CADTH

CADTH COMMON DRUG REVIEW

Pharmacoeconomic Review Report

USTEKINUMAB (STELARA/STELARA I.V.)

Janssen Inc.

Indication: Treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic or have medical contraindications to such therapies.

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Abbreviations

CDR	CADTH Common Drug Review
CT	conventional therapy
ICER	incremental cost-effectiveness ratio
NMA	network meta-analysis
QALY	quality-adjusted life-year
SC	subcutaneous
UC	ulcerative colitis
WTP	willingness to pay

Table 1: Summary of the Sponsor's Economic Submission

Drug product	Ustekinumab (Stelara)
Study question	What is the cost-effectiveness of ustekinumab versus biological drugs or conventional therapy (CT) for adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response to, or were intolerant to, either conventional therapy or a biologic, or have medical contraindications to such therapies?
Type of economic evaluation	Cost-utility analysis
Target population	Patients (≥ 18 years of age) with moderately to severely active UC. Stratified analyses based on past treatment exposure, defined as follows: • Non-biologic failure: Inadequate response to CT • Biologic failure: Inadequate response to other biological drugs
Treatment	Ustekinumab 6 mg/kg IV at week 0 (induction phase), followed by 90 mg SC thereafter (maintenance phase)
Outcome	Quality-adjusted life-years (QALYs)
Comparators	• Tofacitinib (Xeljanz) • Vedolizumab (Entyvio) • Infliximab (Remicade, biosimilars) • Adalimumab (Humira) • Golimumab (Simponi) • Continuing CT (combination of aminosalicylates, corticosteroids, and immunomodulators)
Perspective	Canadian public health care payer
Time horizon	10 years

Results for base case	Sequential incremental cost-effectiveness ratios for:
	• Non-biologic failure population:
	  ○ Infliximab (biosimilar) versus CT: $62,017 per QALY gained
	  ○ Ustekinumab versus infliximab (biosimilar): $68,133 per QALY gained
	• Biologic failure population:
	  ○ Tofacitinib versus CT: $68,006 per QALY gained
	  ○ Ustekinumab versus tofacitinib: $79,040 per QALY gained

Key limitations	• The comparative treatment effects of ustekinumab with relevant comparators, particularly in the maintenance phase, are uncertain, given limitations in the sponsor's submitted network meta-analysis. Considerable heterogeneity was noted in the clinical studies included in the network meta-analysis. • All relevant comparators (i.e., infliximab [including biosimilars] and golimumab) were not considered in the biologic failure population. • The time horizon of 10 years was insufficient to capture all relevant costs and effects that would be incurred over a patient's lifetime for this chronic condition. • The sponsor assumed different proportions of low- and high-dose biologic use. The proportions assumed in the model did not align with the proportions studied within the clinical trials that informed the comparative efficacy data. • Arbitrary definitions (20% of the mean) set to define probabilistic distributions of many model inputs.

CDR estimate(s)	In both subgroups, the CADTH base case applied a random-effects model to inform the treatment effects in the induction phase; extended the time horizon to a lifetime time horizon (50 years); and used trial-reported proportions for low- and high-dose biologic use. • For a non-biologic failure population: Ustekinumab was the optimal therapy at a willingness-to-pay threshold above $53,546 per QALY; below this threshold, CT was the optimal therapy. • Due to the instability of the CADTH base case, a deterministic analysis is reported for the biologic failure subgroup. For a biologic failure population: ustekinumab was the optimal therapy at a willingness-to-pay threshold above $63,058 per QALY; below this threshold, CT was the optimal therapy. • Several methodological concerns were identified with the sponsor-commissioned network meta-analyses, resulting in uncertainty on the effect estimates that informed the economic model. As these could not be addressed, the validity of the economic evaluation is uncertain.

CDR = CADTH Common Drug Review; CT= conventional therapy; SC = subcutaneous; QALY = quality-adjusted life-year.

Drug	Ustekinumab (Stelara/Stelara I.V.)
Indication	Treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response, or were intolerant to either conventional therapy or a biologic, or have medical contraindications to such therapies).
Reimbursement request	As per indication.
Dosage form(s)	Induction: Solution for intravenous infusion single use either at a weight-based dose (approximately 6 mg/kg) of 260 mg, 390 mg, or 520 mg, depending on body weight, or at a fixed dose of 130 mg. Maintenance: subcutaneous injection, at 90 mg every 8 weeks (vial with 90 mg/1.0 mL).
NOC date	January 23, 2020
Sponsor	Janssen Inc.

Executive Summary

Background

Ustekinumab (Stelara) is indicated for use in adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response, or were intolerant to either conventional therapy or a biologic, or have medical contraindications to such therapies.[1] The recommended dose of ustekinumab is a single IV tiered infusion based on body weight (6 mg/kg) during the induction phase, followed by subcutaneous injections of 90 mg every eight weeks during the maintenance phase. The sponsor-submitted price is $2,079.84 per 130 mg/26 mL solution vial for IV infusion and $4,593.14 for a pre-filled syringe of 90 mg/1 mL for subcutaneous injection.[1] The cost of treatment per patient with ustekinumab is estimated to be $33,798 in the first year and increases to $32,152 annually thereafter.

CADTH has reviewed ustekinumab three times previously,[2-4] but not for UC. The CADTH Canadian Drug Expert Committee (CDEC) has previously recommended listing (reimbursement of) ustekinumab for the treatment of adult patients with moderately to severely active Crohn disease (2017) and for the treatment of adult patients with chronic moderate-to-severe plaque psoriasis who are eligible for phototherapy or systemic therapy (2009). The clinical criterion for the active Crohn disease indication was that treatment should be discontinued if patients do not achieve clinical response within eight weeks of induction therapy,[2] while the clinical criteria for the plaque psoriasis indication were: greater than 10% of body surface involvement or significant involvement of face, hands, feet, or genital regions; failed response, contraindications to, or intolerance to methotrexate and cyclosporine; failed response, intolerant to, or unable to access phototherapy.[4] For the treatment of adult patients with active psoriatic arthritis (2014), CDEC recommended that ustekinumab not be listed at the submitted price.[3]

The sponsor submitted a cost-utility analysis comparing ustekinumab with other biologic therapies (infliximab, infliximab biosimilars, adalimumab, golimumab, vedolizumab, tofacitinib) or continuing conventional therapy (CT) (a mix of 5-aminosalicylates, corticosteroids, and immunomodulators) for Canadian adults with moderately to severely active UC and an inadequate, intolerant, or failed response to CT or biological drugs.[5] Two patient populations were modelled separately: the non-biological failure and the biologic

failure subgroups. While infliximab, infliximab biosimilars, and golimumab were compared in the non-biologic failure population, they were not included in the economic analysis for the biologic failure population. A single-dose regimen was modelled in the induction phase, while a dose-mix regimen (i.e., a proportion of patients receive a low dose while the remainder receive a high dose of the biologic) was assumed for the maintenance phase. The analysis was conducted over a 10-year time horizon from the perspective of the Canadian publicly funded health care system, with future costs and benefits discounted at 1.5%.[5] The hybrid model consisted of a decision tree and Markov state transition model which captured patients' disease progression through the treatment induction and maintenance phases, respectively. Patients first entered the decision tree with active UC and started induction with ustekinumab or biologic therapies, or continued with CT. At the end of the induction phase, patients could achieve clinical remission (a Mayo score of ≤ 2 with no individual subscore > 1), respond without clinical remission (decrease from baseline in total Mayo score of > 3 points and at least 30%), fail to respond to induction therapy (i.e., remain in active UC), or die. Thereafter, patients would enter into their corresponding health state within the Markov model, which captured the long-term clinical progression, including the clinical effects of the maintenance phase of treatment and the potential impact from surgical intervention.[5] Patients who demonstrated clinical remission or response without remission would remain in these respective states, whereas patients who lost response to treatment or who failed to respond to induction therapy would transition to the active UC health state and switch over to CT (i.e., discontinue their biologic) or continue receiving CT. The comparative efficacy for ustekinumab and all included comparators was derived from a sponsor-commissioned network meta-analysis (NMA).[5] Utility values for health states and the utility decrement for adverse events were obtained from the literature.[6,7] Costs and resource use data reflected Canadian and UK sources and included costs of drug acquisition, adverse events, and disease management.[8-12]

Based on a sequential analysis of the sponsor's base case, the incremental cost-effectiveness ratio (ICER) for ustekinumab was $68,133 per quality-adjusted life-year (QALY) gained compared with an infliximab biosimilar (Renflexis) in non-biologic failure patients, and $79,040 per QALY gained compared with tofacitinib in biologic failure patients.

Summary of Identified Limitations and Key Results

CADTH identified several limitations with the submitted economic analysis.

There is considerable uncertainty regarding the comparative efficacy for ustekinumab. Relative treatment efficacy in the model's induction and maintenance phases for both subgroups was based on a sponsor-commissioned NMA. Considerable methodological issues were noted with this NMA due to inconsistencies in the body of evidence, the heterogeneity observed between individual trials, intransitivity on the indirect treatment comparison analyses, and the potential risk of bias in individual studies. CADTH clinical reviewers noted that the NMA results demonstrated no clear superiority over other biologics.

The sponsor further failed to consider all relevant comparators in the biologic failure subgroup by excluding infliximab, infliximab biosimilars, and golimumab.[5] Therefore, the cost-effectiveness of ustekinumab relative to all currently used treatments within the biologic failure subgroup is unknown.

Given the chronic nature of UC, a lifetime time horizon would have better reflected the costs and effects of treatments, as recommended in the CADTH guidelines.[13] The sponsor underestimated the expected treatment costs and effects of ustekinumab and other biologic

treatments over the patient's lifetime by selecting a shorter, 10-year time horizon for the economic analysis.[5]

Other limitations included the assumption of varied proportions of patients receiving low- and high-maintenance doses across biologic treatments, the use of a two-week cycle length, and the use of an arbitrary definition of uncertainty. The dose-mix regimen assumed differences in dosing, but these proportions did not align with the proportions studied within the clinical trials that informed the comparative efficacy data. Given that a dose-response relationship exists, the dose-mix regimen assumed in the economic model should be consistent with those studied in the clinical trials. Additionally, the cycle length of two weeks implied that patients' response would be assessed every two weeks, with treatment discontinuation occurring biweekly, whereas CADTH's consultation with the clinical expert indicated that treatment response in clinical practice for the maintenance phase would be approximately every two months. Lastly, incorrect methods were used to define the probabilistic distribution of model inputs.

