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CADTH COMMON DRUG REVIEW

Pharmacoeconomic Review Report

BARICITINIB (OLUMIANT)

(Eli Lilly Canada Inc.)

Indication: For use in combination with methotrexate (MTX) for the treatment of adult patients with moderate to severe rheumatoid arthritis who have responded inadequately to one or more disease-modifying antirheumatic drugs (DMARDs). Baricitinib may also be used as monotherapy in cases of intolerance to MTX.

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Abbreviations

ABTi	abatacept IV
ACR	American College of Rheumatology
ADA	adalimumab
bDMARD	biologic disease-modifying antirheumatic drug
bDMARD-IR	inadequate response to biologic disease-modifying antirheumatic drug
cDMARD	conventional disease-modifying antirheumatic drug
cDMARD-IR	inadequate response to conventional disease-modifying antirheumatic drug
CDEC	CADTH Canadian Drug Expert Committee
CTZ	certolizumab pegol
DAS28	Disease Activity Score-28
DMARD	disease-modifying antirheumatic drug
ETN	etanercept
EQ-5D	EuroQol 5-Dimensions questionnaire
GOL	golimumab
HAQ	Health Assessment Questionnaire
HAQ-DI	Health Assessment Questionnaire–Disability Index
ICUR	incremental cost-utility ratio
IFX	infliximab
NMA	network meta-analysis
QALY	quality-adjusted life-year
RA	rheumatoid arthritis
RTX	rituximab
SAE	serious adverse event
SAR	sarilumab
TCZi	tocilizumab IV
TOF	tofacitinib

Table 1: Summary of the Manufacturer's Economic Submission

Drug Product	Baricitinib (Olumiant) 2 mg tablet
Study Question	To develop a cost-effectiveness model to allow assessment of the economic value of baricitinib for the treatment of moderately to severely active rheumatoid arthritis (RA) in patients with prior inadequate response to conventional disease-modifying antirheumatic drugs (cDMARD) therapy and in patients with prior inadequate response to biologic DMARD (bDMARD) therapy
Type of Economic Evaluation	Cost-utility analysis
Target Population	Adult patients with moderate-to-severe RA who have responded inadequately to ≥ 1 DMARDs
Treatment	Baricitinib (subsequent treatment sequences modelled)
Outcomes	• Quality-adjusted life-years (QALYs)
Comparators	• **Inadequate response to cDMARDs (cDMARD-IR) population:** Etanercept (branded and biosimilar), golimumab, infliximab (branded and biosimilar), abatacept (IV), adalimumab, tofacitinib, certolizumab, sarilumab. The same subsequent treatment sequence was modelled as baricitinib. • **Inadequate response to bDMARDs (bDMARD-IR) population:** Rituximab, golimumab, abatacept (IV), tofacitinib, sarilumab, tocilizumab. The same subsequent treatment sequence was modelled as baricitinib.
Perspective	Canadian public health care payer
Time Horizon	45 years (proxy for lifetime)
Results for Base Case	Manufacturer indicated that baricitinib sequence is dominated, or extendedly dominated, by alternative treatments in both the cDMARD-IR and bDMARD-IR populations.
Key Limitations	• The submitted model was more complex than necessary and lacked transparency. • Infliximab and etanercept costs were based on branded drug prices. • Calculation and coding errors were identified. • The patient populations were highly heterogeneous in terms of age and initial HAQ score. • Serious adverse events were not considered in the manufacturer's analysis. • The model structure did not allow evaluation of treatment response rates that differed by patients' initial disease severity or treatment that resulted in a mortality benefit.
CADTH Estimates	• Based on CADTH reanalyses, the baricitinib sequence is extendedly dominated by a combination of alternative treatments in both analyses. • The baricitinib sequence moved onto the efficient frontier, with a 15% price reduction in patients who have failed to respond to cDMARD therapy ($34,890 per QALY gained versus follow-up sequence alone). • The baricitinib sequence moved onto the efficient frontier, with a 35% price reduction in patients who have failed to respond to bDMARD therapy ($130,998 per QALY gained versus follow-up sequence alone). • When compared with a strategy of only the follow-up regimen (ignoring other treatment alternatives), in both patient populations, baricitinib has lower ICURs when treatment is initiated in patients with a higher HAQ score.

bDMARD = biologic disease-modifying antirheumatic drug; cDMARD = conventional disease-modifying antirheumatic drug; DMARD = disease-modifying antirheumatic drug; HAQ = Health Assessment Questionnaire; ICUR = incremental cost-utility ratio; IR = inadequate response; IV = intravenous; QALY = quality-adjusted life-year; RA = rheumatoid arthritis.

Drug	Baricitinib (Olumiant)
Indication	For use in combination with methotrexate (MTX) for the treatment of adult patients with moderate to severe rheumatoid arthritis who have responded inadequately to one or more disease-modifying antirheumatic drugs (DMARDs). Baricitinib may also be used as monotherapy in cases of intolerance to MTX.
Listing Request	As per indication
Dosage Form	2 mg tablet
NOC Date	August 17, 2018
Manufacturer	Eli Lilly Canada Inc.

Executive Summary

Background

Baricitinib (Olumiant) is indicated for the treatment of moderate-to-severe rheumatoid arthritis (RA) in adult patients who have responded inadequately to one or more disease-modifying antirheumatic drugs (DMARDs). The recommended dosage is 2 mg tablet daily.[1] At the submitted price of $47.92 per 2 mg tablet,[2] the annual cost is $17,490.

The manufacturer submitted a cost-effectiveness analysis based on a discrete-event simulation model. The model compares numerous possible sequences of biologic treatments as current practice for the treatment of RA, including changing to a different treatment, often of a different class, when patients fail their current treatment. The analysis was run over a 45-year time horizon and adopted a Canadian public health system perspective.[3] Two analysis cohorts were considered with moderate-to-severe RA: patients with inadequate response to conventional synthetic DMARDS (cDMARD-IR) and patients with inadequate response to biologic DMARDs (bDMARD-IR). The modelled patient cohorts were not homogenous in terms of characteristics, with wide distributions in age (e.g., cDMARD analysis: average age 52.8 [95% confidence interval (CI), 28 to 77]) and initial disease symptoms (e.g., cDMARD analysis, average Health Assessment Questionnaire [HAQ] score of 1.55, range 0 to 3).[3] Clinical data were based on the manufacturer-provided network meta-analysis (NMA) for both the cDMARD-IR and bDMARD-IR populations. For the cDMARD-IR population, the manufacturer assessed baricitinib followed by a sequence of etanercept (branded and biosimilar) → tocilizumab IV → rituximab → Palliative care, compared with golimumab, infliximab (branded and biosimilar), abatacept IV, adalimumab, tofacitinib, certolizumab, sarilumab, and the follow-up sequence alone. For the bDMARD-IR population, the manufacturer assessed baricitinib followed by a sequence of rituximab → Palliative care, compared with golimumab, abatacept IV, tofacitinib, sarilumab, tocilizumab, and the follow-up sequence alone.

The manufacturer indicated that, for both cDMARD-IR and bDMARD-IR cohorts of patients with moderate-to-severe RA, the baricitinib sequence is dominated or extendedly dominated (i.e., has a higher incremental cost-utility ratio [ICUR] than the reference treatment and the next most cost-effective treatment):

- For patients with inadequate response to cDMARDs, the baricitinib sequence is dominated by the treatment-sequence strategy beginning with tofacitinib, which has an ICUR of $34,100 per quality-adjusted life-year (QALY) gained (compared with etanercept sequence). The next treatment sequence on the efficient frontier begins with sarilumab, with an ICUR of $47,400 per QALY gained, compared with the treatment strategy beginning with tofacitinib.
- For patients with inadequate response to bDMARDs, the baricitinib sequence is dominated by the treatment-sequence strategy beginning with tocilizumab, which has an ICUR of $33,700 per QALY gained.

Summary of Identified Limitations and Key Results

The manufacturer provided an updated model and addendum to the report with additional relevant comparators. CADTH noted that the model was unnecessarily complex and lacked transparency. The manufacturer provided additional information to allow CADTH to validate, as possible, the progression of a limited number of patients through the model. However, CADTH identified several programming and calculation errors throughout the model.

The patient cohorts considered in the manufacturer's analysis were highly heterogeneous in terms of patient age and HAQ score. CADTH's current guidelines for economic evaluations recommend that analyses be stratified where disease progression or treatment effect may vary to inform decision-making.[4]

The manufacturer did not consider biosimilar infliximab and biosimilar etanercept as distinct treatment and assumed a blended comparator of branded and biosimilar products (95% brand, 5% biosimilar). Recent CADTH Canadian Drug Expert Committee (CDEC) recommendations for relevant comparators have recommended listing with a price no higher than the least costly bDMARD alterative for RA. Additionally, the manufacturer did not consider costs and quality-of-life consequences of serious adverse events associated with treatment and may have underestimated the health care costs for RA patients.

The results of the CADTH reanalyses indicated that the patient cohort in the manufacturer's model, which contained individuals over a wide range of ages and initial disease severity, masked important insights into the cost-effectiveness of baricitinib and other biologics for the treatment of RA. CADTH undertook reanalyses that considered more homogeneous patient cohorts (ages 30, 50, and 70 years, and initial HAQ score of 0.5, 1.0, 1.5, 2.0, and 2.5). This analysis revealed that HAQ score at baseline is an important source of heterogeneity in the cost-effectiveness of RA treatment; biologic therapies on the efficient frontier were more cost-effective, in both cDMARD and bDMARD patients, in patients with more severe disease. The CADTH base case assumed that patients entered the model at age 50 with a HAQ score of 1.5, that approximately 80% of patients were female, there was 100% biosimilar use for etanercept and infliximab; serious adverse events were included.

Conclusion

CADTH reanalyses results were generally consistent with the manufacturer's analysis. CADTH analyses identified that, for both cDMARD-IR and bDMARD-IR cohorts of patients with moderate-to-severe RA, baricitinib is dominated (i.e., costs more and provides fewer QALYs than comparators) or extendedly dominated.

Price reductions can improve the cost-efficiency and the cost-effectiveness of baricitinib in patients with moderate disease who are 50 years of age:

- For patients with inadequate response to cDMARDs, a price reduction of 35% results in an ICUR of $130,998 per QALY gained for baricitinib compared with the most efficient treatment strategy. A price reduction of more than 40% is required for baricitinib to achieve an ICUR below $50,000 per QALY compared with the most efficient treatment strategy.
- For patients with inadequate response to bDMARDs, a price reduction of 15% results in an ICUR of $34,890 per QALY gained for baricitinib compared with the most efficient treatment strategy.

While there may be numerical differences between baricitinib and other bDMARDs for some American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) response outcomes, the clinical review concluded that, based on the results of the manufacturer's NMA and other published NMAs, the clinical effects of baricitinib are likely similar to those of existing biologic DMARDs.

Information on the Pharmacoeconomic Submission

Summary of the Manufacturer's Pharmacoeconomic Submission

Overview

The manufacturer submitted an economic model that captured health outcomes in terms of quality-adjusted life-years (QALYs) for cohorts of adult patients with moderate-to-severe rheumatoid arthritis (RA) who have responded inadequately to one or more disease-modifying antirheumatic drugs (DMARDs). The model was designed to evaluate the cost-utility of treatment with baricitinib 2 mg + methotrexate (MTX) in patients with inadequate response to conventional DMARDs (cDMARDs) and in patients with inadequate response to biologic DMARDs (bDMARDs).[3]

Current practice for the treatment of RA includes changing to a different treatment, often of a different class, when patients fail their current treatment. Ultimately, patients initiate treatment alternatives in sequence as they seek to control disease symptoms. As a result, in the health economic analysis submitted by the manufacturer, numerous comparators were evaluated (see Decision Alternatives section).

Model Structure

The manufacturer submitted a discrete-event simulation microsimulation model.[3] Individual patients were assigned an age, gender, and disease severity at the beginning of the model. With each new treatment, patients were assigned an initial level of response, which determined the benefit from treatment. All individuals, regardless of initial response level, had the same distribution of time to treatment failure. The model calculated the time until the first event (death or treatment failure and transition to new treatment). Individual patients were then simulated over 45 years (representing a lifetime horizon for most simulated patients), accruing costs and quality-of-life utilities. The analysis incorporated a discount rate of 1.5% per annum for costs and benefits. To reduce uncertainty associated with variation between individuals, each simulated individual was processed through each of the alternative treatment sequences. Both deterministic and probabilistic results were provided.[3] For each decision alternative, 50,000 individual patients were simulated in the deterministic analysis (1,000 patients for the probabilistic sensitivity analysis). The average total cost and QALYs were then calculated for each decision alternative. The analysis was conducted from the perspective of the Canadian publicly funded health care system.[3]

Patient Cohort

Two patient cohorts with moderate-to-severe RA, as measured by the Disease Activity Score-28 (i.e., DAS28 3.2 or greater), were considered in separate analyses:

- patients with inadequate response to cDMARDs (cDMARD-IR)
- patients with inadequate response to bDMARDs (bDMARD-IR).

Initial patient characteristics including the proportion of the population that was male versus female, the baseline age and distribution, and baseline Health Assessment Questionnaire–Disability Index (HAQ-DI) score. Distributions were based on data from the modified

intention-to-treat population from the clinical trials: for the cDMARD analysis, this was a weighted average of the BUILD and BEAM trials; for the bDMARD analysis, this was based on the BEACON trial.[3] Scenario analyses for patients with moderate disease (DAS28 between 3.2 and 5.1) and severe disease (DAS28 greater than 5.1) were undertaken.[3]

Decision Alternatives

CADTH requested the manufacturer provide an expanded list of comparators, including at least one representative for each possible class of biologic treatment, that would not duplicate treatments in the follow-up sequence.[3,5] The manufacturer assumed the treatment follow-up sequence was consistent across decision alternatives in each analysis. Palliative care was assumed to be a combination of cDMARDs, including leflunomide (15 mg/day), azathioprine (1 mg/kg/day), and cyclosporine (5 mg/kg/day).[3]

In the cDMARD analysis, the biologic treatment-sequence alternatives considered were:

- Baricitinib 2 mg + MTX → etanercept (ETN) → tocilizumab IV (TCZi) → rituximab (RTX) → Palliative care
- Abatacept IV (ABTi) + MTX → ETN → TCZi → RTX → Palliative care
- Adalimumab (ADA) + MTX → ETN → TCZi → RTX → Palliative care
- Certolizumab (CTZ) + MTX → ETN → TCZi → RTX → Palliative care
- Golimumab (GOL) + MTX → ETN → TCZi → RTX → Palliative care
- Infliximab (IFX) + MTX → ETN → TCZi → RTX → Palliative care
- Sarilumab (SAR) + MTX → ETN → TCZi → RTX → Palliative care
- Tofacitinib (TOF) + MTX → ETN → TCZi → RTX → Palliative care
- “Follow-up sequence”: ETN → TCZi → RTX → Palliative care

In the bDMARD analysis, the biologic treatment-sequence alternatives considered were:

- Baricitinib 2 mg + MTX → RTX → Palliative care
- ABTI + MTX → RTX → Palliative care
- GOL + MTX → RTX → Palliative care
- SAR + MTX → RTX → Palliative care
- TOF + MTX → RTX → Palliative care
- TCZi + MTX → RTX → Palliative care
- “Follow-up sequence”: RTX → Palliative care

Model Inputs: Disease Natural-History Parameters

The manufacturer assumed that age- and gender-specific mortality were increased, based on the randomly selected baseline Health Assessment Questionnaire–Disability Index (HAQ-DI; hereafter referred to as HAQ) scores of each patient. Hazard ratios were

estimated based on a large prospective, longitudinal, observational cohort study using the US National Data Bank for Rheumatic Diseases,[6] which found that changes in HAQ did not affect mortality rate when controlling for baseline HAQ. In the model, mortality is determined exclusively by baseline HAQ and is not influenced by treatment. Therefore, no differences in life-years were expected across the treatment sequences.[3]

Model Inputs: Treatment Effectiveness and Treatment Discontinuation

Clinical response to each line of treatment is based on the proportion of patients within each American College of Rheumatology (ACR) response category. The ACR categories indicate the degree of symptom relief. Specifically, ACR20 indicates at least 20% improvement in tender or swollen joint counts were achieved as well as at least 20% improvement in at least three of the other five criteria (patient assessment, physician assessment, pain scale, disability/functional questionnaire, and acute-phase reactant [C-reactive protein or erythrocyte sedimentation rate]). Effectiveness translates into health benefits exclusively through changes in patient quality of life.

