of these treatments include symptom control, remission maintenance, reduced dependence on corticosteroids, and availability of different drug classes that allow for a more tailored treatment plan based on the patient's needs. In the 2022 survey by Crohn's and Colitis Canada, almost all respondents (93%) agreed they took systemic steroids only if needed, with more than 81% of respondents reporting side effects from taking them. More than half of the respondents agreed that using systemic steroids was a burden for managing their IBD. CDHF underscored ongoing challenges with current treatments, including side effects, limited access

due to high costs, insurance gaps, and logistical barriers. This patient advocacy group also emphasized the significant psychosocial impact and diminished quality of life that many patients continue to face.

The GI Society noted that patients with IBD often have difficulty reaching remission or adequate symptom relief. Their 2020 survey indicated that 33% of the respondents (N = 579) did not believe that their IBD was well-controlled by their current medications. In the 2024 survey, 29% of respondents (N = 651) believed that their IBD was not well-controlled, 38% found it well-controlled, and 33% were unsure. At least 82% of respondents were at least somewhat concerned about running out of treatment options. In 1 survey, 63% of respondents reported symptom reduction on biologics and 23% reported confirmed remission.

The GI Society and CDHF patient groups highlighted that each person living with IBD had a different experience, and a treatment that worked for 1 person may not be tolerated by another.

CDHF noted important outcomes are providing treatment options to improve and control burdening symptoms and reducing the feeling of bowel urgency. In addition, the GI Society noted the following important treatment outcomes: access to medications that work, improved quality of life, sustained remission, and/or treatment response over relieving any 1 symptom. Furthermore, Crohn's and Colitis Canada noted that understanding long-term risks of IBD medications and minimizing use of steroids were considered important. They also noted that respondents preferred the treatment as pills (63%), self-injections at home (40%), or IV infusion (31%).

Clinician Input

Input From Clinical Experts Consulted for This Review

Both clinical experts consulted by CDA-AMC indicated that there are no curative treatments available for CD. Despite advancements in treatments for CD, the clinical experts consulted by CDA-AMC noted several unmet needs related to current treatments for CD, such as failure to achieve or sustain clinical response and remission, primary nonresponse or secondary loss of response, long-term safety concerns and tolerability issues related to administration, inadequacy of existing treatments for CD in addressing symptoms, and a paucity of evidence for treatments for CD among certain populations (e.g., patients who are pregnant, pediatric patients, older adults, and patients with postoperative recurrence).

The clinical experts consulted by CDA-AMC noted that mirikizumab would be most suitable for patients who have not had prior treatment with a biologic; it is less challenging to treat these patients than patients with longer disease duration, prior biologic failure(s), or with other challenging disease characteristics, such as perianal disease activity. However, the clinical experts indicated that they did not expect the introduction of mirikizumab to shift the treatment paradigm for moderately to severely active CD in clinical practice in Canada, considering the other available treatment options. The clinical experts agreed that although mirikizumab may represent an additional treatment option for CD, they indicated that it would not be used in a similar manner or before other available therapies for CD (e.g., anti-TNF drugs, vedolizumab, ustekinumab, risankizumab, and upadacitinib). They noted that mirikizumab has the same mechanism of action as other anti-IL-23 drugs for CD, such as risankizumab, which would be the preferred first-line option by clinicians. The clinical experts consulted by CDA-AMC indicated that response to mirikizumab in clinical practice would

be determined by improvement in symptoms, elimination of corticosteroid dependence, normalization of biomarker levels, and improvement in endoscopic outcomes. The clinical experts consulted by CDA-AMC agreed that patients should discontinue treatment with mirikizumab if they do not experience clinical and/or biochemical response by week 12 after the induction treatment period. Although the clinical experts consulted by CDA-AMC agreed that a patient who exhibits any clinical benefit, such as partial clinical response (significant improvement in symptoms and/or C-reactive protein and fecal calprotectin levels), during the induction period may benefit from an additional 12 weeks of mirikizumab treatment. However, if patients do not experience improvement by week 24, mirikizumab should be discontinued. They also agreed that treatment with mirikizumab should be discontinued for patients who exhibit continued dependence on corticosteroids or upon the occurrence of intolerable side effects. The experts noted that treatment with mirikizumab should be discontinued among patients who do not experience clinical or biomarker remission by 24 weeks or who experience disease progression indicated by a need for surgery or hospitalization. The clinical experts consulted by CDA-AMC indicated that treatment with mirikizumab should be prescribed and monitored by a specialist who is trained in the diagnosis and management of CD and/or IBD, which may include gastroenterologists, internal medicine specialists with a special interest in IBD, or general or colorectal surgeons. The clinical experts consulted by CDA-AMC agreed that mirikizumab should be administered in settings with infrastructure and experience in infusion of biologic therapies, which may include hospitals, specialty clinics, infusion centres, community clinics, and outpatient clinics.

Clinician Group Input

No clinician groups provided input for this submission.

Drug Program Input

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

Table 2: Responses to Questions From the Drug Programs

Drug program implementation questions	Clinical expert response
Relevant comparators	
The pivotal trial (VIVID-1) compared mirikizumab with placebo and ustekinumab. Mirikizumab was found to be noninferior to ustekinumab for clinical remission at week 52. Ustekinumab for CD is funded in most (but not all) jurisdictions Risankizumab is a more relevant comparator. It received a positive CDEC recommendation and is funded in most (but not all) jurisdictions.	Comment from the drug programs to inform CDEC deliberations.
Considerations for initiation of therapy	
There is variability in the criteria for advanced therapies for CD between jurisdictions (i.e., definitions of moderately to severely active CD, conventional therapy, and definitions of inadequate response, loss of response, intolerance to therapy, and so on).	Comment from the drug programs to inform CDEC deliberations.

Drug program implementation questions	Clinical expert response
Alignment with initiation criteria for advanced therapies for CD should be considered, as appropriate (i.e., “Eligibility should be based on the criteria used by each of the public drug plans for other biologic [or advanced] therapies for the treatment of adult patients with moderately to severely active CD...”).	Comment from the drug programs to inform CDEC deliberations.
Considerations for continuation or renewal of therapy	
The VIVID-1 trial measured clinical response at week 12; however, the product monograph notes that consideration should be given to discontinuing treatment in patients who have shown no evidence of therapeutic benefit by week 24. What would be an appropriate time frame for assessment of response to treatment?	The clinical experts consulted by CDA-AMC agreed that a patient who exhibits any clinical benefit at week 12 (e.g., partial clinical response [significant improvement in symptoms and/or C-reactive protein or fecal calprotectin levels) may benefit from an additional 12 weeks of mirikizumab treatment. However, the experts agreed that treatment should be discontinued if the patient does not experience improvement by week 24. In the VIVID-1 trial, patients in the mirikizumab group were not required to have a clinical response at the end of the induction period at week 12 to proceed into the maintenance period. CDEC acknowledged input from the clinical experts and ultimately considered it appropriate to align the discontinuation criteria for mirikizumab with the criteria of other advanced therapies used by the public drug plans for the treatment of adults with moderately to severely active CD.
Alignment with renewal criteria for advanced therapies for CD should be considered, as appropriate.	Comment from the drug programs to inform CDEC deliberations.
Considerations for prescribing of therapy	
The recommended induction dosing is 900 mg IV at week 0, week 4, and week 8. The recommended maintenance dosing is 300 mg subcutaneously (given as 2 consecutive injections of 100 mg and 200 mg) every 4 weeks starting at week 12 upon completion of induction dosing. Is there a potential for dose escalation with mirikizumab?	One clinical expert consulted by CDA-AMC indicated that some patients with CD may benefit from dose escalation of treatment. However, both experts consulted by CDA-AMC agree that there is a lack of data to support dose escalation of mirikizumab for the treatment of CD. CDEC agreed that there was insufficient evidence to make a recommendation on dose escalation with mirikizumab.
Is there any evidence to support the use of mirikizumab in combination with other advanced therapies for CD?	The clinical experts consulted by CDA-AMC agreed there is a lack of data to support the use of mirikizumab in combination with other advanced therapies for CD. However, 1 expert noted that anti-IL-23 drugs would potentially be ideal to combine with other therapies due to their excellent safety profile. CDEC agreed there was insufficient evidence to make a recommendation on the use of mirikizumab in combination with other advanced therapies for CD.
Alignment with prescribing criteria for advanced therapies for CD should be considered, as appropriate.	Comment from the drug programs to inform CDEC deliberations.
Care provision issues	
Mirikizumab requires IV induction (for 3 doses), administered by a health care professional in a hospital or infusion clinic setting.	Comment from the drug programs to inform CDEC deliberations.

