CADTH

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

(Draft)

Upadacitinib (Rinvoq)

Indication: for the treatment of adults with active psoriatic arthritis who have had an inadequate response or intolerance to methotrexate or other disease-modifying antirheumatic drugs (DMARDs). Upadacitinib may be used as monotherapy or in combination with methotrexate.

Recommendation: Reimburse with Conditions

Version:	1.0
Publication Date:	July 2021
Report Length:	16 Pages

Single Technology

CADTH

UPADACITINIB (RINVOQ — ABBVIE CORPORATION)

Therapeutic Area: Psoriatic Arthritis, Adults

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that upadacitinib should be reimbursed as monotherapy or in combination with methotrexate for the treatment of adults with active psoriatic arthritis (PsA) who have had an inadequate response or intolerance to methotrexate or other disease-modifying antirheumatic drugs (DMARDs) only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

In two double-blind, randomized controlled trials in adults with moderate-to-severe active PsA who had an insufficient response or intolerance to a non-biologic DMARD and who were biologic DMARD (bDMARD) naive (SELECT-PsA1) or who had insufficient response or intolerance to a bDMARD (SELECT-PsA2), upadacitinib 15 mg once daily was associated with statistically significant and clinically meaningful improvements compared with placebo in the proportion of patients achieving at least a 20% improvement in American College of Rheumatology response criteria (ACR20) at week 12 (the primary efficacy outcome). The difference between the upadacitinib 15 mg group and placebo treatment group was 34.5% (95% confidence interval [CI], 28.2 to 40.7; P < 0.0001) in SELECT PsA1, and 32.8% (95% CI, 24.0 to 41.6; *P* < 0.0001) in SELECT-PsA2. Additionally, in bDMARD naive patients, upadacitinib was non-inferior to adalimumab 40 mg subcutaneous (SC) every other week for the ACR20 response at week 12. The efficacy of upadacitinib compared to adalimumab in bDMARD experienced patients is unknown. In both studies, upadacitinib 15 mg was associated with statistically significant improvements compared with placebo for numerous clinically relevant manifestations of PsA, including function and disability (Health Assessment Questionnaire – Disability Index [HAQ-DI]), PsA symptoms (Functional Assessment of Chronic Illness Therapy-Fatigue [FACIT-F]), Health-related Quality of Life (HRQoL) (Physical Component Summary [PCS] component of the SF-36), skin disease (Psoriasis Area and Severity Index [PASI], and Static Investigator Global Assessment [sIGA]), and other measures of clinical response or disease control such as Minimal Disease Activity (MDA).

Patient input received for this review articulated that there is a need for new PsA treatment alternatives that are effective in reducing PsA symptoms, including joint pain, clearing psoriasis and improving their HRQoL. Based on the results from SELECT-PsA1 and SELECT-PsA2 studies, upadacitinib appears to address some of these important outcomes valued by patients.

Direct comparative evidence for upadacitinib versus bDMARDs (other than versus adalimumab) or targeted synthetic DMARDs (tsDMARDs) was not identified. One sponsor-submitted indirect treatment comparison (ITC) comparing upadacitinib to bDMARDs or tsDMARDs suggested that in both bDMARD-naive and experienced patients, upadacitinib does not show a consistent nor distinct difference in efficacy as measured by ACR, PASI, PsARC, or HAQ-DI when compared to bDMARDs or tsDMARDs. There is uncertainty around the ITC results due to the inherent heterogeneity across trials in the networks.

Using the sponsor submitted price for upadacitinib and publicly listed prices for all other drug costs, upadacitinib was more costly compared with several relevant comparator treatments for adults with active PsA who have had an inadequate response to previous DMARDs or for whom DMARDs are not tolerated or contraindicated. The committee considered that there is insufficient evidence to justify a cost premium over the least expensive bDMARD or tsDMARDs reimbursed for the treatment of adult patients with PsA.

Table 1. Reimbursement Conditions and Reasons

Reimbursement Condition	Reason
Initiation	
1. Eligibility for upadacitinib should be based on the criteria used by each of the public drug plans for reimbursement of bDMARDs for the treatment of active psoriatic arthritis (PsA)	There is no direct evidence that upadacitinib is clinically superior or inferior to other biologic treatments currently reimbursed for the treatment of active PsA. In bDMARD-naive patients (Study SELECT-PsA1), upadacitinib 15 mg orally once daily was non-inferior to adalimumab 40 mg SC every other week in achievement of ACR20 response at Week 12.
Renewal	
1. Upadacitinib should be renewed in a similar manner to other bDMARDs currently reimbursed for the treatment of adult patients with active PsA.	There is no evidence that upadacitinib should be held to a different standard than other reimbursed options when considering renewal.
Prescribing	
1. Patient should be under the care of a rheumatologist or clinicians who have experience treating adult patients with active PsA	Accurate diagnosis and follow up of patients with active PsA is important to ensure that upadacitinib is prescribed to the most appropriate patients. In addition, there are several bDMARD and tsDMARD treatment options that may be considered when selecting the most appropriate therapy for patients, which is best determined by a rheumatologist or clinician who is familiar with this complex treatment paradigm.
2. Upadacitinib should not be reimbursed when used in combination with bDMARDS or other Janus kinase (JAK) inhibitor treatments for active psoriatic arthritis.	There is no evidence to determine the effects of upadacitinib when used in combination with bDMARDs or other JAK inhibitors in patients with active psoriatic arthritis.
Pricing	
1. The cost of upadacitinib should not exceed the drug program cost of treatment with the least costly bDMARD or tsDMARD reimbursed for the treatment of active PsA	Upadacitinib did not demonstrate improved efficacy or harms relative to bDMARDs based on direct (SELECT PsA1) evidence. Indirect evidence for upadacitinib compared with other treatments in patients who were biologic-naïve and biologic-experienced were associated with several limitations. Based on the totality of evidence, CADTH noted that upadacitinib does not show any difference in efficacy in terms of PsARC, PASI, HAQ-DI change and ACR when compared to bDMARDs and tsDMARDs.

