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CADTH Reimbursement Recommendation

Risankizumab (Skyrizi)

Indication: For the treatment of adults with moderately to severely active Crohn's disease who have an inadequate response, intolerance, or demonstrated dependence to corticosteroids; or an inadequate response, intolerance, or loss of response to immunomodulators or biologic therapies

Sponsor: AbbVie Corporation

Final recommendation: Reimburse with conditions

Note: This document was initially published on May 31, 2023, and subsequently revised on August 22, 2023, to correct an error in the results for the cost of the drug.

Summary

What Is the CADTH Reimbursement Recommendation for Skyrizi?

CADTH recommends that Skyrizi be reimbursed by public drug plans for the treatment of moderately to severely active Crohn disease (CD) if certain conditions are met.

Which Patients Are Eligible for Coverage?

Skyrizi should only be covered to treat adult patients with moderately to severely active CD who do not respond to, stop responding to, or who cannot tolerate conventional or biologic therapies.

What Are the Conditions for Reimbursement?

Skyrizi should only be reimbursed if prescribed by a physician experienced in the diagnosis and management of CD, if it is not used in combination with other biologics, and if the cost of Skyrizi is reduced so that it does not cost the drug programs more than the least costly biologic therapy. Patients must respond to treatment in the first 12 weeks of starting Skyrizi to continue receiving the drug.

Why Did CADTH Make This Recommendation?

- Three clinical trials in patients with moderately to severely active CD who had inadequate response or were intolerant to prior conventional or biologic therapies were assessed in this review. In all of these trials, patients treated with Skyrizi showed an improved clinical remission and endoscopic response compared with patients wo were treated with placebo.
- Based on the evidence, Skyrizi may meet some of the needs that were identified as important to patients with CD, such as improving symptoms and health-related quality of life.
- Based on CADTH's assessment of the health economic evidence, Skyrizi 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 Skyrizi compared with other biologic therapies reimbursed for the treatment of adult patients with moderately to severely active CD.
- Based on public list prices, Skyrizi is estimated to cost the public drug plans approximately $56 million over the next 3 years.

What Is CD?

CD is a chronic form of inflammatory bowel disease that can affect any part of the gastrointestinal tract, but commonly affects the small intestine,

Summary

colon, and rectum. For many patients with CD, symptoms are chronic and sporadic, and disease severity can vary widely over time. It is estimated that CD affects more than 135,000 people in Canada.

Unmet Needs in CD

Patients with CD expressed a need for effective treatments that reduce symptoms, achieve sustained remission or response, reduce corticosteroid use, and improve quality of life.

How Much Does Skyrizi Cost?

Treatment with Skyrizi is expected to cost approximately $41,338 per patient in the first year and $29,855 per patient in subsequent years.

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that risankizumab be reimbursed for the treatment of adults with moderately to severely active Crohn disease (CD) who have had an inadequate response, intolerance, or demonstrated dependence to corticosteroids; or an inadequate response, intolerance, or loss of response to immunomodulators or biologic therapies, only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

Evidence from 3 phase III, double-blind, randomized, placebo-controlled trials (MOTIVATE, ADVANCE, and FORTIFY) showed that, compared with placebo, treatment with risankizumab resulted in statistically significant and clinically meaningful improvements in the co-primary outcomes of clinical remission and endoscopic response after 12-week induction treatment (600 mg IV) and 52-week maintenance treatment (360 mg subcutaneous [SC]) in adults with moderate to severe CD who had inadequate response or were intolerant to prior conventional or biologic therapies. In the MOTIVATE induction trial, the adjusted between-group differences (risankizumab versus placebo) at 12 weeks were 22.1% (95% confidence interval [CI], 13.1% to 31.0%; P < 0.001) for the Crohn's Disease Activity Index (CDAI) clinical remission rate, 15.2% (95% CI, 6.4% to 24.0%; P = 0.001) for the stool frequency and abdominal pain score (SF/APS) clinical remission rate, and 17.7% (95% CI, 9.9% to 25.4%; P < 0.001) for the endoscopic response rate. In the ADVANCE induction trial, the adjusted between-group differences at 12 weeks were 20.7% (95% CI, 12.4 to 29.0; P < 0.001) in CDAI clinical remission rate, 21.9% (95% CI, 13.8 to 29.9; P < 0.001) in SF/APS clinical remission, and 28.3% (95% CI, 21.2% to 35.4%; P < 0.001) in endoscopic response rate. The effects observed in the MOTIVATE and ADVANCE trials were maintained over the longer term. In patients who achieved clinical response in the induction trials and continued into the FORTIFY maintenance trial, the adjusted between-group differences at 52 weeks were 14.6% (95% CI, 4.3 to 25.0; P = 0.005) in CDAI clinical remission rate, 15.2% (95% CI, 4.9 to 25.4; P = 0.004) in SF/APS clinical remission rate, and 27.8% (95% CI, 18.7 to 37.0; P < 0.001) in endoscopic response rate. Risankizumab treatment may be associated with improvement in other clinical symptoms (e.g., fatigue) and health-related quality of life (HRQoL) in the induction trials, although in general these improvements could have been affected by bias, due to the subjective nature of the outcomes and because the CIs include the potential for effects that are not clinically important.

Patients indicated there is a need for effective treatments that reduce symptoms, achieve sustained remission or response, reduce corticosteroid use, and improve HRQoL. CDEC concluded that risankizumab may address some of these needs, as it is effective in inducing and maintaining clinical remission and endoscopic response and reducing clinical symptoms, and may improve HRQoL in patients who have inadequate response, lose response, or experience intolerance to other treatments.