Drug program implementation questions	Clinical expert response
System and economic issues	
The sponsor's budget impact analysis indicates that the incremental budget impact for funding mirikizumab will be $5.7 million in year 1, $15.1 million in year 2, and $17.7 million in year 3, for a 3-year incremental budget impact of $38.6 million.	Comment from the drug programs to inform CDEC deliberations.
Ustekinumab (biosimilars) and risankizumab also have confidential negotiated prices.	Comment from the drug programs to inform CDEC deliberations.

CD = Crohn disease; CDEC = Canadian Drug Expert Committee; IL-23 = interleukin-23.

Clinical Evidence

Systematic Review

Description of Studies

One pivotal phase III, multicentre, randomized, double-blind, placebo- and active-controlled, treat-through trial (VIVID-1) evaluated the efficacy and safety of mirikizumab (n = 579) compared with placebo (n = 199) and ustekinumab (n = 287) in patients with moderately to severely active CD. Moderately to severely active CD was defined as an unweighted daily average stool frequency score of 4 or higher (i.e., loose and watery stools defined as Bristol Stool Scale category 6 or 7) and/or an unweighted daily average abdominal pain score (range, 0 [none] to 3 [severe]) of 2 (i.e., moderate) or higher at baseline. Also required was a Simple Endoscopic Score for Crohn's Disease (SES-CD) score (range, 0 to 56, with higher scores indicating more severe disease) of 7 or higher in patients with ileal-colonic disease or of 4 or higher in patients with isolated ileal disease measured within 21 days before randomization. Patients also had to have experienced a previous inadequate response to, loss of response to, or intolerance to at least 1 of corticosteroids, immunomodulators, or approved biologic therapy for CD. Randomization was stratified by failure of biologic therapies, baseline corticosteroid use, baseline SES-CD total score, geographical region, and a combined stratification factor using either a baseline stool frequency score of 7 or more and/or a baseline abdominal pain score of 2.5 or more.

The coprimary objectives of the VIVID-1 trial were to evaluate the superiority of efficacy of mirikizumab compared to placebo as assessed by the following 2 composites: clinical response measured by patient-reported outcome (PRO) (which pertains to 2 of the patient-reported items of the Crohn's Disease Activity Index [CDAI], at least a 30% decrease in stool frequency and/or abdominal pain with neither score worse than baseline) (PRO clinical response) at week 12 plus endoscopic response at week 52 (defined as a 50% or greater reduction from baseline in SES-CD total score) (SES-CD endoscopic response) and PRO clinical response at week 12 plus clinical remission measured by CDAI score (CDAI clinical remission) at week 52. The major secondary objectives of the VIVID-1 trial that assessed the efficacy of mirikizumab compared with placebo and were of interest to the review included the following single end points: endoscopic response assessed at week 12 and assessed at week 52, CDAI clinical remission at week 12 and week 52, endoscopic remission measured by SES-CD (SES-CD endoscopic remission) at week 12, PRO clinical

response at week 12, change in Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) score from baseline to week 12. The major secondary objectives also included 3 composite end points: PRO clinical response at week 12 plus PRO clinical remission at week 52, PRO clinical response at week 12 plus endoscopic remission at week 52, and PRO clinical response at week 12 plus corticosteroid-free remission (from week 40 to week 52) and CDAI clinical remission at week 52. The major secondary end points comparing the efficacy of mirikizumab to ustekinumab were the 2 single end points of CDAI clinical remission at week 52 as a noninferiority end point and SES-CD endoscopic response at week 52 for superiority. Efficacy outcomes were analyzed in the primary analysis set (PAS).

Baseline characteristics were well-balanced between the treatment groups. The mean ages of patients receiving mirikizumab, placebo, and ustekinumab were 36.0 years (standard deviation [SD] = 13.22 years), 36.3 years (SD = 12.71 years), and 36.6 years (SD = 12.72 years), respectively. Most of the study patients were male (55.1%; female = 44.9%) and white (71.7%). Of patients in the PAS population, 0.6% were American Indian or Alaska Native, 25.1% were Asian, 2.2% were Black, and 0.4% identified as having multiple races [categories as reported in study]. Most patients were from Europe and regions outside of Asia and the Americas (55.5%). The treatment arms were well-balanced in terms of the site of disease location, with most patients reporting that both ileum and colon were the most affected (49.8%). Moreover, patients across the 3 treatment groups had similar mean SES-CD scores (mirikizumab: mean = 13.5 points; placebo: mean = 13.1 points; ustekinumab: mean = 13.9 points), abdominal pain (for all treatment groups: mean = 2.1 points), and stool frequency scores (mirikizumab and ustekinumab: mean = 5.7; placebo: mean = 5.8). Corticosteroid use at baseline was similar across the 3 treatment groups. However, a lower proportion of patients in the mirikizumab group reported use of immunomodulators at baseline (25.2%) compared to the placebo (29.1%) and ustekinumab (30.3%) groups. Moreover, a lower proportion of patients in the placebo group reported use of oral aminosalicylates at baseline [redacted] compared to the mirikizumab [redacted] and ustekinumab [redacted] groups.

Efficacy Results

At the time of the data cut-off (date of data cut-off: August 23, 2023), the predefined success criteria for superiority based on all coprimary and major secondary end points comparing mirikizumab and placebo were met. The predefined success criteria for noninferiority based on CDAI clinical remission at week 52 for mirikizumab compared with ustekinumab was met. However, the criteria for superiority based on SES-CD endoscopic response at week 52 for mirikizumab compared with ustekinumab was not met.

PRO Clinical Response at Week 12 and SES-CD Endoscopic Response at Week 52

The proportion of patients who experienced both PRO clinical response at week 12 and SES-CD endoscopic response at week 52 favoured the mirikizumab group (38.0%) compared with the placebo group (9.0%; common risk difference = 28.7%; 99.5% CI, 20.6% to 36.8%; P value < 0.000001). Results from the planned sensitivity and subgroup analyses of PRO clinical response at week 12 plus SES-CD endoscopic response at week 52 showed that point estimates favoured mirikizumab, which was consistent with the results of the primary analysis.

The proportion of patients who experienced both PRO clinical response at week 12 and SES-CD endoscopic response by at week 52 was 38.0% in the mirikizumab group and 37.3% in the ustekinumab group (common risk difference = 0.9%; 99.5% CI, −8.9% to 10.7%; P value = 0.795057).

PRO Clinical Response at Week 12 and CDAI Clinical Remission at Week 52

The proportion of patients who experienced both PRO clinical response at week 12 and CDAI clinical remission at week 52 favoured the mirikizumab group (45.4%) compared with the placebo group (19.6%) (common risk difference = 25.8%; 99.5% CI, 15.9% to 35.6%; P value < 0.000001). Results from the planned sensitivity and subgroup analyses of PRO clinical response at week 12 plus CDAI clinical remission at week 52 showed that point estimates favoured mirikizumab, which was consistent with the results of the primary analysis.

The proportion of patients who experienced both PRO clinical response at week 12 and CDAI clinical remission at week 52 was 45.4% in the mirikizumab group and 40.8% the ustekinumab group (common risk difference = 4.6%; 99.5% CI, −5.4% to 14.7%; P value = 0.193027).

PRO Clinical Response at Week 12 and Week 52

The proportion of patients who experienced PRO clinical response at week 12 favoured the mirikizumab group (70.6%) compared with the placebo group (51.8%) (common risk difference = 18.9%; 99.5% CI, 7.5% to 30.3%; P value = 0.000001). At week 52, the proportion of patients who experienced PRO clinical response continued to favour the mirikizumab group [redacted] compared with the placebo group [redacted] (common risk difference = [redacted] [redacted]CI, [redacted]; P value = [redacted]).

The proportion of patients who experienced PRO clinical response at week 12 was 70.6% in the mirikizumab group and [redacted] in the ustekinumab group (common risk difference = [redacted]; P value = [redacted]). At week 52, the proportion of patients who achieved PRO clinical response was [redacted] the mirikizumab group compared with [redacted] in the ustekinumab group (common risk difference = [redacted] [redacted] CI, [redacted]; P value [redacted]).

CDAI Clinical Remission at Week 12 and Week 52

At week 12, the proportion of patients who experienced CDAI clinical remission favoured the mirikizumab group (37.7%) compared with the placebo group (25.1%) (common risk difference = 12.4%; 99.5% CI, 2.2% to 22.7%; P value = 0.001431). At week 52, the proportion of patients who achieved CDAI clinical remission continued to favour the mirikizumab group (54.1%) compared with the placebo group (19.6%) (common risk difference = 34.6%; 99.5% CI, 24.7% to 44.4%; P value < 0.000001).

