CADTH

CADTH REIMBURSEMENT REVIEW

Stakeholder Feedback on Draft Recommendation

RISANKIZUMAB (SKYRIZI)

AbbVie Corporation

Indication: Skyrizi (risankizumab injection) is indicated for the treatment of adults with moderately to severely active Crohn's disease 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 (i.e., tumour necrosis factor-alpha [TNF-α] antagonists, gut-selective anti-inflammatory biologics, interleukin 12/23 inhibitors).

April 27, 2023

CADTH Reimbursement Review

Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0767-000
Brand name (generic)	Skyrizi (Risankizumab)
Indication(s)	Crohn's disease
Organization	Pan-Canadian Inflammatory Bowel Disease (IBD) Specialist Group
Contact information	Name: Jesse Siffledeen, MD

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☐
	No	☒

The Pan-Canadian Inflammatory Bowel Disease Specialist Group acknowledges the CADTH Canadian Drug Expert Committee (CDEC) and its dedicated efforts to providing the recommendation that risankizumab be reimbursed for treatment of adults with moderate-severe Crohn's disease (CD). We hereby provide our feedback and rationale for disagreement on the following recommendations:

- Reimbursement condition 1 (Initiation), page 4, Table 1:
  - The Canadian Specialist Group disagrees with aligning risankizumab with other biologics and recommend highlighting the unique mechanism of action, robustness of the clinical and endoscopic endpoints evaluated (this is the first therapy that has ever been evaluated to meet the treatment goals of both clinical and endoscopic endpoints as co-primary endpoints during induction and maintenance therapy) and excellent safety profile of risankizumab.
  - We note that "conventional therapy" is an imprecise term that can allude to many treatment options and has resulted in non-uniform public health reimbursement rules. As an example, there is no need for the failure of a conventional or immunosuppressive therapy (apart from corticosteroids) in Ontario, Quebec and British Columbia to qualify for biologics reimbursement. The Canadian specialist group recommends that failure of conventional therapy be clarified to mean failure of 5ASA or corticosteroids OR an immune modulator (methotrexate or thiopurine) for eligibility for risankizumab in moderate-severe CD.
    - We further note that conventional therapies do not meet modern treatment goals, including endoscopic remission and intestinal mucosal healing, which have been demonstrated to reduce the chance of future flares, hospitalizations, and surgeries.[1,2] Transition from a conventional therapy to biologic therapy should therefore not be unnecessarily delayed.
  - The Canadian Specialist Group disagrees with the statement, *"Stelara® (ustekinumab) is not an appropriate comparator because it is not widely prescribed in Canada"* (Section on external validity last sentence of page 13) and request that the statement be revised. Despite Stelara® (ustekinumab) not being listed under most public drug plans, it is nevertheless the most commonly prescribed first-line biologic for Crohn's Disease in clinical practice (through private payor coverage or compassionate provision), and is therefore considered a most appropriate comparator to risankizumab in the SEQUENCE trial. The Canadian Specialist Group therefore also recommend that the second paragraph of the "Relevant Comparators" section of table 2 (page 8) also be amended to reflect this.

- Reimbursement condition 2 (Renewal), page 4, Table 1:
  - The Canadian Specialist Group disagrees with the statement, *"The patient must have achieved clinical response to induction therapy after twelve weeks of treatment to continue to maintenance therapy"* and recommends this treatment period be extended to 24 weeks.
  - In line with this, we note that the dose of risankizumab used in the second induction period (Period 2) does, in fact, align with the recommended dosage in the Health Canada product monograph. One-third of patients in Period 2 (inadequate responders at week 12) received risankizumab 360mg sc therapy at week 12 and week 20, with 58 of 91 patients in this group demonstrating a clinical response (CDAI reduction of 100 from baseline). As such, we recommend that the last paragraph of page 5 (under section heading "Discussion Points") be amended to reflect this and for the treatment response evaluation be extended to 24 weeks to continue to maintenance therapy, in order that the greatest proportion of patients who are capable to respond to risankizumab treatment are allowed to.
  - Given the known disconnect between symptom response and the response reflected in objective markers of inflammation,[3,4] patients may experience a treatment benefit, yet have symptoms related to factors other than Crohn's disease activity. The Canadian Specialist Group therefore recommends the initial assessment of treatment response to risankizumab to allow for a clinical response, OR biochemical evidence of improvement (reduction in C-reactive protein, or fecal calprotectin), OR endoscopic evidence of response, if available. These treatment endpoints reflect those defined as primary, or secondary endpoints in the MOTIVATE and ADVANCE trials.