The manufacturer measured health-related quality of life using the HAQ, a disease-specific measure used in RA clinical trials that has shown correlation with the EuroQol 5-Dimensions (EQ-5D) questionnaire. In the base case, the manufacturer's model maps HAQ scores to EQ-5D utilities using a classification-based regression method.[7] Alternative regression approaches with linear and quadradic coefficients for HAQ, developed for two different patient populations, were considered in sensitivity analysis.[3] The differences in the mapping approaches between HAQ and QALY weights were not highlighted by the manufacturer.

After initiating a new treatment, patients were assigned an ACR response category after 24 weeks of treatment. Individuals with less than ACR20 discontinued therapy with no change in their HAQ. Patients with ACR20 or higher were each assigned their own unique HAQ improvement from a beta distribution, with parameters determined by the ACR response level.[3] The average change in HAQ score by ACR response level was derived from a study by Carlson et al.[8] The mean change in HAQ score was a reduction of 1.07 (95% confidence interval [CI], 0.92 to 1.22) for ACR70 responders, a reduction of 0.76 (95% CI, 0.58 to 0.94) for ACR50 responders, and a reduction of 0.44 (95% CI, 0.33 to 0.55) for ACR 20 responders. These levels of HAQ improvement were consistent with the observed levels in the baricitinib clinical trials (BEAM, BUILD, and BEACON).

While on treatment, the manufacturer assumed HAQ gains were maintained. However, when treatment was terminated, the manufacturer's model assumed that the patients returned to their pre-treatment HAQ.[3]

Long-term discontinuation on treatment (after 24 weeks) was estimated based on the distribution of treatment failure times reported in a conference abstract presentation for 598 Canadian patients on bDMARD monotherapy compared with combination therapy with cDMARDs. This study reported a mean time to failure of 4.3 years.[9] Treatment discontinuation rates were the same across ACR response categories; the manufacturer's report noted that this was due to a lack of published Canadian data.[3]

After initiating and ultimately stopping each of the treatments in the treatment sequence, patients transitioned to "Palliative care." The manufacturer assumed class-based HAQ progression after patients progressed to Palliative care, using a latent-class growth mixture modelling approach proposed by Norton et al., which identified four distinct patient subgroups stratified on initial HAQ and progression trajectories.[3,10,11] The manufacturer

estimated the fraction of patients in each of the four trajectory classes based on the observed distribution of patients across the classes in the analysis of Norton et al. Individual patients were then assigned to a class that would ultimately determine their initial HAQ upon beginning Palliative care and HAQ trajectory until death (or the analysis time horizon). In a scenario analysis, the manufacturer considered an alternative approach of increasing HAQ linearly at an average rate of 0.06/year for patients in Palliative care.[3]

Model Inputs: Adverse Events

In the base-case analysis, the manufacturer did not include serious adverse events (SAEs). The manufacturer included SAEs in a sensitivity analysis using observed rates from the BUILD and BEAM clinical trials: 8% per year for baricitinib 2 mg + methotrexate, 4.9% per year for patients on other biologics, and 9.5% per year for patients in Palliative care.[3]

Model Inputs: Costs

The manufacturer incorporated treatment costs based on data from the IQVIA Delta PA database and made assumptions regarding the use of these treatments in Canadian practice (partially informed by market research).[3]

The manufacturer's submission assumes no administrative costs for intravenous injections, stating that those costs would be borne by the manufacturer.[3]

The manufacturer assumed monitoring costs, which were applied evenly to each treatment (Table 15).[3] The frequency of monitoring activities was estimated based on expert opinion, and the unit costs of those activities was estimated based on older versions of the Ontario Schedule of Benefits for Physician Services.[3]

The manufacturer included hospitalization costs, based on specific disease severity, from data from the Alberta Rheumatoid Arthritis Biologics Pharmacosurveillance Program between April 2004 and March 2009.[12] Total health care costs were reported, as well as the fraction of all health care costs that were related to RA and the distribution of costs over sources (hospital, ER, outpatient clinic, and physician) (Table 18).

Deterministic and Probabilistic Analysis

The manufacturer suggested cohorts of 50,000 patients through each decision alternative to ensure stable estimates of total costs and total QALYs in the deterministic analysis. Due to computational limits, cohorts of only 1,000 individuals for each decision alternative were run for each of 1,000 probabilistic drawn-input sets for the probabilistic analysis.

Manufacturer's Base Case

The results of the deterministic and probabilistic analysis were extremely similar. Therefore, aside from discussing the cost-effectiveness acceptability analysis, data presented in the text are from the deterministic analysis.

Conventional Disease-Modifying Antirheumatic Drug Analysis

The manufacturer's base-case analysis identified that the "follow-up" treatment sequence (ETN → TCZi → RTX → Palliative care) cost the least (expected lifetime discounted cost of $412,266) and provided the fewest QALYs (expected lifetime discounted QALYs of 12.40). In both the deterministic and probabilistic analysis, the baricitinib 2 mg + methotrexate

sequence was not on the efficient frontier (Table 19). Specifically, it was dominated by a linear combination of the sequence beginning with TOF and the follow-up sequence alone. However, as illustrated on the cost-effectiveness plane (Figure 1), it was extremely close to the frontier.

The treatment-sequence strategy, beginning with the TOF sequence, was on the efficient frontier at an incremental cost-utility ratio (ICUR) of $33,058 per QALY gained, compared with the "follow-up" treatment sequence alone. The next treatment sequence on the efficient frontier began with the SAR sequence, with an ICUR of $48,161 per QALY gained, compared with the sequence beginning with TOF.

Biologic Disease-Modifying Antirheumatic Drug Analysis

The manufacturer's extended base-case analysis identified that the "follow-up" treatment sequence (RTX → Palliative care) cost the least (expected lifetime discounted cost of $256,549) and provided the fewest QALYs (expected lifetime discounted QALYs of 7.711). In both the deterministic and the probabilistic analysis, the alternative treatment beginning with baricitinib (baricitinib 2 mg + methotrexate → RTX → Palliative care) was not on the efficient frontier. The strategy beginning with tocilizumab IV (TCZi → RTX → Palliative care) was on the efficient frontier (

Figure 2). Compared with the follow-up treatment sequence alone (RTX → Palliative care), the strategy beginning with TCZi increased costs by $49,482 and increased QALYs by 1.49, resulting in an ICUR of $33,219 per QALY gained (Table 20).

Summary of Manufacturer's Sensitivity Analysis

The manufacturer's report presented deterministic sensitivity analysis of quality-of-life assumptions for the mapping of HAQ to EQ-5D and HAQ progression while in Palliative care, discount rate, analysis time horizon, initial treatment response rate, patient baseline disease severity, societal perspective, therapy discontinuation rules (discontinue therapy for ≥ ACR 50), and inclusion of SAEs.

These analyses suggested that the results of the cDMARD analysis were robust, as there were few changes in the cost-efficiency frontier based on the sensitivity analyses. However, as several alternatives were very close in terms of total costs and total QALYs, it is reasonable to assume that the results may be sensitive to the uncertainty in several key input parameters alone and in combinations of parameters that were likely to vary together. The results for the bDMARD analysis differed between the probabilistic base case and the deterministic analysis. Thus, the bDMARD analysis may be associated with greater uncertainty.

Limitations of the Manufacturer's Submission

There were several limitations to the manufacturer's analysis:

- **The manufacturer's submission presented analysis of heterogeneous patient populations**. The manufacturer's analysis selected patients based on the age and disease severity distribution represented in the intention-to-treat analysis of the clinical trials. While they presented some sensitivity analysis of disease severity by stratifying the cohorts of DAS28 3.2 to 5.1 (moderate disease) and DAS28 greater than 5.1 (severe disease), the modelled cohorts remained highly heterogeneous, with wide and highly

overlapping ranges of baseline HAQ scores (i.e., HAQ does not appear to be well correlated with DAS28). Patient groups that are identifiably different at treatment initiation (age, gender, other features of medical history) should be separated for the purposes of health economic analysis.

- **The manufacturer's submission included SAEs only in sensitivity analysis**. SAEs increase costs and decrease QALYs and so should be included in health economic analyses.
- **Costs of treatment monitoring were not estimated accurately, and costs of treatment administration for several treatments were potentially underestimated**. Treatment monitoring costs were informed by older versions of the Ontario Schedule of Benefits for Physician Services, and, in some cases, the unit costs have changed substantially (Table 17). Because the biochemical profile was not fully described, CADTH was unable to calculate up-to-date treatment monitoring costs using current unit costs. The manufacturer's submission indicated that treatment administration costs would be borne by the manufacturer, and the acceptability of this assumption was confirmed by CADTH clinical experts. Clinical experts noted that some patients receive infusions at publicly funded outpatient clinics, so administration costs were included in a CADTH sensitivity analysis. CADTH estimated the hourly cost of infusion based on information from Canadian sources,[13] inflated to 2018 Canadian dollars. Treatments received by infusion have annual administration costs, which were assigned as follows: abatacept (0.5 hours per infusion, $787), infliximab (2 hours per infusion, $1,694), rituximab (2.5 hours per infusion, $1,614), and tocilizumab (1 hour per infusion, $1,573).
- **Cost assumptions for comparators were not appropriate.** The manufacturer assumed 95% of the treatment costs for IFX and for ETN were attributed to the branded product and 5% to the biosimilar product. The use of a blended comparator is not typically appropriate; thus, CADTH undertook reanalyses assuming 100% of patients received biosimilar IFX and biosimilar ETN. Additionally, the manufacturer assumed distributions for drug costs. This assumption is not appropriate for treatments with set doses but was considered reasonable for treatments for which the dose could differ based on patient weight or treatment response. The assumption of 10% variance may not be appropriate, but CADTH could not assess the expected distribution based on the recommended dosage of these products.
- **Outpatient care costs appeared to have been underestimated**. The manufacturer's analysis estimated disease-severity-specific hospital, emergency department, and physician costs from a Canadian study by Ohinmaa et al.[12] However, it excluded outpatient costs, which were also reported by this study. The exclusion of outpatient costs was not explained in the manufacturer's report. There may have been concern about double-counting monitoring costs, which were nominally similar to the total annual outpatient costs (manufacturer-estimated annual costs of monitoring: $1,507; annual outpatient costs reported in Ohinmaa et al. ranged from $1,070 to $2,162 [converted to 2018 C$], depending on disease severity). However, the majority (approximately two-thirds) of outpatient costs reported in Ohinmaa et al. were for non-RA diagnoses. The average non-RA outpatient costs of patients on biologics was $807 (converted to 2018 C$). Because it was unclear why the manufacturer excluded these costs and Ohinmaa et al. did not describe the nature of the RA and non-RA outpatient costs, higher outpatient costs (up to 100% of the RA and non-RA outpatient costs described in Ohinmaa et al.) were included in a CADTH reanalysis sensitivity analysis.

- **The manufacturer's analysis contained costs presented in inconsistent constant dollar years**. The manufacturer's report indicated inflation-adjusting to either 2016 and 2018 constant dollars in different places. In the model submitted by the manufacturer, costs other than drug costs were inflation-adjusted to 2016 constant dollars. However, drug costs were presented in 2018 dollars. CADTH tested 2018 dollars, which did not impact the results.

- **The manufacturer's submitted model contained structural constraints limiting the assessment of uncertainty in some assumptions and parameters**. Clinical experts consulted by CADTH indicated that disease management through treatment may reduce mortality, treatment response levels may correlate with disease severity at treatment initiation, and treatment response level may influence time to treatment failure. The costing study by Ohinmaa et al.[12] also indicated that patients who failed one biologic agent and switched to another had annual health care expenses approximately 50% greater than those who sustained a response to treatment (Table 16). This suggests that patients with more severe disease were more likely to switch therapy, consistent with experience described by the CADTH clinical experts. The manufacturer's model did not permit exploration of different responses for patients according to initial disease severity.

- **The manufacturer's submission was unnecessarily complex, and the programming lacked transparency**.

    - The model initially submitted did not accommodate evaluation of additional treatment sequences, as described in the report for the bDMARD scenario, and contained errors in the parameters affecting the HAQ improvement from treatment for the cDMARD scenario.

    - The model provided contained several hidden sheets, many hidden rows and columns containing inputs and assumptions, few labels identifying assumptions, and several inefficient and difficult-to-evaluate layout choices. Selected examples include the following: the indexing (order in which treatments appear on the input sheet) of treatment alternatives was changed between the cDMARD and bDMARD scenarios, which decreased model transparency; the CEplane sheet appeared to contain errors; the "CODA norm probit" and related sheets each contained 1,000 unlabelled columns of output from the NMA; the "Latent-class" sheet contained unnecessary and unused columns of calculations and a row of unlabelled hardcoded numbers across the top of each class group; and some model inputs were overwritten by hardcoded values in the VBA code and not controlled by the apparent input cells in the workbook (e.g., number of patients per arm).

    - Programmed subroutines were extremely lengthy, containing redundant lines of code, repeating lines of code that could have been made separate subroutines, and used many inefficient coding approaches when simpler approaches were readily available. The main code to simulate a patient, for example, contained three different strategies for converting HAQ to QALYs, two different approaches for modelling long-term HAQ after the patient progressed to Palliative care, and two completely different coding approaches to include SAEs. Each of these selections between methods was repeated multiple times within the code, when it could have more efficiently and more cautiously been its own subroutine. The code for accruing costs and benefits calculated a (poorly named) variable *tmp* for the discount factor to avoid repeating calculations and used it for calculations related to productivity loss, but then did not use this discount factor variable for other costs, life-years, and QALYs instead writing

out the discount factor equation in each line. Overall, the code provided was poorly organized, difficult to review, difficult to debug, and poorly commented. This inefficient programming resulted in longer simulation run times than might otherwise have been expected.