Implementation Guidance

1. Upadacitinib may be used as monotherapy or in combination with methotrexate. Approximately 80% of patients in SELECT-PsA1 and 50% of patients in SELECT-PsA2 received concomitant non-biologic DMARDs (mostly methotrexate), and a subgroup analysis found consistent treatment effects regardless of concomitant non-biologic DMARD use.
2. CDEC noted that there is no evidence demonstrating the efficacy of upadacitinib in patients who have been previously treated with another JAK inhibitor. This was considered an important evidence gap by CDEC. The clinical expert noted that patients who do not respond to tofacitinib treatment or were previously treated with tofacitinib for PsA may be treated with upadacitinib but that patients responding to tofacitinib should not be switched to upadacitinib as their subsequent response is unknown. The clinical expert also noted that patients who are successfully treated with biologic therapy should not switch treatment to upadacitinib just because it offers an oral option; however, patients who failed previous treatment with a bDMARDs should be eligible to switch to upadacitinib.

Discussion Points

- CDEC noted that the only long-term comparative evidence available for upadacitinib was compared with adalimumab in bDMARD naïve patients; however, only descriptive statistics were available. With the exception of adalimumab, there is no direct long-term evidence comparing to the other bDMARDs or tsDMARDs available in Canada. In addition, the sponsor submitted ITC used study results collected over a relatively short duration compared to the chronic nature of PsA. Given that PsA requires lifelong treatment, there is uncertainty regarding the long-term effectiveness and safety of upadacitinib over other currently available bDMARDs or tsDMARDs for the treatment of active PsA.

- Patient groups indicated the need for a treatment that would improve HRQoL with minimal adverse effects. The only comparative evidence available is for upadacitinib compared to adalimumab in bDMARD naive patients and most HRQoL outcomes were outside of the statistical testing hierarchy. The sponsor submitted ITC did not assess comparative HRQoL or safety. Hence, there is no evidence that upadacitinib would improve HRQoL or have a lower rate of adverse events compared with other currently available bDMARDs or tsDMARDs for the treatment of active PsA.

Background

Upadacitinib has a Health Canada indication for the treatment of adults with active psoriatic arthritis who have had an inadequate response or intolerance to methotrexate or other DMARDs. Upadacitinib may be used as monotherapy or in combination with methotrexate. Upadacitinib is a JAK inhibitor and modulates the signaling pathway at the point of JAKs, preventing the phosphorylation and activation of signal transducers and activators of transcription pathways. It is available as orally administered extended-release tablets and the Health Canada–approved dose is 15 mg orally once daily.

Sources of Information Used by the Committee

To make their recommendation, the Committee considered the following information:

- A systematic review that included two phase III RCTs in adult patients with an established diagnosis of moderate to severe active PsA who had been previously treated with a DMARD.
- Patients perspectives gathered by patient groups, including the Arthritis Consumer Experts (ACE), the Canadian Spondylitis Association (CSA), The Canadian Association of Psoriasis Patients (CAPP) partnering with the Canadian Psoriasis Network (CPN), and the Canadian Arthritis Patient Alliance (CAPA) partnering with the Arthritis Society
- Input from public drug plans and cancer agencies that participate in the CADTH review process.
- A clinical specialist with expertise in diagnosing and treating patients with PsA.
- A review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

Patient Input

Four inputs were submitted for this review representing six different patient groups: Arthritis Consumer Experts (ACE), the Canadian Spondylitis Association (CSA), The Canadian Association of Psoriasis Patients (CAPP) partnering with the Canadian Psoriasis Network (CPN), and the Canadian Arthritis Patient Alliance (CAPA) partnering with the Arthritis Society. Patient perspectives were obtained from surveys. The following is a summary of key input from the perspective of the patient group(s):

- Survey respondents emphasized pain, stiffness, lack of mobility, and fatigue which impact their activities of daily living, their family lives, and their ability to work and maintain certain hobbies. The impact of PsA extends to others within a person's support circle, including caregivers such as spouses, partners, or children, who may have to take on additional roles or tasks to support the person living with PsA.

- Patients living with psoriatic disease often try a succession of treatments throughout their lives. Responses to medications can vary significantly between individuals, and treatments that are initially effective can become less effective over time. As a result, patients need several treatment options to effectively manage their disease throughout their lives.

- Outcomes that were identified as important to patients with PsA include a reduction in symptoms particularly pain and fatigue, treatments that are effective for psoriasis as well as psoriatic arthritis symptoms, increased mobility, improved quality of life (including ability to work and be productive at work, ability to carry out activities of daily living, ability to effectively carry out parenting tasks and other important social roles), reduced infection rates, route of drug administration (oral vs. infusion vs. self-injections), and affordability of the medication.

Clinician input

Input from clinical experts consulted by CADTH

The clinical expert consulted by CADTH for this review identified an unmet need in the treatment of psoriatic disease as some patients may not respond to any treatment, and only a minority achieve MDA. In the treatment of PsA, numerous domains of disease activity need to be addressed, which might not be accomplished by a single agent. In patients who do not respond or become refractory to treatment, a switch to treatment with a different mechanism of action will be necessary.

The clinical expert indicated that any patient with peripheral joint and skin disease that does not respond to csDMARDs would be eligible for upadacitinib, barring any contraindications. TNF inhibitors and IL-17 inhibitors will generally be prescribed before upadacitinib. However, as clinicians become more experienced with upadacitinib and long-term safety is confirmed, the clinical expert noted that upadacitinib might become the first line treatment for PsA. The caveat with this assumption is that longer term observation in patients on upadacitinib will be needed to confirm the durability of benefit and safety. The clinical expert also identified the oral route of upadacitinib as an advantage, with the improved convenience over SC injections or IV infusions expected to enhance treatment adherence. It is expected that benefit from a JAK inhibitor will be apparent sooner than TNF inhibitors, and lack of response and/or side effects will result in the decision to discontinue treatment.

According to the clinical expert, in clinical practice, the swollen joint count is the most likely measure to assess response, with a reduction in joint count reflecting meaningful response. Other clinically meaningful responses may be measured using the achievement of MDA or patient-reported outcomes.