CADTH undertook reanalyses of the submitted models to address some of the identified limitations by: selecting the NMA random-effects model to inform the treatment effects in the induction phase, incorporating a lifetime time horizon (50 years), and changing the proportion of patients receiving low- and high-dose biologics to the values studied in the trials. Importantly, the CADTH base-case results for the biologic failure population could not be reported probabilistically due to model instability; therefore, a deterministic CADTH base case has been presented for this subgroup.

Conclusions

CADTH reanalyses of the non-biologic failure population determined that CT would be the optimal therapy if the willingness-to-pay (WTP) threshold is up to $53,546 per QALY; thereafter, ustekinumab would be the optimal therapy. In the biologic failure population, deterministic reanalyses by CADTH suggest that CT would be the optimal therapy up to a WTP threshold of $63,058 per QALY; thereafter, ustekinumab would be the optimal therapy. In the non-biologic failure population, ustekinumab had a 13% probability of being the preferred treatment at a WTP threshold of $50,000 per QALY and, at that threshold, a price reduction of at least 10% would be required for ustekinumab to be considered the optimal treatment. For the biologic failure population, deterministic price-reduction analyses suggest that a price reduction of at least 20% may be required for ustekinumab to be considered cost-effective at a WTP threshold of $50,000 per QALY. The cost-effectiveness of ustekinumab compared with infliximab (branded or biosimilars) and golimumab in the biologic failure population is unknown, given the lack of indirect clinical evidence. Furthermore, the validity in the comparative clinical effect estimates that informed the economic model remain uncertain. The sponsor's submitted NMA did not identify clear superiority between ustekinumab over other common biologics with the same indication. Given that considerable uncertainty remains regarding the comparative treatment efficacy of ustekinumab compared with available treatments in both non-biologic failure and biologic failure subgroups, the results of this economic evaluation should be viewed with caution.

Information on the Pharmacoeconomic Submission

Summary of the Sponsor's Pharmacoeconomic Submission

The sponsor submitted a cost-utility analysis of ustekinumab compared with other biologic therapies (infliximab, infliximab biosimilars, adalimumab, golimumab, vedolizumab, tofacitinib) or continuing CT (i.e., a mix of 5-aminosalicylates, corticosteroids, and immunomodulators) in Canadian adults (≥ 18 years of age) with moderately to severely active UC (defined as a Mayo score of 6 to 12 and a Mayo endoscopy subscore ≥ 2).[5] The analysis was done separately for the non-biologic failure subgroup (i.e., those who had failed or were intolerant to treatment with immunomodulators or corticosteroids, but never failed treatment with a biologic) and a biologic failure subgroup (i.e., those who had failed or were intolerant to treatment with a biologic).[5] Comparators included in the analysis differed by subgroup. All biologic therapies and CT were considered as comparators in the non-biologic failure population while in the biologic failure population, infliximab, infliximab biosimilars, and golimumab were omitted as comparators. The economic evaluation was conducted over a 10-year time horizon (ending at approximately 52 years of age for a 42-year old adult starting in the model), from the perspective of the Canadian public health care payer.[5] Costs and clinical outcomes (QALYs) were discounted at 1.5% per annum.[5] The baseline characteristics of each subgroup were derived from the UNIFI pivotal trial.[5]

The hybrid model structure was based on a decision tree and Markov state transition model in which the decision tree (Figure 1) captured patients' response over a variable induction phase, while the Markov model (Figure 2) captured long-term outcomes, including those of the maintenance phase and the potential impact of surgical interventions. Cycle length in the Markov model was defined as every two weeks.[5] Patients all entered the decision tree with active UC and underwent treatment induction with a biologic treatment (a duration of eight weeks for all biologics, except for golimumab or vedolizumab, for which the induction phase was assumed to be six weeks) or continued on CT.[5] Following the induction phase, possible patient's outcomes included:

- achieve clinical remission (defined as a Mayo score of ≤ 2, with no individual subscore > 1)
- achieve clinical response without remission (defined as a minimum reduction of 3 points and a 30% reduction in the total Mayo score, with a corresponding decrease in the subscore for rectal bleeding of at least 1 point, or an absolute subscore for rectal bleeding of 0 or 1)
- remain in the active UC state (defined as a Mayo score of 6 to 12, including a Mayo endoscopy score ≥ 2)
- die.[5]

At the end of the induction phase, all patients entered the Markov cohort model. Nine health states were defined: clinical remission, clinical response without remission, active UC, first surgery, post–first surgery remission, post–first surgery complications, second surgery, post–second surgery remission, and dead.[5] Patients could enter the Markov model in one of four health states, corresponding to the four possible outcomes that were modelled in the decision tree.[5] Patients who achieved clinical remission or response without remission during the induction phase were maintained on the same treatment and would enter remission or response without remission health states, respectively.[5] Patients who did not

achieve clinical remission or response without remission with their biologic at the end of the induction phase but remained alive were assumed to discontinue their treatment, switch to CT and enter the "active UC" health state. Patients who did not achieve clinical remission or response without remission with CT at the end of the induction phase but remained alive were assumed to remain on CT.[5]

Patients who entered the treatment-maintenance phase in remission and response without remission health states would remain in their respective state until loss of response. Loss of response was assessed at every cycle (i.e., every two weeks) and, upon loss of response, patients would discontinue their current treatment and transition to the active UC health state, whereupon they would be managed by CT. Once in the active UC health state, patients could enter the surgical health states. Following the first surgery, patients could be in one of two post-surgery states (i.e., complications or no complications [referred to as "post–first surgery remission"]) with a second surgery possible for patients who experienced or developed complications with their first surgery. The sponsor assumed that patients could undergo no more than two surgeries and no further complications would occur with the second surgery. Further, patients could die in any health state.[5]

Comparative efficacy data, with respect to remission and response without remission, were informed by a sponsor-commissioned NMA.[5] Specifically, treatment efficacy in the induction phase was based on the results of the induction phase NMA while treatment efficacy in the maintenance phase was based on the separate NMA results of a response-based re-randomized design. Odds ratios of treatment compared with CT were applied to the relevant CT transition probabilities to calculate the treatment-specific probabilities in both the induction and maintenance phases.[5] For both non-biologic failure and biologic failure subgroups, the sponsor assumed a single-dose regimen in the induction phase while, in the maintenance phase, the sponsor assumed a dose-mix regimen (i.e., a proportion of patients would be receiving a low dose of the biologic while the remainder would be receiving high doses of the biologic). Low and high doses differed either by the frequency of the dosing interval or the strength of the dose administered (Table 15).[5] Surgery-related model inputs and the risk of serious adverse events during the treatment-maintenance phase were derived from published literature.[14-17] Background (all-cause) mortality was derived from Canadian life tables.[18] Pharmacotherapy was assumed to not affect mortality, although an excess risk of death was assumed for patients undergoing surgery.[19]

Utility inputs for the non-surgical health states were derived from a study conducted in the UK that estimated health utility using EuroQol 5-Dimensions 3-Levels (EQ-5D-3L) in adult patients with UC.[6] Utility values for surgical health states were obtained from a study that compared various treatments among adult patients with steroid-refractory UC based on the time-trade-off method.[7] A utility decrement for serious infection was also obtained from published literature.[20]

The cost of ustekinumab was based on the sponsor's submitted price and assumed no vial sharing.[5] Costs for low- and high-dose regimens were estimated for biologic treatments, with dosing regimen based on their respective product monographs, with the exception of golimumab. Costs related to treatment-related adverse events and disease management were obtained from Canadian and UK sources.[10-12]

Sponsor's Base Case

The sponsor reported probabilistic results based on 5,000 Monte Carlo simulations. For the non-biologic failure subgroup, the sponsor indicated that continuing CT alone would be cost-effective if a decision-maker's WTP threshold was up to $62,017 per QALY; infliximab (biosimilar) would be cost-effective if a decision-maker were willing to pay between $62,017 and $68,133 per QALY; and ustekinumab would be cost-effective at a WTP threshold greater than $68,133 per QALY (Table 2). Ustekinumab had a 0% probability of being cost-effective at a WTP threshold of $50,000 per QALY gained.

Table 2: Summary of Results of the Sponsor's Base Case – Non-Biologic Failure

	Total costs ($)	Total QALYs	Incremental cost per QALY ($)	
			Versus conventional therapy[a]	Sequential ICER[b]
Conventional therapy	43,717	4.01	–	–
Infliximab biosimilar (Renflexis)	66,043	4.37	62,017	62,017
Golimumab	67,388	4.34	71,730	Dominated by infliximab (Renflexis)
Infliximab biosimilar (Inflectra)	67,552	4.37	66,208	Dominated by infliximab (Renflexis)
Adalimumab	70,121	4.19	146,689	Dominated by infliximab (Renflexis)
Tofacitinib	74,142	4.47	66,141	Subject to extended dominance through ustekinumab versus conventional therapy
Infliximab (main)	91,884	4.37	133,797	Dominated by tofacitinib
Vedolizumab	98,499	4.61	91,303	Subject to extended dominance through ustekinumab versus conventional therapy
Ustekinumab	99,428	4.86	65,542	68,133

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

[a] ICER of comparator versus conventional therapy was recalculated due to sponsor's computational errors.

[b] Sequential ICER (probabilistic) as calculated by CADTH due to sponsor's computational errors.

Source: Adapted from the sponsor's pharmacoeconomic submission.[5]

In the sponsor's base case for the biologic failure subgroup, continuing CT alone would be cost-effective up to a WTP threshold of $68,006 per QALY; tofacitinib would be cost-effective if a decision-maker was willing to pay between $68,006 and $79,040 per QALY; and ustekinumab would be cost-effective at a WTP threshold greater than $79,040 per QALY (Table 3). Ustekinumab had a 0% probability of being cost-effective at a WTP threshold of $50,000 per QALY gained.