Other areas of uncertainty identified by CADTH:

- **The manufacturer's analysis considers a limited set of all possible treatment sequences**. When evaluating the economic value of a health care technology, it is important to understand its value in terms of incremental costs and benefits compared with all available alternatives. More treatment sequences were possible than incorporated in the initially submitted model, specifically in the order of the follow-up regimen; however, the expanded set of treatment alternatives submitted by the manufacturer upon request included options from all treatment classes and all representatives within each class that were included in the manufacturer's network meta-analysis of treatment efficacy. Using the same follow-up sequence for all comparisons helps to minimize confounding for the comparisons included in the final submission. However, due to the limited set of treatment sequences considered, the analysis does not identify the optimal sequence of treatments or the optimal position in the care continuum for baricitinib 2 mg + methotrexate.

- **The manufacturer's submitted model did not consider the potential increasing age-specific health care costs or decreasing QALYs by age**. The manufacturer's model included HAQ-specific health care costs and QALYs, but Canadian health care costs increase with age, and quality-of-life decreases with age, due to increasing rates of other (non-RA) comorbidities. Generally, the inclusion of age-specific health care costs is most important when there is an increase in life expectancy, which is not the case in this analysis. Omitting age-specific QALY declines may result in overestimating the benefits of treatment, because the gains from treatment are often limited by the presence of concomitant illness and morbidities. The model structure did not allow for inclusion of these features in the CADTH base case, so the effect of these omissions could not be assessed.

CADTH Common Drug Review Reanalysis

The CADTH reanalysis focused on patient characteristics, including patient age and HAQ score. Specifically, the CADTH base case included SAEs and assumed the cost of biosimilars for both IFX and ETN. While the intent was to run the reanalyses probabilistically, CADTH noted that there were several limitations with the information available for the probabilistic analyses. Additionally, CADTH analysis considered patient cohorts at ages 30, 50, and 70 years, and at initial HAQ scores of 0.5, 1.0, 1.5, 2.0, and 2.5.

CADTH also repeated many of the deterministic sensitivity analyses performed by the manufacturer to gain insight into how these assumptions affected the cost-effectiveness of the various treatment-sequence alternatives.

Inadequate Response to Conventional Disease-Modifying Antirheumatic Drug Population

- At the base-case price of $47.92 per 2 mg vial (annual cost of $17,490), the baricitinib 2 mg + methotrexate sequence is not on the efficient frontier for patients at any age or at any initial disease severity (Table 2).

- CADTH conducted price-reduction analyses on the manufacturer's cohort and on the CADTH base case. Based on the CADTH base case, the baricitinib 2 mg + methotrexate sequence moved onto the efficient frontier when the price was reduced by approximately 35% (Table 4) and required a price reduction of more than 40% to achieve an ICUR below $50,000 per QALY compared with the most efficient alternative. Based on the manufacturer's mixed age and disease-severity patient cohort, a price reduction of less than 5% was required for the baricitinib 2 mg + methotrexate sequence to achieve an ICUR of $50,000 per QALY compared with the most efficient strategy (follow-up regimen). A price reduction of 50% resulted in the baricitinib 2 mg + methotrexate sequence becoming the lowest-cost alternative (dominant).
- Findings of the analysis were robust to patient gender, discount rate, addition of administration costs, inflation-adjustment of all costs in the model to 2018$, and inclusion of societal costs.

Subgroup analyses found that:

- In both younger and older patients, the baricitinib 2 mg + methotrexate sequence is dominated by a linear combination of the sequence beginning with TOF and the follow-up sequence alone (Table 3).
- Holding patient age at treatment initiation constant, treatments on the efficient frontier have higher ICURs in patients with lower disease severity and lower ICURs in patients with higher disease severity (Table 3). For patients at ages 50 and 70 years, no treatments were on the efficient frontier with an ICUR less than $50,000 per QALY gained.
- Holding disease severity at treatment initiation constant, patient age does not have a substantial impact on the ICUR of treatments on the efficient frontier (Table 17).
- If other treatment alternatives are not considered, and the baricitinib 2 mg + methotrexate sequence is compared with the follow-up treatment sequence only, the observed trends affecting treatments on the efficient frontier also affect the direct comparison of the baricitinib 2 mg + methotrexate sequence with the "follow-up" sequence alone (Table 25). Most significantly, the ICUR is higher for patients with lower disease severity and lowest for patients with greater disease severity.

Table 2: CADTH Base-Case Analysis for the Conventional Disease-Modifying Antirheumatic Drug Population

Scenario	Total Cost ($)	Total QALY	Incremental Cost ($)	Incremental QALY	ICER ($)
IFX → ETN → TCZi → RTX → Palliative care	372,831	14.673	–	–	–
ETN → TCZi → RTX → Palliative care	387,262	14.108	14,431	–0.565	Dominated
BAR 2 mg → ETN → TCZi → RTX → Palliative care	427,272	14.770	54,441	0.096	Extended dominance
TOF → ETN → TCZi → RTX → Palliative care	429,286	14.847	56,455	0.173	Extended dominance
GOL → ETN → TCZi → RTX → Palliative care	429,350	14.683	56,518	0.010	Dominated
CTZ → ETN → TCZi → RTX → Palliative care	431,667	14.873	58,836	0.200	Extended dominance
ABTI → ETN → TCZi → RTX → Palliative care	441,498	14.702	68,667	0.028	Dominated
ADA → ETN → TCZi → RTX → Palliative care	445,941	14.759	73,110	0.086	Dominated
SAR → ETN → TCZi → RTX → Palliative care	449,170	15.132	76,338	0.459	166,445

ABTI = abatacept IV; ADA = adalimumab; BAR = baricitinib; CTZ = certolizumab; ETN = etanercept; GOL = golimumab; ICER = incremental cost-effectiveness ratio; IFX = infliximab; QALY = quality-adjusted life-years; RTX = rituximab; SAR = sarilumab; TCZi = tocilizumab IV; TOF = tofacitinib.

Note: Dominated strategy means the strategy is more costly and results in fewer QALYs than at least one other strategy; extended dominance means strategy is more costly and provides fewer QALYs than a linear combination of two other strategies. Detail presented for an example cohort of 50-year-olds, 79% female, with initial HAQ = 1.5. All initial treatment are in addition to methotrexate. Results are presented deterministically, as there were errors identified with the manufacturer's probabilistic analysis.

Table 3: Summary of CADTH Analyses for cDMARD Population — Alternative Baseline Age and HAQ Scores (Results Presented as Sequential ICURs)

Cohort	Follow-Up[a]	IFX→ Follow-Up[a]	GOL→ Follow-Up[a]	ABTi→ Follow-Up[a]	ADA→ Follow-Up[a]	BAR 2 mg → Follow-Up[a]	TOF→ Follow-Up[a]	CTZ→ Follow-Up[a]	SAR→ Follow-Up[a]
30 years, HAQ = 0.5	Ref.	Ext. dom.	Dominated	Dominated	Dominated	Ext. dom.	69,871	62,751	121,774
30 years, HAQ = 1.0	Ref.	Ext. dom.	Dominated	Dominated	Dominated	Ext. dom.	46,327	Ext. dom.	64,029
30 years, HAQ = 1.5	Ref.	Ext. dom.	Dominated	Dominated	Dominated	Ext. dom.	29,084	36,878	45,933
30 years, HAQ = 2.0	Ref.	Dominated	Dominated	Dominated	Dominated	Dominated	Ext. dom.	14,538	28,667
30 years, HAQ = 2.5	Ref.	Dominated	Dominated	Dominated	Dominated	Dominated	12,741	Ext. dom.	20,859
50 years, HAQ = 0.5	Dominated	Ref.	Dominated	Dominated	Dominated	Ext. dom.	Ext. dom.	Ext. dom.	337,817

Cohort	Follow-Up[a]	IFX→ Follow-Up[a]	GOL→ Follow-Up[a]	ABTi→ Follow-Up[a]	ADA→ Follow-Up[a]	BAR 2 mg → Follow-Up[a]	TOF→ Follow-Up[a]	CTZ→ Follow-Up[a]	SAR→ Follow-Up[a]
50 years, HAQ = 1.0	Dominated	Ref.	Dominated	Dominated	Dominated	Ext. dom.	Ext. dom.	Ext. dom.	187,167
50 years, HAQ = 1.5	Dominated	Ref.	Dominated	Dominated	Dominated	Ext. dom.	Ext. dom.	Ext. dom.	166,445
50 years, HAQ = 2.0	Dominated	Ref.	Dominated	Dominated	Dominated	Ext. dom.	Ext. dom.	Ext. dom.	129,986
50 years, HAQ = 2.5	Dominated	Ref.	Dominated	Dominated	Dominated	Ext. dom.	Ext. dom.	Ext. dom.	108,513
70 years, HAQ = 0.5	Dominated	Ref.	Dominated	Dominated	Dominated	Ext. dom.	Ext. dom.	Ext. dom.	365,813
70 years, HAQ = 1.0	Dominated	Ref.	Dominated	Dominated	Dominated	Ext. dom.	Ext. dom.	Ext. dom.	192,330
70 years, HAQ = 1.5	Dominated	Ref.	Dominated	Dominated	Dominated	Ext. dom.	Ext. dom.	Ext. dom.	177,369
70 years, HAQ = 2.0	Dominated	Ref.	Dominated	Dominated	Dominated	Ext. dom.	Ext. dom.	Ext. dom.	150,475
70 years, HAQ = 2.5	Dominated	Ref.	Dominated	Dominated	Dominated	Dominated	Ext. dom.	Ext. dom.	109,438

ABTi = abatacept IV; ADA = adalimumab; BAR = baricitinib; cDMARD = conventional disease-modifying antirheumatic drug; CTZ = certolizumab; Ext. dom. = extended dominance; GOL = golimumab; HAQ = Health Assessment Questionnaire; ICUR = incremental cost-utility ratio; IFX = infliximab; Ref. = reference strategy; SAR = sarilumab; TOF = tofacitinib.

Note: Dominated strategy means strategy is more costly and results in fewer QALYs than at least one other strategy; Ext. dom. (extended dominance) means strategy is more costly and provides fewer QALYs than a linear combination of two other strategies; Ref. (reference strategy) means lowest-cost alternative. Results are presented deterministically as there were errors identified with the manufacturer's probabilistic analysis. All initial treatment are in addition to methotrexate. The order of treatment headings in the sequential analysis is based on the reference case. The order may change based on different analyses.

[a] Follow-up is defined as ETN→TCZi→RTX→Palliative care.

Table 4: CADTH Base-Case Analysis for cDMARD Population — Incremental Cost-Utility Ratios for Strategies on the Efficient Frontier Varying the Cohort Age and Disease Severity

Cohort	Follow-Up[a]	BAR 2 mg → Follow-Up[a]	TOF→ Follow-Up[a]	IFX→ Follow-Up[a]	CTZ→ Follow-Up[a]	GOL→ Follow-Up[a]	SAR→ Follow-Up[a]	ABTi→ Follow-Up[a]	ADA→ Follow-Up[a]
Manufacturer's base-case analysis									
100%	Ref.	Ext. dom.	$33,036	Dominated	Ext. dom.	Dominated	$48,085	Dominated	Dominated
95%	Ref.	$24,151	Ext. dom.	Dominated	Ext. dom.	Dominated	$61,969	Dominated	Dominated
90%	Ref.	$13,707	Ext. dom.	Dominated	Ext. dom.	Dominated	$81,106	Dominated	Dominated
85%	Ref.	$3,263	Ext. dom.	Dominated	Ext. dom.	Dominated	$100,244	Dominated	Dominated
80%	Dominated	Ref.	Ext. dom.	Dominated	Ext. dom.	Dominated	$119,382	Dominated	Dominated
Cohort	**Follow-Up[a]**	**IFX→ Follow-Up[a]**	**BAR 2 mg → Follow-Up[a]**	**TOF→ Follow-Up[a]**	**GOL→ Follow-Up[a]**	**CTZ→ Follow-Up[a]**	**ABTi→ Follow-Up[a]**	**ADA→ Follow-Up[a]**	**SAR→ Follow-Up[a]**
CADTH reanalysis (example cohort: 50-year-olds, 79% female, initial HAQ = 1.5)									
100%	Dominated	Ref.	Ext. dom.	Ext. dom.	Dominated	Ext. dom.	Dominated	Dominated	$166,445
90%	Dominated	Ref.	Ext. dom.	Ext. dom.	Dominated	Ext. dom.	Dominated	Dominated	$166,445
80%	Dominated	Ref.	Ext. dom.	Ext. dom.	Dominated	Ext. dom.	Dominated	Dominated	$166,445
70%	Dominated	Ref.	Ext. dom.	Ext. dom.	Dominated	Ext. dom.	Dominated	Dominated	$166,445
60%	Dominated	Ref.	$68,787	Ext. dom.	Dominated	Ext. dom.	Dominated	Dominated	$192,333
50%	Dominated	Dominated	Ref.	Ext. dom.	Dominated	Ext. dom.	Dominated	Dominated	$225,316

ABTi = abatacept IV; ADA = adalimumab; BAR = baricitinib; cDMARD = conventional disease-modifying antirheumatic drug; CTZ = certolizumab; Ext. dom. = extended dominance; GOL = golimumab; HAQ = Health Assessment Questionnaire; IFX = infliximab; Ref. = reference strategy; SAR = sarilumab; TOF = tofacitinib.

Note: Dominated strategy means strategy is more costly and results in fewer QALYs than at least one other strategy; Ext. dom. (extended dominance) means strategy is more costly and provides fewer QALYs than a linear combination of two other strategies; Ref. (reference strategy) means lowest-cost alternative. Results are presented deterministically as there were errors identified with the manufacturer's probabilistic analysis. All initial treatment are in addition to methotrexate. The order of treatment headings in the sequential analysis is based on the reference case. The order may change based on different analyses.

[a] Follow-up is defined as ETN→TCZi→RTX→Palliative care.

Inadequate Response to Biologic Disease-Modifying Antirheumatic Drug Population

- At the base-case price of $47.92 per 2 mg vial (annual cost of $17,490), the baricitinib 2 mg + methotrexate sequence is not on the efficient frontier for patients at any age or initial disease severity (Table 5).
- CADTH conducted price-reduction analyses on the manufacturer's cohort and on the CADTH base case. Based on the CADTH base case, the baricitinib 2 mg + methotrexate sequence moved onto the efficient frontier when the price was reduced by approximately 15% (Table 7). Based on the manufacturer's mixed age and disease-severity patient cohort, a price reduction of less than 5% was required for baricitinib to achieve an ICUR of $50,000 per QALY compared with the most efficient strategy (follow-up regimen). A price reduction of 60% resulted in the baricitinib 2 mg + methotrexate sequence becoming the lowest-cost alternative (dominant).

- Findings of the analysis were robust to patient gender, discount rate, addition of administration costs, inflation-adjustment of all costs in the model to 2018$, and inclusion of societal costs.