Using the sponsor-submitted price for risankizumab and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for risankizumab was $535,031 per quality-adjusted life-year (QALY) compared to SC vedolizumab in patients with inadequate response, lost response, or intolerance

to biologic therapies; and risankizumab was dominated by (i.e., more costly and less effective than) ustekinumab in patients with inadequate response, lost response, or intolerance to conventional care. At these ICERs, risankizumab is not cost-effective at a $50,000 per QALY willingness to pay (WTP) threshold for adults with moderately to severely active CD who have had an inadequate response, intolerance, or demonstrated dependence to corticosteroids; or an inadequate response, intolerance, or loss of response to immunomodulators or biologic therapies. A price reduction is required for risankizumab to be considered cost-effective at a $50,000 per QALY threshold.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Eligibility for risankizumab should be based on the criteria used by each of the public drug plans for other biologic therapies 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 conventional or biologic therapies.	The results of the MOTIVATE, ADVANCE, and FORTIFY placebo-controlled RCTs demonstrated that risankizumab is an effective and safe treatment for moderately to severely active CD who have had an inadequate response, a loss of response, or intolerance to conventional or biologic therapies. Part 1 of the SEQUENCE trial and the indirect evidence were insufficient to definitively conclude the relative efficacy and safety of risankizumab compared to other biologics currently reimbursed for the treatment of adult patients with moderately to severely active CD.	The definitions of moderately to severely active CD and inadequate response, intolerance, or loss of response to other therapies should align with the definitions used for other reimbursed biologics.
Renewal		
2. The patient must have achieved clinical response to induction therapy after 12 weeks of treatment to continue to maintenance therapy.	In the MOTIVATE and ADVANCE induction trials, patients had to have a clinical response at the end of the induction period at week 12 to continue to the maintenance period in the FORTIFY trial.	Clinical response is defined as a reduction of CDAI score greater than or equal to 100 points, or an HBI score of 5 or less, or a decrease in HBI score of 4 or more. Endoscopic follow-up is not required if clinical response continues to be achieved. CDEC considered the impracticality of requiring endoscopy within 12 weeks of treatment initiation, given the invasive nature of the procedure and potential difficulties with timely access to the procedure. The clinical expert noted that surrogate markers such as fecal calprotectin and resolution of anemia can be used. Ultimately, CDEC considered it appropriate to leave the determination of clinical response up to the clinical judgment of the treating physician.

Reimbursement condition	Reason	Implementation guidance
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 risankizumab.	Patients who lose response to risankizumab are no longer benefiting from treatment.	—
Prescribing		
4. Risankizumab should only be prescribed by a physician experienced in the diagnosis and management of CD.	It is important to ensure that risankizumab is only prescribed for appropriate patients.	—
5. Risankizumab should not be reimbursed when used in combination with other biologic therapies for CD.	There is no evidence to support the use of risankizumab in combination with another biologic therapy for CD.	Risankizumab may be used in conjunction with conventional therapy.
Pricing		
6. Risankizumab should be negotiated so that it does not exceed the drug program cost of treatment with the least costly biologic therapies reimbursed for the treatment of adult patients with moderately to severely active CD.	No definitive conclusions could be drawn on the efficacy and safety of risankizumab relative to active comparators in both conventional care failure and biologic failure patients with CD. As such, there is insufficient evidence to justify a cost premium for risankizumab over the least expensive biologic therapy reimbursed for adult patients with moderately to severely active CD who have had an inadequate response, a loss of response, or intolerance to conventional or biologic therapies.	—

CD = Crohn disease; CDAI = Crohn's Disease Activity Index; CDEC = CADTH Canadian Drug Expert Committee; HBI = Harvey-Bradshaw Index; RCT = randomized controlled trial.

Discussion Points

- Risankizumab provides another treatment option for CD. CDEC noted that there is uncertainty in the relative efficacy and safety of risankizumab versus active comparators in the Canadian setting due to limitations of the indirect comparative evidence. [redacted]. In addition, there were several notable sources of heterogeneity across the trials included in the sponsor-submitted network meta-analysis (NMA). Also, uncertainty was found in the results of 2 published NMAs due to limitations such as inadequately addressed heterogeneity and a lack of detail on how the NMAs were carried out. Due to the uncertainty in the indirect evidence,

CDEC was unable to determine the relative efficacy of risankizumab compared to other biologic therapies.

- CDEC also considered evidence from the SEQUENCE trial, which is an ongoing phase III trial that aimed to evaluate the comparative efficacy and safety of risankizumab compared to ustekinumab. In part 1 of the SEQUENCE trial, preliminary data from an interim analysis showed [redacted]. However, these interim results are at risk of overestimating the treatment effect, as they represent only [redacted] of the patients ongoing in the trial. Due to the limitations of the preliminary data from the SEQUENCE trial, CDEC could not draw definitive conclusions regarding the relative efficacy of risankizumab compared to ustekinumab.
- CDEC concluded that evidence from the MOTIVATE, ADVANCE, and FORTIFY trials demonstrated that induction and maintenance therapy with risankizumab was safe and well tolerated compared to placebo. Due to limitations of the preliminary data from the SEQUENCE trial comparing risankizumab to ustekinumab, and the indirect treatment comparisons, CDEC was unable to determine the relative safety of risankizumab compared to other biologic therapies used to treat CD.
- Patients described negative impacts of CD on quality of life. In both induction trials, multiplicity-adjusted secondary outcomes —Inflammatory Bowel Disease Questionnaire (IBDQ) and SF-36 physical component summary (PCS) scores at week 12 — favoured risankizumab over placebo. As such, CDEC concluded that treatment with risankizumab could have a beneficial effect on HRQoL. However, CDEC noted that the impact of risankizumab on HRQoL beyond 12 weeks is uncertain. In the FORTIFY maintenance trial, which included only clinical responders from the induction trials, the evidence was insufficient to show a difference between risankizumab and placebo for the ranked secondary outcomes IBDQ, FACIT-F, and SF-36 PCS scores change from baseline induction at week 52.
- CDEC noted that some patients in the MOTIVATE and ADVANCE trials did not achieve clinical response in the first induction period, and then achieved clinical response during a second exploratory 12-week induction period with different doses of risankizumab. However, the doses of risankizumab used in the second induction period did not align with the recommended dosage in the Health Canada product monograph. CDEC concluded that there is currently insufficient evidence to support a second induction period and dosing beyond the Health Canada recommended dose.