Table 3: Summary of Results of the Sponsor's Base Case – Biologic Failure

	Total costs ($)	Total QALYs	Incremental cost per QALY ($)	
			Versus conventional therapy[a]	Sequential ICER[b]
Conventional therapy	43,973	3.95	–	–
Tofacitinib	65,055	4.26	68,006	68,006
Adalimumab	79,231	4.31	97,939	Subject to extended dominance through vedolizumab and ustekinumab versus conventional therapy
Vedolizumab	81,613	4.34	96,513	Subject to extended dominance through ustekinumab versus conventional therapy
Ustekinumab	88,767	4.56	73,433	79,040

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

Source: Adapted from the sponsor's pharmacoeconomic submission.[5]

[a] ICER of comparator versus conventional therapy was recalculated due to sponsor's computational errors.

[b] Sequential ICER (probabilistic) as calculated by CADTH, due to sponsor's computational errors.

Summary of the Sponsor's Scenario Analyses

The sponsor conducted several probabilistic scenario analyses to test alternative assumptions for the non-biologic and biologic failure subgroups, respectively. Specifically, the sponsor explored: the impact of "delayed responders" (i.e., patients who did not initially achieve remission or response without remission in the induction phase); the impact of incorporating "direct trial data" (i.e., direct use of maintenance-phase efficacy data from individual pivotal trials from each of the interventions rather than selecting the relative treatment effect estimates within the NMA); varying proportions for low- or high-dose regimens in the maintenance phase; and alternate utility values for health states. It was observed that the model was most sensitive to inputs that impacted treatment costs (i.e., low- and high-dose regimens) or utility values.

The sponsor also conducted deterministic one-way sensitivity analyses to address parameter uncertainty for the two subgroups. These analyses indicated that, for both subgroups, the model results were most sensitive to the pre-surgery health state utilities for remission and active UC, and the rates of remission and response for CT.

The uncertainty around most input parameters in the sponsor's model was assumed to be 20% of the parameter point estimate (e.g., mean value).

Limitations of Sponsor's Submission

CADTH identified the following limitations with the sponsor's model:

- **Comparative treatment efficacy is uncertain**: The sponsor incorporated results from their NMA to inform the treatment efficacy and the transition probabilities within their economic model for both the induction and maintenance phases. Based on the appraisal of the sponsor's commissioned NMA, CADTH clinical reviewers noted several concerns. With respect to the individual studies that were included in the NMA, potential risk of bias was detected related to the randomization process, unclear blinding, and imbalance in the dropout rates between trial arms. When these studies were pooled into the NMA, the assumption of transitivity may have been violated, given that different placebo effect

estimates were observed across studies. Methodological heterogeneity was further observed between the included trials, as different routes of drug administration and dosing were studied. Greater uncertainty exists in the estimates derived for the maintenance phase, as methodological differences exist in the design of the individual trials. Although an imputation process was taken to mimic the expected outcomes of different trial designs (i.e., treat-through design and response-based re-randomized designs), there was no validation of these approaches. Significant imprecision (i.e., wide credible intervals) in the effect estimates were observed, with precision likely overestimated in the maintenance phase. Treatment effect estimates in the economic model were selected from the fixed effect models. Given the imprecision and heterogeneity noted previously, results from a random-effects model approach would have been more conservative. CADTH selected a random-effects model for the induction phase; however, as the results of the maintenance estimates from a random-effects model were unavailable, CADTH was unable to select a random-effects model for the maintenance phase. The comparative clinical efficacy of ustekinumab against other biologics is uncertain, as noted in CADTH's clinical review. As such, a scenario analysis assuming equal treatment efficacy among biologics in the maintenance phase was conducted to assess the impact of this limitation on the CADTH base case.

In the UNIFI trial, a large proportion of patients who did not show a clinical response at eight weeks (i.e., 157 of 233 patients [67%] who did not initially respond at the end of the induction phase) were found to have responded at 16 weeks (i.e., delayed responders). Although the sponsor's base case assumed treatment would be prescribed according to its product monograph (i.e., patients would enter maintenance therapy only if response was observed in the induction phase), the cost-effectiveness of ustekinumab would be different if patients were to continue treatments beyond the induction phase, regardless of treatment response to permit the assessment of delayed responders. CADTH conducted a scenario analysis on delayed responders in which patients who did not respond at the end of the induction phase but who responded during the maintenance phase (i.e., week 16 for ustekinumab) would be permitted to remain on biologic treatment.

Lastly, there is uncertainty about the long-term treatment effects, as there are no long-term extension studies supporting the clinical efficacy of ustekinumab beyond 52 weeks. The sponsor assumed a treatment-specific constant risk of loss of response beyond 52 weeks.

- **Model did not include all relevant comparators for the biologic failure subgroup:** The sponsor excluded infliximab (branded or biosimilars) and golimumab as active comparators from the model in the biologic failure subgroup without providing justification. The sponsor-commissioned NMA similarly included only four biologics in its analysis and, subsequently, these were the four biologics alongside CT that were studied in the sponsor's economic model.[5] However, according to the clinical expert consulted by CADTH, infliximab and golimumab are available options for this indicated population. By not including these comparators in the biologic failure subgroup, the sponsor's model would have implicitly assumed that these patients would have failed treatment with infliximab and golimumab. There may be variability around which biologic is first prescribed to patients. CADTH was unable to fully examine the cost-effectiveness of ustekinumab compared with all biologic treatments in the biologic failure subgroup, given that no comparative clinical data were available.

- **Model time horizon was not suitable to evaluate costs and effects of a chronic condition:** The sponsor selected a 10-year time horizon for the economic analysis rather than a lifetime. According to CADTH guidelines, the time horizon for an economic evaluation should be long enough to sufficiently capture all potential costs and effects. The assumed time horizon may have a substantial influence on the valuation of a health care intervention.[13] Given that UC is a lifelong condition, a lifetime time horizon would be most appropriate to capture relevant lifelong costs and effects. By shortening the time horizon, costs and effects of ustekinumab may be underestimated. CADTH addressed this limitation by changing the time horizon from 10 years to 50 years in the CADTH base case.

- **Dose-mixing regimen in the treatment-maintenance phase was not modelled appropriately:** A dose-mix regimen was assumed in the treatment-maintenance phase for non-biologic failure and biologic failure patients who remained on treatment with their current biologic. The clinical expert consulted by CADTH indicated that within the Canadian standard of practice, dose escalation may be performed upon disease flare or nonresponse, and rarely if a patient is stable and responding well to treatment. Clinical practice guidelines suggest that, in some instances, patients with previous anti–tumour necrosis factor failure (i.e., biologic failure) may benefit from a higher maintenance dose.[21] For the reasons mentioned, it may be reasonable that a dose-mixing regimen was modelled for non-biologic failure and biologic-exposed patients in the indicated population.

  In both models, the sponsor relied on expert opinion to assign the proportion of patients who received either low- or high-dose biologics in the maintenance phase. However, a dose-response relationship exists, as patients who receive a higher dose of a biologic are expected to more likely achieve clinical response or remission, whereas patients who receive a lower dose are less likely to achieve clinical response or remission. It is therefore important for the dose mixes assumed in the model to be consistent with the dose-mix studied in the clinical trials that informed the model's comparative efficacy data. While the approach of relying on expert opinion to inform the proportion of patients on a low- or high-maintenance dose may potentially be more reflective of clinical practice, the clinical efficacy data have not been adjusted accordingly. Whereas the sponsor's model assumed differences in dosing, the NMA incorporated an equal proportion of patients on a high and low dose (50:50) in the non-biologic failure population. If certain biologics are expected to have a higher proportion of patients administered a higher maintenance dose, their efficacy would be expected to be higher than what has been observed in the trials that studied the high and low dose at equal proportions. This limitation was not a concern for vedolizumab or adalimumab, as the dose-mix regimen was reflective of that incorporated in the NMA. It was less of a concern for golimumab as, although the cost of the high dose was assumed in the sponsor's submitted model, the costs of the high- and low-dose regimens are identical (Appendix 1). CADTH therefore changed the proportion of patients within the dose-mix regimen for the remaining treatments to reflect the proportions studied in the trials. For biologic failure patients, all patients in the clinical studies received low-dose biologics in the maintenance phase. CADTH therefore considered it appropriate to set the treatment costs for the biologic failure patients to the costs of a low-dose biologic regimen.

- **Frequency of assessment of treatment response during the maintenance phase is not reflective of clinical practice:** Loss of treatment response was assumed to be reassessed at every cycle (i.e., every two weeks) to determine whether patients would continue their current treatment during the maintenance phase. The clinical expert

consulted by CADTH confirmed that reassessment of treatment response within the context of clinical practice in Canada typically occurs less frequently, with an approximate frequency of every two months. CADTH was unable to address this, given the structure of the model. With more frequent reassessment to determine discontinuation, this may underestimate the expected drug costs for all biologics, with a greater underestimation for biologics that are priced higher.

- **Lack of model stability partly arising from the use of an arbitrary definition of uncertainty within the probabilistic sensitivity analysis:** CADTH noted that the sponsor's model was not stable at 5,000 iterations for the biologic-failure population. Furthermore, when incorporating the proposed changes to CADTH's base case, the model was unstable, even up 20,000 Monte Carlo simulations. CADTH evaluated the potential causes of instability and noted a number of factors that may have contributed. The sponsor applied an arbitrary definition of uncertainty in the probabilistic analysis (i.e., the standard error of the mean was estimated to be 20% of the mean value for parameters) for most parameters in the model. No appropriate justifications were provided for this assumption. This approach in defining probability distributions is inappropriate , as parameters with low sensitivity but higher uncertainty should impact the model's output more than parameters with high sensitivity, but estimated with greater precision. In addition, the CADTH clinical review noted imprecision in the comparative treatment effect estimates, as demonstrated by the considerable number of wide credible intervals around the effect estimates in the NMA. The uncertainty around effect estimates, and the arbitrary definition of uncertainty applied in the probabilistic sensitivity analysis , likely contributed to the instability observed in the probabilistic results. The uncertainty observed in the probabilistic results may therefore not fully reflect the true uncertainty around model parameters. CADTH did not address the impact of uncertainty on the estimated costs and outcomes and, for the biologic failure population, the CADTH reanalyses presents the deterministic results only.