Subgroup analyses found that:

- In both younger and older patients, the baricitinib 2 mg + methotrexate sequence is dominated by a linear combination of the sequence, beginning with TOF and the follow-up sequence alone (Table 3).
- Holding patient age at treatment initiation constant, treatments on the efficient frontier have higher ICURs in patients with lower disease severity and lower ICURs in patients with higher disease severity (Table 6).
- Holding disease severity at treatment initiation constant, patient age does not have a substantial impact on the ICUR of treatments on the efficient frontier (Table 17).

Table 5: CADTH Base-Case Analysis for the Biologic Disease-Modifying Antirheumatic Drug Population

Scenario	Total Cost	Total QALY	Incremental Cost	Incremental QALY	ICER
RTX → Palliative care	$295,257	10.849	–	–	–
BAR 2 mg + MTX → RTX → Palliative care	$329,471	11.590	$34,214	0.741	Ext. dom.
GOL → RTX → Palliative care	$336,348	11.674	$41,092	0.825	Ext. dom.
SAR → RTX → Palliative care	$339,988	11.812	$44,731	0.963	Ext. dom.
TOF → RTX → Palliative care	$344,941	11.997	$49,684	1.148	Ext. dom.
ABTi → RTX → Palliative care	$354,421	11.970	$59,164	1.121	Dominated
TCZi → RTX → Palliative care	$358,068	12.536	$62,811	1.687	$37,226

ABTi = abatacept IV; BAR = baricitinib; Ext. dom. = extended dominance; GOL = golimumab; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; RTX = rituximab; SAR = sarilumab; TCZi = tocilizumab IV; TOF = tofacitinib.

Note: Dominated strategy means strategy is more costly and results in fewer QALYs than at least one other strategy; Ext. dom. (extended dominance) means strategy is more costly and provides fewer QALYs than a linear combination of two other strategies. Results are presented deterministically as there were errors identified with the manufacturer's probabilistic analysis. All initial treatment are in addition to methotrexate. Cohort of 50-year-olds, 82% female, with initial HAQ = 1.5.

Table 6: CADTH Base-Case Analysis for bDMARD Population — Incremental Cost-Utility Ratios for Strategies on the Efficient Frontier Varying the Cohort Age and Disease Severity

Price (As a % of Base Case)	Follow-Up[a]	BAR 2 mg → Follow-Up	GOL→ Follow-Up	SAR→ Follow-Up	TOF→ Follow-Up	ABTi→ Follow-Up	TCZi→ Follow-Up
30 years, HAQ = 0.5	Ref.	Ext. dom.	Ext. dom.	Ext. dom.	Ext. dom.	Dominated	80,334
30 years, HAQ = 1.0	Ref.	Ext. dom.	Ext. dom.	Ext. dom.	Ext. dom.	Dominated	56,921
30 years, HAQ = 1.5	Ref.	Ext. dom.	Ext. dom.	Ext. dom.	Ext. dom.	Dominated	35,879
30 years, HAQ = 2.0	Ref.	Ext. dom.	Ext. dom.	Ext. dom.	Ext. dom.	Dominated	18,776
30 years, HAQ = 2.5	Ref.	Ext. dom.	Ext. dom.	Ext. dom.	Ext. dom.	Dominated	21,123
50 years, HAQ = 0.5	Ref.	Ext. dom.	Ext. dom.	Ext. dom.	Ext. dom.	Dominated	82,264
50 years, HAQ = 1.0	Ref.	Ext. dom.	Ext. dom.	Ext. dom.	Ext. dom.	Dominated	58,556
50 years, HAQ = 1.5	Ref.	Ext. dom.	Ext. dom.	Ext. dom.	Ext. dom.	Dominated	37,333
50 years, HAQ = 2.0	Ref.	Ext. dom.	Ext. dom.	Ext. dom.	Ext. dom.	Dominated	19,573
50 years, HAQ = 2.5	Ref.	Ext. dom.	Ext. dom.	Ext. dom.	Ext. dom.	Dominated	21,632

Price (As a % of Base Case)	Follow-Up[a]	BAR 2 mg → Follow-Up	GOL→ Follow-Up	SAR→ Follow-Up	TOF→ Follow-Up	ABTi→ Follow-Up	TCZi→ Follow-Up
70 years, HAQ = 0.5	Ref.	Ext. dom.	Ext. dom.	Ext. dom.	Ext. dom.	Dominated	86,209
70 years, HAQ = 1.0	Ref.	Ext. dom.	Ext. dom.	Ext. dom.	Ext. dom.	Dominated	60,545
70 years, HAQ = 1.5	Ref.	Ext. dom.	Ext. dom.	Ext. dom.	Ext. dom.	Dominated	41,004
70 years, HAQ = 2.0	Ref.	Ext. dom.	Ext. dom.	Ext. dom.	Ext. dom.	Dominated	23,029
70 years, HAQ = 2.5	Ref.	Ext. dom.	Ext. dom.	Ext. dom.	Ext. dom.	Dominated	25,213

ABTi = abatacept IV; BAR = baricitinib; Ext. dom. = extended dominance; HAQ = Health Assessment Questionnaire; MTX = methotrexate; GOL = golimumab; Ref. = reference strategy; SAR = sarilumab; TCZi = tocilizumab IV; TOF = tofacitinib.

Note: Results are presented deterministically, as there were errors identified with the manufacturer's probabilistic analysis. All initial treatment are in addition to methotrexate. The order of treatment headings in the sequential analysis is based on the reference case. The order may change based on different analyses. Dominated strategy means strategy is more costly and results in fewer QALYs than at least one other strategy; Ext. dom. (extended dominance) means strategy is more costly and provides fewer QALYs than a linear combination of two other strategies; Ref. (reference strategy) means the lowest-cost alternative.

[a] Follow-up: ETN→TCZi→RTX→Palliative care.

Table 7: CADTH Analysis for bDMARD Population — Incremental Cost-Utility Ratios for Strategies on the Efficient Frontier Varying the Price of Baricitinib

Price (As a % of Base Case)	Follow-Up[a]	BAR 2 mg → Follow-Up	GOL→ Follow-Up	SAR→ Follow-Up	TOF→ Follow-Up	ABTi→ Follow-Up	TCZi→ Follow-Up
Manufacturer's submission base-case population							
100	Ref.	Ext. dom.	Ext. dom.	Ext. dom.	Ext. dom.	Ext. dom.	$33,229
90	Ref.	Ext. dom.	Ext. dom.	Ext. dom.	Ext. dom.	Ext. dom.	$33,229
85	Ref.	$31,315	Ext. dom.	Ext. dom.	Ext. dom.	Ext. dom.	$34,848
80	Ref.	$27,608	Ext. dom.	Ext. dom.	Ext. dom.	Ext. dom.	$37,982
75	Ref.	$23,901	Ext. dom.	Ext. dom.	Ext. dom.	Ext. dom.	$41,117
70	Ref.	$20,194	Ext. dom.	Ext. dom.	Ext. dom.	Ext. dom.	$44,251
60	Ref.	$12,779	Ext. dom.	Ext. dom.	Ext. dom.	Ext. dom.	$50,520
50	Ref.	$5,365	Ext. dom.	Ext. dom.	Ext. dom.	Ext. dom.	$56,789
CADTH reanalysis (example cohort: 50-year-olds, 82% female, initial HAQ = 1.5)							
100	Ref.	Ext. dom.	Ext. dom.	Ext. dom.	Ext. dom.	Dominated	$37,333
90	Ref.	Ext. dom.	Ext. dom.	Ext. dom.	Ext. dom.	Dominated	$37,333
85	Ref.	$34,980	Ext. dom.	Ext. dom.	Ext. dom.	Ext. dom.	$39,176
80	Ref.	$30,949	Ext. dom.	Ext. dom.	Ext. dom.	Ext. dom.	$42,333
70	Ref.	$22,888	Ext. dom.	Ext. dom.	Ext. dom.	Ext. dom.	$48,647
60	Ref.	$14,827	Ext. dom.	Ext. dom.	Ext. dom.	Ext. dom.	$54,961
50	Ref.	$6,765	Ext. dom.	Ext. dom.	Ext. dom.	Ext. dom.	$61,275
40	Dominated	Ref.	Ext. dom.	Ext. dom.	Ext. dom.	Ext. dom.	$67,589

ABTi = abatacept IV; BAR = baricitinib; bDMARD = biologic disease-modifying antirheumatic drug; Ext. dom. = extended dominance; GOL = golimumab; Ref. = reference strategy; SAR = sarilumab; TCZi = tocilizumab IV; TOF = tofacitinib.

Note: Dominated strategy means strategy is more costly and results in fewer QALYs than at least one other strategy; Ext. dom. (extended dominance) means strategy is more costly and provides fewer QALYs than a linear combination of two other strategies; Ref. (reference strategy) means the lowest-cost alternative. All initial treatment are in addition to methotrexate.

[a] Follow-up: ETN→TCZi→RTX→Palliative care.

Issues for Consideration

International jurisdictions have recommended a 4 mg tablet of baricitinib, which is not currently available in Canada and has not been assessed in this review.

CADTH reviewed tofacitinib, another JAK inhibitor available in Canada for patients with moderately to severely active RA, in 2015. The CADTH Canadian Drug Expert Committee (CDEC) recommended that tofacitinib be reimbursed with the condition that the "drug plan cost for tofacitinib not to exceed the drug plan costs for the biologic DMARDs reimbursed."[14] More recently, CADTH reviewed tofacitinib for ulcerative colitis, and CDEC recommended the drug plan cost of treatment of ulcerative colitis with tofacitinib not exceed the drug plan costs of treatment of ulcerative colitis with the least costly biologic DMARD.[15]

CADTH reviewed sarilumab for patients with moderately to severely active RA in 2017. CDEC recommended that tofacitinib be reimbursed with the condition that the "drug plan cost for sarilumab not to exceed the drug plan cost of treatment with the least costly alternative biologic."[16] Although sarilumab was not reimbursed by any provinces as of April 1, 2019, the pan-Canadian Pharmaceutical Alliance recently completed negotiations on sarilumab.[17]

Patient Input

Three patient groups provided input: The Arthritis Society, Canadian Arthritis Patient Alliance, and Arthritis Consumer Experts. These patient groups reported that people living with RA reported that the following symptoms have the most negative impact on quality of life: joint stiffness and swelling, joint pain, limitation of mobility, and ongoing fatigue. These factors are captured in the HAQ and ACR scales that were incorporated in the manufacturer's model.

The patient groups also highlighted that RA can significantly restrict patients' ability to perform daily activities; simple tasks most people take for granted can take some patients a long time and much effort or pain to complete. The manufacturer presented an analysis from the societal perspective; the results of this analysis were aligned with the results from the payer perspective for both patient populations.

Conclusions

CADTH reanalyses results were generally consistent with the manufacturer's analysis. CADTH analyses identified that, for both cDMARD-IR and bDMARD-IR cohorts of patients with moderate-to-severe RA, baricitinib is dominated (i.e., costs more and provides less QALYs than comparators) or extendedly dominated.

Price reductions can improve the cost-efficiency and the cost-effectiveness of baricitinib in patients with moderate disease who are 50 years of age:

- For patients with inadequate response to cDMARDs, a price reduction of 35% results in an ICUR of $130,998 per QALY gained for baricitinib compared with the most efficient treatment strategy. A price reduction of more than 40% is required for baricitinib to achieve an ICUR below $50,000 per QALY compared with the most efficient treatment strategy.

- For patients with inadequate response to bDMARDs, a price reduction of 15% results in an ICUR of $34,890 per QALY gained for baricitinib compared with the most efficient treatment strategy.

While there may be numerical differences between baricitinib and other bDMARDs for some ACR and EULAR response outcomes, the clinical review concluded that based on the results of the manufacturer NMA and other published NMAs, it is likely that the clinical effects associated with baricitinib are similar to existing biologic DMARDs.

Appendix 1: Cost Comparison

The comparators presented in Table 8 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 manufacturer's 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 8: CADTH Cost Comparison Table for Janus Kinase Inhibitors and Biologic Treatments for Rheumatoid Arthritis in Adults

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dosage	Average Annual Drug Cost ($)
Janus Kinase Inhibitors					
Baricitinib (Olumiant)	**2 mg**	**Tablet**	**47.9176[a]**	**2 mg daily**	**17,490**
Tofacitinib (Xeljanz)	5 mg	Tablet	23.9588	5 mg twice daily	17,490
Biologics					
Abatacept SC (Orencia)	125 mg/mL	Pre-filled syringe	373.7881	125 mg weekly[b]	19,437
Abatacept IV (Orencia)	250 mg/15 mL	Vial	500.3411	Patients < 60 kg: 500 mg Patients 60 to 100 kg: 750 mg Patients > 100 kg: 1,000 mg 500 to 1,000 mg at weeks 0, 2, and 4 then every 4 weeks	Year 1: 21,014 Thereafter: 19,567
Adalimumab SC (Humira)	40 mg/0.8 mL	Pre-filled syringe or pen	769.9700	40 mg every other week	20,074
Anakinra (Kineret)	100 mg	Pre-filled syringe	49.6990	100 mg daily	18,140
Certolizumab pegol (Cimzia)	200 mg/mL	Pre-filled syringe	664.5100	400 mg at weeks 0, 2, and 4 then 200 mg every 2 weeks	Year 1: 19,271 Thereafter: 17,325
Etanercept (Enbrel)	25 mg	Vial	202.9300	50 mg weekly or two 25 mg doses on same day every week or every 3 or 4 days	21,163
	50 mg/mL	Pre-filled syringe or auto-injector	405.9850		21,169
Etanercept (Brenzys)	50 mg/mL	Pre-filled syringe	255.0000	50 mg weekly	13,296
Etanercept (Erelzi)	25 mg	Vial	127.5000	50 mg weekly or two 25 mg doses on same day every week or every 3 or 4 days	13,296
	50 mg/mL	Pre-filled syringe or auto-injector	255.0000		13,296

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dosage	Average Annual Drug Cost ($)
Golimumab SC (Simponi)	50 mg/0.5 mL	Pre-filled syringe or auto-injector	1,555.1700	50 mg monthly	18,662
Golimumab IV (Simponi)	50 mg/4 mL	Vial	879.5000[b]	2 mg/kg at weeks 0 and 4, then every 8 weeks thereafter	Year 1: 18,470 Average thereafter: 17,197
Infliximab (Remicade)	100 mg	Vial	987.5600	3 mg/kg at weeks 0, 2, and 6, then every 8 weeks thereafter Depending on clinical response, dose can be increased to 10 mg/kg and/or up to every four weeks	Year 1: 23,701 Thereafter: 19,310 Maximum: 102,998
Infliximab (Inflectra)	100 mg	Vial	525.0000		Year 1: 12,600 Thereafter: 10,266 Maximum: 54,750
Infliximab (Renflexis)	100 mg	Vial	493.0000		Year 1: 11,832 Thereafter:9,640 Maximum: 51,413
Rituximab (Rituxan)	100 mg/10 mL 500 mg/50 mL	Vial	474.7100 2,373.5600	A course consists of 1,000 mg infusions at weeks 0 and 2. Reassess for retreatment at week 26, no sooner than 16 weeks after previous	18,988, assuming 2 courses Per course: 9,494
Sarilumab (Kevzara)	200 mg	Vial	700.0000[c]	200 mg SC every two weeks	18,250
Tocilizumab SC (Actemra)	162 mg/ 0.9 mL	Pre-filled syringe	358.9050	Patients < 100 kg: 162 mg SC every two weeks, increasing to weekly based on clinical response Patients ≥ 100 kg: 162 mg SC weekly	9,357 to 18,714
Tocilizumab IV (Actemra)	80 mg/4 mL 200 mg/10 mL 400 mg/20 mL	Vial	182.8000 457.0000 914.0000	4 mg/kg every 4 weeks followed by an increase to 8 mg/kg based on clinical response	9,532 to 19,063

SC = subcutaneous.

