



CADTH Reimbursement Recommendation

Mirikizumab (Omvoh)

Indication: For the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response, loss of response, or were intolerant to conventional therapy, a biologic treatment, or a Janus kinase inhibitor

Sponsor: Eli Lilly Canada

Final recommendation: Reimburse with conditions



Summary

What Is the CADTH Reimbursement Recommendation for Omvoh?

CADTH recommends that Omvoh be reimbursed by public drug plans for the treatment of moderately to severely active ulcerative colitis (UC) if certain conditions are met.

Which Patients Are Eligible for Coverage?

Omvoh should only be covered for patients who are eligible for the reimbursement of other advanced drugs for the treatment of moderately to severely active UC (i.e., biologics and Janus kinase [JAK] inhibitors) based on the criteria used by each public drug plan.

What Are the Conditions for Reimbursement?

Omvoh should only be reimbursed if prescribed by a physician experienced in the diagnosis and management of UC but should not be reimbursed if used in combination with biologic therapies or JAK inhibitors for UC. For ongoing treatment to keep UC under control, Omvoh should only be reimbursed if initial treatment reduces the severity of UC after 24 weeks. Patients should be reassessed every year for renewal. The cost of Omvoh should not exceed the drug program cost of treatment with the least costly biologic reimbursed for the treatment of UC.

Why Did CADTH Make This Recommendation?

- Evidence from 2 clinical trials demonstrated that treatment with Omvoh improved symptoms and reduced severity of UC; this treatment effect with Omvoh was maintained for up to 52 weeks compared with placebo.
- Additionally, fewer patients needed to use corticosteroids with Omvoh compared with placebo; this outcome was identified as important to patients and clinicians.
- Omvoh appears to meet some of the needs identified by patients, including a need for additional treatment options that would help them gain control of UC symptoms and keep them under control.
- Based on CADTH's 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 that there is not enough evidence to justify a greater cost for Omvoh compared with other biologics reimbursed for the treatment of UC.
- Based on public list prices, Omvoh is estimated to cost the public drug plans approximately \$15 million over the next 3 years. However, the



Summary

actual budget impact is uncertain due to limitations with the sponsor-submitted model.

Additional Information

What Is UC?

UC is an inflammatory bowel disease that causes inflammation and ulcers in the lining of the large intestine and rectum. Signs and symptoms include blood in stool, frequent diarrhea, loss of appetite, the strong urge to use the bathroom without necessarily having a bowel movement, abdominal pain, and rectal bleeding. It is estimated that the prevalence of UC in Canada will be 0.44% of the population in 2030.

Unmet Needs in UC

Patients have found it difficult to obtain adequate symptom relief with the currently available treatment options. Patients have also noted that treatment response varies across patients and that response to treatment may stop after prolonged use. Thus, patients have identified a need for additional treatments that reduce the severity of symptoms and keep the symptoms under control, demonstrate long-term safety and tolerability, and improve quality of life and work productivity.

How Much Does Omvoh Cost?

Treatment with Omvoh is expected to cost between \$7,124 and \$14,248 per patient during the 12- to 24-week initiation phase and \$30,977 per patient in the maintenance phase (i.e., per year).

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that mirikizumab be reimbursed for the treatment of adult patients with moderately to severely active UC who have had an inadequate response, loss of response, or were intolerant to conventional therapy, a biologic treatment, or a JAK inhibitor only if the conditions listed in [Table 1](#) are met.

Rationale for the Recommendation

Evidence from 2 phase III, randomized, double-blind, placebo-controlled trials (LUCENT-1, N = 1,281, and LUCENT-2, N = 544) demonstrated that treatment with mirikizumab resulted in clinical benefit for adults with moderately to severely active UC. In the LUCENT-1 trial, a greater proportion of patients in the mirikizumab group (24.2%) compared with the placebo group (13.3%) achieved clinical remission during the induction phase, following 12 weeks of treatment (common risk difference of 11.1%; 99.875% CI, 3.2% to 19.1%; P = 0.00006). In the main analysis of the LUCENT-2 trial, which included patients whose disease responded to mirikizumab in the LUCENT-1 trial, a greater proportion of patients in the mirikizumab group (49.9%) compared with the placebo group (25.1%) achieved clinical remission after 40 weeks of maintenance therapy (i.e., 52 weeks of continuous therapy) (23.2% common risk difference; 95% CI, 15.2% to 31.2%; P < 0.001). Similarly, there were statistically significant between-group differences in favour of the mirikizumab group for alternate clinical remission, clinical response, endoscopic remission, symptomatic remission, bowel urgency improvement, and mucosal healing over 12 weeks. During the 40-week maintenance phase of treatment that was assessed in the LUCENT-2 trial, statistically significant between-group differences in favour of the mirikizumab group were demonstrated for alternate clinical remission, endoscopic remission, histologic endoscopic mucosal remission, bowel movement urgency improvement, and urgency remission, demonstrating a maintenance of treatment effect with mirikizumab for up to 1 year. Additionally, a greater proportion of patients in the mirikizumab group (44.9%) compared with the placebo group (21.8%) achieved corticosteroid-free remission during the maintenance phase (common risk difference of 21.3%; 95% CI, 13.5% to 29.1%; P < 0.001), which was an outcome of importance identified by patients and clinicians. Patients also identified a need for additional treatments that induce and maintain symptomatic remission, exhibit long-term safety and tolerability, and are associated with improved quality of life and work productivity. Mirikizumab appears to meet some of these needs.

At the sponsor-submitted price for mirikizumab and publicly listed prices for all other drug costs, mirikizumab was more costly than the least costly relevant comparator (i.e., biologic) for adults with moderately to severely active UC. Direct comparative evidence to other advanced therapies was not identified and indirect evidence is insufficient to conclude that mirikizumab is superior or inferior to other advanced therapies. As such, the total drug cost of mirikizumab should not exceed the total drug cost of the least costly biologic reimbursed in this patient population.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Eligibility for reimbursement of mirikizumab should be based on the criteria used by each of the public drug plans for the reimbursement of other advanced drugs for the treatment of moderately to severely active UC (i.e., biologics).	The results of the LUCENT-1 and LUCENT-2 studies demonstrate that mirikizumab is an effective treatment for induction and maintenance of UC. The indirect evidence is insufficient to conclude that mirikizumab is superior or inferior to the most relevant comparators (i.e., biologic drugs).	—
Renewal		
2. The patient must have achieved clinical response to induction therapy after 24 weeks of treatment initiation to continue to maintenance therapy.	In the LUCENT-1 study, patients were required to achieve a clinical response at week 12 of the induction period to continue directly into maintenance dosing in the LUCENT-2 study. Patients whose disease did not respond to mirikizumab during induction by week 12 in the LUCENT-1 study were eligible for an extended induction period in the LUCENT-2 study. The clinical expert indicated that 24 weeks would be a reasonable time frame to assess the efficacy of induction therapy as some patients may have disease that is late to respond. This is aligned with results of the LUCENT-1 and LUCENT-2 trials in that more than half of the patients whose disease did not respond after 12 weeks of treatment (146 of 272 patients) exhibited a delayed response after 24 weeks.	A Modified Mayo Score that requires an endoscopy was used to determine clinical response in the LUCENT-1 and LUCENT-2 trials. Given the invasive nature of an endoscopy and the limitations associated with timely access and associated costs of health care resources in Canada, CDEC considered it appropriate to leave the determination of clinical response up to the judgment of the treating physician.
3. Assessment for renewal after the first assessment of treatment response should be performed every year.	The patient must maintain clinical response to therapy to continue receiving mirikizumab. Patients who lose response to mirikizumab are no longer benefiting from treatment.	—
Prescribing		
4. Mirikizumab should only be prescribed by a physician experienced in the diagnosis and management of UC.	It is important to ensure that mirikizumab is only prescribed for appropriate patients.	—
5. Mirikizumab should not be reimbursed when used in combination with biologic therapies or JAK inhibitors for UC.	There is no evidence to support the use of mirikizumab in combination with a biologic therapy or JAK inhibitor for UC.	—

Reimbursement condition	Reason	Implementation guidance
Pricing		
6. The cost of mirikizumab should be negotiated so that it does not exceed the drug program cost of treatment with the least costly relevant comparator (i.e., biologic) reimbursed for the treatment of ulcerative colitis.	There is insufficient clinical evidence to justify a cost premium for mirikizumab over the least costly relevant comparator reimbursed for ulcerative colitis.	–
Feasibility of adoption		
7. The feasibility of adoption of mirikizumab must be addressed.	At the submitted price, the magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of adoption, given CADTH was unable to reassess the sponsor's estimate.	–

CDEC = CADTH Canadian Drug Expert Committee; JAK = Janus kinase; UC = ulcerative colitis.

