CADTH

CADTH Reimbursement Review

# CADTH Reimbursement Recommendation

(Draft)

INFLIXIMAB (REMSIMA SC)

Indication: Maintenance treatment of adults with moderately to severely active ulcerative colitis who have had an inadequate response or were intolerant to conventional therapy. Remsima SC should only be used as maintenance therapy after the completion of an induction period with intravenous infliximab.

Sponsor: Celltrion Healthcare Co., Ltd

Recommendation: Reimburse with Conditions


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Single Technology

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## Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that infliximab subcutaneous (SC) be reimbursed as maintenance treatment for adults with moderately to severely active ulcerative colitis who have had an inadequate response or were intolerant to conventional therapy if the conditions listed in

Table 1 are met.

## Rationale for the Recommendation

One double-blind, placebo controlled, phase III, randomized controlled trial (RCT) (LIBERTY-UC) demonstrated that, compared to placebo, treatment with infliximab SC resulted in added clinical benefit in adults with moderately to severely active ulcerative colitis who have had an inadequate response or were intolerant to conventional therapy. Infliximab SC, compared with placebo, was associated with statistically significant and clinically meaningful improvements in the primary outcome of clinical remission based on modified Mayo score at Week 54 (between group difference = 21.1%; 95% confidence interval [CI], 11.8 to 29.3). The key secondary outcomes, clinical response based on modified Mayo score, endoscopic-histologic mucosal improvement based on modified Mayo score and Robarts Histopathology Index, and corticosteroid-free remission, were also statistically significantly in favor of infliximab SC at Week 54.

Patients identified a need for effective treatments that provide a more convenient route of administration, timely patient access, and improved quality of life. CDEC noted that infliximab SC may meet some of the needs identified by patients by providing a subcutaneous drug option that can be administered in a patient's home; however, CDEC could not reach definitive conclusions regarding the effects of infliximab SC compared to placebo on health-related quality of life (HRQoL) due to a significant decline in the number of patients available to provide assessments over time and the descriptive nature of the analyses. CDEC noted that no new safety concerns were observed with infliximab SC; however, uncertainty remained in the absence of long-term safety data.

At the sponsor submitted price for infliximab SC of $19,357 per patient during the induction year (when inducted with Inflectra) and $15,424 per patient in the subsequent maintenance years would increase costs to drug plans when compared with other infliximab IV biosimilars and adalimumab biosimilars, based on publicly available prices. There is insufficient evidence to justify a cost premium for infliximab SC over the least costly biologic therapy reimbursed for the treatment for adults with moderately to severely active ulcerative colitis who have had an inadequate response or were intolerant to conventional therapy.

## Table 1. Reimbursement Conditions and Reasons

| Reimbursement condition | Reason | Implementation guidance |
|---|---|---|
| **Initiation** | | |
| 1. Eligibility for reimbursement of infliximab SC should be based on the criteria used by each of the public drug plans for biologic therapies for the treatment of adults with moderately to severely active ulcerative colitis who have had an inadequate response or were intolerant to conventional therapy. | The results of the LIBERTY-UC trial demonstrated that infliximab SC is an efficacious maintenance treatment for adult patients with moderately to severely active UC who have had an inadequate response or are intolerant to conventional therapy.<br><br>There is no evidence that infliximab SC should be held to a different standard than biologic therapies currently reimbursed for the treatment of adult patients with moderately to severely active UC when considering initiation of therapy. | The definition of moderately to severely active UC and inadequate response, intolerance, or loss of response to other therapies should align with those used for reimbursed biologic therapies. |
| 2. The patient must have achieved a clinical response to induction therapy with infliximab IV at Week 10 of treatment to continue to maintenance therapy with infliximab SC. | In the LIBERTY-UC trial, patients had to have a clinical response at the end of the induction period with infliximab IV at Week 10 to continue to the maintenance phase with infliximab SC. | A Modified Mayo Score that requires an endoscopy was used to determine clinical response in the LIBERTY-UC trial. However, CDEC considered the invasive nature of an endoscopy and the limitations associated with timely access and associated costs of health care resources in Canada. CDEC heard from the clinical expert that fecal calprotectin level and sigmoidoscopy may be useful tools for assessing patients if endoscopy is not feasible. Ultimately, CDEC considered it appropriate to leave the determination of clinical response up to the judgment of the treating physician. |
| **Renewal** | | |
| 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 infliximab SC. | Patients who lose response to infliximab SC are no longer benefiting from treatment. | — |
| **Prescribing** | | |
| 4. Infliximab SC should only be prescribed by a physician experienced in diagnosing and managing UC. | It is important to ensure that infliximab SC is only prescribed for appropriate patients. | The clinical expert indicated that prescribing infliximab SC should not be limited to IBD specialists. General gastroenterologists would have the expertise required to initiate therapy, and general internists with a particular interest in IBD/GI may have sufficient experience and training to prescribe infliximab SC, which may be important for accessibility. |

| Reimbursement condition | Reason | Implementation guidance |
|---|---|---|
| 5. Infliximab SC should not be reimbursed when combined with biological or other JAK inhibitor treatments for UC. | There is no evidence to support the use of infliximab SC in combination with biological or other JAK inhibitor treatments for UC. | Infliximab SC may be used in conjunction with conventional therapy. |
| **Pricing** | | |
| 6. Infliximab SC should be negotiated so that it does not exceed the drug program cost of treatment with the least costly biologic therapy reimbursed for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response or were intolerant to conventional therapy. | While the LIBERTY-UC trial demonstrated infliximab SC provided benefit to patients compared to placebo, no evidence was available to estimate the comparative effectiveness of infliximab SC to other currently reimbursed treatments for moderately to severely active UC.<br><br>There is insufficient evidence to justify a cost premium for infliximab SC over currently available biologic therapies reimbursed for the indicated patient population. | |

GI = gastrointestinal; IBD = inflammatory bowel disease; JAK = Janus kinase; RCT= randomized controlled trial; SC = subcutaneous; UC = ulcerative colitis