Background

CD is a chronic form of inflammatory bowel disease (IBD) that can affect any part of the gastrointestinal tract, but commonly affects the ileum (i.e., small intestine), colon (i.e., beginning of the large intestine), and rectum. Common symptoms experienced by patients with CD include abdominal pain, rectal bleeding, fatigue, vomiting, diarrhea, perianal disease, weight loss, and bloating. Complications associated with CD can include malnutrition, weight loss, anemia, bowel obstructions, fistulas, anal fissures, intra-abdominal and other abscesses, and ulcers. In addition, patients with colonic CD have been shown to have an increased

risk of developing colon cancer. Smoking, family history of IBD, infectious gastroenteritis, and frequent use of nonsteroidal anti-inflammatory drugs have been identified as risk factors.[4] For many patients with CD, symptoms are chronic and intermittent, and disease activity and severity can vary widely over time. The predicted prevalence of CD in 2018 was 368 per 100,000 population, which translates to approximately 135,000 people in Canada living with CD.

Currently, there is no cure for CD. Therapeutic goals include inducing and maintaining clinical and endoscopic remission. Pharmaceutical treatments for CD include aminosalicylates, immunosuppressants, corticosteroids, tumour necrosis factor alpha (TNF-alpha) antagonists, interleukin (IL) inhibitors, and integrin inhibitors. Medical management is based on a stepwise approach, with treatments used sequentially and escalated to either newer therapies or higher doses as patients fail to respond to each step of treatment. Not all patients respond to available treatments and their disease may become refractory to the current treatment regimens.

Risankizumab (Skyrizi) is a humanized immunoglobulin G1 monoclonal antibody that binds to the p19 subunit of human interleukin 23 cytokine and inhibits IL-23 signalling, including the release of the proinflammatory cytokine, IL-17. Risankizumab is indicated for the treatment of adults with moderately to severely active CD who have had an inadequate response, intolerance, or demonstrated dependence to corticosteroids; or an inadequate response, intolerance, or loss of response to immunomodulators or biologic therapies. The sponsor-submitted reimbursement criteria for risankizumab are the same as in the Health Canada–approved indication. The recommended dose for CD is 600 mg IV infusion at weeks 0, 4, and 8 as induction therapy, followed by 360 mg SC injection at week 12, and every 8 weeks thereafter as maintenance therapy.

Sources of Information Used by the Committee

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

- a review of 4 randomized controlled trials (RCTs) in adult patients with moderate to severe CD, 1 NMA submitted by the sponsor, and 2 published NMAs
- patients' perspectives gathered by 2 patient groups: the Gastroenterological (GI) Society, and Crohn's and Colitis Canada (CCC)
- input from public drug plans that participate in the CADTH review process
- input from 1 clinical specialist with expertise diagnosing and treating patients with CD
- input from 1 clinician group: the Pan-Canadian Inflammatory Bowel Disease Specialist Group
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

The information in this section is a summary of input provided by the patient groups who responded to CADTH's call for patient input and from 1 clinical expert consulted by CADTH for the purpose of this review.

Patient Input

Two patient groups, CCC and the GI Society, provided input for this review. CCC's input was informed by the *Impact of Inflammatory Bowel Disease in Canada* report, a survey involving 687 respondents with moderate to severe CD, and interviews with 3 patients with CD who participated in the risankizumab clinical trial. The GI Society's input was informed by 5 patient surveys involving more than 1,000 participants; interviews with 2 patients with CD who participated in the risankizumab trial; focus groups; patient roundtables; phone, email, and social media interactions; and story submissions.

Both patient groups emphasized the importance of symptom relief, reducing pain, achieving and retaining remission, improving quality of life, minimizing chronic steroid use, and having access to a variety of effective treatment options. In particular, the inability to predict when the next urgent of bowel movement would occur and the inability to control flare-ups had a significant negative impact on the personal and social lives of patients with CD.

Clinician Input

Input From Clinical Expert Consulted by CADTH

The clinical expert noted the following unmet needs of patients with CD: some patients do not respond to available treatments and some become refractory over time, access to biologic agents is challenging or limited, and there is a lack of treatment options for fibrostenotic strictures and perianal or fistulizing CD.

The clinical expert noted that risankizumab is not expected to cause a shift in the treatment paradigm; they indicated it would be used in a similar fashion as other biologic treatments for CD, and likely prescribed alone or with a steroid taper or immunomodulator. The expert also noted that risankizumab could be used as first-line or as a later treatment. However, the expert noted that due to a lack in data for fistulizing CD, these patients should try other treatments such as anti-TNF therapy before risankizumab.

The clinical expert commented that patients who are most in need are those with moderate to severe disease that have failed other biologic therapies, although patients who are naive to biologic therapies may have an even better response. Patients best suited for treatment with risankizumab should have an established diagnosis of CD based on ileocolonoscopy with active disease.

The clinical expert noted the following outcomes are used to determine patient response to treatment: clinical response or remission (e.g., improvement in symptoms such as pain or diarrhea), improvement in biomarkers, mucosal healing (e.g., endoscopic improvement), and improved HRQoL. The clinical expert noted discontinuation of treatment should be based on primary or secondary loss of response, or adverse events (AEs) or symptoms that cannot be managed. It was noted by the expert that a gastroenterologist

should be required to diagnose, treat, and monitor patients who might receive risankizumab, either in a community or hospital setting.

Clinician Group Input

One clinician group input was provided by the Pan-Canadian Inflammatory Bowel Disease Specialist Group, which consists of specialists in gastroenterology caring for patients with CD. Their input was informed by 16 specialists.

The clinician group noted that the goal of treatment should focus on improving clinical symptoms, endoscopic response, and endoscopic remission. The clinician group stated there is a lack of safe and effective treatments for rapidly improving endoscopic outcomes of CD and maintain improvement in the long term. Risankizumab was suggested to be used in patients with moderate to severe CD as first-line therapy, as well as second-line therapy for patients experiencing flares or inadequate response to biologics. The clinician group indicated that risankizumab is not suitable for patients with perianal fistulizing CD, severe peripheral arthritis, uveitis, or a concomitant immune-mediated disease.

The clinician group indicated that administration of risankizumab during the induction phase should occur in a clinic under the supervision of a gastroenterologist. For maintenance therapy, the clinician group indicated patients could self-administer SC risankizumab after training. Aligning with the opinion from the clinical expert consulted by CADTH, the clinician group proposed the following outcomes to determine treatment response with risankizumab: improvements in symptoms (e.g., stool frequency, abdominal pain), reduction in biomarkers (e.g., C-reactive protein, fecal calprotectin) of inflammatory activity by 3 months of therapy, symptomatic remission, discontinuation of corticosteroids by 6 months of treatment, and improvements in HRQoL. The clinician group indicated risankizumab should be discontinued when symptoms worsen or there is inadequate response.