Discussion Points

- Patients described many of the significant negative impacts of UC on quality of life, as well as the effect on participation at school or in the workplace. Although numerical and clinically meaningful improvements in health-related quality of life (HRQoL) based on the Inflammatory Bowel Disease Questionnaire (IBDQ) and Work Life Productivity Activity Index – Ulcerative Colitis (WPAI:UC) were observed in the trials, CDEC noted that a conclusion could not be drawn on HRQoL and productivity outcomes in the LUCENT-1 and LUCENT-2 studies due to lack of control for multiplicity.
- Results from the sponsor's network meta-analysis (NMA) did not demonstrate a difference between mirikizumab and other advanced therapies for moderately to severely active UC in induction clinical remission and response, mucosal healing, all-cause discontinuation, and serious adverse events (SAEs). The NMA suggested differences between mirikizumab and some of the advanced therapies during the maintenance phase; however, there was heterogeneity in terms of patient characteristics, inclusion criteria, prior treatment exposure, and outcome definitions across the included studies, as well as wide credible intervals for most estimates. These limitations contributed to uncertainty in the effect estimates; therefore, it was not possible to conclude that mirikizumab was superior or inferior in efficacy or safety to advanced therapies for UC.
- CDEC discussed that remission with treatment is not universal and patients can lose response to treatment after an initial period of improvement or relapse after long periods of remission on an existing therapy. Moreover, patients expressed a notable concern about the occurrence of disease flares with currently available treatments. Mirikizumab provides another treatment option with a different mechanism of action from other currently available therapies for UC, with efficacy and safety demonstrated for up to 52 weeks of treatment. However, the lack of data beyond 52 weeks represents a gap in the evidence, and with the lack of direct evidence with relevant comparators and

the uncertainty in the results from the sponsor-submitted NMA, any clinical benefit derived from this novel mechanism relative to other therapies is uncertain.

- CDEC discussed the variable length of induction therapy for patients with mirikizumab. A total of 1,178 patients from the LUCENT-1 trial were randomized into the LUCENT-2 trial in either the mirikizumab or placebo group. Of those, 544 patients randomized to mirikizumab IV had disease that responded to 12 weeks of induction dosing in the LUCENT-1 trial and were rerandomized to receive maintenance dosing in the LUCENT-2 trial. A total of 272 patients (23%) who enrolled in the LUCENT-2 trial had received mirikizumab in the LUCENT-1 trial but their disease did not respond to 12-week induction dosing and they subsequently received an additional 12 weeks of induction therapy (i.e., 24 weeks in total). After 24 weeks of treatment, 53.7% of the mirikizumab nonresponder group achieved a delayed clinical response. This information may prove useful for payers when assessing the total cost of treatment to ensure mirikizumab is no more costly than the least costly relevant comparator (i.e., biologic) reimbursed for adults with moderately to severely active UC.
- A request for a minor reconsideration of the initial draft recommendation for mirikizumab was received from the sponsor. The reconsideration included 1 issue, which indicated that “the draft recommendation states that mirikizumab should not be priced higher than tofacitinib due to a lack of direct evidence comparing the 2 molecules. However, this conclusion is refuted by clear differences in safety profiles and utilization.” During the minor reconsideration discussion, a subpanel of the committee discussed the sponsor’s issue and whether tofacitinib, an advanced therapy for the treatment of UC, is the most relevant and least costly comparator reimbursed for UC. Upon reconsidering the issue, CDEC discussed the anticipated place in therapy of mirikizumab, which would be used as a second-line or later-line therapy in both those who are biologic naive and biologic experienced. CDEC concluded that for those who are biologic naive, the most relevant comparators for mirikizumab were those of a similar drug class (i.e., other biologics). Although tofacitinib is used in clinical practice, clinicians indicated that tofacitinib use is often reserved for patients whose disease does not respond to, or who do not tolerate a biologic, and would not be used in the second line.
- Two patient groups provided feedback on the initial draft recommendation for mirikizumab. In their feedback, 1 of the groups did not agree that patients should have to fail conventional therapy before accessing mirikizumab, highlighting patient dissatisfaction with conventional first-line therapies. During the reconsideration meeting, CDEC discussed that the recommendation is aligned with the indication approved by Health Canada, which is for patients who have had an inadequate response, loss of response, or were intolerant to conventional therapy, a biologic treatment, or a JAK inhibitor.

Background

Inflammatory bowel disease (IBD) is a term used to describe disorders that involve chronic inflammation of the digestive tract. UC is 1 such disease as it causes inflammation and ulcers in the digestive tract, affecting the innermost lining of the large intestine (colon) and rectum. UC is characterized by blood in the stool

with mucus, frequent diarrhea, loss of appetite, and tenesmus (strong urge to use the bathroom without necessarily having a bowel movement), in addition to abdominal pain, rectal bleeding, and weight loss. While the etiology of UC is not completely understood, there is growing evidence to suggest that genetic and environmental factors may contribute to the irregular immune response that aberrantly recruits activated immune cells to the colon, which results in chronic inflammation that damages the colon and causes UC symptoms. Majority of individuals living with UC have a mild to moderate disease course; generally, with active disease at diagnosis followed by alternating exacerbations and longer periods of remission. However, aggressive disease course is experienced in 10% to 15% of patients, with a cumulative risk of relapse between 70% to 80% at 10 years postdiagnosis. Regardless of severity, UC is associated with substantial reduction in quality of life, with considerable impact on many aspects of a patient's life, including emotional and psychological functioning, social and physical functioning, and work and academic life.

UC is diagnosed clinically, with endoscopy, biopsy, and stool sampling being common tests used in ruling out other causes of symptoms. Treatment strategies for UC are dependent on the presence of active disease, severity and extent of the UC, and patient preference with the goal of achieving complete remission. Conventional therapies for UC include 5-acetylsalicylic acid (5-ASA) products, corticosteroids, and immunomodulators (such as azathioprine, 5-mercaptopurine, and methotrexate) and advanced therapies consist of adalimumab, golimumab, infliximab, ustekinumab, tofacitinib, ozanimod, and vedolizumab. However, these treatments are unable to meet all current needs of patients in terms of short- or long-term treatment. Remission with treatment is not universal and patients' UC can lose response to treatment after an initial period of improvement and relapse even after long periods of remission on an existing therapy. Accordingly, there is a need for novel therapies targeting alternative pathways. An estimate of 322,600 patients in Canada are living with IBD. In 2030, the number of people living in Canada with IBD is anticipated to be 470,000, accounting for 1.1% of the population, with a prevalence for UC specifically of 0.44%.

Mirikizumab has been approved by Health Canada for the treatment of adult patients with moderately to severely active UC who have had an inadequate response, loss of response, or were intolerant to conventional therapy, a biologic treatment, or a JAK inhibitor. Mirikizumab is a humanized immunoglobulin G4 monoclonal antibody that is available as a 300 mg/15 mL vial for IV injection and 100 mg/mL autoinjector pen or prefilled syringe for subcutaneous (SC) injection and the dosage recommended in the product monograph is 300 mg IV injection for induction dosing, and 200 mg SC injection for maintenance dosing. For patients whose disease does not show adequate therapeutic response at week 12 after induction dosing, extended induction dosing may be considered by administering 300 mg mirikizumab by IV infusion for up to 3 doses given every 4 weeks.

Sources of Information Used by the Committee

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

- a review of 2 clinical trials and 1 indirect treatment comparison in adults with moderately to severely active UC

- patient perspectives gathered by 2 patient groups: the Gastrointestinal (GI) Society and Crohn's and Colitis Canada
- input from the public drug plans that participate in the CADTH review process
- 1 clinical specialist with expertise diagnosing and treating patients with UC
- input from 1 clinician group, a group of gastroenterologists from Canada
- a review of the pharmacoeconomic model and report submitted by the sponsor
- information submitted as part of the request for minor reconsideration (described subsequently).

Stakeholder Perspectives

The information in this section is a summary of input provided by the patient and clinician groups that responded to CADTH's call for input and from a clinical expert consulted by CADTH for the purpose of this review.

Patient Input

Patient input was collected from the GI Society and Crohn's and Colitis Canada. Patient input was collected through a variety of questionnaires (n = 4 to n = 432), focus groups, and individual interviews. In addition, 1-to-1 interviews were conducted with 3 patients with UC who received mirikizumab in a clinical trial. After collating responses, it was noted that UC has a profound effect on daily life – physically, emotionally, and socially – at home and at school or in the workplace. Many patients surveyed by Crohn's and Colitis Canada revealed that they hid aspects of their diagnosis from their friends, coworkers, and classmates, and almost two-thirds (63%) agreed that their family and friends do not understand what they are going through. Patients noted that symptoms can be relentless, embarrassing, and scary. Based on the surveys conducted by Crohn's and Colitis Canada, the most frequently reported UC-related complication reported were mental health and stress (65%), joint inflammation and arthritis (51%), anal fissures and hemorrhoids (40%), anemia (33%), skin conditions (30%), malnutrition (30%), and weight loss (30%). Patients stated that more than anything, sustained remission, and/or treatment response is more important than relieving any 1 symptom of UC. The constant concern that there will be future flares, possibly worse than the last, at unpredictable times, was noted as being disastrously disruptive.