## Discussion Points

- CDEC was unable to determine the relative efficacy and safety of infliximab SC versus currently available biologic therapies in the target patient population, because of the lack of head-to-head comparisons and the limitations associated with the supportive phase I study (Study 1.6 Part 2). While results observed in Study 1.6 Part 2 were suggestive of similar efficacy and safety between infliximab SC and infliximab IV, CDEC could not reach definitive conclusions regarding the comparisons to infliximab IV, because Study 1.6 Part 2 had a small sample size, was not designed or powered to assess comparative efficacy, and dosing of infliximab SC was inconsistent with the Health Canada recommended dose.
- CDEC considered that maintenance infliximab IV administered every 8 weeks is currently available in the target patient population. The committee acknowledged patient and clinical expert input expressing the need for effective treatments that offer a more convenient route of administration, improve patient access, and quality of life. CDEC heard from the clinical expert that a subcutaneous mode of administration may reduce treatment related travel time and the need to be off work, which may facilitate access to treatment and allow patients a sense of independence. The committee noted, however, that some patients may fear self-injection and/ or may find infliximab SC's more frequent administration schedule (i.e., every 2 weeks versus every 8 weeks) burdensome. CDEC noted that the available evidence on HRQoL based on the LIBERTY-UC trial and Study 1.6 Part 2 was insufficient to reach definitive conclusions regarding the effects of infliximab SC compared to placebo or infliximab IV. Overall, CDEC noted that uncertainty remained about the clinical value conferred by infliximab's subcutaneous versus the intravenous mode of administration.
- CDEC heard from the clinical expert that patients who have had prior exposure to 2 or more lines of biologic agents or JAK inhibitors and otherwise meet the trial's eligibility criteria, are currently considered for treatment with infliximab IV in clinical practice. The LIBERTY-UC trial excluded patients who had previously received 2 or more biologic agents, JAK inhibitors, or both biologic agents and JAK inhibitors. CDEC noted that the generalizability of results of LIBERTY-UC to these patients is limited.
- The LIBERTY-UC trial allowed dose adjustments from infliximab SC 120mg to infliximab SC 240mg every 2 weeks starting from Week 22 through Week 102, if patients initially responded but then lost response. This dose escalation explored whether infliximab SC could be used to reinitiate response; however, this is inconsistent with the Health

Canada recommended dose and approved indication, which is for infliximab SC 120mg every 2 weeks as maintenance therapy.

- CDEC heard from the clinical expert that the dose-loading phase with infliximab IV may extend up to 16 weeks in practice to accommodate slow responders, allowing patients to benefit from treatment. CDEC noted that in the LIBERTY-UC trial only patients who experienced clinical response at Week 10 after 3 full doses of infliximab IV, were randomly assigned into the maintenance phase with infliximab SC. Therefore, the generalizability of results of LIBERTY-UC to patients with an extended induction phase with infliximab IV is uncertain. CDEC also noted that the recommended dosage in the Product Monograph is to start maintenance infliximab SC at Week 10 following 3 infliximab IV infusion doses and that extending the induction period to 16 weeks would fall outside the recommended dosage.
- While Study 1.6 Part 2 was suggestive of similar efficacy, no conclusions could be reached about the comparative clinical benefit between infliximab SC and infliximab IV. Consequently, the evidence does not support a price premium for infliximab SC when compared to infliximab IV. The comparative effectiveness and cost-effectiveness of either infliximab SC or IV compared to other biologic treatments currently reimbursed for moderately to severely active UC unknown. Consequently, the evidence also does not support a price premium relative to these treatments.

## Background

Inflammatory bowel disease (IBD) is an umbrella term describing chronic inflammation of the gastrointestinal (GI) tract caused by one of 2 disorders: ulcerative colitis (UC) and Crohn's disease (CD). Canada has the highest prevalence and incidence of IBD compared to other countries in the world with estimates of about 0.8%, amounting to about 322,600 people living with the disease as of 2023. The Canadian prevalence is forecasted to increase to 493 and 436 per 100,000 by 2030, with an average annual percentage change (AAPC) of 2.75% and 2.87% for CD and UC, respectively.

Ulcerative colitis is characterized by inflammation and ulcers in the mucosal layer of the large intestine (colon), typically beginning at the rectum (anus), progressing upwards, and in some cases affecting the entire colon. UC has a worldwide annual incidence rate of 1.2 to 20.3 cases per 100,000 people and a prevalence of 7.6 to 246.0 cases per 100,000 people. UC generally develops in young adulthood and persists throughout life, marked by periods of spontaneous remission and relapse. Symptoms include 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. Although most patients experience a relapsing-remitting disease course, reports show that up to 24% of patients experience continuous UC symptoms.

Ulcerative colitis is diagnosed based on symptoms and clinical tests such as endoscopic evaluations (endoscopy, biopsy), stool sampling, histological, radiological, and/or biochemical investigations at initial diagnosis. Available treatment options depend on the presence of active disease, severity and extent of disease, and patient preference. Conventional therapies for UC include aminosalicylates, corticosteroids, and immunomodulators (such as azathioprine, 5-mercaptopurine, and methotrexate) and advanced therapies consist of adalimumab, golimumab, infliximab, ustekinumab, tofacitinib, ozanimod, and vedolizumab. Current treatments are unable to meet all current needs of patients in terms of short or long-term treatment. Infliximab SC was reviewed by HC and received a notice of compliance (NOC) on February 15, 2024, for the following indication: as maintenance treatment of adults with moderately to severely active ulcerative colitis who have had an inadequate response or were intolerant to conventional therapy. Remsima SC should only be used as maintenance therapy after the completion of an induction period with intravenous infliximab.

Infliximab (REMSIMA™ SC) is a subcutaneous formulation of infliximab, available in a pre-filled syringe with automatic needle guard, and pre-filled pen formats, containing 120 mg of active substance. It is recommended that infliximab SC be initiated as maintenance therapy 4 weeks after the last administration of 3 intravenous infusions of infliximab 5 mg/kg given at weeks 0, 2 and 6. The recommended dose for infliximab SC is 120 mg once every 2 weeks. Infliximab has also been reviewed by the Food and Drug Administration (FDA) and received FDA market authorization on October 20, 2023, for UC (i.e., for reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing, and eliminating corticosteroid use in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy). It also received regulatory authorization at the European Medicines Agency on June 01, 2020, and at the Medicines and Healthcare products Regulatory Agency in July of 2022.

Infliximab (REMSIMA™ SC) was approved in 2021 by Health Canada for use in patients with moderately to severely active rheumatoid arthritis (RA). It received a positive conditional CADTH recommendation for the treatment of adult patients with moderately to severely active RA in 2021.