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	Response
Relevant comparators	
There were 3 multicentre, double-blind, placebo-controlled clinical trials. Two of these are phase III induction studies (MOTIVATE and ADVANCE), and 1 is a phase III maintenance study (FORTIFY). Placebo was not the most appropriate choice of comparator. There is also the SEQUENCE trial, a randomized phase III study comparing risankizumab directly with ustekinumab. Part 1 is a head-to-head trial over 48 weeks. Despite being approved for a similar indication, given that ustekinumab is not listed under most public drug plans, it is not an appropriate comparator.	Comment from the drug plans to inform CDEC deliberations.

Implementation issues	Response
Considerations for initiation of therapy	
The main inclusion criteria for the 2 induction trials included patients whose CDAI score is between 250 and 450 at baseline. Is the CDAI an acceptable and expected score to request on initiation of risankizumab? If an alternative scoring system can be accepted, please specify (e.g., HBI).	The clinical expert noted that CDAI is an acceptable scoring system, although in clinical practice HBI is more commonly used and should be the requested tool. CDEC agreed that both the CDAI and HBI can be used.
One of the exclusions in the trials were patients with a current diagnosis of UC or indeterminate colitis. Can CDEC confirm that patients deemed to have a comorbid diagnosis of UC will not be eligible for coverage?	CDEC noted that patients with a comorbid diagnosis of UC or indeterminate colitis were excluded from the MOTIVATE, ADVANCE, FORTIFY, and SEQUENCE trials; therefore, CDEC did not review evidence supporting the efficacy and safety of risankizumab in these patients. The clinical expert noted that the treatment approach for patients with both CD and UC compared to those with only CD is similar. The clinical expert also noted that it may be possible to use risankizumab in patients with indeterminate colitis, as it is more likely CD than UC.
In the MOTIVATE trial, patients must have had demonstrated intolerance or inadequate response to biologic therapy for CD, and in the ADVANCE trial, patients must have had demonstrated intolerance or inadequate response to conventional therapies OR biologic therapy for CD. Neither induction trial studied only patients who had failed or been intolerant to conventional therapies. Although consistent with the approved indication, this poses a concern for drug plans who might see new beneficiaries, with previous failure or intolerance to a biologic drug for CD, but who would not have met the coverage criteria for that biologic. It creates a "loophole" in obtaining public drug plan coverage.	Comment from the drug plans to inform CDEC deliberations.
The SEQUENCE trial contained 2 parts. Part 2 was an open-label trial to evaluate the long-term safety of risankizumab up to 220 weeks in patients who received risankizumab during part 1 and completed the week 48 visit. It allowed patients who demonstrated inadequate response during part 2 to receive open-label IV risankizumab rescue therapy, comprised of one dose of 600 mg IV followed by 360 mg SC at the next scheduled dose. Patients are eligible to receive up to 2 rescue visits per year, and these must be at least 16 weeks apart. Can CDEC comment if patients would be eligible for rescue doses of risankizumab under recommended criteria?	CDEC did not review part 2 of the SEQUENCE trial because the trial is ongoing, and the data were not available at the time of this review. CDEC did not review evidence supporting rescue doses of risankizumab and therefore could not comment, because it is outside the scope of this review.
Considerations for continuation or renewal of therapy	
The sponsor highlighted that desired CD treatment outcomes should include a focus on deep remission, referring to endoscopic healing and clinical remission. Other treatment goals included improved patient-reported outcomes and avoidance of long-term steroid use. Would endoscopic response, SF/APS, and CDAI all be considered a requirement for therapy renewal or would one, or a combination of the 3 be considered?	The clinical expert noted that stool frequency and abdominal pain are the 2 main symptoms of CD, which are calculated in the HBI. The HBI is considered the standard tool used in Canada and correlates well with CDAI. The clinical expert noted that endoscopy is typically performed every 8 to 12 months. Because of the invasive nature of endoscopy and potential difficulties with timely access to the procedure in Canada, more often people would use surrogate markers like fecal calprotectin and resolution of anemia to

Implementation issues	Response
Which primary outcomes do you feel would be most typical of Canadian practice and therefore most appropriate for consideration when assessing response for renewal purposes? How common is it for patients with CD to undergo regular endoscopic testing to assess treatment response? Is it reasonable to expect patients to undergo endoscopic testing to evaluate response, for consideration of renewal of treatment coverage? If so, when should the testing occur? If CDAI is the most appropriate outcome for assessment, would another scoring system (e.g., HBI) be appropriate for assessment of response for renewal of coverage under public drug plans? If so, what would be the equivalent HBI remission score comparable to CDAI remission of < 150?	assess healing. The clinical expert indicated that mandatory endoscopy for renewal would be unrealistic and stressful for patients. The clinical expert noted that HBI would be acceptable and appropriate for assessment of response for renewal of coverage. The equivalent HBI remission score comparable to CDAI would be 4 or less. CDEC agreed with the responses provided by the clinical expert.
Consideration for discontinuation of therapy	
At what point would a patient be deemed to have an LOR to risankizumab? Which parameters would be most appropriate to determine this?	CDEC agreed with the clinical expert, who noted that LOR would be if the patient is no longer clinically well after maximizing therapy. Many biologics allow for dose optimization or dose escalation, and as such, the patient would have to show a nonresponse to therapy despite being on an optimized dose. Sometimes a patient has a partial response or partial loss of response; therefore, optimizing the therapy should be done before determining LOR. If a patient's fecal calprotectin and HBI is normal, the clinical expert indicated that they likely would not conduct an endoscopy.
If there is a treatment interruption for any reason other than intolerance of LOR, would the patient be eligible for reinitiation dosing?	CDEC agreed with the clinical expert, who indicated that the patient would be eligible for reinitiation of dosing if there is a treatment interruption for any reason other than intolerance.
Considerations for prescribing of therapy	
The dosing consists of 600 mg IV infusion at weeks 0, 4, and 8, then maintenance 360 mg SC starting at week 12, continued every 8 weeks after the first maintenance dose.	Comment from the drug plans to inform CDEC deliberations.
The loading doses of risankizumab for CD is an IV infusion, whereas the maintenance doses are SC.	Comment from the drug plans to inform CDEC deliberations.
GI specialists are not always readily accessible. The loading doses will be given via IV infusion, in hospitals or special infusion clinic settings, which are not available in some areas.	Comment from the drug plans to inform CDEC deliberations.
Care provision issues	
This drug's initiation must be administered in a clinic setting, as it is an infusion. These settings are not available in some areas. Maintenance dosing can be self-administered, as it is SC.	Comment from the drug plans to inform CDEC deliberations.
The most common AEs of special interest in the MOTIVATE and ADVANCE trials were hypersensitivity, serious infections, and hepatic events. The product monograph recommends that liver tests be obtained before initiating treatment. Should	CDEC and the clinical expert indicated that they did not have any concerns related to hepatic events with risankizumab. The clinical expert noted that most hepatic events were elevated liver enzymes and did not lead to change in treatment; none