Drug program input

Input was obtained from the jurisdictions participating in CADTH reimbursement reviews. The following were identified as key factors that could impact the implementation:

- The place in therapy of upadacitinib relative to currently available treatments for psoriatic arthritis.
    - The clinical expert indicated that the place in therapy of upadacitinib would be the same as that of the biologic DMARDs.
- The significance of potential adverse events associated with JAK inhibitors
    - The clinical expert does not expect that upadacitinib would have an impact on cardiovascular morbidity and mortality; patients should be treated for their lipid abnormalities according to their risk and the standard of care; however, the full effect of upadacitinib on cardiovascular morbidity and mortality still need to be assessed.
- The expected dose of upadacitinib used and any potential for dose escalation
    - Due to safety concerns of serious infection and herpes zoster which increased with the upadacitinib 30 mg dose in comparison with the upadacitinib 15 mg dose, the clinical expert indicated that clinicians would be cautious about dose escalation. The clinical expert also stated that it is not expected that dose escalation beyond 15 mg of upadacitinib once daily would happen in the clinical practice of managing patients with PsA.

Clinical Evidence

Pivotal Studies and Protocol Selected Studies

Description of studies

Two multicentre, phase 3, randomised, double-blind, placebo-controlled trials, SELECT-PsA1 and SELECT-PsA2 met the inclusion criteria for this review. Both SELECT studies enrolled adult patients with established diagnosis of moderate to severe active PsA who

had been previously treated with a DMARD. SELECT-PsA1 was conducted in patients who had insufficient response or intolerance to a non-biologic DMARD, whereas PsA2 included patients who had insufficient response or intolerance to a biologic DMARD. Both trials investigated two doses of oral upadacitinib: 15 mg once daily and 30 mg once daily; however, to align with the Health Canada recommended dosage, only results for the upadacitinib 15 mg once daily dose were presented in this review.

Efficacy and safety of upadacitinib was compared with placebo in both studies; SELECT PsA-1 also included adalimumab as an active comparator. Both studies consist of two periods, and at the end of Week 24 in Period 1, all patients on placebo were switched to upadacitinib. In SELECT-PsA1, Period 1 consisted of 56 weeks in duration and included a 24-week double-blind placebo and active comparator-controlled period followed by 32 weeks of blinded active comparator-controlled treatment. SELECT-PsA2 also consisted of Period 1 that was 56-weeks in duration and included 24-weeks of double-blinded placebo-controlled phase, followed by 32 weeks of non-comparative treatment phase. Period 2 is an ongoing open-label long-term treatment extension of up to approximately 5 years for PsA1 and 3 years for PsA2.

In SELECT-PsA1 (N = 1705), eligible participants were randomized at a 2:2:2:1:1 ratio to one of five treatment groups: upadacitinib 15 mg once daily, upadacitinib 30 mg once daily, adalimumab 40 mg subcutaneous (SC) every other week, and placebo followed by upadacitinib 15 mg once daily or placebo followed by upadacitinib 30 mg once daily. Randomization was stratified by extent of psoriasis (≥ 3% body surface area [BSA] or < 3% BSA), current use of at least 1 DMARD, presence of dactylitis, and presence of enthesitis. Patients enrolled into SELECT-PsA2 (N = 642), were randomized in a 2:2:1:1 ratio to one of four treatment groups similar to SELECT-PsA1, but without the adalimumab treatment group: upadacitinib 15 mg once daily, upadacitinib 30mg once daily, and placebo followed by either upadacitinib 15 mg once daily or upadacitinib 30 mg once daily. Randomization was stratified by extent of psoriasis, current use of at least 1 DMARD, and number of prior failed biologic DMARDs (1 vs. >1). Patients were permitted to continue their stable background non-biologic DMARD therapy, which in the majority of patients was methotrexate. Both studies had an appropriate randomization strategy; treatment groups within each study were generally well-balanced. Compared to SELECT-PsA1, PsA-2 enrolled patients had PsA for longer with more significant disease.

The primary endpoint for both SELECT-PsA1 and PsA2 was the proportion of patients who achieved 20% American College of Rheumatology (ACR) response, defined as an improvement of at least 20% in both swollen and tender joint counts and at least three of five additional disease criteria at Week 12. The primary and major secondary efficacy outcomes were assessed using a hierarchical testing procedure to control the overall type I error rate. The multiplicity-adjusted testing hierarchy included the primary endpoint plus 14 ranked key secondary endpoints in SELECT-PsA1, and 7 ranked key secondary endpoints in SELECT-PsA2. Several additional endpoints which were not part of the multiplicity-adjusted analyses but identified in the CADTH systematic review protocol are also discussed in this report.

Efficacy Results

Clinical responses in PsA symptoms

Clinical response in PsA symptoms or overall disease activity were measured using ACR 20, Minimal Disease Activity (MDA), and modified Psoriatic Arthritis Response Criteria (PsARC). In SELECT-PsA1, 70.6% and 36.2% of patients treated with upadacitinib 15 mg and placebo, respectively, achieved ACR20 response, the difference between the upadacitinib 15 mg group and placebo treatment group was 34.5% (95% CI, 28.2 to 40.7; $p < 0.0001$), which was clinically relevant and statistically significant in favour of upadacitinib 15 mg. In SELECT-PsA2, 56.9% and 24.1% of patients treated with upadacitinib 15 mg and placebo, respectively, achieved ACR20 response; the difference between the upadacitinib 15 mg group and placebo treatment group was 32.8% (95% CI, 24.0 to 41.6; $p < 0.0001$), which was clinically relevant and statistically significant in favour of upadacitinib 15 mg. In SELECT-PsA1, results of the pre-specified subgroup analyses by current use of non-biologic DMARD, number of prior non-biologic DMARD (PsA1) and number of prior failed biologic DMARDs (PsA2) were consistent with results from the overall population for the primary endpoint of ACR20 response at Week 12; however, these analyses were not included in the hierarchical statistical analysis and should be interpreted with caution. The clinical expert consulted for this review noted that the differences in ACR20 responses compared with placebo were clinically meaningful.

In SELECT-PsA1, the proportion of patients achieving ACR20 at Week 12 with upadacitinib treatment compared with adalimumab was tested for non-inferiority and superiority as key secondary endpoints. ACR20 response was achieved by 70.6% in the

upadacitinib 15 mg group and by 65.0% of patients in the adalimumab group, the difference between the upadacitinib 15 mg group and adalimumab treatment group was 5.6% (95% CI, −0.6 to 11.8). The adalimumab effect preservation, calculated by (upadacitinib – placebo)/(adalimumab – placebo), was 119.4% (95% CI, 98.0 to 147.9); the lower bound of the 95% CI had exceeded the pre-specified non-inferiority threshold of at least 50% of the placebo-subtracted adalimumab effect, indicating that upadacitinib 15 mg daily was non-inferior to adalimumab 40 mg every other week. In the subsequent testing of superiority, upadacitinib 15 mg was not found to be superior compared to adalimumab 40 mg, as it did not meet the statistical significance for superiority.