- Reimbursement condition 3 (Renewal), page 4, Table 1:
  - In line with above, the Canadian Specialist Group recommends assessment for renewal after the first assessment of treatment response to allow for a clinical response, OR biochemical evidence of improvement (reduction in C-reactive protein, or fecal calprotectin), OR endoscopic evidence of response, to continue receiving risankizumab.

Expert committee consideration of the stakeholder input

2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☐
	No	☒

The following aspects of input from the Canadian Specialist Group were identified as important to emphasize further in the draft recommendations:

- The unique and stringent endoscopic endpoints present in the ADVANCE, MOTIVATE and FORTIFY clinical trials, thus differentiating risankizumab from other available biologic therapies. Achieving these robust endpoints could translate into changing the clinical course of CD.
- The group has previously noted that there is no planned dose escalation with risankizumab, given the lack of evidence supporting it. Therefore, risankizumab dose-escalation should be removed from the cost- effectiveness calculation (Section on the summary of economic evaluation page 15-16).
- The IBD specialist group feel that, in their draft recommendations, the CDEC have not strongly emphasized the importance of the Health-related quality of life (HRQoL) endpoints in the ADVANCE, MOTIVATE and FORTIFY clinical trials, which is of most relevance to the patient. We further suggest that a lack of statistical significance of HRQoL data beyond 12 weeks represents risankizumab's prolonged positive carry-over effect from the induction trials in those clinical

responders who were re-randomized to receive placebo treatment in the maintenance phase. We recommend that the second-last paragraph of page 5 (section title “Discussion Points”) be amended to reflect this.

Clarity of the draft recommendation

3. Are the reasons for the recommendation clearly stated?	Yes	☐
	No	☒

The renewal condition reason (Table 1, page 4) does not include the evidence from patients who received additional 12 weeks of therapy (Period 2) consistent with the recommended dosage in the Health Canada product monograph, two-thirds (58/91) of which achieved a clinical response by the end of period 2 treatment, suggesting that the time to assessment of clinical response to induction therapy should be 24 weeks.

4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☐
	No	☒

- The definition of “loss of response to conventional therapies” remains confusing and should be further specified to be a loss of response, or intolerance to one OR more conventional therapies (i.e. 5-ASA OR thiopurines OR methotrexate OR systemic corticosteroids).
- In line with CDEC recommendations that clinical response be left up to the clinical judgement of the treating physician, the Canadian Specialist Group recommends that the definition of clinical response be expanded to include clinical symptom response OR biochemical response (c-reactive protein, fecal calprotectin) OR endoscopic response.

5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☐
	No	☒

- Under “Considerations for continuation or renewal of therapy” (table 2, page 9), no mention is made of using other objective markers of disease response, which are commonly used in GI practice. While symptom improvement by HBI measure is important, it does not capture the other highly relevant patient reported outcomes (ex. HRQoL) and ignores the use of objective measures of disease activity, which do not always correlate with clinical response, but do reflect a response to treatment. We suggest incorporating clinical OR objective (ex. FCP, endoscopy) response for consideration of continuation/renewal of therapy.
- The comment that ustekinumab is not listed under some public drug plans and is therefore not considered a relevant comparator (Table 2, “Relevant Comparators” section, page 9) is inaccurate. Despite limited public plan listing, Stelara is among the most frequently prescribed biologics for Crohn’s disease and is, therefore a relevant comparator. This comment also does not align with CDEC’s Reimbursement condition 1, which states that eligibility should be based on criteria used by public plans for other biologic therapies.
- The CADTH cost effectiveness model (Section titled “Economic Evidence”, table 2, “Key limitations”, page 16) increases the cost associated with risankizumab therapy by adding dose escalation. This is inaccurate, as escalated doses of risankizumab will not be available. We recommend that the cost model be adjusted to reflect this.

References:

1. Shah SC, Colombel JF, Sands BE, et al. Narula N. Systematic review with meta-analysis: mucosal healing is associated with improved long-term outcomes in Crohn's disease. Aliment Pharmacol Ther. 2016 Feb;43(3):317-33.