## Sources of Information Used by the Committee

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

- a review of 2 trials (1 phase III, open-label induction, double-blind maintenance, RCT and 1 phase I open-label RCT), in patients with moderately to severely active UC.
- patients perspectives gathered by 1 patient group, (Gastrointestinal [GI] Society)
- input from public drug plans and cancer agencies that participate in the CADTH review process
- One clinical specialist with expertise diagnosing and treating patients with Ulcerative colitis

- a review of the pharmacoeconomic model and report submitted by the sponsor

## Stakeholder Perspectives

### Patient Input

One patient input was received by CADTH from the Gastrointestinal (GI) Society and was summarized for this review. The GI Society is a national charity organization with programs and services that support research, advocate for appropriate patient access to healthcare, and promote gastrointestinal and liver health. Information from this input was gathered via questionnaires and interviews. Information was collected from 5 surveys with a total of 1,633 respondents contributing across the surveys. Additional data from a 2020 focus group on persons living with IBD and one-to-one interviews with patients were also assessed for the input.

The GI society highlighted that patients with IBD preferred sustained remission/treatment response over relieving one symptom. Respondents in the surveys expressed different concerns associated with IBD some of which included the fear of running out of medication, how to determine when to go to the ER based on their symptoms, pain, fear of going out due to disease, decrease quality of life, and fear and worry of being faced with mortality at a young age. The patient group highlighted the need for effective treatments for patients that could improve quality of life and cause no symptoms, pain, frustration, or hardship. The patient advocacy group expressed that inadequate access to treatment causes patient suffering such as continual, debilitating disease symptoms; secondary illnesses such as depression and anxiety disorders; and loss of family/social interactions that could have been prevented.

According to the patient advocacy group, treatment of UC requires a multi-faceted strategy that allows for the management of symptom and disease consequences with therapies that target and reduce the underlying inflammation. Treatment options outlined included 5-ASA, corticosteroids, immunosuppressive agents, and biologics. The patient advocacy group highlighted that despite the treatment options available in practice, patients with UC still have trouble achieving remission and adequate symptom relief; thus, there is a need for more treatments that cater to patients' needs. There were no patients interviewed that were currently receiving the treatment under review, however, the majority of patients surveyed had received a biologic. Results from one survey showed that 63% of respondents reported symptom reduction after using a biologic and 23% confirmed remission.

According to the patient advocacy group, patients would like additional effective treatment options with convenient and timely patient access and different administration methods and dosages. The GI society highlighted that major concerns with available therapies included ensuring adequate supply and continuity of care, especially timely communication between patients and their healthcare providers. The patient group noted that receiving intravenous treatments at clinics and untimely communications between patients and healthcare providers could mean frequently taking time off work, which can be difficult and contribute to financial hardship for many patients. According to the patient advocacy group, patients desire options that can be administered at home thereby reducing required time off work.

### Clinician Input

#### *Input From Clinical Experts Consulted by CADTH*

Input from 1 clinical expert with experience treating UC was summarized for this review. The clinical expert highlighted that there is no cure for UC in current practice and early treatment is crucial as the first medication prescribed has the best chance of improving patient symptoms and healing. Treatment goals highlighted for UC patients include symptom resolution (clinical remission), improving patient quality of life (by normalizing bowel movements, resolution of pain, resolution of bowel urgency, resolution of rectal bleeding, normalization of weight/energy level), reducing the need for surgery, and avoiding repetitive use of corticosteroids.

According to the expert, treatment selection is complex for patients with UC and depends on disease phenotype and patient preference. Most advanced treatments (anti-TNF, JAK inhibitors, alpha4beta7 integrin inhibition and IL-23 + IL-12/23 inhibitors) currently available in practice target primary and secondary loss of response in both diseases. The expert did not anticipate any shift in treatment paradigm with the use of infliximab SC apart from the option of switching from the IV route to a subcutaneous option. According to the clinical expert, patients with confirmed moderate to severe UC (based on a pathological and histological diagnosis)

will be best suited for treatment with infliximab SC. The expert highlighted that misdiagnosis is rarely observed in practice although delays in diagnosis may occur. The expert noted that not all patients respond well to anti-TNF therapy. Patients that will be less suitable for infliximab SC will be those that fear self-injection.

The clinical expert consulted noted that the frequency of assessing response to treatment in the LIBERTY-UC trial differs from real-world settings. The expert highlighted that colonoscopy is seldom performed every 12 weeks as was the case of the trial procedures due to logistics and patient preference. Fecal calprotectin is an objective measure to monitor disease activity and treatment response for UC patients in addition to the partial Mayo score (partial and modified Mayo scores were derived in the LIBERTY-UC trial to evaluate clinical remission) according to the clinical expert consulted by CADTH. The expert noted that the modified Mayo score (which includes an endoscopic assessment) is used in clinical practice for initial patient assessment prior to treatment initiation while the partial Mayo score is used routinely for follow-up to assess response. According to the clinical expert consulted by CADTH, factors that will lead to treatment discontinuation will be consistent with those outlined for current advanced therapies. The expert highlighted that patients will be evaluated in practice based on clinical symptoms presentation and objective data assessed. The expert mentioned that some patients may present as primary non-responders during treatment and some patients may experience loss of response during treatment (the clinical expert noted that the standard percentage of patients with UC in clinical practice who experience loss of response in the first year of treatment is approximately 10% to 20%). The clinical expert highlighted that UC diagnosis are made by gastroenterologists. However, general internists with special interest in IBD have sufficient experience to prescribe infliximab for both populations. The expert noted that treatment initiation begins in private infusion centres where costs are covered by the drug manufacturer or other patient support programs. Patients will then be transitioned to using the self-injection for the subcutaneous formulation.

### *Clinician Group Input*

No clinician group input was submitted for this review.