Implementation issues	Response
normal liver function tests be a criterion on initiation of the drug? Are there any concerns related to hepatic events with risankizumab? One of the treatment-emergent AEs that was considered in these 2 trials was "Crohn's disease." Can CDEC clarify if it is appropriate to consider the indication of the study drug to also be an AE of the study drug? In other words, can it be clarified that treatment-emergent symptoms of Crohn disease would be indicative of poor response (rather than attributed to an AE of the drug or placebo), and that they should not have been included in the AE results?	were serious or severe. In the trials, any worsening of a pre-existing condition or illness was considered an AE. CDEC noted that worsening of CD would indicate a lack of response to treatment.
In certain adverse reactions, such as hypersensitivity reactions, supportive medications may be needed.	Comment from the drug plans to inform CDEC deliberations.
If looking at endoscopies again was warranted or required, what would be the optimal timing for repeat endoscopies, for determining treatment response (i.e., week 12, annually)? The studies also included assessment of biomarkers (CRP, ESR, FCP). Would biomarkers be routinely used for follow-up assessment of response to therapy, and if so, would it make sense to include these as criteria for renewal of coverage?	The clinical expert noted that endoscopy should not be required, but optimal timing would be every 6 to 12 months. CDEC agreed with the clinical expert. The clinical expert noted that biomarkers should not be required for renewal of coverage. CDEC agreed with the clinical expert.
System and economic issues	
Risankizumab would allow for another alternate biologic drug for the treatment of CD; however, it will be more costly than other biologics currently listed that offer biosimilar versions. In jurisdictions without a mechanism to tier biologic therapies, patients could potentially meet eligibility criteria for risankizumab in favour of a more cost-effective biosimilar drug. Therefore, risankizumab, for the requested indication, should not cost more than the least costly biologic drug currently reimbursed under public drug plans.	Comment from the drug plans to inform CDEC deliberations.
There are multiple alternative biologic drugs that have confidential PLAs with jurisdictions for the treatment of CD in adults (adalimumab, infliximab, ustekinumab, vedolizumab).	Comment from the drug plans to inform CDEC deliberations.

AE = adverse event; CD = Crohn disease; CDAI = Crohn's Disease Activity Index; CDEC = CADTH Canadian Drug Expert Committee; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; FCP = fecal calprotectin; GI = gastrointestinal; HBI = Harvey-Bradshaw Index; LOR = loss of response; SF/APS = stool frequency/abdominal pain score; SC = subcutaneous; TNF = tumour necrosis factor; UC = ulcerative colitis.

Clinical Evidence

Pivotal Studies and Protocol-Selected Studies

Description of Studies

Four phase III RCTs (MOTIVATE induction, N = 413; ADVANCE induction, N = 559; FORTIFY substudy 1 maintenance, N = 363; SEQUENCE part 1 induction and maintenance ongoing, N = 272) submitted by the sponsor were included in this systematic review. The objectives of the MOTIVATE, ADVANCE, and FORTIFY

trials were to evaluate the efficacy and safety of risankizumab in patients with moderate to severe active CD who had an inadequate response, loss of response, or intolerance to either conventional therapy (Non-Bio-IR) or biologic therapy (Bio-IR). The SEQUENCE trial aimed to evaluate the comparative efficacy and safety of risankizumab compared to ustekinumab in the same population. Both induction trials were of similar design, except that the MOTIVATE trial enrolled patients who were Bio-IR, and the ADVANCE trial enrolled patients who were Bio-IR or Non-Bio-IR. In these 2 trials, eligible patients were randomized to receive 600 mg IV administered at weeks 0, 4, and 8 or matching placebo, in a double-blind manner. Patients without clinical response to risankizumab at week 12 entered an additional exploratory double-blind, 12-week induction period (period 2) and were re-randomized to risankizumab 1,200 mg IV, risankizumab 360 mg SC, or risankizumab 180 mg SC. Clinical responders from the induction trials were eligible to enter the maintenance trial (FORTIFY), as were patients from induction period 2 who achieved clinical response at week 24. Patients who entered the maintenance study were re-randomized to receive blinded risankizumab 360 mg SC or matching placebo every 8 weeks for 52 weeks. The induction and maintenance trials included treatment groups (1,200 mg IV induction and 180 mg SC maintenance doses of risankizumab) not aligned with the Health Canada–approved dose, and for this reason were not included in this review. To meet regional regulatory requirements, all 3 trials included 2 protocols denoted as US (United States) and OUS (Outside of United States) that were identical in design but specified different co-primary and key ranked secondary outcomes. Clinical remission and endoscopic response were co-primary outcomes in both protocols; however, the definition of clinical remission in the US protocol was defined as CDAI score less than 150, whereas in the OUS protocol, it was defined as stool frequency and abdominal pain score (SF/APS) clinical remission (defined as average daily SF ≤ 2.8 and not worse than baseline, and average daily APS ≤ 1 and not worse than baseline). Key secondary outcomes were similar in both protocols but ranked differently. These included clinical remission, clinical response, enhanced SF/APS clinical response and endoscopic response, endoscopic remission, ulcer-free endoscopy, corticosteroid-free clinical remission, Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) score, IBDQ total score, Short-Form 36 health survey (SF-36) PCS and Mental Component score, and safety outcomes.