Regarding current treatments for UC, it was noted that although there are several available options, most patients have difficulty obtaining remission or adequate symptom relief. Based on survey data from the GI Society, only 24% of patients with IBD found the available medications to be adequate, 56% found them to be only somewhat adequate, and 20% found them not at all adequate. More than half (56%) of patients surveyed by Crohn's and Colitis Canada believed that different treatment options could make them feel better. While steroid use is an important part of symptom management for UC, the patients surveyed by Crohn's and Colitis Canada reported not to be particularly supportive of that treatment option. Almost all patients (93%) surveyed by Crohn's and Colitis Canada stated that they only take systemic steroids if absolutely necessary. Patient input from the GI Society stressed that treatment response varies across patients, and in some cases

response to medication may stop after prolonged use. For these reasons, patients noted that it is important to have a variety of treatment options for UC. Patients noted that there is a need for new and effective options to achieve mucosal healing and reduce the debilitating symptoms of UC, as well provide good quality of life. The patients interviewed by Crohn's and Colitis Canada added that any new treatment must be able to protect a patient's ability to work productively, attend school and social events, and conduct basic necessities such as leaving the home to run errands. However, patients interviewed by Crohn's and Colitis Canada also added that potential risks and side effects, especially those related to heart and liver function, are a major source of concern when considering new treatment options. The 3 patients interviewed by the GI Society who received mirikizumab in clinical trials reported that they continue to take the medication at the time they were interviewed. All 3 patients experienced improved gut healing and expressed improvement in quality of life following treatment with mirikizumab. Regarding administration of mirikizumab, 1 patient reported that the initial induction treatment by infusion was exhausting and time consuming, and although this patient did not particularly like the SC administration of mirikizumab, they were willing to tolerate it and described it as manageable.

Clinician Input

Input From Clinical Experts Consulted by CADTH

The clinical expert noted that there is an unmet need for treatments that are better tolerated, improve convenience and compliance, and take into consideration special populations such as those with previous or current malignancies. The clinical expert stated that having available treatments with different administration methods is also important to patients (e.g., IV, SC, or oral), as well as having multiple treatment options, given that a patient's UC will often lose response to treatment and require another therapy. The clinical expert noted that not all patients' UC will respond to available treatments and patients' disease often becomes refractory to current treatment options. According to the clinical expert, mirikizumab is an anti-interleukin-23 drug for UC and would offer a novel treatment mechanism for the disease that is more targeted compared to other therapies such as ustekinumab. The clinical expert anticipated that place in therapy of mirikizumab would be similar to other biologics – as a second-line therapy after 5-ASA, instead of immunomodulators. The clinical expert opined that patients do not need to initiate other therapies and have them fail before being prescribed mirikizumab given the limitations and risks of other therapies. The clinical expert noted that patients whose UC is most likely to respond to treatment with mirikizumab would be those with moderately to severely active UC (who are biologic naive or biologic experienced) that has not responded to conventional therapy. The clinical expert noted that patients least suited for treatment with mirikizumab are patients with active infections, malignancy, severe hepatic impairment, and those who are pregnant. The clinical expert felt that patients with the greatest need for mirikizumab would be those for whom first-line therapy with 5-ASA has failed.

According to the clinical expert, the outcomes used in clinical practice align with those used in the clinical trials, such as clinical remission and clinical response (measured by Partial Mayo Score), endoscopic remission and response, and biomarkers (e.g., fecal calprotectin). The clinical expert noted that clinicians routinely schedule a colonoscopy to check for endoscopic healing 6 to 9 months after a patient has been

started on a biologic therapy or small molecules. If there is concern about response to treatment, the expert indicated that some physicians may try to book a flexible sigmoidoscopy early after the induction period has been completed.

According to the clinical expert, a clinically meaningful response to treatment would be no further rectal bleeding, no rectal incontinence, reduced to no more rectal urgency, reduced to normal frequency of bowel movements, stools becoming more solid, and reduced to no abdominal pain. The clinical expert would expect clinical improvement within 4 weeks, and clinical remission within 12 weeks; however, depending on the severity of disease and previous medication exposure, the clinical expert noted that patients' UC may have a slower response or a delay to remission. In this case, the expert indicated that they would be comfortable with an extended induction period of 12 weeks for those with disease that does not respond to treatment, which is aligned with the product monograph. The clinical expert noted that most gastroenterologists use standard clinical scores (e.g., Partial Mayo Score or Modified Mayo Score [MMS]) for UC in clinic with an endoscopic component if performing colonoscopy.

Regarding discontinuation of treatment, the clinical expert suggested that mirikizumab be discontinued in the event of SAEs, disease progression, or the inability to taper off steroids. The clinical expert would consider stopping treatment after 24 weeks if the patient's disease does not respond. This would include an extended induction phase if the patient's disease was not responding to initial induction (e.g., 12 weeks). According to the clinical expert, it would be expected that approximately 30% of patients with UC that did not have an initial induction response might have disease with a delayed response to induction treatment.

Clinician Group Input

Clinician group input was received by a group of gastroenterologists from Canada. Input from the clinician group was compiled by 9 gastroenterologists recognized as experts in the management of IBD. Based on input from the clinician group, the goals of UC therapy are multifaceted, ranging from controlling symptoms to preventing disease progression, surgery, and disability with early intervention and a treat-to-target approach. The clinician group identified the following unmet needs for the treatment of moderately to severely active UC: a therapy that induces and maintains symptomatic remission, is safe with long-term use, and can rapidly improve endoscopic appearance of the bowel and maintain this in the long term. The clinician group emphasized that none of the available therapies for UC meet all of the current needs of patients in the short or long term. Remission with treatment is not universal and patients' disease can lose response after an initial period of improvement and relapse even when in deep remission on an existing therapy. Accordingly, the clinician group advocated the need for novel therapies targeting alternative pathways. Overall, the clinician group found that mirikizumab has the potential for a broad range of uses in clinical practice from first-line advanced therapy to the treatment of patients whose UC shows inadequate response to, or those who cannot tolerate, multiple advanced therapies.

In regards of treatment with mirikizumab, the clinician group suggested that the aim of treatment should be remission. The clinician group suggests that a meaningful improvement in symptoms as measured by resolution of stool frequency and rectal bleeding should be demonstrated in the first 3 months of therapy. The clinician group would expect patients to be in symptomatic remission and off corticosteroids by 6

months after initiation of mirikizumab. The clinician group added that symptomatic improvement should be accompanied by a decrease in the biomarkers of inflammatory activity (C-reactive protein and fecal calprotectin) in the first 3 months after initiating mirikizumab. The clinician group suggested discontinuing treatment with mirikizumab in the event of worsening symptoms or inadequate response. In circumstances where there is an inadequate response to mirikizumab as a first-line biologic, the clinician group indicated that a switch to another class of drugs, such as anti-tumour necrosis factors (TNFs) is warranted. Based on clinical experience, the clinician group suggests that mirikizumab be administered in clinic by a trained health care professional during the induction phase.

Drug Program Input

The clinical expert consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

Table 2: Responses to Questions from the Drug Programs

Implementation issues	Advice from CADTH
Considerations for initiation of therapy	
<p>Are patients eligible for re-treatment if their disease did not respond to initial mirikizumab treatment?</p>	<p>According to the clinical expert, yes, patients are eligible for re-treatment if their disease no longer responds to the drug. However, they should not be re-treated if their UC does not show response to re-treatment. In the LUCENT-2 study (maintenance trial) extended doses of an additional 12 weeks produced a clinical response in up to 50% of patients whose disease did not show a clinical response to 12 weeks of induction doses. Patients would not be re-treated with mirikizumab if their disease did not respond to extended induction and clinicians would not re-treat with the drug later in the patient’s therapeutic journey after this point.</p> <p>CDEC agreed with the clinical expert and felt the extended induction period was reasonable.</p>
<p>In the LUCENT trials, patients were excluded if they had surgery or were to have surgery to treat their UC. Given that recurrence may happen even after surgery, would patients who have recurrence of UC postsurgical treatment be eligible for mirikizumab?</p>	<p>The clinical expert noted that for UC, surgery refers to colectomy (removal of the whole colon but not the rectal stump). According to the clinical expert, typically, the operating physician will add either a permanent ostomy bag or J-pouch. Patients will stop medications postsurgery and would not normally have recurrence of UC if they have a J-pouch. However, there is a possibility of developing inflammation of the J-pouch, which could develop into Crohn-like phenotype of the pouch that is refractory to antibiotics. Only in this rare case would patients need to go back onto a biologic, which may be mirikizumab if they have not been on it before.</p> <p>CDEC agreed with the clinical expert and noted that this population was not included in the data provided to CADTH.</p>
<p>Should patients be trialed on other biologics before being eligible for mirikizumab? The current criteria proposed by the sponsor is a trial of, at minimum, conventional therapy.</p>	<p>In the opinion of the clinical expert, patients do not need to trial other biologics to be eligible for reimbursement of treatment with mirikizumab. The clinical expert would expect that mirikizumab can be initiated after conventional therapy with 5-ASA.</p>