CADTH Common Drug Review Reanalyses

CADTH conducted separate analyses for non-biologic failure and biologic failure subgroups, as reported in Table 4 and Table 5. The reanalyses addressed the identified limitations that could be modified within the sponsor's model, which included:

- selection of clinical estimates generated from a random-effects model for the induction phase.
- changing the time horizon from 10 years to 50 years to reflect a lifetime time horizon.
- revising dose-mix proportions in the maintenance phase to the proportions studied in trials. This meant that dose-mixing was not permitted for the biologic failure subgroup, while the dose mix was set to (50:50) for the non-biologic failure subgroup.

Results of the stepwise analyses can be found in Table 14 and Table 13 of Appendix 4.

Non-Biologic Failure Population

Given instabilities in the pharmacoeconomic model, the CADTH probabilistic reanalyses were conducted with 7,500 Monte Carlo simulation in order to achieve convergence. Based on the revisions outlined previously, the CADTH base case for the non-biologic failure population found that the least costly comparator was to continue CT. Ustekinumab was the only non-dominated comparator and, at a WTP threshold of less than $53,546 per QALY, CT was the optimal therapy; above that threshold, ustekinumab was the optimal therapy.

Ustekinumab had a 13% probability of being the most likely cost-effective treatment at a WTP threshold of $50,000 per QALY (Table 4).

Table 4: Summary of Results for the Probabilistic CADTH Base-Case Analysis – Non-Biologic Failure

	Total costs ($)	Total QALYs	Incremental cost per QALY ($)	
			Versus conventional therapy	Sequential ICER
Conventional therapy	184,202	13.06	NA	NA
Biosimilar: Renflexis	208,830	13.46	62,070	Subject to extended dominance
Golimumab	209,305	13.47	61,723	Subject to extended dominance
Biosimilar: Inflectra	210,633	13.45	67,596	Dominated
Adalimumab	213,402	13.29	124,120	Dominated
Tofacitinib	224,745	13.71	61,943	Subject to extended dominance
Infliximab	239,239	13.45	141,695	Dominated
Vedolizumab	258,093	14.00	78,563	Subject to extended dominance
Ustekinumab	264,390	14.56	53,546	$53,546

ICER = incremental cost-effectiveness ratio; NA = not applicable; QALY = quality-adjusted life-year.

Biologic Failure Population

Deterministic results were presented for the CADTH base case due to the model's instability. At a WTP threshold of up to $63,058 per QALY, CT was the optimal therapy; above that threshold, ustekinumab was the optimal therapy (Table 5).

Table 5: Summary of Results for the Deterministic CADTH Base-Case Analysis – Biologic Failure Patients

	Total costs ($)	Total QALYs	Incremental cost per QALY ($)	
			Versus conventional therapy	Sequential ICER
Conventional therapy	183,471	12.92	NA	NA
Tofacitinib	195,652	13.09	73,216	Subject to extended dominance
Vedolizumab	198,759	13.06	106,614	Dominated
Adalimumab	201,809	13.15	79,735	Subject to extended dominance
Ustekinumab	204,688	13.26	63,058	$63,058

ICER = incremental cost-effectiveness ratio; NA = not applicable; QALY = quality-adjusted life-year.

CADTH conducted a series of scenario analyses on the probabilistic CADTH base case for the non-biologic failure subgroup and on the deterministic CADTH base case for the biologic failure subgroup:

- Delayed-responders analysis: Pivotal trials on biologic treatments informed the proportion of patients who would be considered delayed responders and the sponsor's mimic treat-through analysis was selected to inform treatment efficacy in the maintenance phase. Of

note, as only point estimates were available for the treatment effects of a mimic treat-through analysis, the standard errors from the mimic response-based analysis were used.

- The dose-mix regimen was removed in the non-biologic failure subgroup, with 100% of patients assumed to be receiving low-dose biologics in the maintenance phase.
- The dose-mix regimen modelled in the non-biologic failure subgroup assumed 100% of patients to be receiving high-dose biologics in the maintenance phase.
- Efficacy estimates for the maintenance phase were based on the mimic treat-through analysis of the NMA in both the non-biologic failure and biologic failure subgroups.
- Equal efficacy for all biologic treatments was assumed in the maintenance phase in both the biologic failure and non-biologic failure subgroups.

Results of the scenario analyses are reported in Appendix 4 (Table 15 to Table 18).

When equal efficacy among biologics was assumed in the maintenance phase, the efficiency frontier consisted of CT and infliximab biosimilars. At a WTP threshold of up to $38,414 per QALY, continuing CT would be the optimal therapy while, if the WTP threshold was between $38,414 and $3.2 million per QALY, an infliximab biosimilar (Renflexis) would be the optimal therapy for the non-biologic failure population. For the biologic failure population, infliximab was not a comparator in the analysis. Deterministic results suggested that at a WTP of up to $85,787 per QALY, continuing CT would be the optimal therapy while, if the WTP were greater, tofacitinib would be the optimal therapy.

The delayed-responder scenario analysis found that the results differed between subgroups. In the non-biologic failure population, the probabilistic ICER of ustekinumab was $51,230 per QALY gained compared with CT; whereas, in the biologic failure population, deterministic results found that the biologics on the efficiency frontier differed and ustekinumab was dominated. Between a WTP threshold of $123,024 and $299,674 per QALY gained, tofacitinib was the optimal therapy. Below a WTP threshold of $123,024 per QALY, CT was the optimal therapy and, above a WTP threshold of $299,674 per QALY, vedolizumab was the optimal therapy.

For the CADTH base case, price-reduction analyses were undertaken by subgroup (Table 6). Probabilistic results show that a price reduction of at least 10% would be required to bring the ICER under $50,000 per QALY in the non-biologic failure subgroup, while deterministic results suggest a price reduction of 20% would be required for the biologic failure subgroup.

Table 6: CDR Reanalysis Price Reduction Scenarios

ICERs of submitted drug versus comparator				
	Non-biologic failure		Biologic failure	
Price	**Base-case analysis submitted by sponsor**	**Probabilistic reanalysis by CADTH[a]**	**Base-case analysis submitted by sponsor**	**Deterministic reanalysis by CADTH**
Submitted	If λ < $62,017 CT is optimal If $68,133 > λ > $62,017 infliximab is optimal	If λ < $53,546 CT is optimal If λ > $53,546 ustekinumab is optimal	If λ < $68,006 CT is optimal If $79,040 > λ > $68,006 tofacitinib is optimal If λ > $79,040 ustekinumab is optimal	If λ < $63,058 CT is optimal If λ > $63,058 ustekinumab is optimal

ICERs of submitted drug versus comparator				
	Non-biologic failure		Biologic failure	
Price	**Base-case analysis submitted by sponsor**	**Probabilistic reanalysis by CADTH[a]**	**Base-case analysis submitted by sponsor**	**Deterministic reanalysis by CADTH**
	If λ > $68,133 ustekinumab is optimal			
10% reduction	If λ < $57,789 CT is optimal If λ > 57,789 ustekinumab is optimal	If λ < $46,740 CT is optimal If λ > $46,740 ustekinumab is optimal	If λ < $65,325 CT is optimal If λ > $65,325 ustekinumab is optimal	If λ < $55,104 CT is optimal If λ > $55,104 ustekinumab is optimal
20% reduction	If λ < $50,184 CT is optimal If λ > $50,184 ustekinumab is optimal	If λ < $40,293 CT is optimal If λ > $40,293 CT ustekinumab is optimal	If λ < $57,036 CT is optimal If λ > $57,036 ustekinumab is optimal	If λ < $63,058 CT is optimal If λ > $63,058 ustekinumab is optimal

CDR = CADTH Common Drug Review; CT = conventional therapy; ICER = incremental cost-effectiveness ratio.

[a] Given instabilities in the pharmacoeconomic model, CADTH probabilistic reanalysis was conducted with 7,500 Monte Carlo simulations to achieve convergence.

Issues for Consideration

Feedback from the clinical expert consulted by CADTH indicated that a patient would not be maintained on a treatment that is failing and, furthermore, clinicians would be unlikely to return a patient to a previously failed treatment. The clinical expert noted an exception would be for patients who had failed several biologics or already exhausted other treatment options and must avoid surgery (less than 5% of cases). In such instances, a clinician may treat these patients with CT, although there would be minimal benefit. This suggests that, in the economic model for the non-biologic failure subgroup, CT may not be a suitable comparator, given the multitude of biologics that are available.

The confidential nature of the negotiated effective price for pharmaceuticals means CADTH is unable to assess the impact of potentially lower prices of comparators on the results. Thus, it is unknown if the reduced effective price of comparators would lead to differing conclusions than the current analysis, based on list prices.

Patient Input

Two patient groups provided input for the ustekinumab submission for UC: Crohn's and Colitis Canada and the Gastrointestinal Society.

Patient's noted that UC is a lifelong condition. As such, a lifetime time horizon would have been appropriate to consider within the economic analysis. The most important outcome for patients with moderate-to-severe UC is clinical remission, and achieving remission does have a substantial impact on patients' quality of life. Remission was a clinical outcome captured as a health state in the submitted economic model and, similarly, the attainment of remission was associated with the highest utility value.

Patient input described that first-line (e.g., 5-aminosalicylates and corticosteroids) and second-line treatments (e.g., immunomodulators or immunosuppressants) are helpful for targeting inflammation, though they may be more effective for patients with moderate rather than severe UC. In the sponsor's model, the first- and second-line treatments, as noted by the patient groups, are included as part of CT. Nonresponders of first- and second-line

treatment may be eligible to receive third-line treatment with biologics (i.e., anti–tumour necrosis factor drugs); however, severe cases may still fail to maintain remission, even with these advanced treatments.