## Drug Program Input

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

### Table 2. Responses to Questions from the Drug Programs

| Drug Plan Questions | Clinical expert response Clinical expert response |
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| **Relevant comparators** | |
| There are no direct phase III head-to-head trials with other therapies used for the treatment of UC.<br><br>Is conducting a head-to-head comparative trial against one of the numerous comparative treatments for UC a reasonable expectation in the target population? What could be the rationale for conducting trials against placebo? | The clinical expert recommended conducting a head-to-head comparative trial against currently listed therapies and future therapies for future trials in the UC setting. However, given that the LIBERTY-UC trial assessed the efficacy of a new mode of administration (i.e., subcutaneous) for infliximab that is already approved based on IV administration for use in the indicated populations, the use of a placebo group was considered appropriate by the clinical expert.<br><br>While CDEC acknowledged the clinical expert input, CDEC noted that comparative evidence is the focus of reimbursement reviews and the lack thereof, poses serious limitations. |
| 1. For what clinical reasons would infliximab IV be selected as therapy for UC, rather than the humanized versions of anti-TNFα agents – adalimumab or golimumab?<br><br>2. When conventional therapies fail, are anti-TNFα agents the preferred therapy to initiate or are other biologics with different | 1. According to the clinical expert, infliximab SC will be selected as a treatment of choice following the same reasons as selecting any other anti-TNFα agents, i.e., the choice of treatment is complex and based on the disease phenotype and patient preference. The clinical expert highlighted that some clinicians believe that IV infusions provide more rapid response compared to subcutaneous options. The expert |

| Drug Plan Questions | Clinical expert response Clinical expert response |
|---|---|
| mechanisms of action being selected due to patient specific factors?<br><br>3. Is there a significant unmet need that infliximab SC fills for the treatment of UC? | added that hospitalized patients with severe UC will be more likely to receive infliximab IV formulation.<br><br>2. The clinical expert noted that treatment choice in this setting is complex and dependent on multiple factors, including patient preference. Anti-TNFα agents are not the automatic preferred agent in this setting.<br><br>In LIBERTY-UC, a total of 432 (99.1%) patients had at least 1 prior medication (292 [98.6%] and 140 [100%] patients in the infliximab SC 120 mg and Placebo SC groups, respectively); most reported medication was corticosteroids for systemic use (338 [77.5%]) in total.<br><br>3. According to the clinical expert, infliximab SC provides a subcutaneous option for patients already receiving infliximab IV in practice. Subcutaneous administration of advanced therapies is often desirable for patients, reducing the need for infusion clinic appointments (time away from work, etc.) and allowing them a sense of independence. Many patients find subcutaneous administrations more convenient.<br><br>CDEC acknowledged and agreed with the clinical expert's responses. |
| **Considerations for initiation of therapy** | |
| LIBERTY-UC assessed the superiority of infliximab SC over placebo in 438 patients with moderately to severely active UC (modified Mayo score 5 to 9, endoscopy subscore ≥2).<br><br>Some jurisdictions use the Harvey-Bradshaw Index in their coverage criteria to determine disease severity. Are there any differences in how the Harvey-Bradshaw Index performs against the Mayo score? | The clinical expert noted that the Mayo score is commonly used for UC in practice and is not comparable to the HBI according to the expert. CDEC acknowledged and agreed with the clinical expert's responses. |
| Infliximab SC is indicated for patients who have had inadequate response or were intolerant to conventional therapy. Also, to be started on infliximab SC, patients must first be initiated on IV infliximab.<br><br>1. How many conventional therapies are typically tried before biologic, JAK inhibitors or S1PRMs are considered for therapy?<br><br>2. Is there a standard definition of an inadequate response to conventional (or biologic) therapy for UC?<br><br>3. In your opinion, what percentage of patients would choose to switch from IV infliximab | 1. The clinical expert highlighted that biologics are now considered as advanced therapies, which include S1PRMs and JAK inhibitors. According to the expert, patients with moderate to severe UC should not have to fail conventional therapy before access to advanced therapies are considered. In terms of corticosteroids, it is not indicated for maintenance of remission in UC populations.<br><br>2. According to the expert, markers to determine inadequate response to conventional therapy include inability of patients to taper off from the use of corticosteroids, lack of clinical remission, lack of endomucosal healing, worsening of objective markers (e.g., fecal calprotectin). |

| Drug Plan Questions | Clinical expert response Clinical expert response |
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| every 8 weeks to a bi-weekly injection of infliximab SC? | 3. The clinical expert expressed that it will be difficult to determine the percentage of patients who will switch from IV infliximab to subcutaneous treatment. According to the expert, many patients already on stable IV therapy may choose to remain on that treatment plan. However, the expert noted that subcutaneous injections often lead to more stable therapeutic drug levels and can be clinically advantageous for some patients. The expert felt that the choice to switch will be made based on a case-by-case approach and after thorough discussion between clinician and patient.<br><br>CDEC acknowledged clinical expert's responses. CDEC noted that as per the Health Canda indication infliximab SC is recommended in patients who have had an inadequate response or were intolerant to conventional therapy; removing the criteria of being intolerant or having an inadequate response is out of scope of this indication. |
| There is variation in how public drug plans reimburse infliximab across Canada. If infliximab SC is recommended for reimbursement by the CDEC, is it reasonable to use existing initiation criteria for infliximab IV in each jurisdiction? | The clinical expert expressed that it will be reasonable to use the existing initiation criteria for infliximab IV in each jurisdiction for infliximab SC, although they would prefer not to include the need for a patient to have intolerant or inadequate response to conventional therapies (immunomodulators) as criteria for initiation.<br><br>CDEC acknowledged the clinical expert's responses. CDEC noted that as per the Health Canda indication infliximab SC is recommended in patients who have had an inadequate response or were intolerant to conventional therapy; removing the criteria of being intolerant or having an inadequate response is out of scope of this indication. |
| **Considerations for continuation or renewal of therapy** | |
| If infliximab SC is recommended for reimbursement by the CDEC, is it reasonable to use existing renewal criteria for infliximab IV in each jurisdiction? | The clinical expert expressed that it will be reasonable to use the existing renewal criteria for infliximab IV in each jurisdiction for infliximab SC. CDEC acknowledged and agreed with the clinical expert's responses. |
| **Considerations for discontinuation of therapy** | |
| LIBERTY-UC:<br><br>Loss of response criteria = an increase in modified Mayo score of ≥ 2 points and ≥ 30% from the Week 10 modified Mayo score with actual value of ≥ 5 points, and endoscopic subscore of ≥ 2 points.<br><br>These patients received infliximab SC 240 mg (double injection [2 shots] every 2 weeks from week 22.<br><br>1. Is the loss of response criteria used in the studies consistent with those used in clinical practice? | 1. According to the clinical expert, definition of loss of response for UC patients is consistent with clinical practice.<br><br>2. According to the clinical expert, loss of response for infliximab 120/240 mg SC is not inevitable for UC patients. The expert noted that many patients will remain on their original advanced therapy for many years. The expert highlighted that they have patients currently in practice that have been on infliximab since starting the medication for their disease. Best chance of achieving remission is commonly observed with the first advanced therapy chosen. |