In the SEQUENCE trial, patients were randomized to receive blinded 600 mg IV induction at weeks 0, 4, and 8, then 360 mg SC maintenance at week 12 and every 8 weeks thereafter; or ustekinumab weight-based IV induction dose at week 0 and then 90 mg SC maintenance every 8 weeks thereafter, over 48 weeks. [redacted].

The trial populations were predominantly white (77% to 91%), with an approximate mean age of 40 years, and a mean CD disease duration of approximately 8 to 12 years. In the MOTIVATE trial, approximately 48% of patients were Bio-IR to 1 therapy, and 52% of patients were Bio-IR to more than 1 therapy. In the ADVANCE trial, 23% to 30% of patients were Bio-IR, 28% to 32% were Bio-IR to more than 1 therapy, and 42% to 45% were Non-Bio-IR. Between 29% and 36% of patients across treatment groups were on concomitant

corticosteroids, and about 19 to 28% of patients were on immunomodulators. In the maintenance trial (FORTIFY), patients' baseline characteristics were generally comparable to those in the induction trials. [redacted].

Efficacy Results

Clinical Remission

In both induction trials (MOTIVATE and ADVANCE), the co-primary outcome of clinical remission at week 12 for both the US and OUS protocols favoured risankizumab over placebo. In the MOTIVATE US protocol, the adjusted between-group difference in CDAI clinical remission rate with risankizumab versus placebo was 22.1% (95% CI, 13.1% to 31.0%; P < 0.001). For the OUS protocol, the adjusted between-group difference in SF/APS clinical remission rate was 15.2% (95% CI, 6.4% to 24.0%; P = 0.001). In the ADVANCE US protocol, the adjusted between-group difference in CDAI clinical remission rate with risankizumab versus placebo was 20.7% (95% CI, 12.4 to 29.0; P < 0.001). For the OUS protocol, the adjusted between-group difference in SF/APS clinical remission was 21.9% (95% CI, 13.8 to 29.9; P < 0.001). In both trials and protocols, all secondary ranked multiplicity-controlled outcomes, including SF and APS remission at week 12, CDAI clinical remission at week 4, SF/APS clinical remission at week 4, favoured risankizumab versus placebo. Results of subgroup analyses by Bio-IR status were consistent with the main analysis. The findings were robust to sensitivity analyses using different methods to account for missing data.

In the maintenance trial (FORTIFY), the co-primary outcome of clinical remission at week 52 in both protocols favoured risankizumab over placebo. For the US protocol, the adjusted between-group difference in CDAI clinical remission rate with risankizumab was 14.6% (95% CI, 4.3 to 25.0; P = 0.005). For the OUS protocol, the adjusted between-group difference in SF/APS clinical remission rate was 15.2% (95% CI, 4.9 to 25.4); P = 0.004). In both protocols, almost all secondary remission outcomes, including SF and APS remission, maintenance of SF/APS or CDAI clinical remission, SF/APS or CDAI clinical remission with endoscopic response, and SF/APS or CDAI deep remission, favoured risankizumab versus placebo. [redacted]. However, except for SF/APS clinical remission (US protocol), the secondary outcomes are at increased risk of type I error (false-positive results) because they were tested after failure of the statistical hierarchy.

[redacted]. However, this was based only on [redacted] of the planned population, and the findings are at risk of overestimating the efficacy of risankizumab versus ustekinumab, although the potential presence and magnitude of the overestimation is unclear.

Clinical Response

In both induction trials and protocols, all of the secondary ranked multiplicity-controlled clinical response outcomes favoured risankizumab over placebo. The between-group adjusted difference in CDAI clinical response at week 12 for risankizumab versus placebo was 23.1% (95% CI, 14.2% to 31.9%) in the ADVANCE trial and 29.4% (95% CI, 19.9% to 39.0%) in the MOTIVATE trial. The between-group adjusted difference for CDAI clinical response and endoscopic response combined at week 12 for risankizumab versus placebo was 24.5% (95% CI, 18.5% to 30.5%) in the ADVANCE trial and 15.0% (95% CI, 8.5% to 21.5%) in the MOTIVATE trial. Results of the sensitivity analysis for all outcomes were consistent with the primary analysis.

In the maintenance trial (FORTIFY), the secondary outcomes of CDAI clinical response and SF/APS enhanced clinical response at week 52 were not formally tested due to failure of the statistical hierarchy, although they were supportive of the primary outcomes.

Mucosal Healing and Endoscopic Response

In the induction trials, the co-primary outcome of endoscopic response and secondary outcomes of endoscopic remission and ulcer-free endoscopy at week 12 favoured risankizumab over placebo. In the MOTIVATE trial, the adjusted between-group difference in endoscopic response rate with risankizumab versus placebo was 17.7% (95% CI, 9.9% to 25.4%; P < 0.001). In the ADVANCE trial, the adjusted between-group difference in endoscopic response rate was 28.3% (95% CI, 21.2% to 35.4%; P < 0.001). In both trials, results of the sensitivity analysis were consistent with the primary analysis.

In the maintenance trial (FORTIFY), the adjusted between-group difference in the co-primary outcome of endoscopic response at week 52 with risankizumab versus placebo was 27.8% (95% CI, 18.7 to 37.0; P < 0.001). The ranked secondary outcomes of ulcer-free endoscopy and endoscopic remission were not formally tested due to failure of the statistical hierarchy, but were supportive of the primary outcomes.

Harms Results

Evidence from the pivotal trials showed induction (600 mg IV) and maintenance (360 mg SC) therapy with risankizumab seemed generally safe and well tolerated. In the MOTIVATE trial, treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and AEs leading to study drug discontinuation were higher in the placebo group than with risankizumab, mainly due to worsening CD. In the ADVANCE (induction) trial, TEAEs occurred with similar frequency in both treatment groups, while SAEs and AEs leading to study drug discontinuation occurred with higher frequency in the placebo group. The most common TEAEs with risankizumab (> 2% of patients) during the 12-week induction period were headache, arthralgia, and nasopharyngitis, whereas with placebo they were CD or worsening of underlying disease, headache, and arthralgia. In both induction trials, the most frequently reported TEAE leading to study drug discontinuation was CD or worsening of the underlying disease. Two deaths were reported, both of which occurred in the ADVANCE placebo group. In the maintenance trial (FORTIFY), TEAEs, SAEs, and AEs leading to discontinuation were similar between treatment groups and induction trials. Across the 3 trials, the incidence of notable harms in treatment groups were comparable and infrequent. [redacted].