Conclusions

CADTH reanalyses of the non-biologic failure population determined that CT would be the optimal therapy if the WTP threshold were up to $53,546 per QALY; thereafter, ustekinumab would be the optimal therapy. In the biologic failure population, deterministic reanalyses by CADTH suggest that CT would be the optimal therapy up to a WTP of $63,058 per QALY; thereafter, ustekinumab would be the optimal therapy. In the non-biologic failure population, ustekinumab had a 13% probability of being the preferred treatment at a WTP threshold of $50,000 per QALY and, at that threshold, a price reduction of at least 10% would be required for ustekinumab to be considered the optimal treatment. For the biologic failure population, deterministic price-reduction analyses suggest that a price reduction of at least 20% may be required for ustekinumab to be considered cost-effective at a WTP threshold of $50,000 per QALY.

The cost-effectiveness of ustekinumab compared with infliximab (branded or biosimilar) and golimumab in the biologic failure population is unknown, given the lack of indirect clinical evidence. Furthermore, the validity in the comparative clinical effect estimates that informed the economic model remain uncertain. The sponsor's submitted NMA did not identify clear superiority between ustekinumab over other common biologics with the same indication. Given that considerable uncertainty remains regarding the comparative treatment efficacy of ustekinumab compared with available treatments in both non-biologic failure and biologic failure subgroups, the results of this economic evaluation should be viewed with caution.

Appendix 1: Cost Comparison

The comparators presented in Table 7 have been deemed to be appropriate by clinical experts. Comparators may be recommended (appropriate) practice, versus actual practice. Comparators are not restricted to drugs but may be devices or procedures. Costs are sponsor list prices, unless otherwise specified. Existing Product Listing Agreements are not reflected in the table and as such may not represent the actual costs to public drug plans.

Table 7: CDR Cost Comparison Table for the Treatment of Ulcerative Colitis

Drug or comparator	Strength	Dosage form	Price ($)	Recommended dosage	Average cost per month ($)	Average cost per year ($)
Ustekinumab (Stelara)	• **130 mg/ 26.0 mL** • **90 mg/ 1.0 mL**	• **Vial for IV infusion** • **Pre-filled syringe for SC injection**	• **$2,079.8400[a]** • **$4,593.1400[a]**	**6 mg/kg IV at week 0, then 90 mg SC every 8 weeks thereafter[a]**	**Year 1: $2,816.53 Thereafter: $2,679.33**	**Year 1: $33,798 Thereafter: $32,152**
Comparators: Biologics						
Adalimumab (Humira)	40 mg/ 0.8 mL	Pre-filled syringe or auto-injector for SC injection	$769.9700	160 mg at week 0, 80 mg at week 2, then 40 mg every other week thereafter[b]	Year 1: $1,924.93 Thereafter: $1,668.27	Year 1: $23,099 Thereafter: $20,019
Golimumab (Simponi)	50 mg/ 0.5 mL 100 mg/ 1 mL	Pre-filled syringe or auto-injector for SC injection	$1,555.1700[o] $1,555.1700[o]	200 mg at week 0, 100 mg at week 2, then 50 mg every 4 weeks thereafter[d]	Year 1: $1,944.42 Thereafter: $1,684.77	Year 1: $23,333 Thereafter: $20,217
Infliximab (Inflectra)	100 mg	Vial for IV infusion	$525.0000	5 mg/kg at week 0, 2, and 6, then every 8 weeks thereafter[e]	Year 1: $1,400.00 Thereafter: $1,225.00	Year 1: $16,800 Thereafter: $14,700
Infliximab (Remicade)	100 mg	Vial for IV infusion	$977.0000[c]	5 mg/kg at week 0, 2, and 6, then every 8 weeks thereafter[f]	Year 1: $2,605.33 Thereafter: $2,279.67	Year 1: $31,264 Thereafter: $27,356
Infliximab (Renflexis)	100 mg	Vial for IV infusion	$493.0000	5 mg/kg at week 0, 2, and 6, then every 8 weeks thereafter[g]	Year 1: $1,314.67 Thereafter: $1,150.33	Year 1: $15,776 Thereafter: $13,804
Tofacitinib (Xeljanz)	5 mg 10 mg	Tablet	$23.9589 $42.3436[h]	10 mg twice daily for at least 8 weeks, then 5 mg twice daily thereafter	Year 1: $1,625.10 Thereafter: $1,453.51	Year 1: $19,501 Thereafter: $17,442
Vedolizumab (Entyvio) (IV only)	300 mg	Vial for IV infusion	$3,291.0000[c]	300 mg at week 0, 2, and 6, then every 8 weeks thereafter[i]	Year 1: $2,194.00 Thereafter: $1,919.75	Year 1: $26,328 Thereafter: $23,037
Comparators: Aminosalicylates						
5-ASA (Asacol, Asacol 800)	400 mg 800 mg	Tablet	$0.5597 $1.1358	Active: 2 to 8 tablets daily in divided doses	$34.05 to $136.19	$409 to $1,634

Drug or comparator	Strength	Dosage form	Price ($)	Recommended dosage	Average cost per month ($)	Average cost per year ($)
				Maint: 4 tablets daily in divided doses[j]		
5-ASA (Mesasal)	500 mg	Enteric tablet	$0.6559	Active: 1.5 to 3 g tablets daily in divided doses Maint: 1.5 g daily in divided doses[k]	$59.85 to $119.70	$718 to $1,436
5-ASA (Mezavant)	1.2 g	Delayed extended-release tablet	$1.7284	Active: 2 to 4 tablets once daily Maint: 2 tablets daily[l]	$105.14 to $210.29	$1,262 to $2,523
5-ASA (Pentasa)	500 mg 1,000 mg	Extended-release tablet	$0.5881 $1.1761	0.5 to 1 g four times daily (2 g daily dose)[m]	$71.55 to $143.09	$859 to $1,717
	1 g	Suppository	$1.9962	1 g daily[m]	$60.72	$729
	1 g/100 mL 4 g/100 mL	Enema Enema	$4.4790 $6.0400	1 to 4 g daily	$136.24 to $183.72	$1,635 to $2,205
5-ASA (Salofalk)	500 mg	Enteric tablet	$0.6445	Active: 3 g to 4 g daily in divided doses[n] Maint: 1.5 to 3 g per day in divided doses[n]	$117.62 to $156.83	$1,411 to $1,882
	500 mg 1,000 mg	Suppository Suppository	$1.5314 $2.2495	1 to 1.5 g/day[b]	$68.42 to $115.00	$821 to $1,380
	4 g/60 g	Rectal suspension	$8.1360	Active: 4 g nightly Maint: 2 g nightly or 4 g every two nights	$247.47 $123.74	$2,970 $1,485
Olsalazine (Dipentum)	250 mg	Capsule	$0.5330	Active: 1 g to 3 g daily in divided doses[h] Maint: 1 g daily in divided doses[h]	Year 1: 64.85 to 194.55 Thereafter: $64.85	Year 1: $778 to $2,335 Thereafter: $778
Sulfasalazine (Salazopyrin, generics)	500 mg	Tablet	$0.1804	Active: 1 g to 2 g three to four times daily[n] Maint: 1 g two to three times daily[n]	Year 1: $32.92 to $65.85 Thereafter: $21.95 to $32.92	Year 1: $395 to $790 Thereafter: $263 to $395

Drug or comparator	Strength	Dosage form	Price ($)	Recommended dosage	Average cost per month ($)	Average cost per year ($)
Comparators: Corticosteroids						
Betamethasone enema (Betnesol)	5 mg/ 100 mL	Enema	$11.8214	5 mg nightly[h]	$359.57	$4,315
Budesonide (Entocort)	3 mg	Capsule	$1.8653[c]	3 mg three times per day up to 8 weeks, followed by 6 mg daily for up to 3 months[h]	$54.48	$654
Hydrocortisone enema (Cortenema, Cortifoam)	100 mg/ 60 mL	Enema	$8.2541	60 mL nightly or every other night	$125.53 to $251.06	$1,506 to $3,013
	15 g/pack (14 doses)	Rectal aerosol	$117.8800	One dose nightly or every other night[h]	$117.88 to $235.80	$1,415 to $2,830
Hydrocortisone (Solu-Cortef)	100 mg 250 mg	Vial	$4.1500[c] $7.2000[c]	100 mg to 500 mg IV daily to induce remission; then switch to other drug[h]	$126.25 to $438.00	$1,515 to $5,256
Prednisone (generic)	1 mg 5 mg 50 mg	Tablet	$0.1095[c] $0.0220 $0.1735	40 mg to 60 mg daily to induce remission; then lower dose[h]	$5.42 to $8.08	$64 to $79 or lower
Comparators: Immunomodulators						
Azathioprine (generic)	50 mg	Tablet	$0.2405	up to 2.5 mg/kg daily[h]	$29.26	$351
Azathioprine (Imuran)	50 mg	Tablet	$1.0927		$132.95	$1,595
Mercaptopurine (Purinethol and generic)	50 mg	Tablet	$2.8610	1.5 to 2.5 mg/kg daily[h]	$261.07 to $348.09	$3,133 to $4,177
Methotrexate (generic)	2.5 mg 10 mg	Tablet	$0.6325 $2.7000[c]	10 to 25 mg weekly[h]	$11.70 to $28.88	$140 to $347

5-ASA = 5-aminosalicylate; CDR = CADTH Common Drug Review; maint = maintenance; SC = subcutaneous.

Note: All weight-based calculations are based on an assumed mean weight of 73.2 kg, taken from sponsor's baseline patient characteristics, and assumes wastage.

[a] Based on sponsor's submission.

[b] Health Canada Drug Product database.

[c] Price obtained from the Saskatchewan Drug Plan (August 2019).

[d] Product monograph for Simponi (golimumab) injection.

[e] Product monograph for Inflectra (infliximab).

[f] Product monograph Remicade (infliximab).

[g] Product monograph Renflexis (infliximab).

[h] CADTH Common Drug Review Pharmacoeconomic Review Report for Xeljanz.

[i] Product monograph for vedolizumab.

[j] 5-ASA Asacol.

[k] 5-ASA Mesasal.

[l] 5-ASA Mezavant.

[m] 5-ASA Pentasa.

[n] RxTx.

[o] Ontario Formulary Exceptional Access Program (EAP)[22] Source: Ontario Drug Benefit Formulary/Comparative Drug Index (effective from August 2019) unless otherwise noted. Annual period assumes 52 weeks, 365 days.

