Common Drug Review
Pharmacoeconomic Review Report

November 2016

Drug	Canakinumab (Ilaris)
Indication	Treatment of active systemic juvenile idiopathic arthritis in patients aged 2 years and older
Reimbursement request	Treatment of active systemic juvenile idiopathic arthritis in patients 2 years and older who are contraindicated to, or have discontinued, any biologic therapy for lack of efficacy or intolerance
Dosage form(s)	150 mg subcutaneous injection
NOC date	December 12, 2013
Manufacturer	Novartis Pharmaceuticals Canada Inc.

This review report was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). In addition to CADTH staff, the review team included two clinical experts in rheumatology and pediatric rheumatology who provided input on the conduct of the review and the interpretation of findings.

Through the CADTH Common Drug Review (CDR) process, CADTH undertakes reviews of drug submissions, resubmissions, and requests for advice, and provides formulary listing recommendations to all Canadian publicly funded federal, provincial, and territorial drug plans, with the exception of Quebec.

The report contains an evidence-based clinical and/or pharmacoeconomic drug review, based on published and unpublished material, including manufacturer submissions; studies identified through independent, systematic literature searches; and patient-group submissions. In accordance with *CDR Update – Issue 87*, manufacturers may request that confidential information be redacted from the CDR Clinical and Pharmacoeconomic Review Reports.

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ABBREVIATIONS

ACR Pedi	American College of Rheumatology Pediatric
BSC	best supportive care
CDR	CADTH Common Drug Review
CHAQ	Childhood Health Assessment Questionnaire
CUA	cost-utility analysis
DMARD	disease-modifying antirheumatic drug
EQ-5D	EuroQoL 5-dimensions (health outcomes questionnaire)
ICUR	incremental cost-utility ratio
ITC	indirect treatment comparison
MAS	macrophage activation syndrome
NSAID	nonsteroidal anti-inflammatory drug
OCCI	Ontario Case Costing Initiative
PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life-year
sJIA	systemic juvenile idiopathic arthritis

TABLE 1: SUMMARY OF THE MANUFACTURER'S ECONOMIC SUBMISSION

Drug Product	Canakinumab (Ilaris) 150 mg subcutaneous injection (single-use vial)
Study Questions	• Primary analysis: "From the Canadian health care system perspective, what is the cost-effectiveness of Ilaris as a first-line biologic for the treatment of active sJIA in patients aged two years and older who have responded inadequately to previous therapy with one or more nonsteroidal anti-inflammatory steroids [NSAID] and corticosteroids as compared to Actemra [tocilizumab]?" • Secondary analysis: "From the Canadian health care system perspective, what is the cost-effectiveness of Ilaris as a second-line biologic for the treatment of active sJIA in patients aged two years and older who have discontinued any biologic therapy for lack of efficacy or intolerance as compared to the best supportive care (BSC)?"
Type of Economic Evaluation	Cost-utility analysis (CUA)
Target Populations	• Primary analysis: first-line biologic treatment in patients two years and older with active sJIA who have responded inadequately due to intolerance or lack of efficacy to NSAIDs and systemic corticosteroids. • Secondary analysis: second-line biologic treatment in patients two years and older with active sJIA who have discontinued any biologic due to intolerance or lack of efficacy.
Treatment	Canakinumab: for patients with a body weight of > 9 kg, 4 mg/kg (max 300 mg) every 4 weeks via subcutaneous injection.
Outcome	Quality-adjusted life-year (QALY)
Comparators	• Primary analysis: tocilizumab intravenous (IV) infusion (12 mg/kg in patients weighing less than 30 kg and 8 mg/kg in patients weighing 30 kg or more) • Secondary analysis: BSC, which is stated to be steroids (e.g., prednisone) and methotrexate.
Perspective	Health care payer perspective
Time Horizon	Up to 18 years (patients remain in the model up to age 20). Mean age in the model was 8.69 years.
Manufacturer Results for Base Case	• First-line biologic treatment (primary analysis), canakinumab vs. tocilizumab, ICUR: $3,273,360 per QALY. When manufacturer's risk-sharing arrangement was applied ([redacted]), the ICUR was $1,036,258 per QALY. • Second-line biologic treatment (secondary analysis), canakinumab vs. BSC, ICUR: $824,830 per QALY. When manufacturer's risk-sharing arrangement was applied, the ICUR was $307,981 per QALY.
Key Limitations	• The data used for the primary and the secondary analyses are not from the specific populations reported to have been modelled (biologic-naive patients for the primary analysis and biologic-experienced patients for the secondary analysis). For both analyses, clinical data were based on a population that had a mix of both patient types. This raises uncertainty of whether the results are reflective of the specific patient populations aimed to be assessed. This could not be tested by CDR because of limited stratified data for biologic-naive and biologic-experienced patients. • The patients' baseline characteristics were based on a single trial (G2301). Efficacy data used to develop the model predictive algorithms was sourced from a different trial than the one used to inform the patients' baseline