At week 12, the proportion of patients who experienced CDAI clinical remission was 37.7% in the mirikizumab and [redacted] in the ustekinumab group (common risk difference = [redacted]; [redacted]CI, [redacted]; P value = [redacted]).

CDAI clinical remission was assessed for noninferiority of mirikizumab compared with ustekinumab at week 52. At week 52, 54.1% of patients who received mirikizumab experienced CDAI clinical remission compared with 48.4% of patients who received ustekinumab. At week 52, mirikizumab was noninferior to ustekinumab

(common risk difference = 5.7%; 95% CI, −1.4% to 12.8%; P value for noninferiority < 0.0001, superiority = 0.113117).

Corticosteroid-Free CDAI Clinical Remission at Week 52

At week 52, the proportion of patients who experienced corticosteroid-free CDAI clinical remission was 51.8% in the mirikizumab group compared with 18.6% in the placebo group (common risk difference for mirikizumab versus placebo = 33.3%; 99.5% CI, 23.5% to 43.0%; P value < 0.000001) and 45.6% in the ustekinumab group (common risk difference for mirikizumab versus ustekinumab = 6.3%; 99.5% CI, −3.8% to 16.4%; P value = 0.082319).

SES-CD Endoscopic Response at Week 12 and Week 52

At week 12, the proportion of patients who experienced SES-CD endoscopic response was 32.5% in the mirikizumab group compared with the 12.6% in the placebo group (common risk difference = 19.7%; 99.5% CI, 11.1% to 28.2%; P value < 0.000001) and [redacted] in the ustekinumab group (common risk difference = [redacted]; [redacted]CI, [redacted]; P value = [redacted]).

At week 52, the proportion of patients who experienced SES-CD endoscopic response continued to favour the mirikizumab group (48.4%) compared with the placebo group (9.0%) (common risk difference = 39.1%; 99.5% CI, 31.0% to 47.2%; P value < 0.000001).

At week 52, the proportion of patients who experienced SES-CD endoscopic response was 48.4% in the mirikizumab group compared with 46.3% in the ustekinumab group (common risk difference = 2.3%; 95% CI, −4.7% to 9.3%; P value = 0.513623).

SES-CD Endoscopic Remission at Week 12 and Week 52

At week 12, the proportion of patients who experienced SES-CD endoscopic remission favoured the mirikizumab group (10.9%) compared with the placebo group (4.0%) (common risk difference = 6.8%; 99.5% CI, 1.6% to 12.1%; P value = 0.003414). At week 52, the proportion of patients who experienced SES-CD endoscopic remission continued to favour the mirikizumab group (19.0%) compared to the placebo group [redacted] (common risk difference = [redacted]; [redacted]CI, [redacted]; P value |[redacted]).

At week 12, the proportion of patients who experienced SES-CD endoscopic remission was 10.9% in the mirikizumab group and [redacted] in the ustekinumab group (common risk difference = [redacted]; [redacted] CI, [redacted] [redacted]; P value = [redacted]). At week 52, the proportion of patients who experienced SES-CD endoscopic remission was 19.0% in the mirikizumab group and 18.1% in the ustekinumab group (common risk difference = 0.9%; 99.5% CI, −6.9% to 8.7%; P value = 0.745430).

PRO Clinical Response at Week 12 and SES-CD Endoscopic Remission at Week 52

The proportion of patients who experienced both PRO clinical response at week 12 and SES-CD endoscopic remission at week 52 was 15.9% in the mirikizumab group compared with 2.0% in the placebo group (common risk difference = 13.8%; 99.5% CI, 8.7% to 18.9%; P value < 0.000001) and [redacted] in the ustekinumab group (common risk difference = [redacted] CI, [redacted]; P value = [redacted]).

PRO Clinical Response at Week 12 and Corticosteroid-Free CDAI Clinical Remission From Week 40 to Week 52

The proportion of patients who experienced PRO clinical response at week 12, remained corticosteroid-free from week 40 to week 52, and experienced CDAI clinical remission at week 52 was 43.7% in the mirikizumab group compared with 18.6% in the placebo group (common risk difference = 33.3%; 99.5% CI, 23.5% to 43.0%; P value < 0.000001) and [redacted] in the ustekinumab group (common risk difference = [redacted]; 99.5% CI,[redacted]; P value = [redacted]).

Change From Baseline in IBDQ Score at Week 12 and Week 52

At week 12, patients in the mirikizumab treatment group had a larger improvement in IBDQ score from baseline (least squares [LS] mean change from baseline = 36.89 points; standard error [SE] = 1.245 points) compared to patients in the placebo group (LS mean change from baseline = 17.39 points; SE = 2.113 points; LS mean difference for mirikizumab compared with placebo = 19.50 points; 95% CI, 14.71 to 24.29 points; P value < 0.000001). At week 52, patients in the mirikizumab treatment group continued to have a larger improvement in IBDQ score from baseline (LS mean = 43.82 points; SE = 1.365 points) compared to patients in the placebo group (LS mean = 15.90 points; SE = 2.316 points; LS mean difference for mirikizumab compared with placebo = 27.92 points; 95% CI, 22.67 to 33.18; P value < 0.000001).

At week 12, improvements in IBDQ score from baseline were observed for the mirikizumab group (LS mean change from baseline = 36.89 points; SE = 1.245 points) and the ustekinumab group (LS mean change from baseline = [redacted]; SE = [redacted]; LS mean difference for mirikizumab compared with ustekinumab = −0.32 points; 95% CI, −4.52 to 3.88 points; P value = 0.880867). At week 52, improvements from baseline were observed for the mirikizumab group (LS mean = 43.82 points; SE = 1.365 points) and the ustekinumab group (LS mean = [redacted]; SE = [redacted]; LS mean difference for mirikizumab compared with ustekinumab[redacted]; 95% CI, [redacted]; P value = [redacted]).

Harms Results

During the overall treatment period, 78.6% of patients who received mirikizumab reported at least 1 TEAE, whereas 73.0% of patients who received placebo and 77.3% of patients who received ustekinumab reported at least 1 TEAE. At least 1 SAE was reported by 10.3% of patients who received mirikizumab, 17.1% of patients who received placebo, and 10.7% of patients who received ustekinumab. During the overall treatment period, 5.1% of patients who received mirikizumab withdrew from treatment due to AEs, whereas 9.5% of patients who received placebo and 2.6% of patients who received ustekinumab reported withdrawals due to AEs. During the overall treatment period, 2 deaths were reported: o 1 patient received placebo and 1 patient received ustekinumab.

According to the product monograph for mirikizumab and the clinical experts consulted by CDA-AMC, the notable harms defined for this review included infections, infusion and injection site reactions, hepatic events, depression, suicide ideation, immediate and nonimmediate hypersensitivity reactions, cerebrocardiovascular events, and malignancies. During the overall treatment regimen period, the rate of infections was similar between the mirikizumab (41.4%) and ustekinumab (42.1%) groups, but lower for the placebo group (34.6%). The following notable harms were observed: injection site reactions (10.8%

for the mirikizumab group,6.5% for the placebo group, and 5.8% for the ustekinumab group), hepatic events (6.2% for the mirikizumab group,4.3% for the placebo group, and 2.6% for the ustekinumab group), immediate hypersensitivity reactions (3.8% for the mirikizumab group, 2.4% for the placebo group, and 2.3% for the ustekinumab group), and nonimmediate hypersensitivity reactions (7.9% for the mirikizumab group, 5.2% for the placebo group, and 5.8% for the ustekinumab group). Suicide ideation was reported by 2 patients receiving mirikizumab and no patients in the placebo or ustekinumab groups. Rates of depression, cerebrocardiovascular events, and malignancies remained low (2% or less) and similar across the 3 treatment groups.