Appendix 2: Additional Information

Table 8: Submission Quality

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?		X	
Comments Reviewer to provide comments if checking "no"	None		
Was the material included (content) sufficient?	X		
Comments Reviewer to provide comments if checking "poor"	None		
Was the submission well organized and was information easy to locate?		X	
Comments Reviewer to provide comments if checking "poor"	None		

Table 9: Authors information

Authors of the pharmacoeconomic evaluation submitted to CDR

☒ Adaptation of Global model/Canadian model done by the sponsor

☐ Adaptation of Global model/Canadian model done by a private consultant contracted by the sponsor

☐ Adaptation of Global model/Canadian model done by an academic consultant contracted by the sponsor

☐ Other (please specify)

	Yes	No	Uncertain
Authors signed a letter indicating agreement with entire document			X
Authors had independent control over the methods and right to publish analysis			X

CADTH

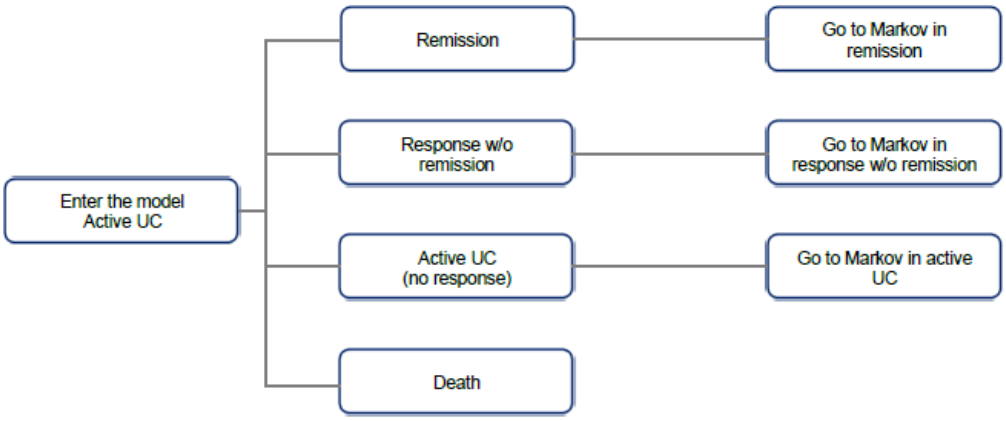
Appendix 3: Summary of Other HTA Reviews of Drug

Stelara was reviewed by the National Institute for Health and Care Excellence (NICE) for this indication and published on June 17, 2020.

Appendix 4: Reviewer Worksheets

Sponsor's Model Structure

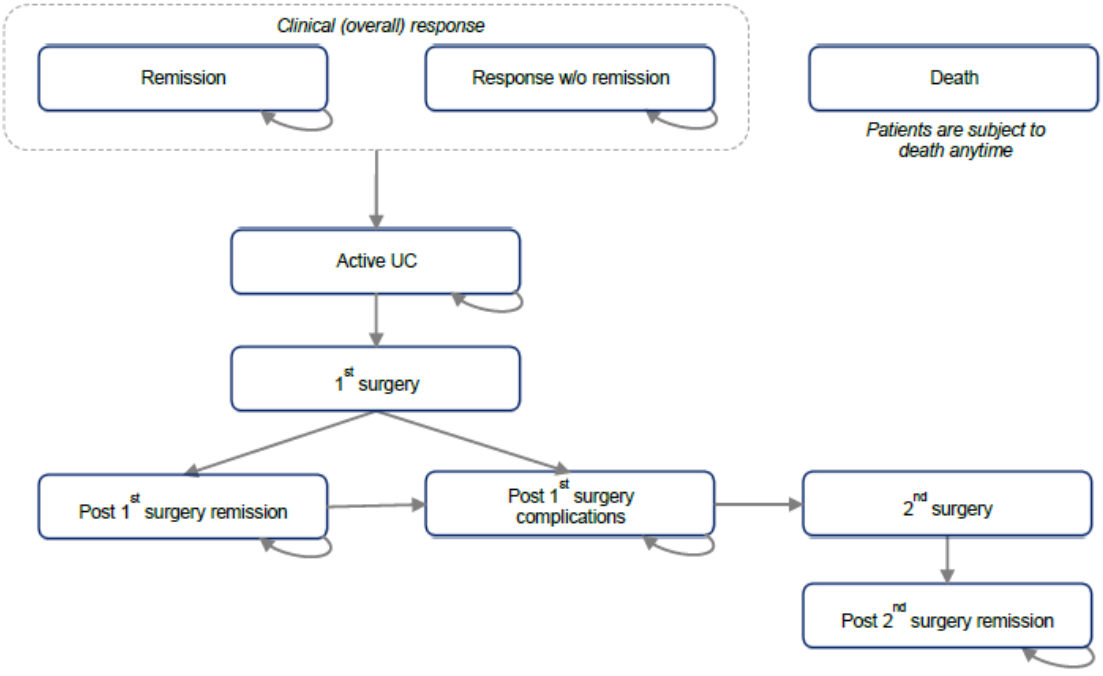
Figure 1: Decision Tree Schematic



UC = ulcerative colitis; w/o = without.

Source: Sponsor's pharmacoeconomic submission.5

Figure 2: Markov Model Schematic



UC = ulcerative colitis; w/o = without.

Source: Sponsor's pharmacoeconomic submission.5

Table 10: Dose Regimen for Intervention Treatment and Comparators

Treatment	Administration mode	Induction phase	Dose regimen: Maintenance phase	
			Low dose % patients	High dose % patients
Biologic drugs				
Ustekinumab (Stelara)	IV at week 0, then SC every 8 weeks	Duration: 8 weeks Based on body weight: ≤ 55 kg: 260 mg > 56 to ≤ 85 kg: 390 mg > 85 kg: 520 mg (Recommended dose: ~6 mg/kg)	90 mg q.12.w.	90 mg q.8.w.
Infliximab (Remicade), Infliximab biosimilars (Infletra, Renflexis)	IV	Duration: 8 weeks	Duration: 8 weeks	Duration: 8 weeks
Golimumab (Simponi)	SC	5 mg/kg at weeks 0, 2, and 6	5 mg/kg at weeks 0, 2, and 6	5 mg/kg at weeks 0, 2, and 6
Adalimumab (Humira)	SC	5 mg/kg q.8.w.	5 mg/kg q.8.w.	5 mg/kg q.8.w.
Vedolizumab	IV	Duration: 6 weeks 300 mg at weeks 0 and 2	300 mg q.8.w.	300 mg q.4.w.
Tofacitinib	Oral	Duration: 8 weeks 10 mg b.i.d. for 8 weeks	5 mg b.i.d.	10 mg b.i.d.
Non-biologic failure subgroup				
Treatment			**Dose regimen: Maintenance phase**	
			Low dose % patients	**High dose % patients**
Ustekinumab			90 mg q.12.w. 43%	90 mg q.8.w. 57%
Infliximab			5 mg/kg q.8.w. 66.7%	10 mg/kg q.8.w. 33.3%
Infliximab biosimilar			5 mg/kg q.8.w. 66.7%	10 mg/kg q.8.w. 33.3%
Infliximab biosimilar			5 mg/kg q.8.w. 66.7%	10 mg/kg q.8.w. 33.3%
Golimumab			50 mg q.4.w. 0%	100 mg q.4.w. 100%
Adalimumab			40 mg q.2.w. 50%	40 mg q.w. 50%
Vedolizumab			300 mg q.8.w. 50%	300 mg q.4.w. 50%
Tofacitinib			5 mg b.i.d. 66.7%	10 mg b.i.d. 33.3%

Biologic failure subgroup		
Treatment	**Dose regimen: Maintenance phase**	
	Low dose % patients	**High dose % patients**
Ustekinumab	90 mg q.12.w. 20%	90 mg q.8.w. 80%
Adalimumab	40 mg q.2.w. 50%	40 mg q.w. 50%
Vedolizumab	300 mg q.8.w. 50%	300 mg q.4.w. 50%
Tofacitinib	5 mg b.i.d. 66.7%	10 mg b.i.d. 33.3%

b.i.d. = twice a day; IV = intravenous; q.4.w. = every four weeks; q.8.w. = every eight weeks; q.12.w. = every 12 weeks; q.w. = every week; SC = subcutaneous.

Table 11: Data Sources

Data Input	Description of Data Source	Comment
Baseline characteristics	Patient characteristics and baseline distributions for the two subgroups of interest were derived from the UNIFI trial.	Appropriate. The CADTH clinical report notes that the UNIFI trial is representative of patients encountered in clinical practice. Non-Biologic failure patients had a mean age of 41.4 years, a mean weight of 73.6 kg, and approximately 60% were male. Biologic failure patients had a mean age of 41.9 years, a mean weight of 72.8 kg, and approximately 61% were male.[5]
Efficacy	Treatment efficacy of ustekinumab, biologics, and CT in the induction phase was estimated from NMA data of clinical trials. Treatment efficacy of ustekinumab, biologics, and CT in the maintenance phase was estimated from NMA data of clinical trials. Extrapolation: The loss of response to treatment observed during the maintenance phase of the trial was assumed to reflect the loss of response observed in the trial, and assumed to occur at a constant loss of response.	Inappropriate. See Limitations of Sponsor's Submission within the main report.
Natural history	Modelled health states represented the natural history of disease, in line with the definitions used in the UNIFI clinical trial. Treatment response in the maintenance phase was evaluated every 2 weeks.	Appropriate. Inappropriate. See Limitations of Sponsor's Submission within the main report.
Time horizon	A time horizon of up to 10 years was assumed in the base case.	Inappropriate. UC is a chronic condition. See Limitations of Sponsor's Submission within the main report.