2. Yzet C, Diouf M, Le Mouel et al, Complete Endoscopic Healing Associated with Better Outcomes Than Partial Endoscopic Healing in Patients with Crohn's Disease. Clin Gastroenterol Hepatol. 2020 Sep;18(10):2256-2261.

3. Cellier C. et al. Correlations between clinical activity, endoscopic severity, and biological parameters in colonic or ileocolonic Crohn's disease. A prospective multicentre study of 121 cases. The Groupe d'Etudes Thérapeutiques des Affections Inflammatoires Digestives
Gut. 1994; 35:231-235; Lewis JD, et al. *Inflamm Bowel Dis* 2020;26(2):304-313.

4. Panaccione R, Colombel JF, Louis E, et al. Evolving definitions of remission in Crohn’s disease. *Inflamm Bowel Dis* 2013; 19:1645–1653.

Appendix 2. Conflict of Interest Declarations for Clinician Groups

A. Assistance with Providing the Feedback		
1. Did you receive help from outside your clinician group to complete this submission?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
B. Previously Disclosed Conflict of Interest		
3. Were conflict of interest declarations provided in clinician group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section C below.	No	☐
	Yes	☒
If yes, please list the clinicians who contributed input and whose declarations have not changed: • Dr. Remo Panaccione • Dr. Hillary Steinhart • Dr. John Marshall • Dr. Jesse Siffledeen • Dr. Michael Stewart • Dr. Christopher Ma • Dr. Cathy Lu • Dr. Cynthia Seow		

C. New or Updated Conflict of Interest Declarations

New or Updated Declaration for Clinician 1	
Name	*Frank Hoentjen*
Position	*Associate Professor of Medicine*
Date	*21-04-2023*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Abbvie	☐	☒	☐	☐
Janssen	☐	☒	☐	☐

Pfizer	☒	☐	☐	☐
Pendopharm	☒			

New or Updated Declaration for Clinician 2	
Name	*Mark Borgaonkar*
Position	*Staff Physician, Eastern Health*
Date	*21-04-2023*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Abbvie	☐	☐	☒	☐
Amgen	☐	☒	☐	☐
AstraZeneca	☒	☐	☐	☐
Biojamp	☒	☐	☐	☐
BMS	☒	☐	☐	☐
Celltrion	☒	☐	☐	☐
Innomar	☒	☐	☐	☐
Janssen	☐	☐	☒	☐
Pendpharm	☒	☐	☐	☐
Pfizer	☐	☐	☒	☐
Sandoz	☒	☐	☐	☐
Takeda	☐	☐	☒	☐

New or Updated Declaration for Clinician 3	
Name	*John Igoe*
Position	*Gastroenterologist, New Brunswick*
Date	*02-04-2023*

☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Abbvie	☐	☐	☒	☐
Janssen	☒	☐	☐	☐
Takeda	☐	☒	☐	☐
Pfizer	☒	☐	☐	☐
Bio-Jamp	☒	☐	☐	☐

New or Updated Declaration for Clinician 4	
Name	*Mark MacMillan*
Position	*Gastroenterology*
Date	*23/Apr/2023*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
AbbVie	☒	☐	☐	☐
Takeda	☒	☐	☐	☐
Janssen	☒	☐	☐	☐
Organon	☒	☐	☐	☐
Vantage	☒	☐	☐	☐

New or Updated Declaration for Clinician 5	
Name	*Sundeep Singh*
Position	*Gastroenterologist, Clinical Instructor, UBC*
Date	*23-04-2023*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Abbvie	☐	☒	☐	☐

CADTH Reimbursement Review

Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0767
Name of the drug and Indication(s)	Risankizumab (Skyrizi) for moderately to severely active Crohn's disease
Organization Providing Feedback	FWG

1. Recommendation revisions Please indicate if the stakeholder requires the expert review committee to reconsider or clarify its recommendation.		
Request for Reconsideration	**Major revisions:** A change in recommendation **category** or patient **population** is requested	☐
	Minor revisions: A change in reimbursement **conditions** is requested	☐
No Request for Reconsideration	**Editorial revisions:** Clarifications in recommendation **text** are requested	☐
	No requested revisions	X

2. Change in recommendation category or conditions Complete this section if major or minor revisions are requested
Please identify the specific text from the recommendation and provide a rationale for requesting a change in recommendation.