Critical Appraisal

Internal Validity

The trials used appropriate methods of randomization and allocation concealment via interactive response technology. In general, baseline characteristics of patients appeared balanced between trial arms, indicating that randomization was successful.

There are some concerns related to risk of bias due to deviation from the intended interventions, primarily due to performing the analysis on the intention-to-treat (ITT) population for the 12-week induction period (ITTA1) (included all randomized patients who received at least 1 dose of study drug and had a baseline eligible Simple Endoscopic Score for Crohn's Disease [SES-CD] of at least 6 (≥ 4 for isolated ileal disease), which included randomized patients who received at least 1 dose of the study drug. As this is not a true ITT population, some concerns for bias were introduced in the ADVANCE and MOTIVATE trials (about 10% of patients were not included), and a high risk of potential bias may be present for the FORTIFY trial (21% of the risankizumab group and 11% of the placebo group were not included). The magnitude and direction of the potential bias cannot be predicted.

For most outcomes, there was minimal concern for missing outcome data. In the induction trials, there was a higher number of discontinuations of study drug (10% in the MOTIVATE trial and 12% in the ADVANCE trial) in the placebo groups compared to the risankizumab groups (2% in both the MOTIVATE and ADVANCE trials). In the maintenance trial, discontinuations were similar, at slightly more than 10% across groups. For the primary outcomes, acceptable methods were used to impute missing data, and the findings were robust to sensitivity analyses using different methods to account for missing data. There is concern for bias due to missing outcome data for the HRQoL and fatigue outcomes, due to large and imbalanced amounts of missing data, particularly at the 12-week time point. The direction and magnitude of the potential bias is unclear.

Across all trials, most outcomes were subjective (e.g., SF/APS or CDAI clinical remission or response, FACIT-F, IBDQ, and SF-36) and collected from patient diaries, except for endoscopic outcomes, which were read centrally by a blinded reviewer. Although the subjective outcomes are prone to risk of bias, the double-blind design of the trials mitigated this risk. There is some risk of unblinding that could have affected the subjective outcomes because dropout rates were higher in the placebo groups, which could allow investigators and patients to make inferences on treatment assignment regardless of blinding. However, the extent of the potential bias is unclear.

Statistical analyses in the 3 trials were prespecified. A hierarchical testing procedure was appropriately used in all 3 trials to account for multiplicity in co-primary and key secondary outcomes. The exploratory outcomes of Crohn's Symptom Severity (CSS) and EQ-5D-5L were not adjusted for multiplicity, which limited the ability to draw conclusions regarding these outcomes. In the FORTIFY trial, early failure of the statistical hierarchy precluded formal statistical testing of most secondary outcomes. This lack of adjustment for multiplicity may increase the likelihood of type I error, and as such, P values for these outcomes should be considered supportive and not for drawing conclusions.

In the ongoing SEQUENCE trial, there were 2 key limitations with the interim results that are at risk of overestimating the treatment effect [redacted], although the potential presence and magnitude of the overestimation is unclear. There was a considerable amount of missing data for all outcomes because this was an interim analysis, in which only [redacted] of patients had reached the time point of interest. There was also bias in selection of reported results, as the statistical analyses presented for all exploratory outcomes were not described in the statistical analysis plan. The analysis plan only aimed to describe the outcomes descriptively. Because of these limitations, the interim results cannot support definitive conclusions about the efficacy of risankizumab compared to ustekinumab.

External Validity

According to the clinical expert consulted by CADTH, the inclusion and exclusion criteria of the pivotal trials were generally aligned with selection criteria that would be adopted by most clinicians in Canada when identifying suitable candidates for risankizumab. Based on the available trial data, relative efficacy of risankizumab to other active treatments were not available. In the MOTIVATE, ADVANCE, and FORTIFY trials, placebo was the comparator; in the SEQUENCE trial, ustekinumab was the comparator. Since ustekinumab is not used frequently in Canada, it is not considered the most relevant active treatment. The trials included outcomes that were important to patients and clinicians. All outcomes were considered appropriate by the clinical expert, although the Harvey-Bradshaw Index (HBI) was noted as a more commonly used tool to assess clinical remission in patients in Canada with CD. The clinical expert noted that the time frames used in the trials were appropriate to determine short-term treatment effects with risankizumab, but may not be considered sufficient to fully understand the long-term safety for rare events and those that take longer to develop, such as malignancy.

Indirect Comparisons

Description of Studies

The sponsor-submitted indirect treatment comparison (ITC) was an NMA assessing the efficacy and safety of risankizumab relative to vedolizumab, ustekinumab, adalimumab, infliximab, and placebo in patients diagnosed with moderately to severely active CD.

The 2 published ITCs identified from the CADTH literature search were also NMAs. Barberio et al. (2023) evaluated the efficacy of all biologic therapies and small molecules that have been investigated in phase III clinical trials in luminal CD, compared to placebo or each other. Singh et al. (2021) determined the relative efficacy and safety of infliximab, adalimumab, certolizumab pegol, vedolizumab, ustekinumab, and risankizumab (either alone or in combination with immunosuppressants) for the treatment of moderate to severe CD in patients with or without previous biologic exposure.

Efficacy and Harm Results

[redacted]

[redacted].

For the NMA conducted by Barberio et al. (2023), in the induction phase, both patients naive to biologic therapies and patients previously exposed to biologic therapies, who were treated with risankizumab, had a lower risk of failing to achieve clinical remission or clinical response compared to placebo and some of the active treatments (e.g., ustekinumab, adalimumab). During the maintenance phase, in most cases, the effect estimates were too imprecise to draw conclusions about the efficacy of risankizumab versus placebo or any other active treatments in patients naive to biologic therapies or those previously exposed to biologic therapies. With respect to harms outcomes, the evidence was insufficient to show a difference between risankizumab 600 mg versus placebo or other active treatments in the incidence of any AEs or any infection at the induction phase.