Data Input	Description of Data Source	Comment
Utilities	The sponsor indicated that health state utility values for patients in remission, response without remission, active UC, first and second surgery remission were obtained from a published abstract by Woehl et al. (2008).[6] The sponsor derived utility values for first surgery, post-first surgery complications and second surgery from Arseneau et al. (2006) (time-trade-off method)[7]: • For the first surgery, this was calculated as a weighted average of the utilities for ileostomy and J pouch (or ileal pouch-anal anastomosis), • For post-first surgery complications, the sponsor calculated a weighted average of the utilities for chronic pouchitis, obstruction, and post-colectomy Crohn disease. The utility value for the second surgery health state was assumed to be equal to that of the first surgery health state. Disutility for serious infection was obtained from Stevenson et al. (2016).[20]	Appropriate The patient population in Arseneau et al. (2006) comprised adult UC patients with steroid-refractory disease. The clinical expert consulted by CADTH noted that ileostomy and J pouch are two of several potential surgical options available for patients if medical treatment fails. The clinical expert consulted by CADTH noted that acute complications, such as a wound infection, could occur after a first surgery. However, wound infection was not a complication reported in Arseneau et al. (2006). Conservative assumption. The clinical expert consulted by CADTH indicated that the quality of life in patients following a second surgery would be worse than that of patients who had undergone a first surgery. The second surgery could be a hernia repair, removal of pouch, or bowel obstruction, or an additional surgery stemming from complications from the first surgery. CADTH was unable to validate the utility value of the second surgery health state because no published literature was available. However, the sponsor's model is not sensitive to the utility value for the second surgery. Likely inappropriate, but unlikely to impact model. The disutility for serious infection was obtained from a study reflecting the rheumatoid arthritis population; the face validity of selecting utility weights from this population is unclear.
Adverse events	In the base case, the model included only serious infections from biologic treatments sourced from the PSOLAR study (Kalb et al., 2015), a study in psoriasis patients.[25] The sponsor assumed that the rate of serious infection from golimumab was the same as infliximab (and biosimilars). The rate of serious infection from vedolizumab, tofacitinib, and conventional therapy was assumed to be the same as ustekinumab.[5]	Unclear if appropriate, but unlikely to impact the model. It is uncertain if serious infection rates in patients with UC would be similar to patients with a skin condition.

Data Input	Description of Data Source	Comment
Complications	The rate of first surgery was sourced from Dan et al. (2017) (i.e., a cumulative colectomy rate after 6 years of 7.5% and a probability of 0.0005 per cycle).[14] Second surgery rates were assumed to be equal to probability of first surgery. The risk of post-first surgery complications was derived from Causey et al. (2013).[15] The probability of post-first surgery complications (following first surgery remission) was derived from Suzuki et al. (2012), at a probability of 0.0018 per cycle.[16]	Likely inappropriate. The aim of Dan et al. (2017) was to assess UC-related direct medical costs among patients with UC prior to and after use of biologic treatments, rather than an epidemiological focus on patients with UC. Acceptable. Likely inappropriate as the study was based in Japan. However, model was not sensitive to this parameter.
Mortality	The baseline all-cause mortality risk was adjusted for age and sex, estimated from Statistics Canada life tables. The relative risk of death from surgery (attributed to first surgery and second surgery health states) was sourced from Jess et al. (2007), which reported an approximate 30% higher risk of dying.	Appropriate. The model was not sensitive to the relative risk of death from surgery. The literature suggests that standardized mortality rates in UC are the same as in the general population. Older patients with comorbidities may have increased mortality; however, the literature suggests that mortality rates from emergent or elective colectomy are much lower than 30%.[26,27]
Resource use and costs		
Drug	Recommended doses were based on product monographs; however, the sponsor applied a dose-mix regimen by pooling maintenance doses. Unit costs obtained from the Ontario Drug Benefit Formulary. Cost of ustekinumab based on sponsor's submission. Costs of conventional therapy based on average distribution of all conventional therapy medications from comparator trials.[5]	Inappropriate. See Limitations of Sponsor's Submission within the main report for details. Appropriate. Appropriate.
Administration	Administration costs of IV infusion were not included in the model for the induction phase. The sponsor did not include training costs for self-administration of subcutaneous drugs in the maintenance phase.	Appropriate. The clinical expert consulted by CADTH confirmed that administration costs of induction IV treatment are covered by the sponsor in infusion clinics, and patients mainly self-administer ustekinumab in the maintenance phase. Although inappropriate, its impact is likely to be marginal.

Data Input	Description of Data Source	Comment
	Disease management resource use obtained from published literature (includes costs of outpatient visits, blood tests, endoscopy, in-patient care without hospitalizations attributed to colectomy).	The clinical expert consulted by CADTH noted that costs of elective and emergency endoscopy appeared to be lower than expected in clinical practice, however the model was not sensitive to any alternate plausible costs.
Adverse events	Cost of serious infection was estimated as a weighted average of the costs for psoriasis, cellulitis, and sepsis. Costs were derived from the Ontario Case Costing Initiative database.[5]	Appropriate source.
Disease management by health state	Resource use data for each of the model's health states were obtained from various sources:	
	Consultant visit costs were obtained from OHIP. [8 88]	Appropriate.
	Blood test costs were obtained from Tsai et al. (2008).[12]	Unclear whether reported cost is appropriate since Tsai et al. (2008) reported a substantially lower cost: approximately £2.93. than that which is reflected in the sponsor's submission and as confirmed by clinical expert consulted by CADTH. Unlikely to have a large impact to the model.
	Costs for emergency endoscopy and elective endoscopy were obtained from Sharara et al. (2008).[10]	Likely appropriate, although the clinical expert consulted by CADTH indicated that costs for emergency endoscopy and elective endoscopy may be lower than the costs expected in clinical practice.
	Cost for care without colectomy was obtained from Coward et al. (2015).[11] First and second surgery health state costs were obtained from Sandborn et al. (2016).[28] All resource use costs associated with active UC, first surgery, and second surgery were assumed to be the same. Post-surgery remission costs (for both first and second surgeries) were assumed to be based on the same resource use.	Likely appropriate.

IV = intravenous; NMA = network meta-analysis; UC = ulcerative colitis.

Table 12: Sponsor's Key Assumptions

Assumption	Comment
Assessment of response to treatment induction at 8 weeks (except for golimumab and vedolizumab, at 6 weeks).	Appropriate.
Patients discontinue treatment upon loss of response to treatment with a biologic (i.e., no clinical benefit is achieved).	Appropriate.
Treatment discontinuation due to adverse events was captured under treatment discontinuation due to loss of response.	The sponsor assumed that the risk of adverse events associated with biologic treatment was very low and therefore these patients would already be accounted for among those patients who lost response. The clinical expert consulted by CADTH indicated that biologic treatment should be discontinued if the adverse event is severe, in contrast with milder adverse events which would not require treatment discontinuation. Antibody development could also be a reason for discontinuation with infliximab and could be considered a potential reason for discontinuation with ustekinumab.
Patients who do not respond to biologic therapy are discontinued from treatment and switched to CT.	Likely inappropriate. According to the clinical practice guidelines, consideration of an alternate class of therapy is recommended rather than switching to another drug within the same class [21]. However, there is limited data on the efficacy of subsequent switch therapy.
Patients are assumed to remain in the active UC health state until first surgery (i.e., only patients with active UC were at risk of colectomy).	Appropriate as colectomy should only be an option for patients who do not achieve an adequate treatment response with available pharmacologic options.
Patients remain in the surgical health state for six months.	Appropriate. The clinical expert consulted by CADTH confirmed that this assumption is in line with clinical practice, as surgery procedures are usually completed in two or three stages.
Patients are assumed to undergo up to two surgeries and no further complications occur after a second surgery.	There may be complications that arise from additional surgeries such as bowel obstruction or a hernia repair, although these are rare.
Adverse events (i.e., rate of serious infection from ustekinumab) were assumed to occur only in the maintenance phase.	Inappropriate, as adverse events may occur in both the induction and maintenance phases.
No vial sharing was assumed in the base case.	Appropriate.

CT= conventional therapy; UC = ulcerative colitis.

CADTH Common Drug Review Reanalyses

Results of the CADTH stepwise reanalyses for the biologic failure and non-biologic failure subgroups are reported in Table 13 and Table 14, respectively. CADTH assessed the impact of the induction NMA random-effects model for the induction phase and found that the model was sensitive to the use of a random-effects model, changes in the time horizon, and revised utility inputs. The model was less sensitive to equal proportions of patients receiving low- and high-dose biologics in the non-biologic failure subgroup or in the no dose-mix regimen in the biologic failure subgroup.

Table 13: CDR Stepwise Reanalyses (Probabilistic) – Non-Biologic Failure Subgroup

			Total costs ($)	Total QALYs	Incremental cost per QALY
					Sequential ICER
	Sponsor's base case	Conventional therapy	43,717	4.01	–
		Infliximab biosimilar: Renflexis	66,043	4.37	$62,017
		Golimumab	67,388	4.34	Dominated by infliximab (Renflexis)
		Infliximab biosimilar: Inflectra	67,552	4.37	Dominated by infliximab (Renflexis)
		Adalimumab	70,121	4.19	Dominated by infliximab (Renflexis)
		Tofacitinib	74,142	4.47	Subject to extended dominance through ustekinumab and conventional therapy
		Infliximab	91,884	4.37	Dominated by tofacitinib
		Vedolizumab	98,499	4.61	Subject to extended dominance through ustekinumab and conventional therapy
		Ustekinumab	99,428	4.86	$68,133
1.	Selection of NMA random-effects model for induction phase[a]	Conventional therapy	43,956	4.01	NA
		Biosimilar: Renflexis	66,532	4.38	$60,610
		Biosimilar: Inflectra	68,294	4.38	Subject to extended dominance
		Golimumab	68,374	4.36	Dominated
		Adalimumab	71,374	4.20	Dominated
		Tofacitinib	75,702	4.50	Subject to extended dominance
		Infliximab	93,207	4.38	Dominated
		Vedolizumab	99,680	4.63	Subject to extended dominance
		Ustekinumab	101,154	4.89	$67,269
2.	Implementing a lifetime time horizon (50 years)[a]	Conventional therapy	184,323	13.06	NA
		Biosimilar: Renflexis	205,197	13.42	Subject to extended dominance
		Biosimilar: Inflectra	206,851	13.41	Dominated
		Golimumab	207,938	13.41	Dominated
		Adalimumab	210,671	13.24	Dominated
		Tofacitinib	216,072	13.59	Subject to extended dominance
		Infliximab	231,851	13.42	Dominated
		Vedolizumab	251,605	13.89	Subject to extended dominance
		Ustekinumab	254,679	14.28	$57,472
3.		Conventional therapy	43,881	4.01	NA
		Golimumab	66,936	4.32	Subject to extended dominance
		Biosimilar: Renflexis	68,465	4.36	Subject to extended dominance