3. Clarity of the recommendation Complete this section if editorial revisions are requested for the following elements
a) Recommendation rationale
Please provide details regarding the information that requires clarification.
b) Reimbursement conditions and related reasons
Please provide details regarding the information that requires clarification.
c) Implementation guidance
Please provide high-level details regarding the information that requires clarification. You can provide specific comments in the draft recommendation found in the next section. Additional implementation questions can be raised here.

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0767-000
Brand name (generic)	Skyrizi (Risankizumab)
Indication(s)	Risankizumab is indicated for the treatment of adults with moderately to severely active Crohn's disease 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. (i.e., tumour necrosis factor-alpha [TNF-α] antagonists, gut-selective anti-inflammatory biologics, interleukin 12/23 inhibitors).
Organization	Crohn's and Colitis Canada
Contact information	Name: Patrick Tohill

Stakeholder agreement with the draft recommendation		
6. Does the stakeholder agree with the committee's recommendation.	Yes	☐
	No	☒

Please explain why the stakeholder agrees or disagrees with the draft recommendation. Whenever possible, please identify the specific text from the recommendation and rationale.

We believe the recommendation is too narrow and restrictive. The feedback we've had from patients and clinical trialists suggests risankizumab would be a great first line treatment as well as a second line or third line treatment. The clinical expert CADTH consulted would seemingly concur as the report notes: "The expert also noted that risankizumab could be used as a first-line or later treatment" (page 7, second paragraph following heading "Clinician input", subheading "Input from clinical expert consulted by CADTH"). The expert clinician also notes that while those "patients who are most in need are those with moderate to severe disease that have failed other biologic therapies" that "those who are bio-naive may have an even better response" (page 7, third paragraph following heading "Clinician input", subheading "Input from clinical expert consulted by CADTH"). It should not be a requirement therefore to have first failed on other treatments.

We further believe that risankizumab has significant quality of life benefits that were noted in our patient input submission but given short shrift in the recommendation report. Patients we interviewed described a range of benefits including ease of administration, convenience of being able to self-administer at home, painlessness and, most importantly, rapid alleviation of symptoms with no or minimal side effects. One described the drug as "a wonder drug" and said it was "life altering". The experience of the other two was similar with one saying they "can drink and eat almost anything" and the other saying their Crohn's "no longer hinders my life". In contrast to these effusive statements about risankizumab's life changing impact, the report seems to downplay this input which is summed up in a single paragraph (second paragraph under heading "Patient Input" appearing on page 7):

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.

As noted in our submission, all three patients interviewed were struggling prior to enrolling in the trial. The first indicated that "quality of life was almost non-existent" noting that their previous treatments had failed "in addressing their symptoms sufficiently" adding that hip surgery had resulted from systemic steroid use and that their right knee had also deteriorated. A second patient reported having been hospitalized shortly before they got into the trial as a result of "severe pain and rectal bleeding". All three patients noted a dramatic improvement in their health and quality of life shortly after they started taking risankizumab.

Expert committee consideration of the stakeholder input

7. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☐
	No	☒

If not, what aspects are missing from the draft recommendation?

- As noted in the response to question 1 above, we believe that patient group input on quality of life improvements was largely ignored as was clinician feedback, including that of the clinical expert consulted by CADTH that risankizumab would be a useful "first line or later treatment" and could be of even greater benefit to those patients who are "bio-naïve" (page 7, second and third paragraph following heading "Clinician input", subheading "Input from clinical expert consulted by CADTH"). Our patient input submission notes that the patients we spoke to described risankizumab as being "life altering", noting significant improvements in their quality of life as well as the convenience of being able to self-administer, ease of administration, painlessness and near immediate alleviation of symptoms with no/minimal side effects. Our feedback suggests risankizumab provides significant quality of life benefits not only as compared to conventional therapy but also to other biologic therapies that are delivered exclusively at infusion centres.

Clarity of the draft recommendation

8. Are the reasons for the recommendation clearly stated?	Yes	☒
	No	☐

If not, please provide details regarding the information that requires clarification.

9. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☐
	No	☐

If not, please provide details regarding the information that requires clarification. Declined to answer this question.

10. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☐
	No	☐

If not, please provide details regarding the information that requires clarification. Declined to answer this question.