For the NMA conducted by Singh et al. (2021), patients naive to biologic therapies and patients with previous biologic exposure, who were treated with risankizumab, were more likely to achieve clinical remission or clinical response compared to placebo in the induction phase. Risankizumab was also superior to vedolizumab in achieving clinical remission in patients with previous biologic exposure in the induction phase. The effect estimates for efficacy outcomes in the maintenance phase were too imprecise to draw conclusions about the comparison of risankizumab versus placebo or any active treatment. No NMA comparative estimates for harms outcomes were available for risankizumab because it was not connected in the evidence networks.

Critical Appraisal

There were several notable sources of heterogeneity across RCTs included in the sponsor-submitted NMA (e.g., differences in patient characteristics, differences in disease duration in the [redacted], differences in the time at which primary outcomes across individual induction trials were accessed), which increase uncertainty in the effect estimates because it is likely that the assumption of exchangeability was violated. The causes of heterogeneity were not explored [redacted]. In addition, [redacted] in the NMA, which does not incorporate heterogeneity across included studies and implied that heterogeneity across included trials had no impact on the magnitude of effect, might yield biased NMA estimates given the notable heterogeneity. Many of the estimates of treatment effects were affected by imprecision. Finally, [redacted] on the internal validity of the NMA effect estimates at the outcome level were not explicitly discussed in the sponsor submitted NMA.

Given the overlap in the included studies, the potential sources of heterogeneity across included studies are likely to be similar between the sponsor-submitted NMA and the 2 published NMAs identified from CADTH literature search (i.e., Barberio et al., 2023; Singh et al., 2021). However, neither of the 2 published NMAs adequately discussed and accounted for the heterogeneity issue. Therefore, there was a considerable uncertainty in the effect estimates from both studies, and no definitive conclusions could be made.

Other Relevant Evidence

No other relevant evidence was submitted by the sponsor or identified from the literature.

Economic Evidence

Cost and Cost-Effectiveness

Table 3: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Decision tree and Markov model
Target populations	Adults with moderately to severely active CD who have had an inadequate response or intolerance to, or demonstrated dependence on corticosteroids; or an inadequate response, intolerance, or loss of response to immunomodulators or biologic therapies (i.e., TNF-alpha antagonists, gut-selective anti-inflammatory biologics, interleukin 12 or interleukin 23 inhibitors)
Treatment	Risankizumab
Dose regimen	600 mg IV infusion for induction therapy at weeks 0, 4, and 8, followed by maintenance therapy with risankizumab 360 mg by SC injection at week 12, and every 8 weeks thereafter
Submitted price	600 mg in 10 mL vial for IV infusion: $4,593.14 360 mg in 2.4 mL prefilled cartridge for SC injection: $4,593.14
Treatment cost	Annual cost of $41,338 in the first year and $29,855 in subsequent years
Comparators	• Adalimumab and adalimumab-biosimilar • Infliximab and infliximab-biosimilar • Ustekinumab • Vedolizumab and vedolizumab-SC • Conventional care (consisting of corticosteroids, amino salicylates, and immunomodulators)
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (60 years)
Key data sources	MOTIVATE, ADVANCE, and FORTIFY trials
Key limitations	• The CADTH Clinical Review found insufficient evidence to draw conclusions about comparative effectiveness of risankizumab compared to all comparators in conventional care failure and biologic failure populations. The sponsor's base case relied on long-term extrapolations of clinical benefits and an assumption of no treatment waning which were not supported by trial evidence and clinical experts felt were overly optimistic. • The sponsor's model did not differentiate between causes of surgery or types of surgery, and does not account for the impacts of surgery and surgical complications on quality of life, risk of recurrence, and future complications. • The sponsor assumed dose escalation during the maintenance period for all biologics except risankizumab, which clinical experts felt to be overly optimistic, and results in underestimating the total costs for risankizumab.

Component	Description
	• How patients moved between health states in the model (transition probabilities) relied on limited evidence and assumptions that propagated uncertainties. The resulting direction and magnitude on risankizumab's cost-effectiveness results is unknown. • The sponsor's model is associated with extremely long processing times and programming errors that prevented CADTH from conducting a probabilistic sensitivity analysis to account for uncertainty around model estimates. In its absence, CADTH conducted all reanalyses deterministically. • Assumptions regarding severe infections arising from adverse events lacked face validity. The sponsor assumed disutilities for severe infections would last a year, which did not represent the expectation of clinical experts consulted by CADTH.

CADTH reanalysis results	• CADTH made the following revisions to address the identified limitations: corrected disutility of severe infection adverse events; and, added the same rate of dose escalation for all biologics.
	• In the CADTH base case:
	  ◦ In the patients with inadequate response, lost response, or intolerance to conventional care: infliximab-biosimilar was associated with an ICER of $188,134 per QALY gained compared to conventional care. Risankizumab was dominated by ustekinumab (i.e., risankizumab is associated with greater total costs [$6,903] and fewer QALYs [0.364]).
	  ◦ In the patients with inadequate response, lost response, or intolerance to biologic failure: risankizumab was associated with an ICER of $535,031 per QALY gained compared to vedolizumab-SC. A price reduction of at least 41.1% would be needed for risankizumab to be cost-effective compared to vedolizumab at a WTP threshold of $50,000 per QALY.

CD = Crohn disease; ICER = incremental cost-effectiveness ratio; LY = life-year; PSM = partitioned survival model; QALY = quality-adjusted life-year; SC = subcutaneous; TNF = tumour necrosis factor; WTP = willingness to pay.

Budget Impact

CADTH identified the following key limitations with the sponsor's budget impact analysis: the estimated proportion of patients that would be eligible for public coverage is uncertain, and using a claims-based approach to estimate the market size introduces additional uncertainty to the anticipated budget impact. The identified issues could not be addressed in CADTH's base case; therefore, it did not differ from the sponsor's analysis, which found the anticipated budget impact was $10,897,238 in Year 1, $12,300,264 in Year 2, and $32,425,718 in Year 3, for a 3-year total of $55,623,220.

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: March 22, 2023

Regrets: Two expert committee members did not attend.

Conflicts of Interest: None

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