For clinical responses measured with the MDA criteria, patients treated with upadacitinib 15 mg had higher response rates compared with placebo at Week 24 in both SELECT-PsA1 (36.6% for upadacitinib 15 mg and 12.3% for placebo) and PsA2 (25.1% for upadacitinib 15 mg and 2.8% for placebo). The between-group differences were 24.3% (95% CI, 18.8 to 29.8; p = 0.0004) in SELECT-PsA1 trial and 22.3% (95% CI, 16.0 to 28.6; p < 0.0001) in SELECT-PsA2 trial, in both trials, the between group differences were statistically significant in favour of upadacitinib 15 mg.

For modified PsARC response at Week 24, a higher proportion of patients treated with upadacitinib achieved a response compared to patients randomized to adalimumab or placebo in both studies (PsA1: 83.7% for upadacitinib 15 mg, 76.6% for adalimumab 40 mg, and 59.3% for placebo; PsA2: 68.2% for upadacitinib 15 mg and 36.3% for placebo). In PsA1, the response rate difference between the upadacitinib and adalimumab groups was 7.0% (95% CI, 1.7 to 12.3), whereas the difference between upadacitinib and placebo was 24.3% (95% CI, 18.5 to 30.2); in PsA2 the difference between upadacitinib and placebo was 31.9 (95% CI, 22.9 to 40.9). These analyses were not included in the hierarchical statistical analysis.

Measurement of Function and Disability

The improvement in physical function at Week 12 as measured with the Health Assessment Questionnaire – Disability Index (HAQ-DI) was statistically significant. The change in scores from baseline in upadacitinib 15 mg and placebo were −0.42 and −0.14, respectively, in PsA1, and −0.30 and −0.10, respectively, in PsA2. The differences in change from baseline between upadacitinib 15 mg and placebo were −0.28 (95% CI, −0.35 to −0.22; p < 0.0001) in PsA1 and −0.21 (95% CI, −0.30 to −0.12; p < 0.0001) in PsA2. While in both studies, the between-group differences, comparing upadacitinib and placebo, in the improvement of the HAQ-DI score did not exceed the estimated Minimally Important Difference (MID) found in the literature for HAQ-DI of 0.35, it is worth noting that in the SELECT-PsA1 study the proportion of patients who achieved a clinically meaningful improvement in HAQ-DI at Week 12 was 33.4%, 47.2%, and 57.9% in the placebo, adalimumab 40 mg, and upadacitinib 15 mg treatment groups, respectively, while in SELECT-PsA2, the proportion of patients who achieved a clinically meaningful improvement in HAQ-DI at Week 12 was 27.2%, and 44.6% in the placebo and upadacitinib 15 mg treatment groups, respectively.

Work productivity was measured by the Work Productivity and Activity Impairment (WPAI) questionnaire in a portion of study participants in both studies. Numerically greater reductions in work or activity impairment due to disease were observed for the upadacitinib 15 mg group compared to placebo at Week 24. Although it appears the suggested MID was achieved by patients in the upadacitinib group in PsA1 for improvement in presenteeism (≥ 20%) and activity impairment (≥ 20%), the between-group differences in change from baseline with upadacitinib compared to placebo or adalimumab did not exceed this threshold. The least squares (LS) mean difference in the change in scores between upadacitinib and adalimumab was −2.5 (95% CI, −6.2 to 1.2), whereas the LS mean difference between upadacitinib and placebo was −13.4 (95% CI, −17.1 to −9.7) in PsA1 and −12.2 (95% CI, −18.8 to −5.6) in PsA2. With the smaller number of patients included in the analysis, and lack of a confirmed MID for the WPAI instrument, it remains unclear whether differences were clinically meaningful. This was identified as an important outcome by the patient groups, but in both SELECT- PsA1 and PsA2, it was an exploratory variable and was not included in the multiplicity-controlled analyses.

Measurement of PsA Symptoms

PsA symptoms such as fatigue and pain were reported in both studies. A statistically greater improvement in fatigue from baseline, measured using the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), was seen at Week 12 with upadacitinib 15 mg compared to placebo in both studies. The mean changes from baseline were: 6.3 for upadacitinib 15 mg and 2.8 for placebo in SELECT-PsA1 (between group difference of 3.5; 95% CI, 2.4 to 4.7; p=0.0004), and 5.0 for upadacitinib 15 mg and 1.3 for placebo in PsA2 (between group difference of 3.7; 95% CI, 2.0 to 5.4; p < 0.0001). The between-group difference in the improvement in FACIT-F score at Week 12 exceeded the estimated MID (3.1 points) in both studies. The impact of upadacitinib on

pain is uncertain as this endpoint was not part of the hierarchical analysis, and no MID was identified for the Patient's Assessment of Pain Numeric Rating Scale (NRS) in patients with PsA.