Critical Appraisal

Notable strengths of the VIVID-1 trial included its blinding of treatment allocation to patients, study investigators, and study site personnel, as well as the use of a double-dummy design to maintain blinding of treatment throughout the study. The VIVID-1 trial was designed as a treat-through study, in which patients remained on their assigned treatment beyond the initial induction phase without rerandomization. Moreover, there were no concerns with the randomization process, and the clinical experts consulted by CDA-AMC agreed that stratification factors used for randomization were appropriate. The baseline characteristics were generally well-balanced across the 3 treatment groups, supporting the success of the randomization procedure. Although minor differences in certain characteristics were noted among the 3 treatment groups, the clinical experts consulted by CDA-AMC agreed that they would have little effect on the interpretation of results. Clinical remission based on CDAI score at week 52 was assessed for noninferiority between the mirikizumab and ustekinumab groups according to a 10% noninferiority margin, which was selected based on statistical and clinical considerations according to global regulatory guidance. The clinical experts consulted by CDA-AMC agreed that the use of a margin of 10% was considered adequate for performing a noninferiority analysis for a clinical trial in CD. The use of PAS population for the primary analyses deviates from the preferred approach of using the intention-to-treat (ITT) population for efficacy analyses. However, given the consistency of results across the PAS and modified ITT populations and minor differences in the sample sizes of the ITT and modified ITT population, the use of the PAS population was unlikely to introduce bias in the results. In the VIVID-1 trial, higher discontinuation rates in the placebo group were attributed to AEs, lack of efficacy, and patient withdrawal. To address intercurrent events that may lead to missing end point data for the coprimary and binary end points, the VIVID-1 trial implemented a composite strategy, whereby intercurrent events defined for the study included discontinuation of study treatment before the time point of interest.

The strategy to handle intercurrent events in the VIVID-1 trial was deemed appropriate by the CDA-AMC team because the use of nonresponse imputation to handle missing data in primary analyses is generally considered acceptable by regulatory agencies. Similarly, the analysis for LS mean change in IBDQ scores from baseline to week 52 imputed missing data using the modified baseline observation carried forward approach, which was deemed appropriate by the CDA-AMC team. Of note, there remains potential for bias in the results if the reasons for study discontinuation are not clearly related to lack of efficacy. Although most study discontinuations were attributed to lack of efficacy and AEs, there was a higher rate of study discontinuation due to withdrawal among patients in the placebo group compared with those in the

mirikizumab and ustekinumab groups. Although this imbalance may bias results in favour of mirikizumab, the review team deemed that the potential for bias is small. After accounting for intercurrent events, the rates of sporadically missing data due to reasons unrelated to intercurrent events were low (i.e., less than 5%) for the coprimary end points, most major secondary end points, and LS mean change in IBDQ. Sporadically missing data due to reasons unrelated to intercurrent events were imputed based on nonresponse imputation. Although this approach relies on assumptions about the missing data that cannot be verified, the CDA-AMC review team considered it appropriate for most end points because the proportions of missing data were small. However, higher rates of missing data were noted for endoscopic response and remission by SES-CD at week 12 ([redacted] for mirikizumab, [redacted] for placebo, and [redacted] for ustekinumab), which may increase the risk of bias when interpreting the results for those outcomes. However, the direction and magnitude of this risk is unknown. Results of sensitivity analyses performed for the coprimary end points, including a tipping-point analysis and modified nonresponse imputation, were consistent with those of the primary analysis.

The clinical experts consulted by CDA-AMC indicated that the coprimary and major secondary outcomes measured in the VIVID-1 trial were relevant to clinical practice. These outcomes were included in a multiplicity-adjusted testing scheme. Patients who received placebo and were considered to not have had a response at week 12 went on to receive treatment with mirikizumab until the end of the study; the CDA-AMC review team determined that the treatment switch for this group of patients to mirikizumab at week 12 was not expected to significantly affect interpretation of the results. The VIVID-1 trial measured several PROs, which included clinical remission according to CDAI criteria, clinical response based on PROs, and the IBDQ. Data for these outcomes were collected from patient- and physician-reported questionnaires, which may be subject to performance bias if blinding was compromised for patients or physicians. However, the double-blind study design mitigated the potential for bias to be introduced in the results. Subgroup analyses for coprimary and major secondary end points for prior therapy, baseline medication, and baseline demographic and disease characteristics showed results overall consistent with those for the primary analyses, although they were not adjusted for multiplicity and should be interpreted as supportive evidence.

The use of an induction and maintenance treatment phase in the VIVID-1 trial was aligned with phases of treatment for CD administered in clinical practice. The clinical experts consulted by CDA-AMC agreed that the 12-week induction period used in the trial is comparable to other trials for CD and reflects the expected time frame for observing a clinical response after treatment with mirikizumab in clinical practice. The VIVID-1 trial did not include rescue therapy for patients who were assigned to receive either mirikizumab or ustekinumab, whereas patients who were considered to not have had a response to placebo at 12 weeks received treatment with mirikizumab for the remainder of the study. One clinical expert indicated that rescue therapy for CD-related flares could include either a short course of corticosteroid tapering or a dose escalation of existing biologic therapy. The clinical experts consulted by CDA-AMC did not cite major concerns with these differences in terms of generalizability of trial results to Canadian clinical practice.

The clinical experts consulted by CDA-AMC agreed that the eligibility criteria of the VIVID-1 trial are aligned with those for other trials for CD therapies, although they noted that the criteria were not entirely reflective of patients encountered in clinical practice. For instance, the clinical experts agreed there are many patients in clinical practice who would be excluded from the VIVID-1 trial, such as patients who intend to become

pregnant, have an ostomy, have a high risk of infection, or have liver enzyme abnormalities. The clinical experts also indicated that patients with disease isolated to the ileum were underrepresented in the VIVID-1 trial compared to their representation in Canadian clinical practice and previous CD trials. The experts further noted that ileum-isolated disease was more difficult to treat and was expected to lead to poorer treatment outcomes (especially in terms of endoscopic response and endoscopic remission rates) compared to disease affecting other areas of the GI tract. The clinical experts consulted by CDA-AMC also agreed that the proportions of patients with prior anti-TNF therapy failure or failure of 2 or more biologic therapies were lower than what is more commonly seen in drug-exposed populations in clinical practice and previous CD trials. The clinical experts consulted by CDA-AMC also agreed that the patient population of the VIVID-1 trial appeared to have an overall lower endoscopic disease burden (as represented by mean SES-CD score of 13.1 points [SD = 6.0 points] versus mean SES-CD score of 13.9 points [SD = 6.6 points] across treatment groups in VIVID-1) compared to patient populations observed in previous CD trials and clinical practice. The baseline SES-CD scores for evidence for risankizumab ranged from a mean of 14.0 points (SD = 7.1 points) to a mean of 14.8 points (SD = 7.8 points) in the ADVANCE and MOTIVATE trials, respectively. The baseline SES-CD scores for upadacitinib ranged from a mean of 13.6 points (SD = 7.0 points) to a mean of 15.8 points (SD = 7.6 points) across the U-EXCEL, U-EXCEED, and U-ENDURE trials. Based on these factors, the clinical experts consulted by CDA-AMC suggested that patients in the VIVID-1 trial may have a more moderate severity of CD compared to patient populations with moderately to severely active CD in previous CD trials and clinical practice.

The VIVID-1 trial assessed the efficacy and safety of mirikizumab compared to placebo and ustekinumab. The latter has been used previously as an active comparator in other trials for CD. The sponsor noted that ustekinumab was the only available therapy with an IL-23 inhibition mechanism of action at the time of initiation of the VIVID-1 trial. The dose of ustekinumab administered in the trial was aligned with the dose recommended in the Health Canada product monograph. Although the clinical experts consulted by CDA-AMC agreed that ustekinumab was part of the treatment options for CD in Canada, they indicated that ustekinumab is less commonly used to treat CD compared to risankizumab, upadacitinib, and anti-TNF drugs. Because the VIVID-1 trial did not compare mirikizumab with other relevant comparators for CD, the stand-alone results of the trial may not provide a full assessment of the efficacy and safety of mirikizumab compared to existing treatments for CD in Canadian clinical practice. The VIVID-1 trial measured outcomes that were relevant to patients and clinicians. Notably, the clinical experts indicated that endoscopic response and remission were the most important outcomes related to the treatment of CD, citing that these outcomes provided the most reliable measures of disease activity and drug performance. The clinical experts consulted by CDA-AMC indicated that although QoL measures related to CD are important for patients, they are not routinely measured in clinical practice. They agreed that improvements related to QoL (e.g., fatigue and depression) would naturally result from improvements in endoscopic outcomes. The clinical experts consulted by CDA-AMC also agreed that the incidence of injection site reactions was an important safety outcome related to the administration of mirikizumab due to the frequency of injections required for treatment and its effect on overall patient experience.