Note: All prices are from the Ontario Drug Benefit Formulary[18] or the Ontario Exceptional Access Drug Program price list[19] (accessed January 2019) unless otherwise indicated and do not include dispensing fees. All weight-based doses assume an average patient weight of 75 kg and wastage of excess medication in vials.

[a] Manufacturer's submitted price.

[b] Saskatchewan Formulary (January 2019).

[c] CADTH Pharmacoeconomic Report for Kevzara.[20]

Appendix 2: Summary of Key Outcomes

Table 9: When Considering Only Costs, Outcomes, and Quality of Life, How Attractive Is Baricitinib Relative to All The Identified Comparators?

Baricitinib Versus Complete Set of Comparators	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	NA
Costs (total)			X			
Drug treatment costs alone			X			
Clinical outcomes			X			
Quality of life			X			
Incremental CE ratio or net benefit calculation	cDMARD patients: Baricitinib is dominated by alternative biologic therapies bDMARD patients: Baricitinib is dominated by alternative biologic therapies					

bDMARD = biologic disease-modifying antirheumatic drug; cDMARD = conventional disease-modifying antirheumatic drug; CE = cost-effectiveness; NA = not applicable.

Appendix 3: Additional Information

Table 10: Submission Quality

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?			X
Comments	Overall, this was a poor-quality submission. The methods were not clear and transparent, despite the additional information provided by the manufacturer in response to several requests from CADTH. The spreadsheet and VBA code were poorly organized, poorly documented, and contained several unnecessary layers of embedded complexity and redundant disorganized code, making the manufacturer's submission difficult to evaluate. It required multiple revisions due to programming errors in the manufacturer's original submission. See specific details.[a]		
Was the material included (content) sufficient?			X
Comments	See notes[a]		
Was the submission well organized and was information easy to locate?			X
Comments	See notes[a]		

[a] The following issues were identified:

- The model provided contained several hidden sheets, many hidden rows and columns containing inputs and assumptions, few labels identifying assumptions, and several inefficient and difficult-to-evaluate layout choices. Selected examples include the following: the indexing (order in which treatments appear on the input sheet) of treatment alternatives was changed between the conventional disease-modifying antirheumatic drug (cDMARD) and biologic DMARD (bDMARD) scenarios, which decreased model transparency; the CEplane sheet appeared to contain errors; the "CODA norm probit" and related sheets each contained 1,000 unlabelled columns of output from the network meta-analysis; the "Latent-class" sheet contained unnecessary and unused columns of calculations and a row of unlabelled hardcoded numbers across the top of each class group; and some model inputs (such as the number of patients per arm) were overwritten by hardcoded values in the VBA code and not controlled by the apparent input cells in the workbook.
- Programmed subroutines were extremely lengthy, containing redundant lines of code, repeating lines of code that could have been made separate subroutines, having multiple embedded levels of IF statements, and using many inefficient coding approaches when simpler approaches were readily available. The EventLoop subroutine contained 408 lines of code. The main code to simulate a patient, for example, contained three different strategies for converting Health Assessment Questionnaire (HAQ) scores to quality-adjusted life-years (QALYs), two different approaches for modelling long-term HAQ after the patient progressed to Palliative care, and two completely different coding approaches to include serious adverse events (SAEs). The code for accruing costs and benefits calculated a (poorly named) variable *tmp* for the discount factor to avoid repeating

calculations and used it for calculations related to productivity loss, but then did not use this discount factor variable for other costs, life-years, and QALYs instead writing out the discount factor equation in each line. Overall, the code provided was poorly organized, difficult to review, difficult to debug, and poorly commented.

- The manufacturer's model contained mathematical errors. For example, when calculating the distribution parameters for the baseline population as a mixture of the clinical trial distributions, the manufacturer's model erroneously implemented the variance of a mixture distribution as

$$\sigma_{Mix}^2 = \alpha\sigma_1^2 + (1-\alpha)\sigma_2^2 + \alpha[\mu_1 - (\alpha\mu_1 + (1-\alpha)\mu_2)]^2 + (1-\alpha)[\mu_2 - (\alpha\mu_1 + (1-\alpha)\mu_2)]^2$$

  when the correct formula for the variance of a mixture distribution was

$$\sigma_{Mix}^2 = \alpha(\sigma_1^2 + \mu_1^2) + (1-\alpha)(\sigma_2^2 + \mu_2^2) - [\alpha\mu_1 + (1-\alpha)\mu_2]^2$$

  Similarly, there appeared to be other calculation errors in cells AB26 and AD26.

- The manufacturer's report was inconsistent in terms of the year for which cost values were presented. Monitoring costs were described as being inflated to 2016 dollars (page 30) and 2018 dollars (page 31), hospital costs described as being inflated to 2018 dollars (page 32). In the actual model file, it appears that all costs were represented in 2016 dollars.
- Inefficient programming resulted in longer simulation run times overall.
- Submitted model and report analyses did not correctly identify strategies on the efficient frontier due to errors in the method in the manufacturer's submitted spreadsheet. Specifically, the manufacturer's submission (spreadsheet and reports) included incremental cost-utility ratios (ICURs) for dominated strategies and misidentified extendedly dominant strategies when CADTH tested alternative scenarios.

Table 11: Authors Information

Authors of the Pharmacoeconomic Evaluation Submitted to CDR			
☐ Adaptation of global model/Canadian model done by the manufacturer ☒ Adaptation of global model/Canadian model done by a private consultant contracted by the manufacturer ☐ Adaptation of global model/Canadian model done by an academic consultant contracted by the manufacturer ☐ 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		

CDR = CADTH Common Drug Review.

Appendix 4: Summary of Other Health Technology Assessment Reviews of Drug

In 2017, both the Scottish Medicines Consortium (Scotland) and the National Institute for Health and Care Excellence (UK) reviewed baricitinib for the treatment of rheumatoid arthritis (RA) and recommended it for reimbursement under specific clinical criteria and confidential patient access schemes.[21,22] In contrast, the Pharmaceutical Benefits Advisory Committee (Australia) recommended that baricitinib be listed on a cost-minimization basis against the least costly biologic disease-modifying antirheumatic drug (DMARD) reimbursed for RA.[23]

Table 12: Other Health Technology Assessment Findings

	NICE (June 2017)[21]	PBAC (July 2017, November 2017, March 2018)[23-25]	SMC (August 2017)[22]
Treatment	Baricitinib 2 mg and 4 mg tablets (patients receive 4 mg daily, 2 mg in people aged 75 years and older)		
Price	£805.56 per 28 tab pack	Redacted	£803.41 per 28 tab pack (calculated from annual cost)
Similarities with CDR submission	DES, efficacy informed by NMA, lifetime time horizon	DES, efficacy from NMA, patients by ACR, HAQ mapped to EQ-5D (method unclear)	DES, efficacy from NMA, utilities from HAQ scores (per NICE bDMARD MTA)
Differences with CDR submission	Utilities from HAQ not in line with NICE bDMARD MTA, patients categorized by EULAR response at 6 months, UK-specific HC resources use/costs, focus on 4 mg	5-year TH, versus ADA, Australia HC resource use/costs. Subsequent analyses: CMA versus TOF (BAR 4 mg = TOF 10 mg); focus on 4 mg	• CMAs versus biologics. TH 2 to 10 years • CUA versus BSC of cDMARDs, TH 45 years, patients by EULAR response, focus on 4 mg
Manufacturer's results	After cDMARDs Moderate disease: £37,420/QALY versus cDMARDs Severe: dominant except for CZP (£18,400/QALY versus BAR) After bDMARDs: dominated or extendedly dominated all comparisons except CZP (£16,201/QALY versus BAR)	Base case: BAR 4 mg > ADA sequence versus ADA > TOF sequence was A$15,000 to A$45,000 per QALY.[25] Results of other sequences analyzed were not clearly reported. Recommendation made on cost-minimization basis versus TOF	CMA at 10 years (severe disease, no PAS): BAR 4 mg more expensive versus abatacept and TCZ; less expensive versus other bDMARDs CUA: patients with moderate disease not presented as they included patient access scheme
Issues noted by the review group	Concerns with cost calculations, bDMARD efficacy post-bDMARD failure overestimated, PAS for comparators not considered, limitations in NMA, issues how HAQ data used in model, issues with probabilistic analysis including programming errors	Effectiveness for subsequent bDMARDs inappropriate, HRQoL based on ACR mapped to HAQ – unable to verify, base case not include SAEs. When updated price for ADA used, ICUR > $200,000 per QALY	Weaknesses in NMA, no analyses provided for BAR 4 mg monotherapy, results were sensitive to method used to model HAQ progression
Results of reanalyses by review group	New ICURs calculated based on confidential comparator prices, not reported	PBAC preferred CMA based on the least costly biologic comparator[23]	CUA baricitinib (without PAS) in patients with moderate disease versus BSC: £48,223/QALY

	NICE (June 2017)[21]	PBAC (July 2017, November 2017, March 2018)[23-25]	SMC (August 2017)[22]
Recommendation	Recommended with MTX if inadequate response to combination cDMARDs, disease severe, and discount provided Recommended with MTX if inadequate response to or who cannot have other DMARDS including ≥ 1 biologic, disease severe, patient cannot have RTX, discount provided May use as monotherapy if patient cannot take MTX and previous criteria met	Decision deferred twice, final recommendation: list BAR 4 mg on a cost-minimization basis against the least costly bDMARD for RA	Accepted for restricted use in patients with severe disease (a DAS28 > 5.1) who have not responded to intensive therapy with combination cDMARDs. In patients with severe disease inadequately controlled by bDMARD, may be used in patients ineligible for RTX

ACR = American College of Rheumatology; ADA = adalimumab; BAR = baricitinib; bDMARD = biologic disease-modifying antirheumatic drug; BSC = best supportive care; cDMARD = conventional disease-modifying antirheumatic drug; CDR = CADTH Common Drug Review; HRQoL = health-related quality of life; CMA = cost-minimization analysis; CUA = cost-utility analysis; CZP = certolizumab pegol; DAS28 = Disease Activity Score-28; DES = discrete-event simulation; EQ-5D = EuroQol 5-Dimensions questionnaire; EULAR = European League Against Rheumatism; HAQ = Health Assessment Questionnaire; HC = health care; HTA = health technology assessment; ICUR = incremental cost-utility ratio; MTA = multiple technology assessment; MTX = methotrexate; NICE = The National Institute for Health and Care Excellence; NMA = network meta-analysis; PAS = patient access scheme; PBAC = Pharmaceutical Benefits Advisory Committee; QALY = quality-adjusted life-year; RTX = rituximab; SAE = serious adverse event; SMC = Scottish Medicines Consortium; TCZ = tocilizumab; TH = time horizon; TOF = tofacitinib.

Appendix 5: Reviewer Worksheets

Manufacturer's Model Structure

The manufacturer submitted an economic model that captured health outcomes in quality-adjusted life-years (QALYs) for cohorts of adult patients with moderate-to-severe rheumatoid arthritis (RA) who have responded inadequately to one or more disease-modifying antirheumatic drugs (DMARDs). The manufacturer submitted a discrete-event simulation model.[12] Individual patients were simulated over 45 years (representing a lifetime horizon for most simulated patients), accruing costs and quality-of-life utilities.

Table 13: Data Sources

Data Input	Description of Data Source	Comment
Efficacy	Manufacturer-funded NMA[26]	The clinical review of the manufacturer-submitted NMA indicated that there were some methodological limitations and identified other published NMAs. The results of the published NMAs were congruent with the findings of the manufacturer's NMA
Natural history	Assumption[3]	Highly uncertain (see assumption table)
Utilities	NICE MTA[27,28] and Hernandez et al. 2012[7]	Alternative approaches to mapping from HAQ to QALY were explored in sensitivity analysis
Adverse events	Summary SAE rate included only in sensitivity analysis (estimated from JADX and JADV trials) Discontinuation due to a SAE is captured under the ACR nonresponse category	SAEs increase costs and decrease QALYs, and so should be included in the base case
Mortality	Baseline age-specific mortality rates based on average Canadian life tables[3]	Baseline mortality source appropriate; see assumptions table regarding adjustments
Resource use (for monitoring)	Expert opinion[3]	Acceptable
Costs		
Drug	Manufacturer-submitted prices and IQVIA Delta PA database[3]	Drug cost estimates were consistent with CADTH estimates
Monitoring	Ontario Schedule of Benefits for physician services[3]	Appropriate, although costs used were not up to date
AEs	The only specific AEs described were cellulitis and herpes zoster. When individuals experienced an SAE in the sensitivity analysis, they incurred the cost of $4,438.21 and a reduction of –0.012 QALYs[3]	Due to relatively small sample size and given the relative rarity of adverse events, less common but more severe events may not have been observed in the trials' observation period
Health state (disease severity)	Hospitalization costs based on specific disease severity were sourced from Ohinmaa et al., a peer-reviewed paper that reported the costs for 1,222 patients with an average age of 55 years in the Alberta Rheumatoid Arthritis Biologics	The manufacturer's analysis included the proportion of total health care costs accounting for hospital, emergency room, and physician services, although the report does not explain why outpatient clinic costs were not included

Data Input	Description of Data Source	Comment
	Pharmacosurveillance Program between April 2004 and March 2009, stratified by HAQ score[12]	

ACR = American College of Rheumatology; AE = adverse event; HAQ = Health Assessment Questionnaire; MTA = multiple technology assessment; NICE = The National Institute for Health and Care Excellence; NMA = network meta-analysis; QALY = quality-adjusted life-year; SAE = serious adverse event.