Implementation issues	Advice from CADTH
	As there is no evidence to suggest mirikizumab is superior or inferior to other advanced therapies, CDEC agreed with the clinical expert that a trial of other biologics is not required to be eligible to receive mirikizumab.
Considerations for continuation or renewal of therapy	
Will response to induction therapy be the requirement for reimbursement of maintenance therapy in a similar manner to ustekinumab?	The clinical expert recommended that a patient should have achieved clinical response to induction therapy within 24 weeks (an extended induction period) for reimbursement of treatment with mirikizumab to continue to maintenance therapy. CADTH noted that this is aligned with the product monograph. CDEC agreed with the clinical expert regarding requirements for reimbursement.
Considerations for prescribing of therapy	
Who should be able to prescribe mirikizumab? Can this be extended to internists in remote and/or rural areas?	According to the clinical expert, a gastroenterologist should prescribe the treatment, but in the case of rural and remote areas, a general internist or endoscopist trained for IBD management may also prescribe mirikizumab. CDEC agreed with the clinical expert and noted that family physicians who are trained as endoscopists could also prescribe mirikizumab.
System and economic issues	
Mirikizumab requires IV administration for induction and would likely be administered in an outpatient IV clinic. This is an additional cost that should be taken into consideration. Once on maintenance, the drug will be administered subcutaneously. It is necessary to consider the cost of IV administration, including the clinic, staff, materials, and so forth.	Comment from the drug programs to inform CDEC deliberations.

5-ASA = 5-acetylsalicylic acid; CDEC = CADTH Canadian Drug Expert Committee; IBD = inflammatory bowel disease; UC = ulcerative colitis.

Clinical Evidence

Pivotal Studies and Randomized Controlled Trial Evidence

Description of Studies

Two double-blind, multicentre, parallel-arm, randomized placebo-controlled trials, LUCENT-1 and LUCENT-2, were submitted by the sponsor. LUCENT-1 (N = 1,281) was a 12-week induction trial in which patients were randomized 3:1 to either mirikizumab 300 mg IV every 4 weeks or placebo. The aim of the study was to assess whether mirikizumab 300 mg IV would induce clinical remission at week 12 in adults with moderately to severely active UC. Major secondary objectives included alternate clinical remission, clinical response, clinical response in patients who were biologic experienced, endoscopic remission, symptomatic remission, bowel urgency improvement, and histologic endoscopic mucosal improvement (HEMI), all at week 12. HRQoL was also evaluated at week 12 using the IBDQ, EQ-5D, and the 36-item Short-Form Health Survey

(SF-36). The Work Productivity and Impairment Questionnaire: UC (WPAI:UC) was also evaluated at week 12 among patients employed at baseline. At baseline, patients had a mean age of 42.1 years (standard deviation = 13.85), with the majority being male (60.1%) and white (74.7%). There was an equal number of patients with moderate UC and severe UC based on MMS. The proportion of patients reporting prior biologic or tofacitinib failure was also similar between treatment groups (41.6% and 40.1% of patients randomized to mirikizumab and placebo, respectively).

LUCENT-2 (N = 544 in the primary analysis) was a 40-week maintenance trial in which patients were randomized 2:1 to either mirikizumab 200 mg SC every 4 weeks or placebo. The aim of the trial was to assess whether mirikizumab 200 mg SC would achieve clinical remission from baseline at week 40 in adults with moderately to severely active UC whose UC had previously achieved a clinical response at week 12 of the LUCENT-1 trial. Major secondary objectives included alternate clinical remission, corticosteroid-free remission, durable clinical remission, endoscopic remission, bowel urgency remission and improvement, and histologic endoscopic mucosal remission (HEMR), all at week 40 (i.e., 52 weeks of treatment in total). The WPAI:UC was also evaluated at week 40 among patients employed at baseline. The baseline characteristics in the LUCENT-2 trial were similar to those of the LUCENT-1 trial. The majority of the patients in the main cohort had a mean age of 42.3 years (standard deviation = 13.5), were male (58.4%), and were white (71.3%). Based on the MMS, approximately half of the patients in each treatment arm were categorized as having moderate UC severity and 35.1% in the mirikizumab group and 35.8% in the placebo group had a history of biologic or tofacitinib failure. Overall, the baseline characteristics were well-balanced between the treatment arms.

The LUCENT-2 trial also enrolled 405 patients from the LUCENT-1 trial whose disease had not responded to 12 weeks of induction dosing with either mirikizumab or placebo. These patients received open-label mirikizumab (300 mg IV) for 12 weeks. This was referred to as an extended induction period for patients who had previously received 12 weeks of induction dosing (i.e., 24 weeks of continuous therapy).

Efficacy Results

A summary of key efficacy results from the LUCENT-1 and LUCENT-2 trials are summarized in the following.

Induction Period – The LUCENT-1 Trial

Clinical Response

In the LUCENT-1 study, clinical response was evaluated using the MMS. After 12 weeks of treatment, a greater proportion of patients receiving mirikizumab 300 mg IV (versus placebo) achieved clinical response, with a common risk difference of 21.4% (99.875% confidence interval [CI], 10.8% to 32.0%; $P < 0.00001$). Sensitivity analyses in the intent-to-treat (ITT) population were consistent with the modified ITT (mITT) population results. In both the biologic-naïve and biologic-experienced subgroups, more patients achieved clinical response with mirikizumab than with placebo, with a common risk difference of 19.8% (95% CI, 11.3% to 28.3%; $P < 0.001$) and 23.9% (95% CI, 14.3% to 33.5%; $P < 0.001$), respectively. The magnitude of effect for both subgroups was consistent with the primary analysis. In the subgroups of patients using corticosteroids or immunomodulators at baseline, the observed effect sizes for clinical response in the mirikizumab

group compared to the placebo group were numerically positive but small when compared to the overall population. No subgroup differences were observed.

Clinical Remission

Clinical remission was assessed using 2 different outcomes in the LUCENT-1 trial: clinical remission and alternate clinical remission. Clinical remission was based on the MMS and defined as a stool frequency subscore of 0 or 1, with at least a 1-point decrease from baseline; a rectal bleeding subscore of 0; and an endoscopic subscore of 0 or 1 (excluding friability). Alternate clinical remission used the same definition except it excluded the need for an at least 1-point decrease from baseline. These were considered appropriate measures by the clinical expert.

Clinical Remission Rate

A greater proportion of patients receiving mirikizumab 300 mg IV (24.2%) versus placebo (13.3%) achieved clinical remission at week 12, with a common risk difference of 11.1% (99.875% CI, 3.2% to 19%; $P = 0.00006$). Analyses in the per-protocol and ITT population were consistent with the mITT population results. Results of the sensitivity analyses assessing the impact of attrition and missing data were consistent with the results from the primary analysis. In terms of the tipping point analysis, there was no significant difference between groups when imputing missing data as “responder” for the placebo group and “nonresponder” [from original source] for the mirikizumab group.

In both the biologic-naive and biologic-experienced subgroups, more patients receiving mirikizumab achieved clinical remission than those receiving placebo, with a common risk difference of 15.1% (95% CI, 8.3% to 21.9%; $P < 0.001$) and 6.8% (95% CI, 0.5% to 13.0%; $P = 0.065$), respectively. The magnitude of effect for the biologic-naive subgroup was consistent with the primary analysis. In the subgroups of patients using corticosteroids or immunomodulators at baseline, the observed effect sizes for clinical remission in the mirikizumab group compared to the placebo group were numerically positive but small when compared to the overall population.

Alternate Clinical Remission Rate

The results for alternate clinical remission, a slightly less stringent definition of remission, were aligned with the results of clinical remission.

Endoscopic Improvement

At week 12 of the LUCENT-1 trial, 36.3% of patients receiving mirikizumab achieved endoscopic improvement versus 21.1% of patients receiving placebo, with a common risk difference of 15.4% (99.875% CI, 6.3% to 24.5%; $P < 0.00001$). The analyses of the ITT population were consistent with the mITT population results.

In both the biologic-naive and biologic-experienced subgroups, more patients receiving mirikizumab achieved endoscopic improvement at week 12 than those receiving placebo, with a common risk difference of 17.9% (95% CI, 9.8% to 25.9%; $P < 0.001$) and 12.3% (95% CI, 5.2% to 19.4%; $P = 0.003$), respectively.

In the subgroups of patients using corticosteroids or immunomodulators at baseline, the observed effect sizes for endoscopic improvement in the mirikizumab group compared to the placebo group

were numerically positive but small when compared to the overall population. No subgroup differences were observed.



Symptomatic Remission

At week 12 of the LUCENT-1 study, 45.5% of patients receiving mirikizumab and 27.9% of patients receiving placebo achieved symptomatic remission, with a common risk difference of 17.5% (99.875% CI, 7.5% to 27.6%; $P < 0.00001$). The analyses of the ITT population were consistent with the mITT population results.