			Total costs ($)	Total QALYs	Incremental cost per QALY
					Sequential ICER
	Changed proportion of patients receiving low- and high-dose drug regimens to reflect proportions studied in treatment arms (i.e., 50:50)[a]	Adalimumab	70,137	4.18	Dominated
		Biosimilar: Inflectra	70,264	4.36	Dominated
		Tofacitinib	77,259	4.46	Subject to extended dominance
		Infliximab	97,020	4.36	Dominated
		Ustekinumab	97,885	4.86	$63,472
		Vedolizumab	99,704	4.63	Dominated
4.	CADTH base case[a] (combining 1 to 3)	Conventional therapy	184,202	13.06	NA
		Biosimilar: Renflexis	208,830	13.46	Subject to extended dominance
		Golimumab	209,305	13.47	Subject to extended dominance
		Biosimilar: Inflectra	210,633	13.45	Dominated
		Adalimumab	213,402	13.29	Dominated
		Tofacitinib	224,745	13.71	Subject to extended dominance
		Infliximab	239,239	13.45	Dominated
		Vedolizumab	258,093	14.00	Subject to extended dominance
		Ustekinumab	264,390	14.56	$53,546

CDR = CADTH Common Drug Review; ICER = incremental cost-effectiveness ratio; NA = not applicable; NMA = network meta-analysis; QALY = quality-adjusted life-year.

[a] Given instabilities in the pharmacoeconomic model, CADTH probabilistic reanalysis was conducted with 7,500 Monte Carlo simulations to achieve convergence.

Table 14: CDR Stepwise Reanalyses (Deterministic) – Biologic Failure Subgroup

			Total costs ($)	Total QALYs	Incremental cost per QALY
					Sequential ICER
	Sponsor's base case (probabilistic)	Conventional therapy	43,973	3.95	–
		Tofacitinib	65,055	4.26	$68,006
		Vedolizumab	81,613	4.34	Subject to extended dominance through vedolizumab and ustekinumab (versus conventional therapy)
		Adalimumab	79,231	4.31	Subject to extended dominance through ustekinumab versus conventional therapy
		Ustekinumab	88,767	4.56	$79,040
1.	Selection of NMA random-effects model for induction phase	Conventional therapy	44,321	3.95	NA
		Tofacitinib	61,151	4.15	$83,129
		Vedolizumab	65,127	4.09	Dominated
		Adalimumab	71,652	4.19	Subject to extended dominance
		Ustekinumab	75,490	4.31	$88,884
2.	Implementing a lifetime horizon (50 years)	Conventional therapy	183,471	12.92	NA
		Tofacitinib	199,334	13.11	$82,112
		Vedolizumab	203,720	13.06	Dominated
		Adalimumab	209,854	13.15	Subject to extended dominance
		Ustekinumab	212,963	13.27	$86,087

			Total costs ($)	Total QALYs	Incremental cost per QALY
					Sequential ICER
3.	Removing the dose-mix regimen	Conventional therapy	44,321	3.95	NA
		Tofacitinib	57,344	4.12	Subject to extended dominance
		Vedolizumab	60,198	4.10	Dominated
		Adalimumab	63,739	4.19	Subject to extended dominance
		Ustekinumab	67,184	4.30	$65,796
4.	CADTH base case (combining 1 to 3)	Conventional therapy	183,471	12.92	Subject to extended dominance
		Tofacitinib	195,652	13.09	Dominated
		Vedolizumab	198,759	13.06	Subject to extended dominance
		Adalimumab	201,809	13.15	$55,104
		Ustekinumab	202,012	13.26	Subject to extended dominance

ICER = incremental cost-effectiveness ratio; NA = not applicable; NMA = network meta-analysis; QALY = quality-adjusted life-year.

Note: Deterministic results, unless otherwise specified.

The following scenario analyses were undertaken to consider alternate scenarios from the CADTH base-case analysis:

Scenario 1. Delayed-responder analysis based on mimic treat-through data in the maintenance phase for:

a. Non-biologic failure subgroup

b. Biologic failure subgroup

Scenario 2. 100% of patients receiving a low-dose regimen in the maintenance phase for the non-biologic failure subgroup.

Scenario 3. 100% of patients received a high dose in the maintenance phase for the non-biologic failure subgroup.

Scenario 4. Equal efficacy across all biologic treatments for:

a. Non-biologic failure subgroup

b. Biologic failure subgroup

Table 15: Results of CADTH Scenario Analysis 1 (Delayed Responders)

	Total costs ($)	Total QALYs	Incremental cost per QALY	
			Versus conventional therapy ($)	Sequential ICER
Non-biologic failure subgroup[a]				
Conventional therapy	183,560	13.06	NA	NA
Biosimilar: Renflexis	205,755	13.38	$71,106	Subject to extended dominance
Biosimilar: Inflectra	207,479	13.37	$77,109	Dominated
Golimumab	207,579	13.40	$71,882	Subject to extended dominance
Adalimumab	208,781	13.24	$147,333	Dominated
Infliximab	233,915	13.38	$157,265	Dominated

	Total costs ($)	Total QALYs	Incremental cost per QALY	
			Versus conventional therapy ($)	Sequential ICER
Tofacitinib	243,916	14.07	$60,306	Subject to extended dominance
Vedolizumab	308,888	14.57	83,188	Subject to extended dominance
Ustekinumab	332,030	15.96	51,230	$51,230
Biologic failure subgroup[a]				
Conventional therapy	183,471	18.77	NA	NA
Adalimumab	198,126	18.84	190,312	Subject to extended dominance
Tofacitinib	208,966	18.97	123,024	$123,024
Ustekinumab	209,760	18.95	139,510	Dominated
Vedolizumab	240,408	19.08	182,399	$299,674

ICER = incremental cost-effectiveness ratio; NA = not applicable; QALY = quality-adjusted life-year.

[a] Given instabilities in the pharmacoeconomic model, CADTH's probabilistic scenario analysis for the non-biologic failure population was conducted with 7,500 Monte Carlo simulations to achieve convergence. Results of the biologic failure population are based on a deterministic analysis.

Table 16: Results of CADTH Scenario Analysis 2 (All Patients on Low-Dose Biologic Regimen)

	Total costs ($)	Total QALYs	Incremental cost per QALY	
			Versus conventional therapy	Sequential ICER
Non-biologic failure subgroup[a]				
Conventional therapy	184,603	13.09	NA	NA
Biosimilar: Renflexis	208,921	13.48	62,489	Subject to extended dominance
Golimumab	209,382	13.49	62,340	Subject to extended dominance
Biosimilar: Inflectra	210,980	13.48	67,719	Dominated
Adalimumab	213,130	13.32	128,022	Dominated
Tofacitinib	224,307	13.73	62,401	Subject to extended dominance
Infliximab	239,584	13.48	141,380	Dominated
Vedolizumab	259,547	14.05	78,371	Subject to extended dominance
Ustekinumab	262,852	14.55	53,831	$53,831

ICER = incremental cost-effectiveness ratio; NA = not applicable; QALY = quality-adjusted life-year.

[a] Given instabilities in the pharmacoeconomic model, CADTH probabilistic scenario analysis was conducted with 7,500 Monte Carlo simulations to achieve convergence.

Table 17: Results of CADTH Scenario Analysis 3 (All Patients on High-Dose Biologic Regimen)

	Total costs ($)	Total QALYs	Incremental cost per QALY	
			Versus conventional therapy	Sequential ICER
Non-biologic failure subgroup[a]				
Conventional therapy	$183,850	13.07	NA	NA
Golimumab	$211,175	13.53	$59,182	$59,182
Biosimilar: Renflexis	$220,331	13.53	$79,282	Dominated
Biosimilar: Inflectra	$222,814	13.52	$86,005	Dominated
Adalimumab	$227,432	13.36	$148,878	Dominated
Tofacitinib	$246,668	13.87	$78,273	Subject to extended dominance
Infliximab	$263,617	13.53	$175,042	Dominated
Ustekinumab	$299,702	14.85	$65,249	$67,381
Vedolizumab	$324,678	14.45	$102,151	Dominated

ICER = incremental cost-effectiveness ratio; NA = not applicable; QALY = quality-adjusted life-year.

[a] Given instabilities in the pharmacoeconomic model, CADTH probabilistic scenario analysis was conducted with 7,500 Monte Carlo simulations to achieve convergence.

Table 18: Results of CADTH Scenario Analysis 4 (Equal Efficacy Among Biologics in the Maintenance Phase)

	Total costs ($)	Total QALYs	Incremental cost per QALY	
			Versus conventional therapy ($)	Sequential ICER
Non Biologic failure subgroup[a]				
Conventional therapy	183,259	13.08	NA	NA
Golimumab	239,974	14.42	42,289	Subject to extended dominance
Biosimilar: Renflexis	249,727	14.81	38,414	$38,414
Biosimilar: Inflectra	255,663	14.81	41,799	$3,186,852
Tofacitinib	257,560	14.53	51,241	Dominated
Ustekinumab	261,592	14.53	54,032	Dominated
Adalimumab	268,862	14.30	69,643	Dominated
Vedolizumab	298,072	14.68	71,386	Dominated
Infliximab	340,427	14.81	90,742	Dominated
Biologic failure subgroup[a]				
Conventional therapy	183,471	18.77	NA	NA
Adalimumab	199,278	18.85	193,750	Subject to extended dominance
Tofacitinib	200,169	18.96	85,787	$85,787
Vedolizumab	204,230	18.90	155,714	Dominated
Ustekinumab	204,688	18.95	113,751	Dominated

ICER = incremental cost-effectiveness ratio; NA = not applicable; QALY = quality-adjusted life-year.

[a] Given instabilities in the pharmacoeconomic model, CADTH probabilistic scenario analysis for the non-biologic failure population was conducted with 7,500 Monte Carlo simulations to achieve convergence. Results of the biologic failure population are based on a deterministic analysis.

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