Table 14: Manufacturer's Key Assumptions

Assumption	Comment
Treatment Response / Progression	
The manufacturer assumed that treatment improved HAQ and that HAQ would remain constant until treatment failure. Once the patient progressed to Palliative care (last line of therapy), assumed HAQ progression based on a "Latent-class" growth mixture model.	Uncertainty in HAQ progression while on treatment was not explored (specifically, that treatment failure would correspond to a change in HAQ) After treatment failure, patient returns to their pre-treatment HAQ. As a result, during the active treatment sequence (prior to Palliative care), the patient's HAQ can never be worse than their initial HAQ, which inherently favours longer treatment sequences. HAQ progression to Palliative care was explored in sensitivity analysis
Initial HAQ change is determined by ACR response observed at the primary assessment time point (derived from a study by Carlson et al.). ACR response category determined for each treatment from NMA. Impact of using change in HAQ was derived from pooled data from studies BEAM and BUILD for the cDMARD-IR population and BEACON for the bDMARD population, tested in scenario analyses	Acceptable
No HAQ progression was assumed after 15 years for patients remaining on cDMARDs beyond that period	Uncertain: assumption was not tested in sensitivity analysis to determine whether it impacted results
Treatment response rates were assumed to be independent of patient age, BMI, prior treatment history, and current HAQ. Duration of treatment response was also assumed to be independent of patient age, BMI, prior treatment response, and current level of treatment response	Uncertain: model was not designed well for exploration of the impact of these assumptions
Utilities / Quality of Life	
Quality of life in the model does not decrease with age, which is expected because of additional health conditions related to aging	Assuming patients at all ages have the same QALY weight generally inflates gains. The model was programmed in such a way that this assumption could not be explored
Quality of life in the model was tracked using the disease-specific Health Assessment Questionnaire–Disability Index (HAQ-DI) measure. In the base case, HAQ was converted to QALYs using a latent-class regression model	HAQ does not appear to be well correlated with DAS28, which was the disease-severity metric used to define clinical trial cohorts Latent-class approach was unnecessarily complicated, as in the HAQ-to-QALY mapping model Alternative approaches to mapping from HAQ to QALY were explored in sensitivity analysis
It was assumed that adverse events were not a key driver of the model; thus, they were not included. The manufacturer considered that it was not feasible to conduct an NMA on the rate of SAEs, as these were either defined differently or not consistently reported in the trials included for evidence synthesis. In addition, no statistically significant differences	SAEs increase costs and decrease QALYs and so should be included in the base case

Assumption	Comment
were observed in the incidence of SAEs between baricitinib and adalimumab in the BEAM trial	
Mortality	
Mortality rate increased according to initial HAQ score	Limited evidence that HAQ improvement corresponds to a mortality benefit, so the hazard ratio for mortality was assumed not to update with HAQ. The model was programmed in such a way that this assumption could not be explored
Cost and Resource Use	
Model does not include baseline health care costs increasing with age, which is expected because of additional health conditions related to aging	Ignoring baseline health care costs generally decreases the incremental costs of interventions, which lead to life extension. Because no life extension occurs in this analysis, the impact of this assumption is likely minimal. The model was programmed in such a way that this assumption could not be explored
Assumed no cost to health system because drug administration would occur at manufacturer-funded infusion clinics	Manufacturer's drug does not require infusion, so this assumption lowered the cost of comparators. Clinical expert confirmed the assumption is true for most patients
95% of patients receiving infliximab and etanercept received the branded product and 5% received the biosimilar product	Inappropriate assumption. Separate analyses should be undertaken, considering each product (assuming equivalent efficacy)

ACR = American College of Rheumatology; bDMARD = biologic disease-modifying antirheumatic drug; BMI = body mass index; cDMARD = conventional disease-modifying antirheumatic drug; cDMARD-IR = inadequate response to cDMARDs; DAS28 = Disease Activity Score-28; HAQ = Health Assessment Questionnaire; HAQ-DI = Health Assessment Questionnaire–Disability Index; NMA = network meta-analysis; QALY = quality-adjusted life-year; SAE = serious adverse event.

Table 15: Monitoring Costs Presented in the Manufacturer's Analysis

	Treatment Initiation		First 6 Months		Maintenance (Annual)	
Monitoring Activity	**Units**	**Cost**	**Units**	**Cost**	**Units**	**Cost**
Full blood count	1	$11.43	10	$114.30	12	$137.16
Erythrocyte sedimentation rate	1	$2.14	3	$6.42	36	$77.04
Biochemical profile	1	$50.02	10	$500.20	12	$600.24
Chest X-ray	1	$32.65	0	$0.00	0	$0.00
Urinalysis	0	$0.00	0	$0.00	0	$0.00
Hospital outpatient attendance	1	$79.85	4.33	$345.75	8.67	$692.30
Total costs		$176.09		$966.67		$1,506.74

Source: Manufacturer's pharmacoeconomic submission.[3]

Table 16: Annual Health Care Utilization Costs, Excluding Cost of Drug Therapy (2008 Canadian Dollars, as Reported by Ohinmaa et al.), Stratified by Patient Treatment Group

Patient Group	N	Total Costs (2008$)
DMARD sustained response	75	6,652
Failed DMARD treatment, switched to anti-TNF biologic during follow-up	68	6,018
Anti-TNF biologic sustained response	**731**	**4,848**
Failed one anti-TNF therapy, switched to another drug during follow-up	**212**	**7,340**
Overall	1,086	5,531

DMARD = disease-modifying antirheumatic drug; TNF = tumour necrosis factor.

Source: Ohinmaa et al.[12]

Table 17: Unit Costs for Monitoring Activities in the Manufacturer's Analysis Compared With the Costs in the Current-Year Ontario Schedule of Benefits for Physician Services

	Source	Unit Cost	Reference Year	Inflation-Adjusted Cost, 2016$ (Manufacturer's Analysis)	Cost in Current Schedule
Full blood count	Ontario SoB L393	$11.27	1999	$11.43	$3.98
Erythrocyte sedimentation rate	Ontario SoB L451	$2.11	1999	$2.14	$1.79
Biochemical profile	Ontario SoB, compilation of tests, 70 total units	$49.32	1999	$50.02	Unspecified series
Chest X-ray	Ontario SoB, X091H + X091P (2 views)	$32.65	2016	$32.65	$32.65
Urinalysis	Ontario SoB L253 + L254	$4.93	1999	$5.00	$3.59
Hospital outpatient attendance	Ontario SoB, code A483 (med. Specific. Assessment)	$79.85	2016	$79.85	$79.85

SoB = Schedule of Benefits.

Source: Manufacturer's pharmacoeconomic submission;[3] Ontario Schedule of Benefits (2018).[29,30]

Table 18: Annual Health Care Utilization Costs, Excluding Cost of Drug Therapy, Stratified by Health Assessment Questionnaire Score

		2008$			2018$		
HAQ Score	N	Annual Hospital, ER, and Physician Cost	Annual Outpatient Cost	Total Health Care Costs	Annual Hospital, ER, and Physician Cost	Annual Outpatient Cost	Total Health Care Costs
0.0 to 0.5	421	3,242	915	4,157	3,790	1,070	4,860
0.6 to 1.0	149	3,855	1,218	5,073	4,507	1,424	5,931
1.1 to 1.5	126	4,347	1,298	5,645	5,082	1,518	6,600
1.6 to 2.0	61	7,987	1,874	9,861	9,338	2,191	11,529
2.1 to 3.0	27	12,376	1,849	14,225	14,469	2,162	16,631

ER = emergency department; HAQ = Health Assessment Questionnaire.

Source: Ohinmaa et al.[12]

Manufacturer's Base-Case Results

Table 19: Summary of Results of the Manufacturer's Base Case — Conventional Disease-Modifying Antirheumatic Drug Analysis

	Deterministic Analysis			Probabilistic Analysis		
	Total Costs ($)	Total QALYs	Incremental Cost Per QALY Gained[a]	Total Costs ($)	Total QALYs	Incremental Cost Per QALY Gained[a]
ETN → TCZi → RTX → Palliative care	412,266	12.40		412,882	12.44	
BAR 2 mg → ETN → TCZi → RTX → Palliative care	**430,565**	**12.93**	**Ext. dom.**	**431,508**	**12.97**	**Ext. dom.**
TOF → ETN → TCZi → RTX → Palliative care	431,256	12.98	$33,058	432,524	13.02	$34,105
IFX → ETN → TCZi → RTX → Palliative care	432,079	12.85	Dominated	433,246	12.88	Dominated
CTZ → ETN → TCZi → RTX → Palliative care	432,958	13.00	Ext. dom.	433,995	13.04	Ext. dom.
GOL → ETN → TCZi → RTX → Palliative care	435,195	12.86	Dominated	436,264	12.89	Dominated
SAR → ETN → TCZi → RTX → Palliative care	442,929	13.22	$48,161	444,112	13.26	$47,416
ABTi → ETN → TCZi → RTX → Palliative care	444,782	12.87	Dominated	445,754	12.90	Dominated
ADA → ETN → TCZi → RTX → Palliative care	447,786	12.91	Dominated	448,678	12.95	Dominated

ABTi = abatacept IV; ADA = adalimumab; BAR = baricitinib; CTZ = certolizumab; ETN = etanercept; Ext. dom. = extended dominance; GOL = golimumab; IFX = infliximab; MTX = methotrexate; QALY = quality-adjusted life-year; RTX = rituximab; SAR = sarilumab; TCZi = tocilizumab IV; TOF = tofacitinib.

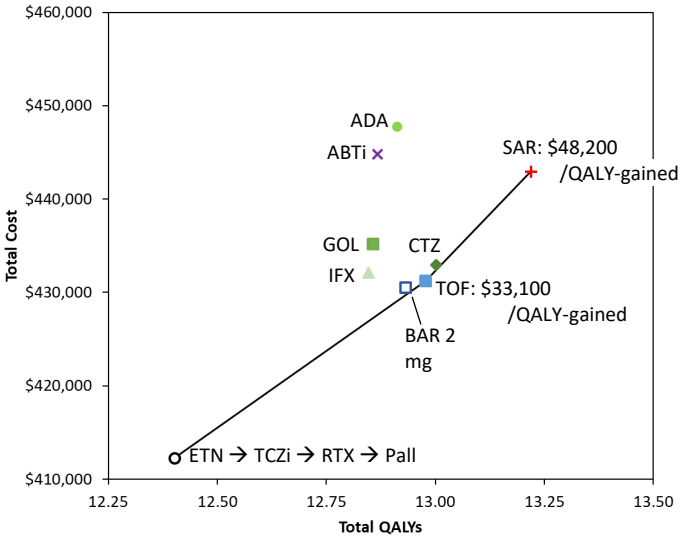
Note: All initial treatment are in addition to methotrexate.

[a] Sequential ICUR.

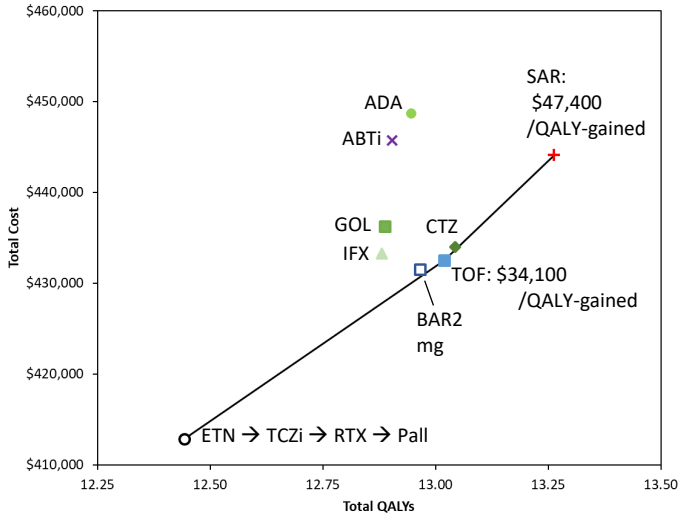
Source: Manufacturer-submitted economic information.[5,10]

Figure 1: Cost-Effectiveness Plane, Manufacturer's Base-Case Conventional Disease-Modifying Antirheumatic Drug; Analysis

(A) Deterministic results



(B) Probabilistic results



ABTi = abatacept IV; ADA = adalimumab; BAR = baricitinib; CTZ = certolizumab; ETN = etanercept; GOL = golimumab; IFX = infliximab; MTX = methotrexate; Pall = Palliative care; QALY = quality-adjusted life-year; RTX = rituximab; SAR = sarilumab; TCZi = tocilizumab IV; TOF = tofacitinib.

Note: All initial treatment are in addition to methotrexate.

Source: Created by CADTH based on the manufacturer's submitted economic information.

Table 20: Summary of Results of the Manufacturer's Base Case — Biologic Disease-Modifying Antirheumatic Drug Analysis

	Deterministic Analysis			Probabilistic Analysis		
	Total Costs ($)	Total QALYs	Incremental Cost Per QALY Gained[a]	Total Costs ($)	Total QALYs	Incremental Cost Per QALY Gained[a]
RTX → Palliative care	256,549	7.71		256,647	7.74	
BAR 2 mg → RTX → Palliative care	**285,504**	**8.39**	**Ext. dom.**	**285,391**	**8.40**	**Ext. dom.**
GOL → RTX → Palliative care	291,417	8.46	Ext. dom.	291,144	8.47	Ext. dom.
SAR → RTX → Palliative care	293,703	8.58	Ext. dom.	293,536	8.58	Ext. dom.
TOF → RTX → Palliative care	296,779	8.74	Ext. dom.	296,972	8.74	Ext. dom.
ABTi → RTX → Palliative care	305,209	8.71	Dominated	305,201	8.72	Dominated
TCZi → RTX → Palliative care	306,031	9.20	33,219	305,813	9.20	33,709

ABTi = abatacept IV; BAR = baricitinib; GOL = golimumab; MTX = methotrexate; QALY = quality-adjusted life-year; RTX = rituximab; SAR = sarilumab; TCZi = tocilizumab IV; TOF = tofacitinib.

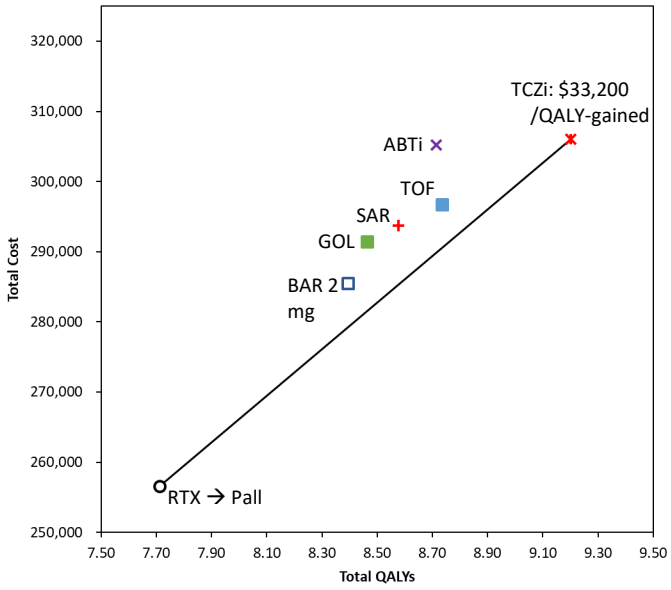
Note: There were some mistakes in the identification of the efficient frontier and which strategies were dominated in the manufacturer's submitted analysis. This table corrects those errors. All initial treatment are in addition to methotrexate.

[a] Sequential ICUR.