	characteristics. The patient characteristics were not stratified for biologic-naive and biologic-experienced patients. CDR tested the impact of varying the patient characteristics. • Treatment response was based on the ACR Pedi 30, while the CDR clinical expert suggested the ACR Pedi 50 is typically used in clinical practice. CDR used the ACR Pedi 50 in reanalyses. • There is uncertainty associated with the utility mapping algorithm used by the manufacturer. This approach was chosen despite the collection of EQ-5D scores in the trials. CDR tested the impact of utility values. • The primary analysis comparing canakinumab with tocilizumab was based on an indirect treatment comparison (ITC), [redacted]. CDR tested the assumption of equal efficacy of the drugs.
CDR Best Estimate	CDR undertook scenario analyses varying patient's baseline characteristics, the utility mapping algorithm and using the ACR Pedi 50 as a response measure. The CDR best estimate was: • In first-line biologic treatment, for canakinumab vs. tocilizumab, an ICUR range of $1,846,134 to $6,521,275 per QALY. Including the risk-sharing arrangement, the ICUR ranges from $576,249 to $2,034,598 per QALY. • In second-line biologic treatment, for canakinumab vs. BSC, an ICUR range of $459,068 to $1,584,896 per QALY. Including the risk-sharing arrangement, the ICUR ranges from $171,111 to $591,272 per QALY. For the first-line biologic treatment scenario assuming equal efficacy for canakinumab and tocilizumab, it resulted in canakinumab being $776,024 more costly than tocilizumab over the ~10 year average time horizon. Considering the risk-sharing arrangement, canakinumab cost $[redacted] more than tocilizumab. Given the high uncertainty associated with the data used for modelling, which do not systematically correspond to the patient population aimed to be assessed (refer to key limitation 1), the true cost-effectiveness of canakinumab compared with tocilizumab (first-line biologic) and BSC (second-line biologic) is highly uncertain.

ACR Pedi = American College of Rheumatology Pediatric score; BSC = best supportive care; CDR = CADTH Common Drug Review; EQ-5D = EuroQoL 5-dimensions (health outcomes questionnaire); ICUR = incremental cost-utility ratio; NSAID = nonsteroidal anti-inflammatory disease; QALY = quality-adjusted life-year; sJIA = systemic juvenile idiopathic.

EXECUTIVE SUMMARY

Background

Canakinumab (Ilaris) is a fully human monoclonal antibody that selectively binds and neutralizes interleukin-1 beta (IL-1 beta), available as a single-use vial containing 150 mg powder for solution for subcutaneous injection, for the treatment of active systemic juvenile idiopathic arthritis (sJIA) in patients 2 years and older.[1] The recommended dose is 4 mg/kg (up to a maximum of 300 mg), administered every four weeks via subcutaneous injection, for patients with a body weight greater of 9 kg or greater.[2] The manufacturer submitted a price of $16,000 per vial of 150 mg canakinumab,[3] which corresponds to an annual cost of $208,000 for patients weighing up to 37 kg and $416,000 for patients weighing 38 kg or more.[3] The manufacturer is requesting reimbursement of canakinumab for the treatment of active sJIA in patients two years and older who are contraindicated to or have discontinued any biologic therapy for lack of efficacy or intolerance.[1]

Canakinumab was previously submitted for review to the CADTH Common Drug Review (CDR) in 2010 for cryopyrin-associated periodic syndrome (CAPS). The CADTH Canadian Expert Drug Advisory Committee (CEDAC; the predecessor to the CADTH Canadian Drug Expert Committee [CDEC]) recommended that canakinumab not be listed by participating drug plans for reimbursement; as although the clinical studies reported a significant reduction in disease flare-ups, there was no significant difference in quality of life (Physician Global Assessment score), and the studies did not provide evidence that canakinumab reduces or reverses severe disease complications.[4]

Currently, the only treatment indicated for sJIA and reimbursed by some public drug programs is tocilizumab, which is administered as a weight-based intravenous infusion (8 mg or 12 mg per kg) every four weeks. The annual cost ranges from $9,400 to $28,200 per patient annually (assuming a patient weight range from 12 kg to 60 kg). Other biologic treatments may also be used off label for sJIA in some jurisdictions.

The manufacturer undertook a cost-utility analysis (CUA) that compared canakinumab and tocilizumab as first-line biologic treatment for patients two years and older with active sJIA who have responded inadequately due to intolerance or lack of efficacy to NSAIDs and systemic corticosteroids. For this analysis, the manufacturer concluded that the incremental cost-utility ratio (ICUR) for canakinumab compared with tocilizumab was more than $3,000,000 per quality-adjusted life-year (QALY) gained. Additionally, the manufacturer undertook a secondary analysis, in line with the requested reimbursement criteria, comparing canakinumab and best supportive care (BSC) as second-line biologic treatment for patients two years and older with active sJIA who are contraindicated to or have discontinued any biologic therapy for lack of efficacy or intolerance. For this analysis, the manufacturer reported that the ICUR for canakinumab compared with BSC was approximately $824,000 per QALY gained.