| Drug Plan Questions | Clinical expert response Clinical expert response |
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| 2. Is a loss of response to infliximab SC 120 mg or 240 mg inevitable for most patients based on the pathophysiology of UC?<br><br>3. In clinical practice, could infliximab SC doses be escalated above 240 mg if patients initially respond to a higher dose but then experiences a loss of response?<br><br>4. Are the loss of response rates in the LIBERTY-UC trial consistent with loss of response to infliximab IV in your clinical practice? | 3. The clinical expert noted that there is currently no data on the use of escalated doses of infliximab SC above 240 mg in current practice. According to the expert, since infliximab SC is a subcutaneous formulation, the likelihood of a patient benefitting from the treatment at a higher dose would be minimal except in specific cases (like severe perianal disease patients and patients with other penetrating disease phenotypes).<br><br>The LIBERTY-UC trial allowed dose adjustments from infliximab SC 120mg to infliximab SC 240mg every 2 weeks starting from Week 22 through Week 54, if patients initially responded but then lost response; these patients were considered as non-responders or non-remitters in primary and secondary efficacy analyses.<br><br>4. The clinical expert noted that the standard percentage of patients with UC in clinical practice who experience loss of response in the first year of treatment is approximately 10% to 20%. In the trials, 11.9% of patients with UC showed loss of response.<br><br>CDEC acknowledged the responses from the clinical expert. CDEC noted that escalating the dose of infliximab SC to 240mg is outside of the Health Canada recommended dose for infliximab SC. |
| If infliximab SC is recommended for reimbursement by CDEC, is it reasonable to use existing discontinuation criteria for infliximab IV in each jurisdiction? | The clinical expert expressed that it will be reasonable to use the existing discontinuation criteria for infliximab IV in each jurisdiction for infliximab SC. CDEC acknowledged and agreed with the clinical expert's responses. |
| **Considerations for prescribing of therapy** | |
| If infliximab SC is recommended for reimbursement by CDEC, is it reasonable to use existing prescribing criteria for infliximab IV in each jurisdiction? | The expert expressed that it will be reasonable to use the existing prescribing criteria for infliximab IV in each jurisdiction for infliximab SC, although they would prefer not to include the need for a patient to have intolerant or inadequate response to conventional therapies (immunomodulators) as criteria for prescribing. CDEC acknowledged the clinical expert's response. CDEC noted that as per the Health Canda indication infliximab SC is recommended in patients who have had an inadequate response or were intolerant to conventional therapy; removing the criteria of being intolerant or having an inadequate response is out of scope of this indication. |
| **Generalizability** | |
| The LIBERTY-UC trial did not evaluate patients < 18 years of age and did not enroll many patients > 65 years of age. | The expert noted that there may be a need for access to infliximab SC in pediatric populations by pediatric gastroenterologists for patients less than 18 years of age. The expert added that anti-TNFα agents are currently used in patients above 65 years of age. |

| Drug Plan Questions | Clinical expert response Clinical expert response |
|---|---|
| Is there any desire to use infliximab SC in patients who are outside the age range of 18 to 65, or are there adequate treatment options for these patients? | CDEC acknowledged that there is currently insufficient evidence to guide a recommendation for infliximab SC for patients aged below 18 or above 65 years of age. CDEC noted that Health Canada has not authorized an indication for pediatric use and recommends caution when treating the elderly as clinical studies with infliximab SC did not include sufficient numbers of patients aged 65 and older to determine whether they respond differently than younger patients. |
| **System and economic issues** | |
| Costs of IV infusions are paid by public drug plans (not sponsors) as these services are intentionally negotiated as part of the total reimbursed price.<br><br>Since infliximab SC maintenance therapy does not require IV infusion services, should its reimbursed price be lower than infliximab IV? Would the lowest priced SC biologic be a reasonable price target? | The clinical expert highlighted that all patients in the trials received IV induction therapy, which is different from other SC advanced therapies currently approved.<br><br>CDEC noted that there is no evidence to support a price premium for infliximab SC over other advanced treatment options. |

CDEC= Canadian Drug Expert Committee; IV= intravenous; JAK inhibitor= janus kinase inhibitors; S1PRMs = Sphingosine 1-phosphat receptor modulators; TNF= Tumour necrosis factor; UC= ulcerative colitis.

## Clinical Evidence

### Systematic Review

*Description of Studies*

The LIBERTY-UC (n= 438) trial was a randomized, double-blind, placebo-controlled, phase III, trial designed to assess the superiority of infliximab SC (120 mg) administered every 2 weeks over placebo in adult patients (18 to 75 years) with moderately to severely active UC that had an inadequate response to conventional therapy. It consisted of an induction phase, where enrolled patients received 5 mg/kg doses of infliximab intravenously; a maintenance phase, which consisted of patients that had no safety concerns and were considered clinical responders before week 10, randomized in a 2:1 ratio to receive infliximab SC or placebo as maintenance treatment for up to 54 weeks; and an extension study phase, consisting of patients who had completed treatment at week 54 in both arms that were administered open-label infliximab SC for up to week 102. The extension phase is ongoing.

The primary endpoint of LIBERTY-UC trial was clinical remission measured using the modified Mayo score. Key secondary endpoints included clinical response (based on modified Mayo score), endoscopic-histologic mucosal improvement, and corticosteroid-free remission at Week 54. Health-related quality of life, another secondary outcome, was measured using the short inflammatory bowel disease questionnaire (SIBDQ), the patient global scale and VAS (for local site pain assessment). Baseline characteristics were generally well balanced between the 2 treatment groups in the trial. The mean age of patients ranged between 38 and 40 years, most patients were males, and majority of the population were white.