GRADE Summary of Findings and Certainty of the Evidence

For the pivotal studies and randomized controlled trials identified in the sponsor's systematic review, GRADE was used to assess the certainty of the evidence for outcomes considered most relevant to inform expert committee deliberations and a final certainty rating was determined as outlined by the GRADE Working Group:

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

- Efficacy outcomes (PRO clinical response at week 12 and SES-CD endoscopic response at week 52; PRO clinical response at week 12 and CDAI clinical remission at week 52; PRO clinical response at week 12 and corticosteroid-free from week 40 to week 52 and CDAI clinical remission at week 52; PRO clinical response at week 12 and SES-CD endoscopic remission at week 52; CDAI clinical remission at week 12 and week 52; endoscopic response at week 52; and endoscopic remission at week 52)
- HRQoL (LS mean change in IBDQ total score from baseline to week 52)
- Harms (SAEs up to week 52)

Table 3: Summary of Findings for Mirikizumab vs. Placebo for Patients With Moderately to Severely Active CD

Outcome and follow-up	Patients, N (studies)	Relative effect (99.5% CI)[a]	Absolute effects (99.5% CI)[a]			Certainty	What happens
			Placebo	Mirikizumab	Difference		
Clinical response and endoscopic response							
Proportion of patients achieving PRO clinical response[b] at week 12 and SES-CD endoscopic response[c] at week 52	778 (1 RCT)		90 per 1,000	380 per 1,000 (323 per 1,000 to 437 per 1,000)	287 more per 1,000 (206 more per 1,000 to 368 more per 1,000)	High[d]	Mirikizumab results in a clinically important increase in the proportion of patients achieving PRO clinical response at week 12 and SES-CD endoscopic response at week 52 compared with placebo.
Clinical response and clinical remission							
Proportion of patients achieving PRO clinical response[b] at week 12 and CDAI clinical remission[e] at week 52	778 (1 RCT)		196 per 1,000	454 per 1,000 (396 per 1,000 to 512 per 1,000)	258 more per 1,000 (159 more per 1,000 to 356 more per 1,000)	High[d]	Mirikizumab results in a clinically important increase in the proportion of patients achieving PRO clinical response at week 12 and CDAI clinical remission at week 52 compared with placebo.
Clinical response and 12-week corticosteroid-free clinical remission							
Proportion of patients achieving PRO clinical response[b] at week 12 and corticosteroid-free from week 40 to week 52 and CDAI clinical remission[f] at week 52	778 (1 RCT)		186 per 1,000	437 per 1,000 (379 per 1,000 to 495 per 1,000)	250 more per 1,000 (152 more per 1,000 to 347 more per 1,000)	High[d]	Mirikizumab results in a clinically important increase in the proportion of patients achieving PRO clinical response at week 12 and corticosteroid-free from week 40 to week 52 and CDAI clinical remission at week 52 compared with placebo.
Clinical response and endoscopic remission							
Proportion of patients achieving PRO clinical response[b] at week 12 and SES-CD endoscopic remission[g] at week 52	778 (1 RCT)		20 per 1,000	159 per 1,000 (116 per 1,000 to 202 per 1,000)	138 more per 1,000 (87 more per 1,000 to 189 more per 1,000)	High[d]	Mirikizumab results in a clinically important increase in the proportion of patients achieving PRO clinical response at week 12 and SES-CD endoscopic remission at week 52 compared with placebo.

Outcome and follow-up	Patients, N (studies)	Relative effect (99.5% CI)[a]	Absolute effects (99.5% CI)[a]			Certainty	What happens
			Placebo	Mirikizumab	Difference		
Clinical remission							
Proportion of patients achieving CDAI clinical remission[e] Follow-up: 12 weeks	778 (1 RCT)		251 per 1,000	377 per 1,000 (320 per 1,000 to 433 per 1,000)	124 more per 1,000 (22 more per 1,000 to 227 more per 1,000)	Moderate[h]	Mirikizumab likely results in little to no clinically important difference in the proportion of patients achieving CDAI clinical remission at week 12 compared with placebo.
Endoscopic response							
Proportion of patients achieving SES-CD endoscopic response[b] Follow-up: 52 weeks	778 (1 RCT)		90 per 1,000	484 per 1,000 (425 per 1,000 to 542 per 1,000)	391 more per 1,000 (310 more per 1,000 to 472 more per 1,000)	High[i]	Mirikizumab results in a clinically important increase in the proportion of patients achieving SES-CD endoscopic response at week 52 compared with placebo.
Endoscopic remission							
Proportion of patients achieving SES-CD endoscopic remission[g] Follow-up: 52 weeks	778 (1 RCT)			190 per 1,000 (144 per 1,000 to 236 per 1,000)		High[j]	Mirikizumab results in a clinically important increase in the proportion of patients achieving SES-CD endoscopic remission at week 52 compared with placebo.
HRQoL (IBDQ)							
LS mean change from baseline to week 52 in IBDQ total score (range, 32 to 224, with higher scores indicating better HRQoL) Follow-up: 52 weeks	774 (1 RCT)		15.90	43.82 (NR)	27.92 more (95% CI, 22.67 to 33.18 more)	High[k]	Mirikizumab results in a clinically important increase in LS mean change from baseline to week 52 in IBDQ total score compared with placebo.
Harms							
Proportion of patients with SAEs Follow-up: 52 weeks	841 (1 RCT)		171 per 1,000	103 per 1,000 (NR)	63.8 less per 1,000 (95% CI, 125.2 less per 1,000 to 2.5 less per 1,000)	Low[l]	Mirikizumab may result in little to no difference in the proportion of patients with SAEs compared with placebo.

CD = Crohn disease; CDAI = Crohn's Disease Activity Index; CI = confidence interval; IBDQ = Inflammatory Bowel Disease Questionnaire; LS = least squares; NR = not reported; PRO = patient-reported outcome; RCT = randomized controlled trial; SAE = serious adverse event; SES-CD = Simple Endoscopic Score for Crohn's Disease.

Notes: Study limitations (which refer to internal validity or risk of bias), 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 level of certainty being rated down are documented in the table footnotes.

The following outcomes were not adjusted for multiplicity and should be considered supportive evidence: SES-CD endoscopic response at week 52, SES-CD endoscopic remission at week 52, and LS mean change from baseline to week 52 in IBDQ total score.

[a]Unless otherwise specified.

[b]PRO clinical response is defined as at least a 30% decrease in stool frequency and/or abdominal pain with neither score worse than baseline.

[c]Endoscopic response was defined as a ≥ 50% reduction from baseline in SES-CD total score.

[d]There is no established between-group minimal important difference (MID) for this outcome, but the clinical experts consulted by CDA-AMC considered a 7% difference between groups could be considered a threshold of clinical importance.

[e]Clinical remission is defined as a CDAI score < 150 points.

[f]Corticosteroid-free remission was defined as being corticosteroid-free from week 40 to week 52 and in CDAI clinical remission at week 52 in patients who were treated with corticosteroids at baseline.

[g]SES-CD endoscopic remission ≤ 4 was defined as SES-CD total score ≤ 4 and at ≥ 2-point reduction from baseline and no segmental subscore > 1.

[h]Rated down 1 level for serious imprecision. There is no established between-group MID for this outcome, but the clinical experts consulted by CDA-AMC considered a 15% difference between groups could be considered a threshold of clinical importance. Based on this threshold, the point estimate and lower bound of the 99.5% CI for the between-group difference suggested no clinically important difference between mirikizumab vs. placebo while the upper bound of the 99.5% CI suggested a clinically important difference between the 2 groups.

[i]There is no established between-group MID for this outcome, but the clinical experts consulted by CDA-AMC considered a 10% difference between groups in this outcome could be considered a threshold of clinical importance.

[j]There is no established between-group MID for this outcome, but the clinical experts consulted by CDA-AMC considered a 7% difference between groups in this outcome could be considered a threshold of clinical importance.

[k]A MID of 16 points for change in IBDQ total score was identified from the published literature.

[l]Rated down 2 levels for serious imprecision and serious indirectness. There is no established between-group MID for the proportion of patients with SAEs at 52 weeks, but the clinical experts consulted by CDA-AMC considered a 10% difference between groups for this outcome could be considered a threshold of clinical importance. The point estimate and upper bound of the 95% CI for the between-group difference suggested no clinically important difference between the 2 groups, while the lower bound of the 95% CI suggested a clinically important difference for mirikizumab vs. placebo based on a 10% threshold. Additionally, there was indirectness related to the inclusion of worsening of CD and other CD-related events (e.g., flares, exacerbation, aggravation) as an SAE, which complicates interpretation of the result.

Source: I6T-MC-AMAM (VIVID-1) Clinical Study Report. Details included in the table are from the sponsor's Summary of Clinical Evidence.