Appendix 1. Conflict of Interest Declarations for Patient Groups

A. Patient Group Information	
Name	*Patrick Tohill*
Position	*Director, Advocacy and Government Affairs*
Date	*18-04-2023*
☒	I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

B. Assistance with Providing Feedback		
1. Did you receive help from outside your patient group to complete your feedback?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
2. Did you receive help from outside your patient group to collect or analyze any information used in your feedback?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		

C. Previously Disclosed Conflict of Interest		
1. Were conflict of interest declarations provided in patient group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section D below.	No	☐
	Yes	☒

D. New or Updated Conflict of Interest Declaration

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0767
Brand name (generic)	SKYRIZI (risankizumab)
Indication(s)	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.
Organization	AbbVie Corporation

Stakeholder agreement with the draft recommendation		
11. Does the stakeholder agree with the committee's recommendation.	Yes	☒
	No	☐

AbbVie agrees with the recommendation to reimburse SKYRIZI (Risankizumab) for the treatment of adults with moderately to severely active Crohn's disease. AbbVie would like to highlight the response criteria is not align with the current clinical guidelines as well as clinical practice.

The CADTH draft recommendation mentions: 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 (page 4, Table 1)

However, in the ADVANCE and MOTIVATE trial the criteria for response (to continue into maintenance) was a 30% decrease in abdominal pain score or stool frequency score of the PRO2. The PRO2 is now the preferred clinical endpoint for CD trials and is required as a co-primary endpoint by most major pharmaceutical regulatory bodies. (FDA. EMEA, Health Canada). As CDAI is rarely used in clinical practice and is being usurped in trials by the PRO 2, the utility of using HBI in clinical practice has come into question. Moreover, the HBI requires a physical exam to score presence/absence of abdominal mass, so is not suitable for remote collection. The PRO2 based only on abdominal pain and stool frequency can be collected/measured by patients, do not require a clinic visit and are far more relatable to a patient than HBI score. From clinical guideline point of view the recently released STRIDE 2 guidelines from IOIBD suggested that the short-term target is symptomatic response and this aligns with Canadian, US and European gastroenterology associations.

AbbVie would recommend that the CDEC aligns their response criteria to the recently released STRIDE 2 guidelines.

Expert committee consideration of the stakeholder input

12. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☐
	No	☒

AbbVie disagrees with the interpretation of the SEQUENCE trial interim results. In the draft recommendation it was mentioned: 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 non-inferiority of risankizumab compared with ustekinumab based on the proportion of patients who achieved clinical remission. However, these interim results are at risk of overestimating the treatment effect as they represent only 50% 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. (page 5, Discussion points, bullet point number 2)

AbbVie would like to clarify that the SEQUENCE trial has two co-primary endpoints: 1) to demonstrate non-inferiority of Risankizumab compared to Ustekinumab on CDAI remission at week 24 in 50% of the subjects, and 2) to show superiority of endoscopic remission at week 48 in 100% of the subjects. The data reported from week 24 is for a pre-specified co-primary endpoint, not per protocol or an interim lock. It's worth noting that the full enrollment at week 24 for the entire population is a ranked secondary endpoint. As per the protocol, the primary analysis of clinical remission at week 24 will be conducted after the first 50% of ITT1 subjects have completed the Week 24 visit or have withdrawn from the study before Week 24. After all ongoing subjects have completed the Week 48/PD visit, the database will be locked for Part 1, and all other planned analyses at Week 24 and Week 48 will be performed. The recent SEAVUE head-to-head trial between Adalimumab and Ustekinumab failed to show superiority on any endpoints, including endoscopy. Therefore, if Risankizumab demonstrates superiority on endoscopy in the co-primary endpoint at week 48, it would clearly demonstrate that Risankizumab has greater efficacy than other MOAs in patients with documented endoscopic inflammation, as required for trial entry. Endoscopic healing has a positive association with decreased disability, surgery, and hospitalization, which are the greatest drivers of cost for CD patients in Canada. Therefore, comparable cost-effectiveness models should be developed based on the ability to heal the mucosa. Finally, the goal of endoscopic improvement is now the long-term target in CD according to STRIDE 2 making Risankizumab the first approved product with Ph. 3 endpoints that align to latest practice guidelines on achieving targets.

Clarity of the draft recommendation

13. Are the reasons for the recommendation clearly stated?	Yes	☒
	No	☐

If not, please provide details regarding the information that requires clarification.

14. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☒
	No	☐

If not, please provide details regarding the information that requires clarification.		
15. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☒
	No	☐
If not, please provide details regarding the information that requires clarification.		