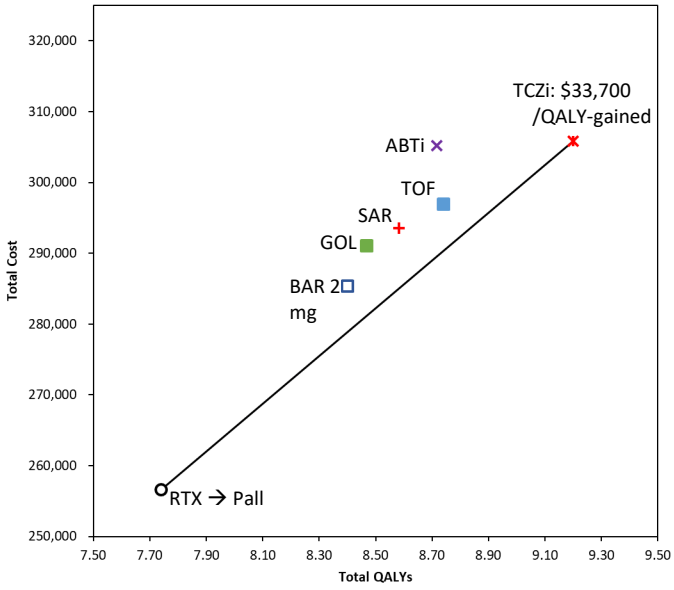
Source: Adapted from manufacturer-submitted economic information.[5]

Figure 2: Cost-Effectiveness Plane, Manufacturer's Base-Case Biologic Disease-Modifying Antirheumatic Drug Analysis

Deterministic Results



Probabilistic Results



ABTi = abatacept IV; BAR = baricitinib; GOL = golimumab; QALY = quality-adjusted life-year; MTX = methotrexate; RTX = rituximab; SAR = sarilumab; TCZi = tocilizumab IV; TOF = tofacitinib.

Note: All initial treatment are in addition to methotrexate.

Source: Created by CADTH based on the manufacturer's submitted economic information, based on deterministic analysis results.

CADTH Reanalyses

Conventional Disease-Modifying Antirheumatic Drug Analyses

Table 21: CADTH Base-Case Analysis for Conventional Disease-Modifying Antirheumatic Drug Population — Component Analysis

Scenario	Treatment	Total Cost ($)	Total QALY	ICER ($)
Manufacturer's base case	ETN → TCZi → RTX → Palliative care	412,266	12.40	–
	BAR 2 mg → ETN → TCZi → RTX → Palliative care	430,565	12.93	Ext. dom.
	TOF → ETN → TCZi → RTX → Palliative care	431,256	12.98	33,058
	IFX → ETN → TCZi → RTX → Palliative care	432,079	12.85	Dominated
	CTZ → ETN → TCZi → RTX → Palliative care	432,958	13.00	Ext. dom.

Scenario	Treatment	Total Cost ($)	Total QALY	ICER ($)
	GOL → ETN → TCZi → RTX → Palliative care	435,195	12.86	Dominated
	SAR → ETN → TCZi → RTX → Palliative care	442,929	13.22	48,161
	ABTi → ETN → TCZi → RTX → Palliative care	444,782	12.87	Dominated
	ADA → ETN → TCZi → RTX → Palliative care	447,786	12.91	Dominated
Revised baseline age	ETN → TCZi → RTX → Palliative care	451,325	13.66	–
	BAR 2 mg → ETN → TCZi → RTX → Palliative care	471,460	14.23	Ext. dom.
	TOF → ETN → TCZi → RTX → Palliative care	472,850	14.29	34,019
	IFX → ETN → TCZi → RTX → Palliative care	473,345	14.14	Dominated
	CTZ → ETN → TCZi → RTX → Palliative care	474,070	14.31	Ext. dom.
	GOL → ETN → TCZi → RTX → Palliative care	477,039	14.15	Dominated
	SAR → ETN → TCZi → RTX → Palliative care	484,923	14.54	49,050
	ABTi → ETN → TCZi → RTX → Palliative care	486,879	14.16	Dominated
	ADA → ETN → TCZi → RTX → Palliative care	490,104	14.20	Dominated
Revised baseline HAQ score	ETN → TCZi → RTX → Palliative care	404,810	12.783	–
	BAR 2 mg → ETN → TCZi → RTX → Palliative care	422,178	13.366	Ext. dom.
	TOF → ETN → TCZi → RTX → Palliative care	423,188	13.425	28,607
	IFX → ETN → TCZi → RTX → Palliative care	423,627	13.271	Dominated
	CTZ → ETN → TCZi → RTX → Palliative care	424,637	13.454	Ext. dom.
	GOL → ETN → TCZi → RTX → Palliative care	426,918	13.281	Dominated
	SAR → ETN → TCZi → RTX → Palliative care	434,567	13.683	44,187
	ABTi → ETN → TCZi → RTX → Palliative care	436,402	13.299	Dominated
	ADA → ETN → TCZi → RTX → Palliative care	439,471	13.347	Dominated
Include SAEs	ETN → TCZi → RTX → Palliative care	417,311	12.41	–
	BAR 2 mg → ETN → TCZi → RTX → Palliative care	436,079	12.91	Ext. dom.

Scenario	Treatment	Total Cost ($)	Total QALY	ICER ($)
	TOF → ETN → TCZi → RTX → Palliative care	436,378	12.97	33,616
	IFX → ETN → TCZi → RTX → Palliative care	437,027	12.82	Dominated
	CTZ → ETN → TCZi → RTX → Palliative care	437,854	13.00	Ext. dom.
	GOL → ETN → TCZi → RTX → Palliative care	439,875	12.83	Dominated
	SAR → ETN → TCZi → RTX → Palliative care	448,099	13.21	49,304
	ABTi → ETN → TCZi → RTX → Palliative care	449,631	12.86	Dominated
	ADA → ETN → TCZi → RTX → Palliative care	452,277	12.89	Dominated
IFX and ETN are biosimilar versions of the product, revised distributions (no impact on deterministic analysis results)	IFX → ETN → TCZi → RTX → Palliative care	344,979	12.86	–
	ETN → TCZi → RTX → Palliative care	356,789	12.43	Dominated
	BAR 2 mg → ETN → TCZi → RTX → Palliative care	393,439	12.94	Ext. dom.
	TOF → ETN → TCZi → RTX → Palliative care	395,744	13.00	Ext. dom.
	GOL → ETN → TCZi → RTX → Palliative care	396,274	12.87	Dominated
	CTZ → ETN → TCZi → RTX → Palliative care	398,114	13.02	Ext. dom.
	ABTI → ETN → TCZi → RTX → Palliative care	407,688	12.89	Dominated
	ADA → ETN → TCZi → RTX → Palliative care	411,119	12.92	Dominated
	SAR → ETN → TCZi → RTX → Palliative care	413,335	13.24	183,934
CADTH base case	IFX → ETN → TCZi → RTX → Palliative care	372,831	14.673	–
	ETN → TCZi → RTX → Palliative care	387,262	14.108	Dominated
	BAR 2 mg → ETN → TCZi → RTX → Palliative care	427,272	14.770	Ext. dom.
	TOF → ETN → TCZi → RTX → Palliative care	429,286	14.847	Ext. dom.
	GOL → ETN → TCZi → RTX → Palliative care	429,350	14.683	Dominated
	CTZ → ETN → TCZi → RTX → Palliative care	431,667	14.873	Ext. dom.
	ABTI → ETN → TCZi → RTX → Palliative care	441,498	14.702	Dominated

Scenario	Treatment	Total Cost ($)	Total QALY	ICER ($)
	ADA → ETN → TCZi → RTX → Palliative care	445,941	14.759	Dominated
	SAR → ETN → TCZi → RTX → Palliative care	449,170	15.132	166,445

ABTi = abatacept IV; ADA = adalimumab; BAR = baricitinib; CTZ = certolizumab; ETN = etanercept; GOL = golimumab; HAQ = Health Assessment Questionnaire; ICER = incremental cost-effectiveness ratio; IFX = infliximab; QALY = quality-adjusted life-year; RTX = rituximab; SAE = serious adverse event; SAR = sarilumab; TCZi = tocilizumab IV; TOF = tofacitinib.

Note: Results are presented deterministically as there were errors identified with the manufacturer's probabilistic analysis. All initial treatment are in addition to methotrexate. Dominated strategy means the strategy is more costly and results in fewer QALYs than at least one other strategy; extended dominance means strategy is more costly and provides fewer QALYs than a linear combination of two other strategies.

Table 22: CADTH Base-Case Analysis for Conventional Disease-Modifying Antirheumatic Drug Population

Scenario	Total Cost ($)	Total QALY	Incremental Cost ($)	Incremental QALY	ICER ($)
IFX → ETN → TCZi → RTX → Palliative care	365,853	14.720	–	–	–
ETN → TCZi → RTX → Palliative care	388,884	14.235	23,023	-0.485	Dominated
BAR 2 mg → ETN → TCZi → RTX → Palliative care	427,863	14.723	62,010	0.003	Ext. dom.
TOF → ETN → TCZi → RTX → Palliative care	430,694	14.809	64,842	0.089	Ext. dom.
CTZ → ETN → TCZi → RTX → Palliative care	440,466	15.054	64,813	0.333	223,919
GOL → ETN → TCZi → RTX → Palliative care	440,542	14.813	74,689	0.093	Dominated
ABTi → ETN → TCZi → RTX → Palliative care	443,434	14.721	77,581	0.000	Dominated
SAR → ETN → TCZi → RTX → Palliative care	445,745	15.007	79,682	0.287	Dominated
ADA → ETN → TCZi → RTX → Palliative care	448,025	14.756	82,172	0.036	Dominated

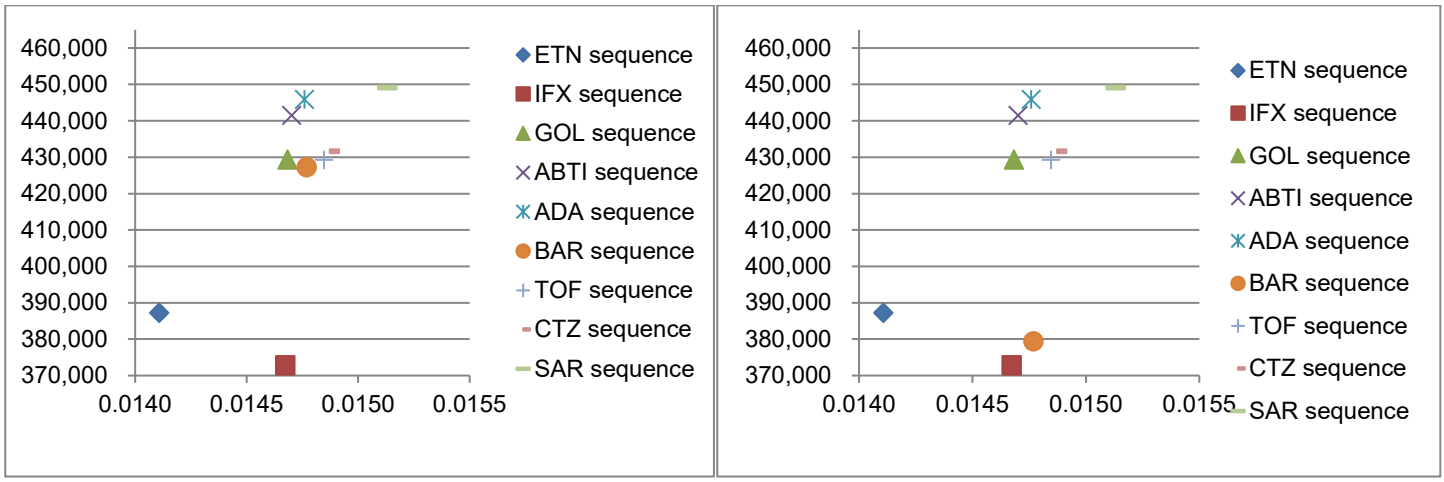
ABTi = abatacept IV; ADA = adalimumab; BAR = baricitinib; CTZ = certolizumab; ETN = etanercept; GOL = golimumab; ICER = incremental cost-effectiveness ratio; IFX = infliximab; MTX = methotrexate; QALY = quality-adjusted life-year; RTX = rituximab; SAR = sarilumab; TCZi = tocilizumab IV; TOF = tofacitinib.

Note: Dominated strategy means the strategy is more costly and results in fewer QALYs than at least one other strategy; extended dominance means strategy is more costly and provides fewer QALYs than a linear combination of two other strategies. Detail presented for an example cohort of 50-year-olds, 79% female, with initial HAQ = 1.5 (probabilistic results). All initial treatment are in addition to methotrexate.

Figure 3: Cost-Effectiveness Plane, CADTH Conventional Disease-Modifying Antirheumatic Drug Base Case

(A) Base case (BAR 2 mg; annual cost: $17,490)

(B) 40% price-reduction analysis (BAR 2 mg; annual: $10,494)



ABTi = abatacept IV; ADA = adalimumab; BAR = baricitinib; CTZ = certolizumab; ETN = etanercept; GOL = golimumab; IFX = infliximab; SAR = sarilumab; TOF = tofacitinib.

Note: Presented for an example cohort of 50-year-olds, 82% female, with initial HAQ = 1.5. All initial treatment are in addition to methotrexate. Vertical axis = incremental costs; Horizontal axis = incremental QALYs.

Source: Created by CADTH based on the manufacturer's submitted economic information, based on deterministic analysis results.

Table 23: CADTH Base-Case Analysis for Biologic Disease-Modifying Antirheumatic Drug Population: Component Analysis

Scenario	Treatment	Total Cost ($)	Total QALY	ICER ($)
Manufacturer's base case	RTX → Palliative care	256,549	7.71	–
	BAR 2 mg → RTX → Palliative care	285,504	8.39	Ext. dom.
	GOL → RTX → Palliative care	291,417	8.46	Ext. dom.
	SAR → RTX → Palliative care	293,703	8.58	Ext. dom.
	TOF → RTX → Palliative care	296,779	8.74	Ext. dom.
	ABTi → RTX → Palliative care	305,209	8.71	Dominated
	TCZi → RTX → Palliative care	306,031	9.20	33,219
Revised baseline age	RTX → Palliative care	303,185	9.03	–
	BAR 2 mg → RTX → Palliative care	335,913	9.82	Ext. dom.
	GOL → RTX → Palliative care	342,904	9.91	Ext. dom.
	SAR → RTX → Palliative care	345,929	10.05	Ext. dom.
	TOF → RTX → Palliative care	350,324	10.25	Ext. dom.
	ABTi → RTX → Palliative care	359,724	10.22	Dominated
	TCZi → RTX → Palliative care	360,754	10.80	32,596
Revised baseline HAQ score	RTX → Palliative care	242,469	9.24	–
	BAR 2 mg → RTX → Palliative care	273,599	9.93	Ext. dom.
	GOL → RTX → Palliative care	280,124	9.99	Ext. dom.
	SAR → RTX → Palliative care	283,094	10.10	Ext. dom.
	TOF → RTX → Palliative care	287,483	10.27	Ext. dom.
	ABTi → RTX → Palliative care	296,111	10.25	Dominated
	TCZi → RTX → Palliative care	298,146	10.71	37,795
Include SAEs	RTX → Palliative care	264,287	7.75	–
	BAR 2 mg → RTX → Palliative care	291,815	8.38	Ext. dom.