Table 4: Summary of Findings for Mirikizumab vs. Ustekinumab for Patients With Moderately to Severely Active CD

Outcome and follow-up	Patients, N (studies)	Relative effect (99.5% CI)[a]	Absolute effects (99.5% CI)[a]			Certainty	What happens
			Ustekinumab	Mirikizumab	Difference		
Clinical response and endoscopic response							
Proportion of patients achieving PRO clinical response[b] at week 12 and SES-CD endoscopic response[c] at week 52	866 (1 RCT)	[redacted]	373 per 1,000	380 per 1,000 (323 per 1,000 to 437 per 1,000)	9 more per 1,000 (89 less per 1,000 to 107 more per 1,000)	Low[d]	Mirikizumab may result in little to no clinically important difference in the proportion of patients achieving PRO clinical response at week 12 and SES-CD endoscopic response at week 52 compared with ustekinumab.

Outcome and follow-up	Patients, N (studies)	Relative effect (99.5% CI)[a]	Absolute effects (99.5% CI)[a]			Certainty	What happens
			Ustekinumab	Mirikizumab	Difference		
Clinical response and clinical remission							
Proportion of patients achieving PRO clinical response[b] at week 12 and CDAI clinical remission[e] at week 52	866 (1 RCT)	[redacted]	408 per 1,000	454 per 1,000 (396 per 1,000 to 512 per 1,000)	46 more per 1,000 (54 less per 1,000 to 147 more per 1,000)	Moderate[f]	Mirikizumab likely results in little to no clinically important difference in the proportion of patients achieving PRO clinical response at week 12 and CDAI clinical remission at week 52 compared with ustekinumab.
Clinical response and corticosteroid-free clinical remission							
Proportion of patients achieving PRO clinical response[b] at week 12 and corticosteroid-free from week 40 to week 52 and CDAI clinical remission[g] at week 52	866 (1 RCT)	[redacted]	[redacted]	437 per 1,000 (379 per 1,000 to 495 per 1,000)	[redacted]	Moderate[f]	Mirikizumab likely results in little to no clinically important difference in the proportion of patients achieving PRO clinical response at week 12 and corticosteroid-free from week 40 to week 52 and CDAI clinical remission at week 52 compared with ustekinumab.
Clinical response and endoscopic remission							
Proportion of patients achieving PRO clinical response[b] at week 12 and SES-CD endoscopic remission[h] at week 52	866 (1 RCT)	[redacted]	[redacted]	159 per 1,000 (116 per 1,000 to 202 per 1,000)	[redacted]	Moderate[f]	Mirikizumab likely results in little to no clinically important difference in the proportion of patients achieving PRO clinical response at week 12 and SES-CD endoscopic remission at week 52 compared with ustekinumab.
Clinical remission							
Proportion of patients achieving CDAI clinical remission[e] Follow-up: 12 weeks	866 (1 RCT)	[redacted]	[redacted]	377 per 1,000 (320 per 1,000 to 433 per 1,000)	[redacted]	High[i]	Mirikizumab results in little to no clinically important difference in the proportion of patients achieving CDAI clinical remission at week 12 compared with ustekinumab.

Outcome and follow-up	Patients, N (studies)	Relative effect (99.5% CI)[a]	Absolute effects (99.5% CI)[a]			Certainty	What happens
			Ustekinumab	Mirikizumab	Difference		
Proportion of patients achieving CDAI clinical remission[e] (noninferiority) Follow-up: 52 weeks	866 (1 RCT)	[redacted]	484 per 1,000	541 per 1,000 (95% CI, 500 per 1,000 to 581 per 1,000)	57 more per 1,000 (95% CI, 14 less per 1,000 to 128 more per 1,000)	Moderate[j]	Mirikizumab likely results in little to no clinically important difference in the proportion of patients achieving CDAI clinical remission at week 52 compared with ustekinumab.
Endoscopic response							
Proportion of patients achieving SES-CD endoscopic response[c] Follow-up: 52 weeks	866 (1 RCT)	[redacted]	463 per 1,000	484 per 1,000 (95% CI, 443 per 1,000 to 524 per 1,000)	23more per 1,000 (95% CI, 47 less per 1,000 to 93 more per 1,000)	High[k]	Mirikizumab results in little to no clinically important difference in the proportion of patients achieving SES-CD endoscopic response at week 52 compared with ustekinumab.
Endoscopic remission							
Proportion of patients achieving SES-CD endoscopic remission[h] Follow-up: 52 weeks	866 (1 RCT)	[redacted]	181 per 1,000	190 per 1,000 (144 per 1,000 to 236 per 1,000)	9 more per 1,000 (69 less per 1,000 to 87 more per 1,000)	Low[l]	Mirikizumab may result in little to no clinically important difference in the proportion of patients achieving SES-CD endoscopic remission at week 52 compared with ustekinumab.
HRQoL (IBDQ)							
LS mean change from baseline to week 52 in IBDQ total score (range, 32 to 224, with higher scores indicating better HRQoL) Follow-up: 52 weeks	863 (1 RCT)	[redacted]	[redacted]	43.82 (NR)	[redacted]	High[m]	Mirikizumab results in little to no clinically important difference in LS mean change from baseline to week 52 in IBDQ total score compared with ustekinumab.

Outcome and follow-up	Patients, N (studies)	Relative effect (99.5% CI)[a]	Absolute effects (99.5% CI)[a]			Certainty	What happens
			Ustekinumab	Mirikizumab	Difference		
Harms							
Proportion of patients with SAEs Follow-up: 52 weeks	939 (1 RCT)	[redacted]	107 per 1,000	103 per 1,000 (NR)	3.6 less per 1,000 (95% CI, 45.5 less per 1,000 to 38.2 more per 1,000)	Moderate[n]	Mirikizumab likely results in little to no clinically important difference in the proportion of patients with SAEs compared with ustekinumab.

CD = Crohn disease; CDAI = Crohn's Disease Activity Index; CI = confidence interval; HRQoL = health-related quality of life; IBDQ = Inflammatory Bowel Disease Questionnaire; LS = least squares; NR = not reported; PRO = patient-reported outcome; RCT = randomized controlled trial; SAE = serious adverse event; SES-CD = Simple Endoscopic Score for Crohn's Disease.

Notes: 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 level of certainty being rated down are documented in the table footnotes.

For mirikizumab compared with ustekinumab, only CDAI clinical remission at week 52 and endoscopic response at week 52 were included in the multiple testing procedure. The remaining outcomes were not adjusted for multiplicity and should be considered supportive evidence.

[a]Unless otherwise specified.

[b]PRO clinical response is defined as at least a 30% decrease in stool frequency and/or abdominal pain with neither score worse than baseline.

[c]Endoscopic response was defined as ≥ 50% reduction from baseline in SES-CD total score.

[d]Rated down 2 levels for very serious imprecision. There is no established between-group minimal important difference (MID) for this outcome, but the clinical experts consulted by CDA-AMC considered that a 7% difference between groups could be considered a threshold of clinical importance. Based on this threshold, the point estimate suggested no clinically important difference between mirikizumab and ustekinumab. However, the upper bound of the 99.5% CI for the between-group difference suggested a clinically important difference in favour of mirikizumab, whereas the lower bound suggested a clinically important difference in favour of ustekinumab.

[e]Clinical remission is defined as a CDAI score less than 150 points.

[f]Rated down 1 level for serious imprecision. There is no established between-group MID for this outcome, but the clinical experts consulted by CDA-AMC considered a 7% difference between groups could be considered a threshold of clinical importance. Based on this threshold, the point estimate and lower bound of the 99.5% CI for the between-group difference suggested no clinically important difference between mirikizumab vs. ustekinumab while the upper bound of the 99.5% CI suggested a clinically important difference between the 2 groups.

[g]Corticosteroid-free remission was defined as being corticosteroid-free from week 40 to week 52 and in CDAI clinical remission at week 52 in patients who were treated with corticosteroids at baseline.

[h]SES-CD endoscopic remission ≤ 4 was defined as SES-CD total score ≤ 4 and at least a 2-point reduction from baseline and no segmental subscore > 1.

[i]There is no established between-group MID for this outcome, but the clinical experts consulted by CDA-AMC considered a 15% difference between groups could be considered a threshold of clinical importance.

[j]Rated down 1 level for serious imprecision. As this outcome was assessed for noninferiority, the threshold of clinical importance was selected to align with the noninferiority margin of 10%. Based on this threshold, the point estimate and lower bound of the 95% CI of the between-group difference suggested no clinically important difference between the mirikizumab and ustekinumab groups, whereas the upper bound of the 95% CI suggested a clinically important difference between the 2 groups.

[k]There is no established between-group MID for this outcome, but the clinical experts consulted by CDA-AMC considered a 10% difference between groups could be considered a threshold of clinical importance.