Study 1.6 (n= 131) was an open-label, parallel-group, phase I, randomized trial comparing pharmacokinetic (PK) parameters, efficacy, and safety of infliximab 5mg/kg IV administered every 8 weeks versus infliximab SC120 mg or 240 mg, administered every 2 weeks in adult patients (18 to 75 years) with active UC and CD. The study had two parts, part 1 was a PK study designed to find the optimal dose of REMSIMA$^{TM}$ SC and has not been include in this report. Part 2 of the study evaluated a PK outcome, as primary end point ($C_{trough,\ week22}$) and clinical efficacy endpoints as secondary outcomes (CDAI-70 and 100 response, clinical remission, endoscopic response, clinical response [based on total Mayo and partial score]), mucosal healing and SIBDQ scores. Patients in the infliximab IV arm received IV infliximab up to week 22 and switched to infliximab SC by Week 30 and continued up to Week 54. Baseline characteristics were generally well balanced between the 2 treatment groups in the trial; most patients were white, males, and mean age between 35 and 36 years across the 2 groups.

*Efficacy Results*

**LIBERTY-UC Trial**

Primary Outcomes

*Clinical remission*

The proportion of patients achieving clinical remission at Week 54 in the infliximab SC group was higher (127 [43.2%] patients) compared to placebo (30 [20.8%] patients), with a 21.1% treatment difference (95% CI: 11.8 to 29.3) and a P value of <.0001. Sensitivity and other supportive analyses were consistent with the primary analyses in the LIBERTY-UC trial.

Key secondary outcomes

*Clinical response*

The proportion of patients who achieved clinical response at Week 54 was higher in the infliximab SC group (158 [53.7%]) compared to the placebo group (45 [31.3%]) at Week 54, with an estimated treatment difference of 21.1% (95% CI: 11.2 to 30.1) and a P value of <0.0001.

*Endoscopic-histologic mucosal improvement*

A greater proportion of patients in the infliximab SC group (105 [35.7%]) achieved endoscopic-histologic mucosal improvement at Week 54 compared to the placebo group (24 [16.7%] with an estimated treatment difference of 18.0% [95% CI: 9.1 to 25.7], P value of <0.0001).

*Corticosteroid-free remission*

More patients in the infliximab SC group (44 of 120 [36.7%]) achieved corticosteroid-free remission compared to the placebo group (11 of 61 [18.0%]) at Week 54 with an estimated treatment difference of 17.3% (95% CI: [3.1 to 28.9], P value of 0.01).

*Maintenance of clinical remission*

Among patients with clinical remission at Week 10, a higher number of patients in the infliximab SC group 91 (63.6%) achieved maintenance of clinical remission compared to the placebo group (18 [27.3%]) at Week 54, with a treatment difference of 35.5% (95% CI: 21.1 to 47.5) and a P value of <0.0001.

*Total and partial clinical remission*

The number of patients who achieved total remission at Week 54 in the infliximab SC group was 117 (39.8%) compared to 26 (18.1% in the placebo group (treatment difference: 20.4% [95% CI: 11.3 to 28.3, P value <0.0001]). The number of patients who achieved partial clinical remission at week 54 in the infliximab SC arm was 127 (43.2%) compared to 39 (27.1%) in the placebo group (treatment difference of 14.7% [95%CI: 5.1 to 23.5], P value of 0.0017)

*Health-related Quality of Life (HRQoL)*

Fewer patients completed patient reported outcomes using the SIBDQ in the LIBERTY-UC trial at Week 54 compared to baseline in both groups (infliximab SC group [n= 185 at week 54 versus 294 at baseline, respectively] and placebo group [n= 61, at week 54 versus n=144 at baseline, respectively]). The LS mean at week 54 for SIBDQ in the infliximab SC group was 57.7, and 54.9 in the placebo group. The estimated treatment difference between the 2 groups was 2.9 (95% CI: -0.3 to 6.0; P value= 0.08). The LS mean change from baseline at Week 54 was 21.9 in the infliximab SC group versus 18.9 in the placebo group (estimated treatment difference was 3.0 95% CI: -1.0 to 6.9; P value= 0.14).

**Study 1.6**

The mean percent coefficient of variation ([CV]%) observed $C_{trough, week22}$ was higher in the infliximab SC 120/240 mg group than the infliximab IV 5 mg/kg group at Week 22 (21.5 [46.0] and 2.9 [89.0] µg/mL, respectively). The ratio of the geometric LS means was 1154.2 with a lower bound 90% CI of 786.4%, which was greater than 80%, suggesting that infliximab SC was noninferior to infliximab IV in terms of PK (noninferior margin of 80%). The geometric LS mean observed $C_{trough, week22}$ was 20.9 and 1.8 µg/mL in the infliximab SC 120/240 mg group and infliximab IV 5 mg/kg treatment group, respectively.

*Secondary outcomes*

UC population within Study 1.6 trial

The proportion of patients achieving clinical response at Week 22 based on the total Mayo score was higher for patients receiving infliximab SC (n= 24, 63.2%) compared to infliximab IV (n= 17, 43.6%). At Week 22, the proportion of patients achieving clinical response according to partial Mayo scores was 32 (84.2%) in the infliximab SC group compared to 30 (76.9%) in the infliximab IV group. At Week 54, the proportion of patients achieving clinical response was 63.2% (n= 24) in infliximab SC group versus 61.5% (n= 24) in the infliximab IV group (partial Mayo scores were as follows: Infliximab SC [n=31, 81.6%] infliximab IV [n=28, 71.8%]).

The proportion of patients achieving clinical remission at Week 22 based on total Mayo score was higher in the infliximab SC group (n= 17, 44.7%) compared to the infliximab IV group (n= 10, 25.6%). The proportion of patients achieving clinical remission according to partial Mayo scores at week 22 was 23 (60.5%) in the infliximab SC group versus 15 (38.5%) in the infliximab IV group. At Week 54, the proportion of patients achieving clinical remission in the infliximab SC group was 52.6% (n= 20), versus 48.7% (n= 19) in the infliximab IV group (partial Mayo scores were as follows: Infliximab SC [n=26, 68.4%] infliximab IV [n=24, 61.5%]).

The proportion of patients achieving mucosal healing at Week 22 was higher in the infliximab SC group (n= 18, 47.4%) compared to the infliximab IV group (n= 12, 30.8%). At Week 54, the proportion of patients achieving mucosal healing in the infliximab SC group was 55.3% (n= 21) versus 56.4% (n=22) in the infliximab IV group.