Scenario	Treatment	Total Cost ($)	Total QALY	ICER ($)
	GOL → RTX → Palliative care	297,406	8.45	Ext. dom.
	SAR → RTX → Palliative care	299,704	8.57	Ext. dom.
	TOF → RTX → Palliative care	303,421	8.74	Ext. dom.
	ABTi → RTX → Palliative care	311,771	8.71	Dominated
	TCZi → RTX → Palliative care	311,885	9.20	32,960
IFX and ETN are biosimilar versions of the product, revised distributions (no impact on deterministic analysis results)	RTX → Palliative care	255,611	7.72	–
	BAR 2 mg → RTX → Palliative care	283,392	8.40	Ext. dom.
	GOL → RTX → Palliative care	289,357	8.47	Ext. dom.
	SAR → RTX → Palliative care	291,760	8.58	Ext. dom.
	TOF → RTX → Palliative care	303,548	8.72	Ext. dom.
	ABTi → RTX → Palliative care	295,262	8.74	Dominated
	TCZi → RTX → Palliative care	304,227	9.21	32,725[a]
CADTH base case	RTX → Palliative care	295,257	10.85	–
	BAR 2 mg → RTX → Palliative care	329,471	11.59	Ext. dom.
	GOL → RTX → Palliative care	336,348	11.67	Ext. dom.
	SAR → RTX → Palliative care	339,988	11.81	Ext. dom.
	TOF → RTX → Palliative care	344,941	12.00	Ext. dom.
	ABTi → RTX → Palliative care	354,421	11.97	Dominated
	TCZi → RTX → Palliative care	358,068	12.54	$37,226

ABTi = abatacept IV; BAR = baricitinib; ETN = etanercept; Ext. dom. = extended dominance; GOL = golimumab; HAQ = Health Assessment Questionnaire; ICER = incremental cost-effectiveness ratio; IFX = infliximab; MTX = methotrexate; QALY = quality-adjusted life-year; RTX = rituximab; SAE = serious adverse event; SAR = sarilumab; TCZi = tocilizumab IV; TOF = tofacitinib.

Note: Results are presented deterministically as there were errors identified with the manufacturer's probabilistic analysis. All initial treatment are in addition to methotrexate. Dominated strategy means the strategy is more costly and results in fewer QALYs than at least one other strategy; extended dominance means strategy is more costly and provides fewer QALYs than a linear combination of two other strategies.

[a] Difference due to different seeding used.

Table 24: CADTH Base-Case Analysis for Biologic Disease-Modifying Antirheumatic Drug Population — Probabilistic Analysis

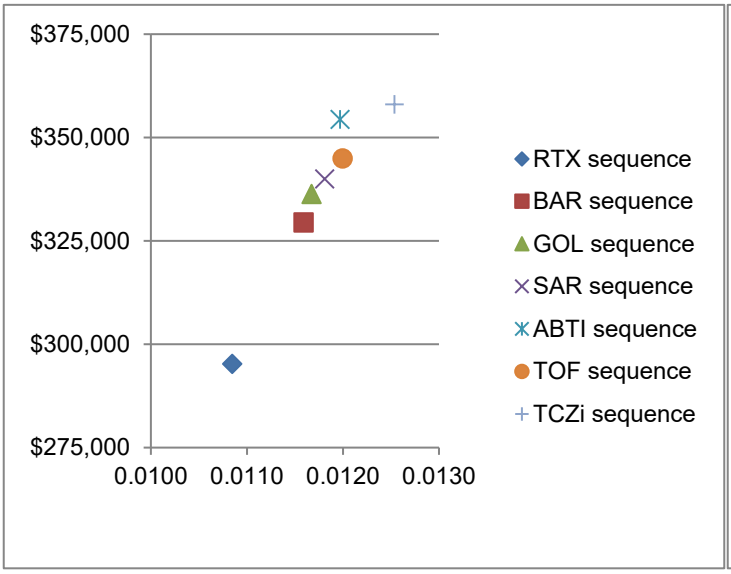
Scenario	Total Cost ($)	Total QALY	Incremental Cost ($)	Incremental QALY	ICER ($)
RTX → Palliative care	289,329	10.544	–	–	–
SAR → RTX → Palliative care	295,403	10.546	6,074	**0.003**	**Ext. dom.**
GOL → RTX → Palliative care	310,892	10.890	**21,563**	0.347	**Ext. dom.**
BAR 2 mg → RTX → Palliative care	330,439	11.453	41,110	0.910	**Ext. dom.**
TCZi → RTX → Palliative care	337,632	11.787	43,302	1.243	38,853
TOF → RTX → Palliative care	341,817	11.786	52,488	1.242	Dominated
ABTI → RTX → Palliative care	345,910	11.605	56,581	1.061	Dominated

ABTi = abatacept IV; BAR = baricitinib; Ext. dom. = extended dominance; GOL = golimumab; ICER = incremental cost-effectiveness ratio; RTX = rituximab; QALY = quality-adjusted life-year; SAR = sarilumab; TCZi = tocilizumab IV; TOF = tofacitinib.

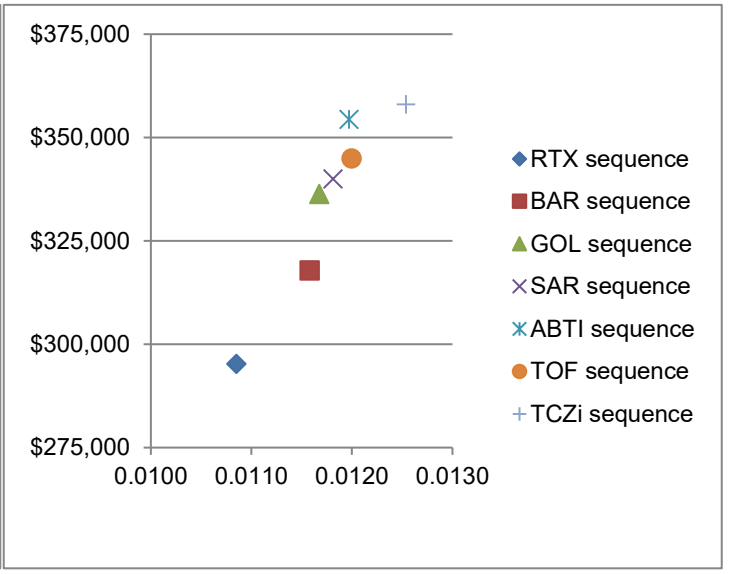
Note: Dominated strategy means the strategy is more costly and results in fewer QALYs than at least one other strategy; extended dominance means strategy is more costly and provides fewer QALYs than a linear combination of two other strategies. Cohort of 50-year-olds, 82% female, with initial HAQ = 1.5. Results are presented deterministically as there were errors identified with the manufacturer's probabilistic analysis. All initial treatment are in addition to methotrexate.

Figure 4: Cost-Effectiveness Plane, CADTH Biologic Disease-Modifying Antirheumatic Drug Analysis

(A) Base case (BAR 2 mg annual cost: $17,490)



(B) 20% price-reduction (BAR 2 mg annual: $13,992)



ABTi = abatacept IV; BAR = baricitinib; GOL = golimumab; RTX = rituximab; SAR = sarilumab; TCZi = tocilizumab IV; TOF = tofacitinib.

Note: Presented for an example cohort of 50-year-olds, 82% female, with initial HAQ = 1.5. All initial treatment are in addition to methotrexate. Vertical axis = incremental costs; Horizontal axis = incremental QALYs.

Source: Created by CADTH based on the manufacturer's submitted economic information, based on deterministic analysis results.

CADTH Scenario Analyses

Conventional Disease-Modifying Antirheumatic Drug Analyses

Table 25: Summary of ICURs for Baricitinib Compared With the "Follow-Up Sequence" Based on CADTH cDMARD Base Case (Ignoring All Other Treatment-Sequence Alternatives)

Cohort	$ per QALY				
	HAQ = 0.5	HAQ = 1.0	HAQ = 1.5	HAQ = 2.0	HAQ = 2.5
30 years	72,031	49,152	31,246	16,245	14,569
40 years	112,573	77,202	56,277	36,576	14,070
50 years	125,914	81,907	60,480	40,356	41,722
60 years	142,502	92,926	65,820	46,699	49,177
70 years	155,269	107,994	80,500	57,574	61,886
80 years	185,675	125,288	107,561	100,700	104,495

cDMARD = conventional disease-modifying antirheumatic drug; HAQ = Health Assessment Questionnaire; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

Biologic Disease-Modifying Antirheumatic Drug Analyses

Table 26: Summary of ICURs for Baricitinib Compared With the "Follow-Up Sequence" Based on the CADTH bDMARD Base Case (Ignoring All Other Treatment-Sequence Alternatives)

Cohort	$ per QALY				
	HAQ = 0.5	HAQ = 1.0	HAQ = 1.5	HAQ = 2.0	HAQ = 2.5
30 years	92,163	67,399	43,159	24,379	30,751
40 years	95,222	72,392	44,840	25,714	29,744
50 years	98,696	74,291	47,072	27,283	32,171
60 years	104,099	74,724	48,514	28,535	36,934
70 years	116,974	79,385	54,244	35,354	45,990
80 years	112,614	87,744	71,857	52,249	66,174

bDMARD = biologic disease-modifying antirheumatic drug; HAQ = Health Assessment Questionnaire; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

CADTH Exploratory Analyses

Table 27: CADTH Base Case for Conventional Disease-Modifying Antirheumatic Drug Population, Excluding Sarilumab

Scenario	Total Cost ($)	Total QALY	Incremental Cost ($)	Incremental QALY	ICER ($)
IFX → ETN → TCZi → RTX → Palliative care	372,831	14.673	–	–	–
ETN → TCZi → RTX → Palliative care	387,262	14.108	14,431	-0.565	Dominated
BAR 2 mg → ETN → TCZi → RTX → Palliative care	427,272	14.770	54,441	0.096	Ext. dom.
TOF → ETN → TCZi → RTX → Palliative care	429,286	14.847	56,455	0.173	Ext. dom.
GOL → ETN → TCZi → RTX → Palliative care	429,350	14.683	56,518	0.010	Dominated
CTZ → ETN → TCZi → RTX → Palliative care	431,667	14.873	58,836	0.200	291,099
ABTi → ETN → TCZi → RTX → Palliative care	441,498	14.702	68,667	0.028	Dominated
ADA → ETN → TCZi → RTX → Palliative care	445,941	14.759	73,110	0.086	Dominated

ABTi = abatacept IV; ADA = adalimumab; BAR = baricitinib; CTZ = certolizumab; ETN = etanercept; Ext. dom. = extended dominance; GOL = golimumab; ICER = incremental cost-effectiveness ratio; IFX = infliximab; MTX = methotrexate; QALY = quality-adjusted life-year; RTX = rituximab; TCZi = tocilizumab IV; TOF = tofacitinib.

Note: Results are presented deterministically, as there were errors identified with the manufacturer's probabilistic analysis. All initial treatment are in addition to methotrexate.

Table 28: CADTH Base Case for Conventional Disease-Modifying Antirheumatic Drug Population, Original Baseline Characteristics

Scenario	Total Cost ($)	Total QALY	Incremental Cost ($)	Incremental QALY	ICUR ($)
IFX → ETN → TCZi → RTX → Palliative care	347,416	12.810	–	–	–
ETN → TCZi → RTX → Palliative care	359,678	12.382	12,261	–0.427	Dominated
BAR 2 mg → ETN → TCZi → RTX → Palliative care	396,529	12.908	49,113	0.098	Ext. dom.
TOF → ETN → TCZi → RTX → Palliative care	397,846	12.963	50,429	0.154	Ext. dom.
GOL → ETN → TCZi → RTX → Palliative care	398,191	12.820	50,775	0.010	Dominated
CTZ → ETN → TCZi → RTX → Palliative care	400,433	12.989	53,017	0.180	Ext. dom.
ABTi → ETN → TCZi → RTX → Palliative care	409,542	12.842	62,126	0.033	Dominated
ADA → ETN → TCZi → RTX → Palliative care	413,220	12.888	65,804	0.079	Dominated
SAR → ETN → TCZi → RTX → Palliative care	413,220	12.888	67,730	0.378	179,020

ABTi = abatacept IV; ADA = adalimumab; BAR = baricitinib; CTZ = certolizumab; ETN = etanercept; Ext. dom. = extended dominance; GOL = golimumab; ICUR = incremental cost-utility ratio; IFX = infliximab; MTX = methotrexate; QALY = quality-adjusted life-year; RTX = rituximab; SAR = sarilumab; TCZi = tocilizumab IV; TOF = tofacitinib.

Note: Results are presented deterministically, as there were errors identified with the manufacturer's probabilistic analysis. All initial treatment are in addition to methotrexate.

Table 29: CADTH Base Case for Biologic Disease-Modifying Antirheumatic Drug Population, Excluding Sarilumab

Scenario	Total Cost ($)	Total QALY	Incremental Cost ($)	Incremental QALY	ICUR ($)
RTX → Palliative care	295,257	10.849	–	–	–
BAR 2 mg → RTX → Palliative care	329,471	11.590	34,214	0.741	Ext. dom.
GOL → RTX → Palliative care	336,348	11.674	41,092	0.825	Ext. dom.
TOF → RTX → Palliative care	344,941	11.997	49,684	1.148	Ext. dom.
ABTi → RTX → Palliative care	354,421	11.970	59,164	1.121	Dominated
TCZi → RTX → Palliative care	358,068	12.536	62,811	1.687	37,226

ABTi = abatacept IV; BAR = baricitinib; Ext. dom. = extended dominance; GOL = golimumab; ICUR = incremental cost-utility ratio; MTX = methotrexate; QALY = quality-adjusted life-year; RTX = rituximab; TCZi = tocilizumab IV; TOF = tofacitinib.

Note: Results are presented deterministically, as there were errors identified with the manufacturer's probabilistic analysis. All initial treatment are in addition to methotrexate.

Table 30: CADTH Base Case for Biologic Disease-Modifying Antirheumatic Drug Population, Original Baseline Characteristics

Scenario	Total Cost ($)	Total QALY	Incremental Cost ($)	Incremental QALY	ICER ($)
RTX → Palliative care	262,254	7.681	–	–	–
BAR 2 mg → RTX → Palliative care	290,698	8.359	28,445	0.679	Ext. dom.
GOL → RTX → Palliative care	296,115	8.425	33,861	0.744	Ext. dom.
SAR → RTX → Palliative care	298,263	8.527	36,009	0.847	Ext. dom.
ABTi → RTX → Palliative care	310,003	8.669	47,750	0.988	Dominated
TOF → RTX → Palliative care	301,794	8.694	39,540	1.013	Ext. dom.
TCZi → RTX → Palliative care	310,218	9.147	47,964	1.466	32,722

ABTi = abatacept IV; BAR = baricitinib; Ext. dom. = extended dominance; GOL = golimumab; ICER = incremental cost-effectiveness ratio; MTX = methotrexate; QALY = quality-adjusted life-year; RTX = rituximab; SAR = sarilumab; TCZi = tocilizumab IV; TOF = tofacitinib.

Note: Results are presented deterministically, as there were errors identified with the manufacturer's probabilistic analysis. All initial treatment are in addition to methotrexate.

References

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