In both the biologic-naive and biologic-experienced subgroups, more patients achieved symptomatic remission at week 12 with mirikizumab than with placebo, with a common risk difference of 17.1% (95% CI, 8.7% to 25.4%; $P < 0.001$) and 18.8% (95% CI, 10.1% to 27.4%; $P < 0.001$), respectively.

In the subgroups of patients using corticosteroids or immunomodulators at baseline, the observed effect sizes for symptomatic remission in the mirikizumab group compared to the placebo group were numerically positive but small when compared to the overall population. No subgroup differences were observed.

Bowel Urgency Improvement – Urgency Numerical Rating Score

The Urgency Numerical Rating Score (UNRS) is an instrument used to assess patient-reported severity of bowel urgency in adults with UC with a 24-hour recall period. Using the UNRS, the least squares means (LSM) change from baseline at week 12 in the mirikizumab group was -2.59 points and -1.63 points in the placebo group, a difference of -0.95 points (99.875% CI, -1.5 points to -0.4 points; P value < 0.00001). The analyses of the ITT population were consistent with the mITT population results.

In the biologic naive subgroup, a greater improvement in UNRS was seen in the mirikizumab group (-2.7 points) versus the placebo group (-2.1 points), with an LSM difference of -0.6 points at week 12 (95% CI, -1.0 points to -0.2 points; $P = 0.002$). Similar results were seen in the biologic-experienced subgroup, but with a larger LSM difference of -1.5 points at week 12 (95% CI, -2.0 points to -1.0 points; $P < 0.001$).

In the subgroups of patients using corticosteroids or immunomodulators at baseline, the observed effect sizes for bowel urgency improvement in the mirikizumab group compared to the placebo group were numerically positive but small when compared to the overall population. No subgroup differences were observed.

Health-Related Quality of Life

HRQoL was assessed in the LUCENT-1 study based on IBDQ score, 5-Level EQ-5D score, and SF-36 score.

IBDQ Score

The IBDQ consists of a 32-item list, subdivided into 4 dimensions, including systemic symptoms, bowel symptoms, emotional function, and social function. Total scores range from 32 to 224, with a higher score

indicating a better HRQoL. The IBDQ has been consistently shown to have good internal consistency and test-retest reliability, as well as responsiveness to change in IBD. The available studies have suggested that an improvement of 30 points from baseline or an improvement of at least 15 points above placebo may constitute a minimal important difference (MID). In the LUCENT-1 trial, the mean change from baseline to week 12 in IBDQ score was 38.4 points for the mirikizumab group and 25.2 points for the placebo group, representing a difference of 13.2 points ($P < 0.001$) in favour of mirikizumab during the induction phase. The MID for IBDQ score was defined as a change greater than 30 points from baseline as well as an MID of greater than 15 points over placebo. While the improvement within the mirikizumab group demonstrated clinical benefit (exceeding the MID threshold of 30 points), it fell short of meeting the MID threshold of at least 15 points compared to the placebo group as defined by previous studies. Nevertheless, the clinical expert believed that the observed change was clinically meaningful in terms of improving quality of life.

SF-36 Score

In the LUCENT-1 trial, the mean change from baseline to week 12 in the SF-36 physical component summary (PCS) score was 5.97 points in the mirikizumab group and 3.90 points in the placebo group, with an LSM difference of 2.07 points (95% CI, 1.21 points to 2.93 points; $P < 0.001$). The mean change from baseline to week 12 in the SF-36 mental component summary (MCS) score was 5.02 points in the mirikizumab group and 3.42 points in the placebo group, with an LSM difference of 1.60 points (95% CI, 0.56 points to 2.63 points; $P = 0.002$). The change in the mirikizumab group was clinically important, but the clinical importance of the difference between groups is uncertain (i.e., MID = 3 points to 5 points).

Mucosal Healing – HEMI

In the LUCENT-1 trial, mucosal healing was assessed based on the HEMI outcome, which considers both histologic and endoscopic outcomes. At week 12, 27.1% of patients receiving mirikizumab achieved HEMI versus 13.9% of patients receiving placebo, with a common risk difference of 13.4% (99.875% CI, 5.5% to 21.4%; $P < 0.00001$). The analyses of the ITT population were consistent with the mITT population results.

In both the biologic-naïve and biologic-experienced subgroups, more patients who received mirikizumab than who received placebo achieved HEMI at week 12, with a common risk difference of 17.1% (95% CI, 9.8% to 24.3%; $P < 0.001$) and 8.4% (95% CI, 2.5% to 14.3%; $P = 0.022$), respectively. The magnitude of the difference in the biologic-naïve subgroup was consistent with the mITT population.

In the subgroups of patients using corticosteroids or immunomodulators at baseline, the observed effect sizes for HEMI in the mirikizumab group compared to the placebo group were numerically positive but small when compared to the overall population. No subgroup differences were observed.

Work Productivity

In the LUCENT-1 trial, work productivity was assessed using WPAI:UC score at week 12. The WPAI:UC is a self-administered, disease-specific scale that measures the level of work impairment due to UC. The

WPAI:UC considers the 4 domains of absenteeism, presenteeism, overall work performance, and nonwork activities. The 4 domains comprise a total of 6 items and the final scores for each domain are a percentage of total impairment, ranging from 0% to 100%, with a higher number indicating greater impairment in that domain. The WPAI:UC is a valid and responsive instrument for use in UC.

Among those employed at baseline (n = 566), patients receiving mirikizumab experienced a mean change in WPAI:UC of -20.65 compared to -14.91 in the placebo group (-5.74 point LSM difference; 95% CI, -10.06 to -1.42; P = 0.009).

Maintenance Period – The LUCENT-2 Trial

Clinical Remission

Clinical remission was assessed using 3 different outcomes in the LUCENT-2 trial: clinical remission, alternate clinical remission, and durable clinical remission. The same definition of clinical remission and alternate clinical remission used in the LUCENT-1 trial were used in the LUCENT-2 trial. Durable clinical remission was achieved if patients who achieved clinical remission at week 12 in the LUCENT-1 trial had ongoing remission at week 40 in the LUCENT-2 trial (i.e., 52 weeks of continuous clinical remission). These were considered appropriate measures by the clinical expert.

Clinical Remission

A greater proportion of patients receiving mirikizumab 200 mg SC (49.9%) versus placebo (25.1%) achieved clinical remission after 40 weeks of maintenance therapy (23.2% common risk difference; 95% CI, 15.2% to 31.2%; P < 0.001). The analyses of the per-protocol and ITT populations were consistent with the mITT population results. In addition, the results of the sensitivity analyses were consistent with the results from the primary analysis. In terms of the tipping point analysis, the difference between groups did not reach statistical significance when imputing missing data as “responder” for the placebo group and “nonresponder” for the mirikizumab group.

In terms of subgroups, more patients receiving mirikizumab than placebo were clinical remitters at the end of the LUCENT-2 trial for both the biologic-naive subgroup (51.5% versus 30.7%) and the biologic-failed subgroup (46.1% versus 15.6%; P < 0.001) with a common risk difference of 20.8% (95% CI, 10.2% to 31.5%; P < 0.001) and 30.5% (95% CI, 18.1% to 42.9%; P < 0.001), respectively. The magnitude of the effect in both subgroups was consistent with the primary analysis.

The subgroup results for baseline corticosteroid use (yes and no), immunomodulator use (no), and patients with severe UC at baseline were consistent with the results of the primary analysis. The subgroup results for immunomodulator use (yes) and patients with moderate UC at baseline were numerically positive but small when compared to the overall population. No subgroup differences were observed.

Alternate Clinical Remission

The results for alternate clinical remission, a slightly less stringent definition of remission, were similar to those of clinical remission.

Durable Clinical Remission

Of patients who achieved clinical remission at week 12 of the LUCENT-1 trial, 63.6% who were randomized to mirikizumab 200 mg SC were still in clinical remission at week 40 of the LUCENT-2 trial, compared to 36.9% of those randomized to placebo SC, with a common risk difference of 24.8% (95% CI, 10.4% to 39.2%; $P < 0.001$). The analyses of the ITT population were consistent with the mITT population results.

In the biologic-naïve subgroup, a greater number of patients in the mirikizumab group (62.5%) versus the placebo group (46.8%) achieved durable clinical remission at the end of the LUCENT-2 trial, with a common risk difference of 15.7% (95% CI, -1.3% to 32.7%; $P = 0.078$), although the effect size was small compared to the overall population. In the biologic-failed subgroup, a greater proportion of patients in the mirikizumab versus placebo group achieved durable clinical remission (66.7% versus 11.1%), with a common risk difference of 55.6% (95% CI, 34.4% to 76.7%; $P < 0.001$). However, the sample sizes for this subgroup were quite small.

The subgroup results for baseline corticosteroid use (no), baseline immunomodulator use (no), and patients with moderate and severe UC at baseline were consistent with the results of the primary analysis. The subgroup results of patients with baseline corticosteroid use (yes) and immunomodulator use (yes) were numerically positive but small when compared to the overall population. No subgroup differences were observed.