Harms

**LIBERTY-UC trial**

Treatment emergent adverse events (TEAEs) reported were more common in the infliximab SC group (67.6%) compared to placebo (59.3%) in the maintenance phase of the LIBERTY-UC. The majority of TEAEs were grade 1 or 2 in intensity. The number of patients with at least 1 serious AE in the maintenance phase was 19 (6.4%) and 4 (2.9%) in the infliximab SC and placebo groups, respectively. The most common serious AEs (infliximab SC versus placebo) included GI disorders (1.4% versus 1.4%) and infections and infestations (2.4% versus 0.7%).

In the LIBERTY-UC trial, the most common grade 3 AEs reported in the infliximab group were neutrophil count decreased (3.7%), anemia (2.0%), and creatine phosphokinase increased (1.7%); the most commonly reported grade 4 AE was creatine phosphokinase (CPK) increased (1.4%). In the placebo group, CPK increased (2.9%) was the most common grade 3 AE and the most common grade 4 AE (1.4%).

Adverse events of special interest (infliximab SC versus placebo) included infection (28.0% versus 25.7%), systemic injection reaction (4.1% versus 2.9%), injection related reaction (4.1% versus 2.9%), and systemic injection reaction (4.1% versus 2.9%).

There were no deaths reported in the LIBERTY-UC trial.

**Study 1.6**

There was a higher proportion of patients in the infliximab SC group (74.2%) of Study 1.6 reporting TEAEs during the maintenance phase compared to the infliximab IV group (58.5%). The most common AEs in Study 1.6 reported during the maintenance phase (infliximab SC versus infliximab IV) included localized injection site reactions (22.7% vs 4.6%), colitis ulcerative (4.5% vs 12.3%), and neutropenia (7.6% vs 4.6%).

The proportion of patients who experienced at least 1 TEAE on or after Week 30 (i.e., post Week 30 includes pooled safety results of the two treatment groups after switching to or continue with infliximab SC at Week 30) was slightly higher in the infliximab SC treatment group (31 [47.0%] and 21 [32.3%] patients for the infliximab SC and infliximab IV treatment groups, respectively)

The most common adverse events of special interests reported during the maintenance phase (infliximab SC versus infliximab IV) included infections (31.8% versus 29.2%), localized injection site reaction (22.7% versus 4.6%), systemic injection reaction (3.0% versus 0%), and malignancy (1.5% versus 0%). Adverse events of special interests classified as systemic injection reaction on or after Week 30 was reported for 1 (1.5%) patient in the infliximab SC group only.

There were no deaths reported in Study 1.6.

### *Critical Appraisal*

*Internal Validity*

LIBERTY-UC Trial

The LIBERTY-UC was a randomized, placebo controlled, multicentre, phase III study designed with an open-label induction phase, a double-blind treatment phase (maintenance phase), and an open-label extension phase. Appropriate methods for blinding, treatment allocation, and randomization were employed.

The primary and key secondary outcomes in the LIBERTY-UC were considered appropriate and recommended by the FDA and EMA for assessing treatment effects for UC patients in the trial settings. Outcomes assessed in the LIBERTY-UC trial (modified Mayo score, patient reported outcomes, and safety outcomes) were subjective and potentially prone to assessment bias, which could bias results in both groups in either direction.

There were imbalances in study treatment exposures between the 2 groups in the LIBERTY-UC trial as there were more dose adjustments observed in the placebo group from week 22 compared to infliximab SC. There is also a potential bias from treatment awareness in the trial due to the frequent dose adjustments. This may have impacted the assessment of subjective outcomes in both populations in the LIBERTY-UC trial. The direction and magnitude of this potential bias are uncertain. There was also a concern for potential bias due to missing outcome data for the HRQoL especially in the placebo group in both trials at week 54, rendering the results inconclusive.

Concomitant drug use in the maintenance phase was similar in both groups. There was a potential for residual drug effect of continued use of corticosteroids in the maintenance phase which may have impacted disease symptoms in the placebo and infliximab SC groups in the LIBERTY-UC trial.

**Study 1.6**

Study 1.6 study is an open-label, randomized, parallel-group, multicentre, phase I study. Appropriate methods for randomization and treatment allocation were implemented. Baseline characteristics were similar between the 2 treatment groups in the trial, suggesting successful randomization.

The key rationale of Study 1.6 was to assess the non-inferiority of infliximab SC against infliximab IV based on primary outcome PK parametre $C_{trough}$ at week 22. $C_{trough}$ assessment in the study was considered appropriate and aligned with regulatory guidelines. The assessment of plasma concentration of infliximab ($C_{trough}$ at week 22) was considered appropriate by the clinical expert consulted by CADTH and it aligns with regulatory guideline requirements and published literature. A noninferiority margin of 80%, 1-sided alpha level 5%, expected ratio of 1.3, and percent coefficient of variation (CV%) of 100% were assumed for part 1 of the study and 20% drop-out rate. The study was powered to detect a statistical difference between the 2 groups of interest for the PK outcome.

Study 1.6 was not designed or powered to formally assess comparative efficacy outcomes (i.e., CDAI response, clinical response, clinical remission, endoscopic response and remission, mucosal healing, or HRQoL) making assessments of relative therapeutic efficacy of infliximab SC against infliximab IV challenging. The sample size of Study 1.6, i.e., n= 135, was considered relatively small to assess efficacy outcomes in the UC and CD populations. Treatment effect estimates observed may not be replicable in a larger study sample. The protocol did not pre-specify a degree of difference from which to formally conclude non-inferiority between

infliximab SC and infliximab IV in terms of efficacy outcomes. While the evidence from Study 1.6 suggests infliximab SC is comparable to infliximab IV in terms of PK parameters, the lack of robust evidence on efficacy outcomes (efficacy outcomes were presented descriptively without any statistical comparison), precludes firm conclusions to support switching from infliximab IV to infliximab SC. The clinical experts consulted by CADTH did not anticipate clinically meaningful differences in efficacy between infliximab SC and infliximab IV due the products' same active ingredient, i.e., infliximab. The clinical expert did not anticipate any clinical concerns switching from the IV route to a subcutaneous option of infliximab as long as the choice to switch was made based on a case-by-case approach and after thorough discussion between clinician and patient.