Health-related Quality of Life

HRQoL was measured by Short Form (36) Health Survey (SF-36) and EuroQol 5-Dimensions 5-Levels (EQ-5D-5L) in SELECT-PsA1 and PsA2. Only the Physical Component Summary (PCS) component of the SF-36 was part of the multiplicity-adjusted testing hierarchy in the SELECT studies, and the difference between the two groups were statistically significant. In PsA1, the difference in mean change from baseline for upadacitinib 15 mg versus placebo was 4.67 (95% CI, 3.67 to 5.67; p = 0.0004) in favour of upadacitinib 15 mg; in PsA2 the difference in mean change from baseline for upadacitinib 15 mg versus placebo was 3.52 (95% CI, 2.07 to 4.98; p < 0.0001) in favour of upadacitinib 15 mg. For the Mental Component Summary (MCS), a numerically greater improvement from baseline was seen for upadacitinib compared to placebo in both trials; the difference in mean change from baseline between the two treatment groups was 1.70 (95% CI, 0.58 to 2.82) in PsA1 and 2.98 (95% CI, 1.44 to 4.52) in PsA2. The results from the EQ-5D-5L suggest that there were greater improvements in the utility index and the visual analogue scale (VAS) scores from baseline to Week 24 in the upadacitinib treatment group compared to patients randomized to placebo in both studies, as well as adalimumab in PsA1. For the utility index, the difference in mean change from baseline between upadacitinib and adalimumab was 0.03 (95% CI, 0.00 to 0.05), whereas the difference in mean change from baseline between upadacitinib and placebo was 0.09 (95% CI, 0.06 to 0.11) in PsA1 and 0.10 (95% CI, 0.06 to 0.14) in PsA2. For the VAS, the difference in mean change from baseline between upadacitinib and adalimumab was 2.8 (95% CI, 0.0 to 5.6), whereas the difference in mean change from baseline between upadacitinib and placebo was 10.9 (95% CI, 8.0 to 13.7) in PsA1 and 6.8 (95% CI, 2.5 to 11.1) in PsA2. For the comparison of upadacitinib to placebo in both PSA1 and PsA2, the mean between-group differences in the EQ-5D-5L utility index reached the MID threshold identified in the literature for the general Canadian population (summarized mean of 0.056; SD = 0.011). These results suggested that treatment with upadacitinib 15 mg was associated with improved HRQoL. Even though HRQoL was identified as an important outcome by the patient groups, the outcome measures of EQ-5D-5L and MCS of SF-36 were not part of the hierarchical analysis plan and were not adjusted for multiple comparisons; therefore, the results should be interpreted with caution due to the risk of inflated type I error.

Measurement of Skin Disease

The extent and severity of skin disease was measured in both studies using a Psoriasis Area and Severity Index (PASI), Static Investigator Global Assessment (sIGA), and Self-Assessment of Psoriasis Symptoms (SAPS). Only patients with psoriasis involving 3% or greater BSA baseline had a PASI assessment. In SELECT-PsA1, the proportion of patients achieving PASI 75 response in the upadacitinib 15 mg treatment group was 62.6% compared to 21.3% in the placebo treatment group, the difference between the upadacitinib 15 mg group and placebo treatment group was 41.3% (95% CI, 32.8 to 49.8; p < 0.0001), which was statistically significant in favour of upadacitinib 15 mg. In PsA2, the proportion of patients achieving PASI 75 response in the upadacitinib treatment group was 52.3% compared to 16.0% in the placebo treatment group, and the difference between the upadacitinib 15 mg group and placebo treatment group was 36.3% (95% CI, 25.6 to 46.9; p < 0.001), which was statistically significant in favour of upadacitinib 15 mg. The clinical expert consulted for this review indicated that the between-group differences in PASI 75 were considered clinically relevant, although the true effect should be derived from separate studies that are specifically designed for patients with skin disease.

Only patients with a sIGA score of ≥ 2 at baseline, and at least 2-point improvement from baseline at Week 16 were included in the assessment. In both SELECT-PsA1 and PsA2, a statistically significant difference in the proportion of patients achieving a response (sIGA of psoriasis score of 0 or 1) was seen, in favour of upadacitinib. At Week 16, the proportion of responders were: 41.9% for upadacitinib 15 mg, 10.9% for placebo (between group difference 31.1% [95% CI, 24.7 to 37.5], p < 0.0001) in PsA1 and 36.8% for upadacitinib 15 mg, 9.2% for placebo (between group difference 27.6% [95% CI, 19.2 to 36.1], p < 0.0001) in PsA2.

A greater reduction in SAPS score from baseline was reported for patients in the upadacitinib group compared to placebo at Week 16. In PsA1, the difference in LS mean change from baseline between upadacitinib and placebo was −17.1 (95% CI, −19.6 to −14.6) for upadacitinib 15 mg versus placebo. Testing for superiority of upadacitinib compared to placebo was part of the multiplicity-adjusted analyses in PsA1; however, it was ranked after where the hierarchical analysis failed and stopped thus no appropriate statistical comparisons can be made. In SELECT-PsA2 the difference between groups in the LS mean change from baseline in SAPS scores was statistically significant, favouring upadacitinib compared to placebo (−22.9 [95% CI, −27.4 to −18.4], p < 0.0001).

Measurement of Other Musculoskeletal Disease

Impact of treatment on musculoskeletal disease was assessed by measuring resolution of enthesitis (with the Leeds Enthesitis Index [LEI]), resolution of dactylitis (with the Leeds Dactylitis Index [LDI]) and change in axial disease using the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). For patients with enthesitis at baseline, resolution of enthesitis (LEI = 0) was achieved by a statistically significantly higher proportion of patients in the upadacitinib 15 mg treatment group (53.7%) compared to placebo (32.4%) at Week 24 in SELECT-PsA1 (between group difference 21.3% [95% CI, 13.0 to 29.7], p = 0.0004). In PsA2, a numerically higher proportion of patients in the upadacitinib 15 mg treatment group achieved resolution of enthesitis at Week 24 compared to patients in the placebo group, with a difference of 27.6% (95% CI, 17.3 to 37.8); however, this endpoint was not part of the multiplicity-controlled analyses in PsA2. As there is a risk of inflated type I error, no appropriate statistical comparisons can be made. Resolution of dactylitis (LDI = 0) was achieved by a numerically higher proportion of patients in the upadacitinib group compared to the placebo group at Week 24 in both trials. The difference between the two treatment groups was 36.8% (95% CI, 25.7 to 47.9) in PsA1 and 30.1% (95% CI, 13.0 to 47.1) in PsA2. In SELECT-PsA1, this endpoint was included in the hierarchical statistical analysis; however, it was ranked after where the hierarchical analysis failed and stopped. In SELECT-PsA2, this endpoint was not part of the multiplicity-controlled analyses. Thus, results for this endpoint are considered exploratory in both trials.

Change in axial disease was assessed in patients with the presence of psoriatic spondylitis at baseline. The improvement in BASDAI score from baseline to Week 24 numerically favoured the upadacitinib 15 mg treatment group compared to placebo in both studies and compared to adalimumab in PsA1. In SELECT-PsA1, the difference in the LS mean change in scores from baseline between upadacitinib and adalimumab was −0.57 (95% CI, −1.09 to −0.05), and between upadacitinib and placebo was −1.42 (95% CI, −1.94 to −0.90). In PsA2, the difference between upadacitinib and placebo was −1.85 (95% CI, −2.55 to −1.15). However, this outcome assessment was not included in the hierarchical statistical analysis and should be considered inconclusive because of the potential for inflated type 1 error.