Corticosteroid-Free Remission

Corticosteroid-free remission was defined as clinical remission at week 40, symptomatic remission at week 28, and no corticosteroid use for at least 12 weeks before week 40.

At week 40, a greater number of patients randomized to mirikizumab achieved corticosteroid-free remission than those randomized to placebo (44.9% versus 21.8%; 21.3% common risk difference; 95% CI, 13.5% to 29.1%; $P < 0.001$).

In both the biologic-naïve and biologic-failed subgroups, more patients receiving mirikizumab than receiving placebo achieved corticosteroid-free remission, with a common risk difference of 20.4% (95% CI, 10.1% to 30.8%; $P < 0.001$) and 26.6% (95% CI, 14.5% to 38.6%; $P < 0.001$), respectively. The magnitude of effect in both subgroups was consistent with the primary analysis.

The subgroup results for baseline corticosteroid use (yes and no), immunomodulator use (yes and no), and patients with moderate and severe UC at baseline were consistent with the results of the primary analysis.

Endoscopic Remission

At week 40 of the LUCENT-2 trial, 58.6% of patients receiving mirikizumab achieved endoscopic remission versus 29.1% of patients receiving placebo, with a common risk difference of 28.5% in favour of mirikizumab (95% CI, 20.2% to 36.8%; $P < 0.001$). The analyses in the ITT population were consistent with the mITT population results.

In both the biologic-naive and biologic-failed subgroups, more patients achieved endoscopic remission at week 40 receiving mirikizumab than receiving placebo, with a common risk difference of 28.2% (95% CI, 17.5% to 39.0%; $P < 0.001$) and 30.5% (95% CI, 17.3% to 43.6%, $P < 0.001$), respectively.

Subgroup results for baseline corticosteroid use (yes and no), immunomodulator use (yes and no), and patients with moderate and severe UC at baseline were consistent with the results of the primary analysis.

Bowel Urgency

In the LUCENT-2 trial, bowel urgency outcomes consisted of bowel urgency remission and bowel urgency improvement as measured by the UNRS. The UNRS is an instrument used to assess patient-reported severity of bowel urgency in adults with UC with a 24-hour recall period.

Bowel Urgency Remission

Of the patients with a UNRS score of at least 3 at the LUCENT-1 trial baseline, 42.9% receiving mirikizumab and 25% receiving placebo at week 40 achieved bowel urgency remission, with a common risk difference of 18.1% in favour of mirikizumab (95% CI, 9.8% to 26.4%; $P < 0.001$). The analyses of the ITT population were consistent with results of the mITT population.

In both the biologic-naive and biologic-failed subgroups, more patients receiving mirikizumab than receiving placebo achieved bowel urgency remission at week 40, with a common risk difference of 17.9% (95% CI, 7.0% to 28.8%; $P = 0.002$) and 30.5% (95% CI, 17.3% to 43.6%; $P < 0.001$), respectively. The magnitude of the effect was similar to the primary analysis.

The subgroup results for baseline corticosteroid use (yes and no), immunomodulator use (yes and no), and patients with moderate and severe UC at baseline were consistent with the results of the primary analysis.

Bowel Urgency Improvement (Change in UNRS)

At week 40 of the LUCENT-2 trial, patients receiving mirikizumab experienced a -3.80 point change in UNRS versus the LUCENT-1 trial baseline, while patients randomized to placebo had a -2.74 point change in UNRS score from the LUCENT-1 trial baseline (-1.06 LSM difference; 95% CI, -1.51 to -0.61; $P < 0.001$). Patients receiving mirikizumab experienced a clinically significant improvement in bowel urgency from baseline, while those receiving placebo did not meet the MID threshold (MID = 3 points from baseline) for clinically significant improvement.

Health-Related Quality of Life

HRQoL was assessed in the LUCENT-2 trial based on IBDQ score, 5-Level EQ-5D score, and SF-36 score.

IBDQ Score

The IBDQ consists of a 32-item list, subdivided into 4 dimensions, including systemic symptoms, bowel symptoms, emotional function, and social function. Total scores range from 32 to 224, with a higher score indicating a better HRQoL. The IBDQ has been consistently shown to have good internal consistency and test-retest reliability, as well as responsiveness to change in IBD. The available studies have suggested that an improvement of 30 points from baseline or an improvement of at least 15 points above placebo may constitute an MID. In the LUCENT-2 trial, the LSM change from the LUCENT-1 trial baseline to week 40 in

the IBDQ score was 49.8 points for those in the mirikizumab group and 25.4 points for those in the placebo group, representing a statistically significant difference of 25.2 points in favour of mirikizumab (95% CI, 19.2 points to 31.3 points; $P < 0.001$). The difference between groups was considered clinically meaningful as the difference was above the MID of at least 15 points above placebo.

SF-36 Score

Only the LUCENT-2 trial evaluated change in the health outcome of the SF-36. At week 40, patients randomized to mirikizumab experienced an LSM change in SF-36 PCS of 9.0 points, compared to 6.7 points in patients randomized to placebo, a 2.3 point difference between groups ($P < 0.001$). In SF-36 MCS, patients receiving mirikizumab had an LSM change of 7.0 points, compared to 5.5 points in the placebo group (LSM change difference between groups = 1.5 points; $P = 0.031$). The change from baseline in the mirikizumab group appeared clinically important (i.e., an MID threshold of at least 3 points), but it is unclear whether the difference between groups is clinically important given that no MID was identified.

Mucosal Healing – HEMR

A greater proportion of patients randomized to mirikizumab achieved HEMR (a stricter outcome than HEMI) than those randomized to placebo at week 40 (43.3% versus 21.8%; 19.9% common risk difference; 95% CI, 12.1% to 27.6%; $P < 0.001$). The analyses of the ITT population were consistent with the mITT population results.

In both the biologic-naive and biologic-failed subgroups, HEMR occurred more often in patients receiving mirikizumab than those receiving placebo, with a common risk difference of 20.8% for the biologic-naive population (95% CI, 10.5% to 31.2%) and 21.2% for the biologic-failed population (95% CI, 10.9% to 31.4%). The magnitude of the effect was consistent with the primary analysis.

The subgroup results for baseline corticosteroid use (yes and no), immunomodulator use (yes and no), and patients with moderate and severe UC at baseline were consistent with the results of the primary analysis.

Work Productivity

The WPAI:UC is a self-administered, disease-specific scale that measures the level of work impairment due to UC. The WPAI:UC considers the 4 domains of absenteeism, presenteeism, overall work performance, and nonwork activities. The 4 domains comprise a total of 6 items and the final scores for each domain are a percentage of total impairment, ranging from 0% to 100%, with a higher number indicating greater impairment in that domain. The WPAI:UC is a valid and responsive instrument for use in UC. At week 40 of the LUCENT-2 trial, patients randomized to the mirikizumab group had an LSM of -31.72 points from the LUCENT-1 trial baseline, and patients randomized to placebo had an LSM of -22.59 points from the LUCENT-1 trial baseline, equating to an LSM difference of -9.13 points between groups (95% CI, -14.26 points to -4.01 points; $P < 0.001$). An MID was not identified for this outcome.

LUCENT-2 Extended Induction

Patients whose disease did not respond to mirikizumab or placebo during induction (12 weeks) in the LUCENT-1 trial went on to the LUCENT-2 trial to receive extended induction (additional 12 weeks) with open-label mirikizumab 300 mg IV for 3 doses. Of the patients receiving mirikizumab induction whose disease did not respond during the LUCENT-1 trial, 272 patients entered the open-label extended induction arm of the LUCENT-2 trial in the mITT population. Of these, 146 patients (53.7%) achieved a delayed clinical response (95% CI, 47.8% to 59.6%) at week 12 of the LUCENT-2 trial (i.e., after 24 weeks of continuous mirikizumab 300 mg IV every 4 weeks, for a total of 6 doses). Additionally for this cohort of 272 patients, at week 12 of the LUCENT-2 trial, the rates of clinical remission, endoscopic remission, and symptomatic remission were 11.4% (95% CI, 7.6% to 15.2%), 16.5% (95% CI, 12.1% to 21.0%), and 37.1% (95% CI, 31.4% to 42.9%), respectively. When considering clinical response at the end of the initial 12-week induction period and the extended induction period, it can be noted that 80% (697 of 868) of patients receiving mirikizumab 300 mg IV achieved a clinical response by the end of the 24 weeks.

Of the 146 patients whose disease showed a delayed response at week 12 in the LUCENT-2 trial, 144 (99%) entered the open-label maintenance period and 104 (72.2%) maintained clinical response at week 40 versus [REDACTED] of patients from the placebo group who entered the maintenance period. Clinical response at week 40 was not evaluated in the LUCENT-2 trials for the induction group of those whose disease responded to treatment from the LUCENT-1 trial; hence, no comment can be made on the difference in treatment effects between these 2 cohorts at week 40.

Harms Results

The key harms results from the pivotal trials are summarized in the following.