There were concerns related to missing data between the 2 groups for HRQoL data assessed using the SIBDQ and VAS (for local site pain assessment) as fewer patients completed questionnaires at Week 30 and Week 54 compared to baseline for CD and UC populations, which may have impacted the findings. It is therefore uncertain whether switching patients from infliximab IV to infliximab SC at week 30 in Study 1.6 resulted in comparable HRQoL outcomes in the UC and CD populations, respectively.

*External Validity*

LIBERTY-UC and Study 1.6 Part 2

LIBERTY-UC and Study 1.6 Part 2 were multicentre, international trials that recruited adult patients aged 18 to 75 years old. The inclusion and exclusion criteria of the trials were generally aligned with the selection criteria used in current practice to identify suitable patients for infliximab according to the clinical expert consulted by CADTH. However, the exclusion of patients with prior experience with 2 or more lines of biological therapy and or JAK inhibitors was inconsistent with clinical practice as patients with prior exposure to other biological agents including JAK inhibitors are currently considered for treatment with infliximab IV in clinical practice according to the clinical expert consulted by CADTH. Baseline disease characteristics of the study patients in the LIBERTY-UC such as Mayo scores, the proportion of patients with moderate to severe disease, type of prior surgeries conducted, and other important objective outcomes such as C-reactive protein, and fecal calprotectin, that are important for monitoring patients in practice were presented. There were no major differences between baseline characteristics in the infliximab SC group compared to placebo in the LIBERTY-UC trial.

The primary and key secondary outcomes were considered relevant to decision-making and adequately reflected measures of both efficacy and harms, according to the clinical expert consulted by CADTH. Concomitant medications used in the trial were reflective of clinical practice (except for mesazaline, which is seldom used in current practice). Corticosteroid tapering was consistent with regulatory guidelines although the rates differed slightly from clinical practice.

Although the study design (induction and maintenance phases) in the 2 trials is consistent with regulatory guidelines and reflects clinical practice, it generates an enriched population in the trial setting consisting of responders who can better tolerate and respond to infliximab. The induction period was also considered short (4 weeks for Study 1.6 and 10 weeks for the LIBERTY-UC trial) and failed to accommodate slow responders, which is inconsistent with current practice according to the clinical expert consulted by CADTH (dose-loading periods may extend up to 16 weeks). The duration of the maintenance phase was considered adequate by the clinical expert consulted to assess treatment effect. The trial frequency of assessments (endoscopic assessments) was considered standard for trials but differed from current practice due to the logistic constraints associated with conducting the assessments (practical limitations and the invasiveness of the procedure) and patient preferences.

The clinical expert consulted by CADTH noted that clinicians may consider higher doses of infliximab IV for patients with more severe disease in the induction/ dose-loading phase, which could then be further adjusted based on patient response, patient preference, and safety profile. The dose of infliximab SC in Study 1.6 differed from the dose, which is recommended by Health Canada for infliximab SC, in that weight-based dosing was performed (i.e.,120 or 240 mg infliximab SC based on body weight [<80 kg and ≥80 kg, respectively]) dose escalation to infliximab SC 240 mg every 2 weeks was allowed from Week 30, and patients received only 2 doses during induction phase rather than 3 doses as per Health Canada recommendations. There is some uncertainty if results of Study 1.6 are generalizable to the use of infliximab SC as per Health Canda recommended dosage.

## Indirect Comparisons

No indirect treatment comparison (ITC) was submitted for this review.

## Economic Evidence

### Cost and Cost-Effectiveness

At the submitted price, the first-year costs of infliximab SC depend on which infliximab IV product is chosen for the induction period. Costs per patient when Inflectra is chosen for the induction are $19,357 per patient for the first year and $15,424 in each subsequent year.

The sponsor submitted a cost comparison assessing infliximab SC compared with other infliximab IV biosimilars (Inflectra, Renflexis and Avsola), adalimumab biosimilars, adalimumab (Humira), Golimumab SC (Simponi), Vedolizumab (Entyvio) IV and SC, and Ustekinumab (Stelara).

CADTH identified the following limitations with the sponsor's submitted cost comparison:

- The comparative efficacy of infliximab SC with respect to non-infliximab comparators is uncertain.
- The sponsor submitted pricing for infliximab SC at parity on a per mg basis does not align with annual costs.

The annual costs associated with infliximab SC are less than those associated with the branded IV product (Remicade) and with other branded biologic comparators such as adalimumab (Humira), Golimumab SC (Simponi), Vedolizumab (Entyvio) IV and SC, and Ustekinumab (Stelara). Alternatively, infliximab SC is associated with increased annual costs when compared to other infliximab IV biosimilars (Inflectra, Renflexis and Avsola) and adalimumab biosimilars, even though it is priced at parity of the least costly biosimilar per mg. These incremental costs or savings are based on publicly available list prices and may not reflect actual prices paid by Canadian drug plans.

Based on publicly available list prices, the price of infliximab SC would have to be reduced by 16% for the annual cost of treatment acquisition to be equivalent to that of the least costly infliximab IV (Renflexis and Avsola). Similarly, the submitted price of infliximab SC would have to be reduced by 40% to be equivalent to the treatment acquisition costs of other bDMARDs.

### Budget Impact

CADTH identified the following key limitations with the sponsor's analysis; use of a claims-based approach to estimate market size introduces uncertainty with the anticipated budget impact of infliximab; average patient population weight did not align with clinical expectations; and actual prices paid for the biologic comparators by Canadian jurisdictions is unknown.

CADTH did not conduct a base case analysis, as the sponsor's submission provided adequate presentation of the budget impact for infliximab SC. The sponsor's base case suggested three-year budgetary cost savings of $732,628 over 3 years.

CADTH presented a series of scenario analyses to test the impact of alternative assumptions on the estimated budget impact. Budget impact was sensitive to assumptions about the average patient weight and the price of infliximab SC.

## CDEC Information

### Members of the Committee:

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunsky, Dr. Edward Xie, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Peter Jamieson, Mr. Morris Joseph, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Dr. Trudy Huyghebaert, Dr. Danyaal Raza, and Dr. Peter Zed.

### Meeting date: February 28, 2024

### Regrets:

2 expert committee members did not attend.

### Conflicts of interest:

None