[l]Rated down 2 levels for very serious imprecision.

[l]There is no established between-group MID for this outcome, but the clinical experts consulted by CDA-AMC considered a 7% difference between groups could be considered a threshold of clinical importance. Based on this threshold, the point estimate suggested no clinically important difference between mirikizumab and ustekinumab. However, the upper bound of the 99.5% CI for the between-group difference suggested a clinically important difference in favour of mirikizumab, whereas the lower bound suggested a clinically important difference in favour of ustekinumab.

[m]A MID of 16 points for change in IBDQ total score was identified from the published literature.

[n]Rated down 1 level for serious indirectness. There is no established between-group MID for the proportion of patients with SAEs at 52 weeks, but the clinical experts consulted by CDA-AMC considered a 10% difference between groups for this outcome could be considered a threshold of clinical importance. There was indirectness related to the inclusion of worsening of CD and other CD-related events (e.g., flares, exacerbation, aggravation) as a SAE, which complicates interpretation of the result.

Source: I6T-MC-AMAM (VIVID-1) Clinical Study Report. Details included in the table are from the sponsor's Summary of Clinical Evidence.

Long-Term Extension Studies

Description of Studies

One ongoing phase III, multicentre, open-label, long-term extension study (VIVID-2) was submitted. VIVID-2 evaluates the long-term efficacy and safety of mirikizumab in patients with CD. Patients were separated into 2 treatment groups according to their response in the VIVID-1 trial: endoscopic response and endoscopic nonresponse. Those patients in the endoscopic response group were defined as participants who achieved a 50% or greater reduction from baseline in SES-CD score, irrespective of their prior treatment group, at week 52 of the VIVID-1 trial.

Patients in the endoscopic response group continued the same subcutaneous mirikizumab dosing as in the VIVID-1 trial (300 mg every 4 weeks), while those in the endoscopic nonresponse group received reinduction with IV mirikizumab (900 mg every 4 weeks for 3 doses) at the start of the VIVID-2 trial followed by 300 mg subcutaneous dosing every 4 weeks. The interim analysis did not include patients who entered the VIVID-2 trial after August 1, 2023, to ensure that all patients in this interim analysis had completed 1 year of treatment in the VIVID-2 trial. Analyses were based on the data cut-off date of August 2, 2024.

The coprimary end points were endoscopic response (≥ 50% reduction from baseline in SES-CD total score) at week 104 (week 52 of the VIVID-2 trial), and CDAI clinical remission (CDAI score < 150 points) at week 104. The secondary end points included endoscopic remission based on SES-CD total score at week 104, PRO clinical response based on stool frequency and abdominal pain at week 104, and quality of life by IBDQ at week 104.

Patients who were eligible included those who completed week 52 of the VIVID-1 trial, including an endoscopy to evaluate response or nonresponse status and who, in the opinion of the investigator, would derive clinical benefit from treatment with mirikizumab. Patients were not eligible for the VIVID-2 long-term extension (LTE) trial if any of the following occurred:

- they had previously reported a SAE while receiving mirikizumab
- they developed conditions before the LTE trial that would disqualify them from treatment with mirikizumab
- they had previously discontinued the study drug or had a temporary interruption of the study drug such that, in the opinion of the investigator or sponsor, would make restarting mirikizumab an unacceptable risk
- they had a significant uncontrolled neuropsychiatric disorder or were assessed as being at risk of suicide
- they had been diagnosed with a serious infection or had an unstable or uncontrolled illness.

Efficacy outcomes were assessed in the overall population of patients with baseline SES-CD score of 7 or higher (≥ 4 for those with isolated ileal disease). Safety was assessed from the first dose of mirikizumab in the VIVID-2 trial to the cut-off date (August 2, 2024). Discontinuations or missing data were handled using modified nonresponse imputation. Sporadically missing data and data from patients who discontinued treatment due to extraordinary circumstances (study treatment supplies, site termination) were imputed

by multiple imputation. Patients who discontinued for other reasons were considered as part of the nonresponse group.

For patients in the endoscopic response group, the mean age was 37 years (SD = 12.89 years), mean duration of CD was 7.8 years (SD = 8.0 years), mean CDAI score was 319 points (SD = 82 points), and mean SES-CD score was 15 points (SD = 7 points). For patients in the endoscopic nonresponse group, the mean age was 38 years (SD = 14 years), mean CDAI score was 328 points (SD = 88 points), mean duration of CD was 9.8 years (SD = 8.4 points), and mean SES-CD score was 12 points (SD = 6 points). In both groups, most patients were male (> 55%) (female: < 45%) and were [redacted]

Efficacy Results

The efficacy data summarized includes only data from patients with a baseline SES-CD of 7 points or higher (or ≥ 4 points for isolated ileal disease) who were randomized to receive mirikizumab in the VIVID-1 trial.

Coprimary End Points

Endoscopic Response at Week 104 (Week 52 of the VIVID-2 Trial)

Among patients in the endoscopic response group at week 52 of the VIVID-1 trial who continued to receive mirikizumab subcutaneously (n = 251), 81.8% maintained endoscopic response at week 104 (week 52 of the VIVID-2 trial).

Among patients in the endoscopic nonresponse group who received reinduction with mirikizumab (n = 179), 30.9% gained endoscopic response at week 104 (week 52 of the VIVID-2 trial).

CDAI Remission at Week 104 (Week 52 of the VIVID-2 Trial)

Among patients receiving mirikizumab in the endoscopic response group at week 52 of the VIVID-1 trial (n = 251), 79.0% maintained clinical remission at week 104 (week 52 in the VIVID-2 trial). In addition, among of patients in the endoscopic response group who were also in clinical remission at week 52 of the VIVID-1 trial (n = 179), 78.3% maintained both clinical remission and endoscopic response at week 104. In addition, among patients in the endoscopic response group who were in corticosteroid-free clinical remission at week 52 (n = 170), 86.5% maintained this outcome at week 104.

Among patients receiving mirikizumab in the endoscopic nonresponse group (n = 179) at week 52 of the VIVID-1 trial, clinical remission was maintained by 86.9% of patients who were in CDAI remission. Of the 67 patients who were not in clinical remission at the end of the VIVID-1 trial, 55.8% gained CDAI remission at week 104 (week 52 of the VIVID-2 trial).

Secondary End Points

Endoscopic Remission

At week 104, among patients in the endoscopic response group, endoscopic remission was maintained by 72.5% of patients who were in endoscopic remission at week 52 of the VIVID-1 trial (n = 137) and gained by 33.3% of patients who were not in endoscopic remission at week 52 of the VIVID-1 trial (n = 112).

At week 104, among patients in the endoscopic nonresponse group, endoscopic remission was gained by 12.1% of patients who were not in endoscopic remission at week 52 of the VIVID-1 trial (n = 174).

PRO Clinical Remission

At week 104 (week 52 of the VIVID-2 trial), clinical remission by PRO was experienced by [redacted] of patients who were in the endoscopic response group at week 52 of the VIVID-1 trial. Information on clinical remission by PRO for patients in the endoscopic nonresponse group at week 52 of the VIVID-1 trial was not provided by the sponsor.

Health-Related Quality of Life

At week 104 (week 52 of the VIVID-2 trial), IBDQ remission was experienced by [redacted] of patients who were in the endoscopic response group at week 52 of the VIVID-1 trial. In addition, IBDQ response was experienced by [redacted] of patients who were in endoscopic response at week 52 of the VIVID-1 trial.

Information on IBDQ remission and response for patients in the endoscopic nonresponse group at week 52 of the VIVID-1 trial was not provided by the sponsor.

Harms Results

Adverse Events

In the endoscopic response group, 171 (64.0%) patients reported 1 or more TEAEs. In the endoscopic nonresponse group, 130 (65.0%) patients reported 1 or more TEAEs. The most common TEAEs (reported in ≥ 5% of patients) in both groups were COVID-19 ([redacted] in both groups) and upper respiratory tract infection (endoscopic response group: [redacted] endoscopic nonresponse group: [redacted]). Nasopharyngitis was reported in [redacted] patients in the endoscopic response group.

Serious Adverse Events

In each of the response and nonresponse groups, 18 patients reported at least 1 SAE. No particular AE accounted for majority of SAEs.