For both the LUCENT-1 and LUCENT-2 trials, the overall rate of adverse events (AEs) was similar between groups, though numerically slightly higher in the placebo groups compared to the respective treatment groups. In the LUCENT-1 trial, 44.5% and 46.1% of patients reported an AE in the mirikizumab and placebo groups, respectively. In the LUCENT-2 trial, 64.5% and 68.8% of patients reported an AE in the mirikizumab and placebo groups, respectively. In the LUCENT-1 trial, the most common AEs for patients receiving mirikizumab 300 mg IV included nasopharyngitis (mirikizumab = 4.1%; placebo = 3.1%), anemia (mirikizumab = 3.3%; placebo = 5.9%), and headache (mirikizumab = 3.3%; placebo = 2.8%). In the LUCENT-2 trial, the most common AEs for patients receiving mirikizumab 200 mg SC included nasopharyngitis (mirikizumab = 7.2%; placebo = 5.7%), arthralgia (mirikizumab = 6.7%; placebo = 4.2%), and UC (mirikizumab = 6.7%; placebo = 20.8%).

The rate of SAEs in the LUCENT-1 study was found to be lower in patients treated with mirikizumab than placebo (2.8% versus 5.3%); however, this was due to UC being included as a harm. In the LUCENT-2 trial, 3.3% and 7.8% of patients reported an SAE in the mirikizumab and placebo groups, respectively. In the LUCENT-1 trial, the most common SAEs in those receiving mirikizumab IV included UC (mirikizumab = 0.8%; placebo = 3.1%) and pneumonia (mirikizumab = 0.2%; placebo = 0%). In the LUCENT-2 trial, no SAE (at the “preferred term” level) occurred in more than 1 patient receiving mirikizumab SC.

Withdrawals due to an AE occurred at a lower rate in patients treated with mirikizumab than patients treated with placebo in the LUCENT-1 and LUCENT-2 trials. In the LUCENT-1 trial, 1.6% and 7.2% of patients withdrew from the trial due to an AE in the mirikizumab and placebo groups, respectively. In the LUCENT-2 study, 1.5% and 8.3% of patients withdrew from the trial due to an AE in the mirikizumab and placebo groups, respectively. [REDACTED]

In the LUCENT-1 trial, no deaths were recorded. In the LUCENT-2 trial, 1 (0.5%) death was recorded in the placebo group due to COVID-19.

Most AEs of special interest occurred at a similar rate between patients treated with mirikizumab and those treated with placebo in the LUCENT-1 and LUCENT-2 studies. One exception is the rate of injection site reactions in the LUCENT-2 trial, in which 8.7% of patients receiving mirikizumab SC experienced this AE of special interest compared to 4.2% of patients receiving placebo SC. The rates of opportunistic infection, cerebrocardiovascular events, malignancy, depression, suicide and/or self-injury, and hepatic-related AEs were low overall and similar between groups for both the LUCENT-1 and LUCENT-2 trials.

Critical Appraisal

Internal Validity

Overall, LUCENT-1 and LUCENT-2 were well-conducted trials. They were adequately powered to detect a difference between mirikizumab and placebo in the primary end point and employed an appropriate prespecified graphical multiple testing approach to control key secondary outcomes for multiplicity. Many of the primary and secondary outcomes, including clinical remission, alternate clinical remission, clinical response, symptomatic remission, bowel urgency remission and improvement, HRQoL, and work productivity, may be at risk of reporting bias and recall bias due to the subjective nature of the patient electronic reporting diary. However, the direction and magnitude of the bias are unknown. As well, there was a risk of attrition bias against mirikizumab due to higher attrition in the placebo arm compared with the intervention; however, sensitivity analyses of the primary end point and the key secondary end points of clinical remission and clinical response assessed the impact of missing data and showed that the results were consistent with the primary analysis, which increases the certainty of the findings. MIDs were provided by the sponsor for the IBDQ, EQ-5D, and SF-36 (PCS and MCS), which were in line with thresholds reported in the literature. Numerically, statistically significant improvements were observed in the mirikizumab group compared to the placebo group [REDACTED]. Notably, the IBDQ did reach the MID threshold for the change from baseline score (i.e., > 30 points) in the mirikizumab treatment groups in both the LUCENT-1 and LUCENT-2 trials, which the clinical expert acknowledged as a meaningful improvement. As for the between-group treatment difference, in the LUCENT-2 trial there was a greater change in the mirikizumab group versus the placebo group for IBDQ score, exceeding the MID threshold mentioned in the literature of greater than 15 points above placebo. However, in the LUCENT-1 trial, the IBDQ score fell short of reaching this 15-point MID threshold above the placebo group.

External Validity

In general, the clinical expert consulted by CADTH considered the baseline demographic and disease characteristics in the pivotal trials to be reflective of the patients with moderately to severely active UC seen in Canadian clinical practice. Concomitant medication use was also reflective of Canadian clinical practice, except for prednisolone, which is not typically used in Canada. In the LUCENT-2 trial, a corticosteroid taper was trialled on all patients in the main cohort. Patients who did not taper their steroid use were allowed to continue their treatment; however, this is in contrast to the input received from the clinical expert, in which patients would be considered treatment failures and discontinue therapy if they could not taper or stop concomitant corticosteroid use by the time of the maintenance phase (i.e., after the induction or extended induction period); therefore, the efficacy of mirikizumab in the trials may appear to be biased given that patients who could not taper were included in the primary analysis even though their UC would have been considered treatment failures in clinical practice. However, the direction and magnitude of this bias are unknown given that both groups underwent the same tapering protocol. Furthermore, the generalizability of the results may be limited to Canadian clinical practice given the discrepancy in tapering protocol. The number of screening failures were quite high in the LUCENT-1 trial (35%); however, this is similar to other UC trials. According to the clinical expert, potential reasons for the higher screening failure could be due to how patients were referred to the trial.

To be eligible for enrolment in the primary cohort of the LUCENT-2 trial, patients were required to achieve clinical response following 12 weeks of induction treatment in the LUCENT-1 trial. This requirement may have resulted in an enriched patient population that was included in the primary analysis of the maintenance trial as it does not take into consideration those whose disease had delayed response. Per the product monograph, mirikizumab is indicated for patients whose disease has delayed response; hence, by excluding these patients in the primary analysis, there is uncertainty about the efficacy of maintenance treatment in the broader population of patients with moderately to severely active UC. Other UC trials have similar concerns regarding enrichment given that they have used a similar study design. Patients who entered the LUCENT-2 trial as “nonresponders” received open-label mirikizumab; therefore, the results should be interpreted with caution given the potential risk of detection or performance bias due to the open-label nature. The clinical expert noted that the duration of follow-up in the LUCENT-1 trial (12 weeks) was not a sufficient amount of time to note a difference in endoscopic remission. However, the issue of insufficient duration is addressed by the LUCENT-2 trial, which measures end points to week 40 (e.g., 52 weeks of continuous therapy). Long-term data beyond 52 weeks are not available; hence, long-term outcomes (e.g., loss of response, harms) may not be sufficiently captured between the 2 trials.

Long-Term Extension Studies

There are currently no published or unpublished long-term extension phase III or IV randomized controlled trials (RCTs) or real-world evidence studies evaluating mirikizumab. The sponsor noted that there is an ongoing phase III, open-label, long-term extension trial enrolling patients from the LUCENT-2 trial and the phase II study (NCT02589665) into the LUCENT-3 trial (I6T-MC-AMAP), with an expected primary completion date of June 6, 2025.

Indirect Comparisons

Description of Studies

One sponsor-conducted indirect treatment comparison that compared the treatment effect of mirikizumab to other advanced therapies in adults with moderately to severely active UC via an NMA was included in the sponsor's submission. [REDACTED]

[REDACTED]

Critical Appraisal

The NMA was based on studies identified from a sponsor-conducted systematic literature review of relevant randomized evidence of European Medicines Agency- and FDA-approved treatments for adults with moderately to severely active UC. The systematic literature reviewed was based on a PICO (patient and population, intervention, comparison, and outcomes)-defined a priori and the literature search involved multiple electronic databases, clinical registries, and supplementary manual searches, thereby minimizing

error and bias in the study selection and data extraction process. The sponsor identified [REDACTED] other sources of heterogeneity across the included UC studies: [REDACTED]. To account for [REDACTED] in UC, the NMA evaluated an [REDACTED]. The network for this subgroup, however, was small, consisting of [REDACTED] studies at induction and maintenance, respectively, evaluating [REDACTED] interventions. To mitigate heterogeneity due to trial design (treat-through versus rerandomized designs), [REDACTED]. However, the CADTH review team was unable to confirm whether the method employed adequately adjusted for differences in design trial without introducing bias. Moreover, [REDACTED] were unlikely to account for the potential issues as [REDACTED]. To account for the potential for heterogeneity due to treatment history (biologic naive versus biologic experienced), [REDACTED]. However, the CADTH review team determined that the definition of biologic naive and biologic experience varied across studies (TNF naive versus TNF experienced; no biologic or JAK inhibitor failure versus biologic or JAK inhibitor failure; biologic naive versus biologic experience; no biologic failure versus biologic failure) [REDACTED]. The use of [REDACTED] would not account for these differences. The CADTH review team identified several other sources of heterogeneity that could not be adjusted for in the NMA, including differences in definitions of clinical response and remission, prior biologics exposure (due to time periods in which the studies occurred), permitted concomitant medications, outcome assessment methods and definitions, and duration of the maintenance period. The inclusion of comparator treatments not relevant to the Canadian setting (i.e., [REDACTED]) provided information to the network and is not expected to significantly impact the heterogeneity of the NMA above the previously mentioned other sources of heterogeneity mentioned. Violation of exchangeability assumptions for efficacy outcomes is likely due to heterogeneity, and several estimates were affected by wide credible intervals that increased uncertainty. Moreover, network consistency or coherence could not be assessed due to the lack of relevant closed loops when comparing mirikizumab to other active treatments. As a result, the NMA evidence was considered to be indirect, thus reducing certainty in the study findings.