Radiographic changes

Radiographic change was assessed only in SELECT-PsA1 using the Sharp/van der Heijde Score (SHS). At Week 24, the differences in LS mean change from baseline in SHS was statistically significant, favouring the upadacitinib 15 mg treatment group over placebo (−0.29; 95% CI, −0.44 to −0.14; p = 0.0004). According to the clinical expert consulted on this review, the numerically small changes seen are unlikely to be clinically meaningful to patients over a period of only 24 weeks and noted that it is difficult to extrapolate the significance of these changes over the lifetime of a patient with PsA. In particular, it is uncertain whether the radiographic changes seen in SELECT-PsA1 correlate with a direct, meaningful improvement in a patient's physical function, quality of life, or permanent disability. However, the observations satisfy the regulatory requirement that upadacitinib can inhibit radiographic progression.

Harms Results

By Week 24, the proportion of patients in SELECT-PsA1 who experienced a treatment-emergent AE (TEAE) was higher in the upadacitinib 15 mg and adalimumab treatment groups compared to the placebo group. In PsA2, the proportion of patients who experienced a TEAE was similar between the upadacitinib and placebo groups. Generally, the majority of adverse events (AEs) were mild or moderate in severity, and the most frequently reported AE in both studies was upper respiratory tract infection. The frequency of serious adverse events (SAEs) and withdrawal due to adverse events (WDAEs) were low across all treatment groups and generally below 5%, with the exception of the upadacitinib 15 mg treatment group of SELECT-PsA2 which had the highest proportion of patients experiencing a SAE (5.7%) or WDAE (7.1%) across both studies. None of the specific SAEs were reported by more than 2 patients. Two treatment-emergent deaths were reported by Week 24, both in the placebo group. One non-treatment-emergent death (i.e., occurring more than 30 days after the last dose) was reported in the upadacitinib 15 mg group.

Critical Appraisal

- Key endpoints comparing upadacitinib to adalimumab were measured at Week 12. According to the clinical expert consulted on this review, this may not have provided adequate time for adalimumab to show maximal benefit. The benefit of JAK inhibitors is thought to be seen generally sooner than TNF inhibitors, as such, endpoints measured at Week 12 may be biased in favour of upadacitinib. While results of both upadacitinib and adalimumab were consistent until 24 weeks, it is uncertain whether upadacitinib 15 mg is non-inferior to adalimumab due to lack of statistical testing at Week 24. Also, the non-inferiority and

superiority comparison between upadacitinib and adalimumab was conducted for the ACR20 efficacy outcome only; hence it is unclear whether upadacitinib would be non-inferior to adalimumab for other important outcome measures.

- Some endpoints measured in this trial may not be considered clinically meaningful to patients, despite showing statistically significant differences in the trials. For example, subjective measures such as fatigue or the small changes seen in SHS may not reflect clinically meaningful improvement especially when measured over such a short length of time relative to the long disease course. The clinical expert consulted on this review noted that it is difficult to extrapolate the significance of these changes over the lifetime of a patient with PsA. Also, several outcomes that were identified in the CADTH review protocol and reported in the studies fell outside the statistical testing hierarchy and thus need to be interpreted with consideration of type I error. Furthermore, the results of the prespecified subgroup analyses performed for the primary endpoint should be interpreted with caution due to the small sample sizes, lack of control for type 1 error, and also because the trial was not powered to test specific hypotheses in subgroups. As with the endpoints which were not part of the statistical testing hierarchy, the results of these subgroup analyses should be interpreted with caution.
- SELECT-PsA1 required patients to have the presence of either 1 or more erosion on x-ray or high-sensitivity C-Reactive Protein (hs-CRP) greater than the upper limit of normal for inclusion into the study, which may impact the generalizability of this study's results. According to the clinical expert consulted on this review, a substantial proportion of patients seen in clinical practice generally do not have evident erosions or inflammatory markers elevated to this degree and yet still require treatment with biologic DMARDs.
- Although long term data were reported for up to Week 56 for both studies, placebo-controlled data for upadacitinib exists only up to Week 24.
- Upadacitinib was compared to active treatment (adalimumab) only in patients with no prior exposure to biologic DMARD treatment. It is unknown if the same relative benefit can be expected from patients who have failed prior treatment with biologic DMARDs.

Indirect Comparisons

Description of studies

Other than the inclusion of upadacitinib in SELECT-PsA1 and SELECT-PsA2, there are no studies in which upadacitinib has been compared directly to other biologic or targeted synthetic DMARDs. Therefore, the sponsor conducted an indirect comparison that comprised a network meta-analysis (NMA) that compared the efficacy of upadacitinib to that of TNF inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab), IL-17 inhibitors (secukinumab, ixekizumab), IL-12/23 inhibitor (ustekinumab), IL-23 inhibitor (guselkumab), CTLA4-Ig (abatacept), JAK inhibitors (tofacitinib), and PDE4 inhibitor (apremilast). Results from the ITC are summarized below only for relevant comparators identified in the CADTH systematic review. Efficacy was compared at 12 and 24 weeks, and the ITC reported results for biologic DMARD-naïve and biologic DMARD-experienced patients separately.

Efficacy Results

Overall, in biologic-naïve patients, the NMA suggests that upadacitinib 15 mg is more efficacious for ACR response at Week 12 compared to some comparators, specifically an IL-17 inhibitor (secukinumab 15 mg), IL-12/23 inhibitor (ustekinumab 45 mg), and IL-23 inhibitor (guselkumab), but this advantage was only seen for the IL-12/23 inhibitor at 24 weeks. Upadacitinib was also shown to be more efficacious than etanercept at both Weeks 12 and 24 for PASI response; however this was not seen with other TNF-inhibitors. On the other hand, the IL-17 inhibitors (secukinumab 300 mg, ixekizumab) and IL-23 inhibitor (guselkumab) appear to be more efficacious than upadacitinib for PASI at Week 12, though only the IL-23 inhibitor was favoured over upadacitinib at Week 24. For PsARC, upadacitinib was more efficacious than tofacitinib but only at Week 12; this was not seen at Week 24. For HAQ-DI measured in PsARC responders at Week 12, etanercept was shown to be more efficacious than upadacitinib; this benefit was not seen with other TNF-inhibitors. At Week 24, adalimumab appeared to be more efficacious than upadacitinib. Of note, the number of comparators included in some analyses (i.e., HAQ-DI at 24 weeks) was very limited. For other analyses conducted, no difference was seen between upadacitinib and the relevant comparators. Thus, no consistent benefit of upadacitinib over biologic DMARDs or tsDMARDs was demonstrated across all measured endpoints Weeks 12 and 24.