Withdrawal Due to Adverse Events

[redacted] patients in the endoscopic response group discontinued treatment due to AEs. Reasons for discontinuations were [redacted] and [redacted]

[redacted] patients in the endoscopic nonresponse group discontinued treatment due to AEs. Reasons for discontinuations were [redacted] and [redacted]

Adverse Events of Special Interest

Infections occurred in [redacted] patients and [redacted] patients in the endoscopic response and endoscopic nonresponse groups, respectively. Other commonly reported AEs of special interest included hepatic TEAEs (endoscopic response group: 5.3%; endoscopic nonresponse group: 3.0%) and hypersensitivity events occurring on the day of study drug administration (immediate) (endoscopic response group: 2.3%;

endoscopic nonresponse group: 4.0%) or otherwise (nonimmediate) (endoscopic response group: [redacted]; endoscopic nonresponse group: [redacted]).

Deaths

Two deaths occurred and both were considered not related to the study drug.

Critical Appraisal

The single-group design of the VIVID-2 trial without a comparator group does not permit inherent causal interpretations about the effect of longer-term mirikizumab treatment. The open-label nature of the study may increase the risk of bias in the evaluation of subjective efficacy and harm outcomes. It may also influence patients' and clinicians' behaviour during the trial, such as the use of concomitant medications. The effect of permitted concomitant medications for CD on efficacy outcomes is unknown because no information on concomitant medications was reported. The sample sizes in both groups were reduced from the original VIVID-1 population because only patients who had not discontinued treatment with mirikizumab before week 52 and were judged by the investigator to potentially derive benefit from further treatment were included.

Of the patients considered to have experienced endoscopic response at the end of the VIVID-1 trial and continued to receive mirikizumab subcutaneously during the VIVID-2 LTE trial, discontinuation from the study was generally low and mainly due to AEs or patient request. The use of multiple imputation for sporadically missing data for patients who discontinued treatment due to extraordinary circumstances (study treatment supplies, site termination) may be appropriate because these reasons would likely be unrelated to patient outcomes. The use of nonresponse imputation for the remainder of discontinuations may be considered conservative in a single-arm design. Although most patients maintained endoscopic response, remission, and clinical remission at week 52 of the VIVID-2 trial, long-term sustainability and/or durability has yet to be determined because the study is ongoing.

In general, because the LTE trial enrolled patients from the pivotal study, the eligibility concerns raised in the pivotal study remain valid for the LTE population. Rescue therapy was not permitted. Patients who completed VIVID-1 and who the investigator thought would benefit from further treatment were included in the trial, which may have led to a more selective population compared to the baseline population in VIVID-1. Endoscopic response, clinical remission, and HRQoL were considered important outcomes, and these were measured and reported. One of the clinical experts consulted by CDA-AMC indicated that re-treatment with mirikizumab would be considered only under certain circumstances, such as incomplete induction (missed doses), partial response suggesting that reinduction may be needed to achieve further improvement, or clear reasons for prior failure of induction, such as pre-existing strictures or *Clostridioides difficile* infection. The other clinical expert noted that re-treatment with mirikizumab would not be considered and that they would likely pivot to another mechanism of action or even another anti-IL-23 drug. The harms results in the VIVID-2 trial were generally aligned with the pivotal study, with no new AEs identified. There were fewer patients who reported injection site reactions in the LTE trial compared to the pivotal study.

Indirect Comparisons

Description of Studies

The direct comparison of efficacy and safety of mirikizumab with ustekinumab was included in the pivotal study (VIVID-1). In the absence of randomized controlled trials providing a direct comparison of all other treatments of interest in the Canadian clinical setting, the sponsor submitted an indirect treatment comparison in the form of an NMA. The NMA was conducted to compare the efficacy and safety of mirikizumab with all potentially relevant comparators of interest (including adalimumab, infliximab, ustekinumab, vedolizumab, upadacitinib, and risankizumab) for the treatment of moderately to severely active CD.

Efficacy Results

In the treatment of patients with moderately to severely active CD who have experienced treatment failure with either conventional care or biologics in both the induction and maintenance treatment periods, evidence from the NMA was insufficient to determine whether mirikizumab differs in efficacy compared to relevant comparators for enhanced clinical response (decrease in CDAI score ≥ 100 points), clinical remission (defined as CDAI score < 150 points), endoscopic response (SES-CD score > 50% from baseline or 2-point SES-CD reduction patient had isolated ileal disease and a baseline SES-CD score of 4 points), and endoscopic remission (SES-CD score ≤ 4 points and at least a 2-point reduction versus baseline and no subscore > 1 point).

No HRQoL outcomes were assessed in the NMA.

Harms Results

Evidence from the NMA was insufficient to determine whether mirikizumab differs in safety during the induction phase compared to relevant comparators. No analysis was done to inform comparative safety in the maintenance phase.

Critical Appraisal

Overall, the sponsor's NMA was conducted according to accepted methodological guidance. A key limitation of the NMA was that the considerable clinical and methodological heterogeneity across the included studies, such as differences in study design, differences in baseline demographic and disease characteristics, potential differences of the conventional care (i.e., the standard care for the CD has evolved over time), potential differences of concomitant medications used in the trials, and differences in follow-up times when outcomes were assessed. The sources of heterogeneity suggest that the assumption of similarity across the included studies may not hold true for the NMA, which increases the likelihood of bias and uncertainty about the validity of the results for determining the comparative efficacy of mirikizumab with all relevant comparators.

Although a variety of approaches were used to reduce the level of heterogeneity in some of these analyses, these may introduce other limitations. Relevant studies were excluded to reduce heterogeneity in the network; however, this approach involved subjective decisions which may be a source of bias in the analysis. Stratifying the analyses by populations with conventional care failure and biologic failure was relevant, but it

limited the generalizability of the results to the broader indicated population in Canada. The ability to assess potential clinical heterogeneity within these groups was limited, and the report did not confirm whether randomization was stratified for these subgroups to ensure prognostic balance was upheld. The baseline risk adjustment for heterogeneity in placebo response was appropriately considered across all analyses and was applied for most of the induction analyses. This adjustment could not be extended to the maintenance analyses (e.g., models did not converge) in which between-trial heterogeneity was potentially greater due to variations in study design.

Other potential limitations included sparsity of evidence networks and that most of the connections between treatment nodes were informed by only 1 trial. There were relatively few closed loops between nodes, inherently limiting the ability to comprehensively examine the consistency assumption. Comparative effect estimates were often accompanied by wide credible intervals, which demonstrates an additional source of uncertainty in the findings.

Economic Evidence

Cost and Cost-Effectiveness

- Mirikizumab is available as a solution for injection (100 mg per 1 mL solution and 200 mg per 2 mL solution) and as a solution for infusion (20 mg/mL). At the submitted price of $2,536.14 per 300 mg (either as a single vial for infusion or a carton of prefilled syringes or pens), the annual cost of mirikizumab is expected to be $50,773 per patient in the first year of treatment and $33,083 per patient in subsequent years, based on the Health Canada–recommended dosage.
- Clinical efficacy in the economic analysis was derived from a sponsor-submitted NMA, with the efficacy of mirikizumab informed by the VIVID-1 trial. Indirect evidence submitted by the sponsor was insufficient to show a difference between mirikizumab and relevant comparators. Due to the significant limitations associated with the NMA (e.g., risk of bias, important clinical and methodological heterogeneity, imprecision), no definite conclusion can be drawn on the comparable efficacy and safety of mirikizumab versus existing comparators in the treatment of patients with moderately to severely active CD who have had prior conventional care failure or biologic treatment failure (refer to the CDA-AMC clinical review).
- CDA-AMC estimates that the budget impact of reimbursing mirikizumab for the treatment of adult patients with moderately to severely active CD who have had an inadequate response, a loss of response, or intolerance to either conventional therapy or a biologic treatment will be approximately $50.3 million over the first 3 years of reimbursement compared to the amount currently spent on biologics, with an estimated expenditure of $120 million on mirikizumab over this period. The actual budget impact of reimbursing mirikizumab will depend on the number of people eligible for treatment and the uptake of mirikizumab.
- Given that the sponsor-submitted indirect evidence suggests that there may be no difference between mirikizumab versus other biologics currently available for the treatment of adult patients with

moderately to severely active CD who have had prior conventional care failure or biologic treatment failure, there is insufficient evidence to suggest that mirikizumab should be priced higher than any other biologics for moderately to severely active CD. Thus, to ensure cost-effectiveness, mirikizumab should be priced no higher than the lowest cost biologic that is funded for the treatment of adult patients with moderately to severely active CD.

All feedback received in response to the draft recommendation is available on the CDA-AMC website.

CDEC Information

Members of the Committee

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

Meeting date: July 23, 2025

Regrets: Three expert committee members did not attend.

Conflicts of interest: None

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

ISSN: 2563-6596

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

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