Studies Addressing Gaps in the Pivotal and RCT Evidence

No relevant studies addressing gaps in the pivotal and RCT evidence were submitted.

Economic Evidence

Note that the sponsor's application was filed on a pre-Notice of Compliance basis and the pharmacoeconomic submission is reflective of the indication and proposed dosage regimen that was initially submitted to Health Canada and CADTH. The sponsor's submission included a reinduction dosage regimen for patients who experience a loss of response during maintenance treatment, which has not been included in the Health Canada-approved product monograph.

Cost and Cost-Effectiveness

Table 3: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Decision tree with Markov model
Target population	Adults with moderately to severely active UC who have had an inadequate response, lost response, or were intolerant to either conventional therapy, a biologic treatment, or a JAK inhibitor or have medical contraindications to such therapies. The 2 key subgroups were reported separately: patients who were biologic naive and patients who were biologic experienced.
Treatment	Mirikizumab
Dose regimen	The recommended induction dose is 300 mg IV at week 0, 4, 8, and 12. If patients do not have adequate therapeutic response at week 12, consider extending the induction dose, 300 mg IV, at weeks 12, 16, and 20. The recommended maintenance dose is 200 mg, given as 2 consecutive SC injections of 100 mg each, every 4 weeks.
Submitted price	300 mg/15 mL: \$2,374.66 per vial 100 mg/mL: \$1,187.33 per autoinjector pen for SC injection 100 mg/mL: \$1,187.33 per prefilled syringe for SC injection
Treatment cost	Induction phase: \$7,123.98 per patient (at 12 weeks of treatment) to \$14,247.96 per patient (at 24 weeks of treatment) Maintenance phase: \$30,977 per patient
Comparators ^a	<ul style="list-style-type: none"> • TNF inhibitors (adalimumab [brand and biosimilar], infliximab [brand and biosimilar], golimumab) • JAK inhibitors (tofacitinib, upadacitinib 45 mg/15 mg, upadacitinib 45 mg/30 mg) • Alpha4beta7 integrin inhibitor (vedolizumab [IV and SC]) • S1P receptor (ozanimod) • CT (combination of aminosalicylates, corticosteroids, and immunomodulators)
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (assumed to be 50 years)
Key data sources	LUCENT-1 trial, LUCENT-2 trial, and a sponsor-commissioned unpublished NMA
Key limitations	<ul style="list-style-type: none"> • The CADTH clinical review identified several key sources of heterogeneity in the sponsor-submitted NMA comparing mirikizumab with other advanced therapies (i.e., biologics, JAK inhibitors, and small molecule drugs). These data were used to inform comparative effectiveness as well as loss of response over time, the latter of which was a key driver of the modelled results. Given the limitations with the indirect evidence, the comparative clinical efficacy of mirikizumab and advanced therapies is uncertain. • The relative treatment effect of extended induction and/or reinduction with mirikizumab is uncertain due to the observational nature of the data collected in the LUCENT trials. • Loss of response was assumed to remain constant over the duration of the maintenance phase. Published literature note attenuation of response over time. • As long-term efficacy data beyond 52 weeks are not available for mirikizumab, its relative

Component	Description
	<p>long-term effectiveness is uncertain.</p> <ul style="list-style-type: none"> The price of tofacitinib in the sponsor’s analysis does not reflect the current formulary price. The comparators in the sponsor’s analyses do not reflect the current relevant comparators for mirikizumab. Upadacitinib was under review at CADTH and did not have Health Canada approval for use in UC at the time the CADTH reports were completed for review by the committee.^b Furthermore, infliximab and golimumab were excluded from the biologic-experienced population. The model lacked transparency and flexibility, and produced errors when running probabilistically.
CADTH reanalysis results	<ul style="list-style-type: none"> CADTH conducted reanalyses by applying the following changes: assuming an equal probability of clinical response, remission, loss of response, and serious infections between mirikizumab and all advanced therapies; excluding the treatment effect of mirikizumab extended induction; and excluding upadacitinib as a comparator. In the CADTH base case, CT, tofacitinib, and mirikizumab were on the cost-effectiveness frontier in both the biologic-naive and biologic-experienced populations. <ul style="list-style-type: none"> Compared with tofacitinib, mirikizumab was associated with an ICER of \$3,758,347 per QALY (incremental costs = \$159,805; incremental QALYs = 0.043) in the biologic-naive population and an ICER of \$2,608,809 per QALY (incremental costs = \$89,769; incremental QALYs = 0.034) in the biologic-experienced population. This incremental benefit was primarily due to the way utility values were calculated in the induction phase and the difference in duration for mirikizumab compared with other advanced therapies. A price reduction of approximately 65% would be needed for mirikizumab to be cost-effective at a WTP threshold of \$50,000 per QALY based on the CADTH analysis. CADTH allowed for the consideration for dose escalation of comparators in line with clinical expert feedback in its base case. Assuming equal efficacy, safety, and treatment usage between mirikizumab and advanced therapies, a price reduction of at least 83% is required for mirikizumab to be no more costly than the publicly available price of the least costly advanced therapy (tofacitinib).

CT = conventional therapy; ICER = incremental cost-effectiveness ratio; JAK = Janus kinase; LY = life-year; NMA = network meta-analysis; QALY = quality-adjusted life-year; SC = subcutaneous; S1P = sphingosine 1-phosphate; TNF = tumour necrosis factor; UC = ulcerative colitis; WTP = willingness to pay.

^aThe comparators were the same for the biologic-naive and biologic-experienced cohorts except that golimumab and infliximab were excluded from the biologic-experienced cohort due to a lack of data to facilitate a comparison for that population.

^bUpadacitinib subsequently received a draft recommendation from CADTH to reimburse with conditions and criteria, after receiving its Notice Of Compliance for this indication from Health Canada.

Budget Impact

CADTH identified the following key limitations with the sponsor’s analysis: the sponsor’s use of a claims-based approach to estimate market size and treatment costs introduced uncertainty with the anticipated budget impact of mirikizumab. The comparators from which the market share of mirikizumab was captured was uncertain and the market share of comparators was uncertain. Due to the limitations with the sponsor’s claims-based analysis, which could not be adequately validated or addressed, CADTH did not conduct base-case reanalyses. Given that mirikizumab has a higher acquisition cost than its comparator treatments, at the submitted price it will lead to an incremental cost to the CADTH-participating public drug plans. It should be noted that the sponsor’s estimated incremental cost of \$15,384,071 over 3 years is highly uncertain.

Request for Minor Reconsideration

The sponsor filed a request for minor reconsideration of the draft recommendation for mirikizumab, indicated for the treatment of adult patients with moderately to severely active UC who have had an inadequate response, loss of response, or were intolerant to conventional therapy, a biologic treatment, or a JAK inhibitor. In their request, the sponsor identified 1 issue.

- According to the sponsor, tofacitinib is not appropriate as the sole comparator for mirikizumab.
 - “The draft recommendation states that mirikizumab should not be priced higher than tofacitinib due to a lack of direct evidence comparing the 2 molecules. However, this conclusion is refuted by clear differences in safety profiles and utilization.”

In the meeting to discuss the sponsor’s request for minor reconsideration, the CDEC committee subpanel considered the following sources of information:

- feedback from the sponsor
- feedback from 1 clinician group, a group of gastroenterologists from Canada
- feedback from 2 patient groups, the GI Society and Crohn’s and Colitis Canada
- information from the initial submission relating to the issue identified by the sponsor
- input from participating drug plans
- input from 1 clinical specialist with expertise in the diagnose and management of patients with UC.

All stakeholder feedback that was received from clinician groups, patient groups, and the public drug programs in response to the draft recommendation is available on the CADTH website.

CDEC Information

Members of the Committee

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunsky, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Mr. Morris Joseph, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, and Dr. Peter Zed

Meeting date: July 27, 2023

Regrets: Three expert committee members did not attend.

Conflicts of interest: None

Minor reconsideration CDEC committee subpanel meeting date: November 2, 2023



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