In biologic-experienced patients, upadacitinib 15 mg was favoured only when compared to tofacitinib (JAK inhibitor) in PASI response at Week 12; this comparison was not performed at Week 24. No difference in treatment effect was demonstrated in all other comparisons between upadacitinib and included IL-inhibitors. Of note, not all IL-inhibitors were included in every analyses, and in particular, the IL-23 inhibitor was absent from many comparisons. Furthermore, TNF-inhibitors were not included in any of the NMA analyses since there were insufficient eligible data in the biologic DMARD-experienced patient population, thus no conclusions can be drawn on the comparative efficacy of upadacitinib in these patients. Also, JAK inhibitors were not included in any of the Week 24 analyses, thus long-term comparative efficacy of upadacitinib compared to tofacitinib is unknown.

Harms Results

The sponsor's submitted ITC did not report safety outcomes.

Critical Appraisal

There are several limitations that increase the uncertainty in the results of the ITC discussed in this review. The included studies were highly heterogeneous in terms of inclusion criteria and patient characteristics. Significant differences were noted in potential effect modifiers, such as duration of disease, use of prior DMARDs, and disease severity. These factors are heightened due to the variation in inclusion and exclusion criteria across included studies. Yet, no sensitivity analysis or subgroup analysis was conducted to assess the impact of these potential effect modifiers on the comparison of upadacitinib and other biologics. The ITC also did not include any analyses of other clinically meaningful outcomes such as PsA symptoms (e.g., pain and fatigue) or HRQoL, or safety.

Overall, there is uncertainty due to the inherent heterogeneity across trials in the networks. The robustness of the comparative efficacy was further compromised by the lack of precision in the findings, hence results from the sponsor-submitted ITC must be interpreted with caution.

Other Relevant Evidence

Description of studies

Each of the two SELECT studies included two study periods. At the time of this review, data up to the end of Period 1 (Week 56) was available. Period 1 for SELECT-PsA1 included 24 weeks of randomized, double-blind, placebo- and active comparator-controlled treatment followed by an additional 32 weeks of blinded active comparator-controlled treatment. Period 1 for SELECT-PsA2 included 24 weeks of randomized, double-blind, placebo-controlled treatment followed by an additional 32 weeks of upadacitinib treatment. In both studies, all patients assigned to placebo were switched to pre-assigned upadacitinib 15 mg or 30 mg daily in a 1:1 ratio at Week 24. Data reported at Week 56 used the As Observed data set, and no adjustments for multiple testing was employed.

Efficacy Results

In both studies, results from the end of Period 1 (Week 56 data) suggest that the improvements in clinical and patient-reported outcomes observed at Week 24 in patients who received upadacitinib 15 mg once daily starting at Day 1 were maintained throughout the 56-week blinded treatment period. Patients who switched from placebo to upadacitinib 15 mg once daily at Week 24 also showed improvements in clinical and patient-reported outcomes at Week 56; the trajectory for the achievement of response or improvement in endpoints after starting upadacitinib was similar to those observed in patients who started upadacitinib on Day 1 of both studies. Numerically greater improvement with upadacitinib compared to adalimumab was also demonstrated for several endpoints in SELECT-PsA1. For example, the difference in ACR20 response rate between the upadacitinib 15 mg treatment group (including those switched to upadacitinib 15 mg from placebo), and adalimumab was 6.3% (95% CI, 0.3 to 12.2), and the difference in the proportion of patients achieving MDA was 7.6% (95% CI, 0.4 to 14.8).

Harms Results

The safety profile of oral upadacitinib 15 mg once daily over 56 weeks was consistent with that observed during the 24-week double-blind period in both SELECT-PsA1 and PsA2, with no unexpected safety signals reported. Harms for the Week 56 analysis were presented as exposure-adjusted event rates and were also pooled, such that data reported for the upadacitinib exposure combined the upadacitinib 15 mg and placebo switched to upadacitinib 15 mg groups. In SELECT-PsA1, one or more AEs were reported at an exposure-adjusted incidence of 265.9 events per 100 patient-years (PY) in the adalimumab group and 281.1 events per 100 PY in

the upadacitinib group. In SELECT-PsA2, one or more AEs were reported at a rate of 260.6 events per 100 PY (pooled upadacitinib group). With longer exposure to treatment, a greater proportion of patients treated with upadacitinib compared to adalimumab experienced infectious adverse events, including the following which are presented as events per 100 PY: urinary tract infections (3.6 adalimumab, 6.7 for upadacitinib in PsA1, 9.8 for upadacitinib in PsA2), bronchitis (2.9 for adalimumab, 5.7 for upadacitinib in PsA1, 8.8 for upadacitinib in PsA2), hypertension (2.7 for adalimumab, 5.6 for upadacitinib in PsA1, 5.7 for upadacitinib in PsA2), and influenza (0.8 for adalimumab, 3.2 for upadacitinib in PsA1, 5.2 for upadacitinib in PsA2). Herpes zoster was also reported in a higher proportion of patients treated with upadacitinib across both studies (3.9 per 100 PY and 3.8 per 100 PY in PsA1 and PsA2, respectively, compared to those treated with adalimumab (0.5 per 100 PY). Other notable adverse events that showed an imbalance in groups include CPK elevation and hepatic disorder, which were reported at a higher incidence by both upadacitinib and adalimumab treatment groups in PsA1 compared to PsA2. Elevated CPK levels were reported at an incidence per 100 PY of 7.3 for adalimumab, 11.9 for upadacitinib in PsA1, and 5.2 for upadacitinib in PsA2. Hepatic disorder was reported in a higher proportion of patients treated with adalimumab (per 100 PY: 24.9 for adalimumab, 19.1 for upadacitinib in PsA1, 4.8 for upadacitinib in PsA2), and may be confounded overall by the higher usage of concomitant methotrexate treatment in SELECT-PsA1 patients. Withdrawal of treatment due to adverse events was reported at an incidence of 7.4 per 100 PY for adalimumab, and 4.6 per 100 PY and 10.0 per 100 PY for upadacitinib in PsA1 and PsA2, respectively. In total, five deaths occurred in the relevant treatment groups by the end of Period 1, inclusive of those counted under Week 24 data. These include both treatment-emergent (occurring within 30 days of last dose for upadacitinib or 70 days for adalimumab) and non-treatment-emergent deaths. One treatment-emergent death occurred in the adalimumab group, and two non-treatment-emergent deaths occurred in the upadacitinib 15 mg treatment group. The remaining two deaths had occurred in the placebo groups.

Critical Appraisal

The interpretation of the long-term efficacy and safety outcomes at Week 56 is limited by a lack of placebo-control in both SELECT-PsA1 and PsA2, as well as lack of a comparator in the SELECT-PsA2 study. Also, background therapies were allowed to be modified. As a result, it is difficult to disentangle the drug effect from the changes in the background therapies on the reported outcomes. Furthermore, given that all patients were aware that they were receiving an active treatment (upadacitinib or adalimumab), results for patient-reported outcomes may be subject to bias. No adjustment was made for multiplicity to evaluate long-term data; thus, given the large number of analyses performed, there is a risk of inflated type I error. As such, the 56 Week data should be interpreted with caution.

Economic Evidence

Cost and Cost-Effectiveness

Table 2: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost utility analysis Markov Model
Target population	Adults (age 18 years or older) with active PsA who have had an inadequate response to previous DMARDs or for whom DMARDs are not tolerated or contraindicated.
Treatment	A drug sequence initiating with upadacitinib as monotherapy or in combination with a non-biologic DMARD (not stratified)
Submitted price	$48.68 per upadacitinib 15 mg tablet
Treatment cost	The sponsor assumed 58% of patients would receive concomitant methotrexate as part of treatment (7.5 mg weekly), therefore the combined total annual drug acquisition costs of upadacitinib with or without methotrexate was $17,867.
Comparators	Drug sequences initiating with: Biologic-naïve population: • Anti-TNFs (i.e., etanercept, infliximab, certolizumab pegol, adalimumab, golimumab) • IL-17s (i.e., secukinumab, ixekizumab) • IL 12/23 (i.e., ustekinumab)

Component	Description
	• PDE4 (i.e., apremilast) Biologic-experienced population: • IL-17 (i.e., secukinumab, ixekizumab) • IL 12/23 (i.e., ustekinumab)
Perspective	Canadian publicly funded health care payer
Outcome	QALYs
Time horizon	Lifetime (48.5 years)
Key data source	• Unpublished sponsor-commissioned NMAs to inform efficacy (i.e., ACR 20/50/70, PsARC, HAQ-DI score, and PASI 50/75/90). • SELECT-PSA 1 and SELECT-PSA 2 to inform health state utilities (i.e., EQ-5D) and patient baseline characteristics.
Submitted results	Biologic-naïve population: • The apremilast sequence and upadacitinib sequence comprised the efficiency frontier with all other treatments being dominated or extendedly dominated • ICER = $37,233 per QALY ($16,483 inc. costs; 0.443 inc. QALYs) vs. apremilast sequence Biologic-experienced population: • The efficiency frontier was comprised of the upadacitinib sequence only with all other treatments being dominated
Key limitations	• The treatments modelled were not fully reflective of Canadian clinical practice. The inclusion of apremilast for biologic-naïve patients was not appropriate given an agreement on price has not been reached with the pCPA; while the generalizability of results may be limited as treatments were not stratified as monotherapy or combination therapy. • The modelled clinical effectiveness of upadacitinib is uncertain. While the sponsor-commissioned NMAs were associated with limitations which lead to the CADTH clinical review noting that the results should be viewed with caution, based on the totality of evidence, the CADTH clinical review noted that upadacitinib does not show any difference in efficacy in terms of PsARC, PASI, HAQ-DI change and ACR when compared to bDMARDs and tsDMARDs. Additionally, the long-term efficacy of upadacitinib is highly uncertain given the lack of available data. • The sponsor modelled a change in PsARC within the model. Feedback from the clinical expert consulted by CADTH noted that while required by some jurisdictions, PsARC is not commonly used as a measure of response in practice. • Inclusions of subsequent treatments biased the results in terms of costs and effects in favour of upadacitinib, while still not being reflective of Canadian clinical practice.
CADTH reanalysis results	• CADTH undertook reanalyses excluding apremilast and subsequent treatments, and including wastage for infliximab. CADTH also undertook a scenario analysis assuming all patients receiving adalimumab received the biosimilar at the available list price. CADTH could not address limitations with the clinical data. • The results of the CADTH reanalyses indicate that upadacitinib was dominated by (i.e., more costly and less effective than) etanercept in the biologic-naïve population, and by secukinumab in the biologic-experienced population. • Based on the CADTH base case, a price reduction of 5% to 27% is required for upadacitinib to move onto the cost-effectiveness frontier.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis:

- Market growth for use of bDMARDs in patients with psoriatic arthritis is uncertain and may have been overestimated.
- There is uncertainty in the market uptake assumptions for upadacitinib, including how it would displace the market shares of comparator treatments, and how functional and generalizable the budget impact is for the Canadian setting.
- The cost of adalimumab moving forward is overestimated, given the new availability of biosimilar products.
- Additionally, CADTH noted that patient copayments were included in the base case. These were removed in reanalyses.

CADTH reanalyses included removing patient co-payments, and additional administrative costs reduced the cost savings associated with upadacitinib. When the price of biosimilar adalimumab was assumed for all adalimumab patients, upadacitinib was no longer cost saving. A larger incremental cost occurred when assuming 100% biosimilar costs for infliximab and etanercept as well as adalimumab.

As CADTH was unable to easily revise treatments displaced by upadacitinib, and the actual prices paid by drug programs is unknown, the budget impact of reimbursing upadacitinib for this indication is associated with some uncertainty.

CDEC Members

Dr. James Silvius (Chair), Dr. Ahmed Bayoumi, Dr. Sally Bean, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Mr. Allen Lefebvre, Dr. Kerry Mansell, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

June 16, 2021 Meeting

Regrets

One CDEC member did not attend.

Conflicts of Interest

None

CADTH

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.