The manufacturer also presented a confidential risk-sharing arrangement, [redacted], which improved the cost-effectiveness ratios of the above two analyses, but not to a point that they could be considered cost-effective at conventionally accepted thresholds. The manufacturer undertook various sensitivity analyses, which indicated that in no circumstance was canakinumab cost-effective as a second-line treatment (compared with BSC) at a willingness-to-pay threshold of $200,000 per QALY.[3]

Summary of Identified Limitations

CDR identified several limitations with the manufacturer's economic analysis. The most notable limitations were that the submitted patient-level simulation model lacks transparency and flexibility; and that the data used to model the primary analyses (first-line biologic treatment) were not based on stratified analyses but on a mixed population (comprised of biologic-naive and biologic-experienced patients), and the data used for the secondary analysis (second-line biologic treatment) were only partially from the population under assessment. CDR was unable to test this limitation as data for the stratified populations were not available. Other identified limitations, which were tested by CDR include: patients' baseline characteristics; the mapping algorithm used to derive utility scores; and the response to treatment threshold applied for the manufacturer's analysis. Finally, the primary analysis comparing canakinumab and tocilizumab was based on an indirect treatment comparison (ITC) [redacted]. Hence CDR tested the assumption of equal efficacy of the drugs.

Results and Conclusions

The limitation regarding the true population assessed by the primary (biologic-naive) and secondary (biologic-experienced) analyses — both analyses actually assessed a population comprising a mixture of biologic-naive and biologic-experienced patients —is critical; and the true cost-effectiveness of canakinumab compared with tocilizumab (first-line biologic) and BSC (second-line biologic) is thus highly uncertain. This uncertainty also questions the results of the CDR reanalyses. Nevertheless, the variation of patients' baseline characteristics and utility scores by CDR may provide some indications of the cost-effectiveness of canakinumab with regard to disease severity.

Varying patient baseline characteristics, utility scores, and applying a response criterion at an American College of Rheumatology Pediatric (ACR Pedi) score 50, as a second-line biologic treatment after failure on another biologic (as per the reimbursement request), the CDR best estimate indicated the ICUR for canakinumab may range from $459,000 to $1,584,000 per QALY compared with BSC. When including the manufacturer's risk-sharing arrangement, the ICUR ranged from $171,000 to $591,000 per QALY for canakinumab compared with BSC. It is notable that patients receiving canakinumab accrued less than 0.8 incremental QALYs compared with patients receiving BSC during the analysis time horizon (average of ~10 years).

When used as a first-line biologic treatment for patients with sJIA, the CDR best estimate indicated the ICUR may range from $1,846,000 to $6,521,000 per QALY compared with tocilizumab, when a slight treatment benefit is assumed for canakinumab. When including the manufacturer's risk-sharing arrangement, the ICUR ranged from $576,000 to $2,034,000 per QALY for canakinumab compared with tocilizumab. If equivalent efficacy is assumed, based on the findings from the manufacturer's ITC, total costs are substantially higher for canakinumab compared with tocilizumab (incremental cost of $776,000 over the average ~10 year time horizon; reduces to $[redacted] when considering the risk-sharing arrangement).

In terms of interpreting the above presented range results, based on the variations tested by CDR, a range of disease severity is represented; the lower ICURs being for higher disease severity.

Based on the CDR best estimates, a price reduction of 79% to 94% is required to improve the ICUR of canakinumab to $100,000 per QALY compared with BSC. A price reduction of 86% to 90% is required to improve the ICUR of canakinumab to $100,000 per QALY compared with tocilizumab (APPENDIX 5: REVIEWER WORKSHEETS for price reduction analyses considering the risk-sharing arrangement).

Assuming equivalent efficacy, the vial cost of canakinumab would have to be reduced by more than 93% to have an annual cost equivalent to that of tocilizumab to treat a patient weighing 20 kg, or by more than 89% for a patient weighing 50 kg.

INFORMATION ON THE PHARMACOECONOMIC SUBMISSION

1. SUMMARY OF THE MANUFACTURER'S PHARMACOECONOMIC SUBMISSION

The manufacturer presented two cost-utility analyses (CUAs) to assess the cost-effectiveness of canakinumab in Canada. The manufacturer's primary analysis compared canakinumab and tocilizumab for first-line biologic treatment for patients two years and older with systematic juvenile idiopathic arthritis (sJIA) who have responded inadequately due to intolerance or lack of efficacy to nonsteroidal anti-inflammatory drugs (NSAIDs) and systemic corticosteroids. The manufacturer's secondary analysis compared canakinumab and best supportive care (BSC) for second-line biologic treatment for patients two years and older with active sJIA who are contraindicated to or have discontinued any biologic therapy for lack of efficacy or intolerance (as per the manufacturer's drug reimbursement request).

The manufacturer's analyses were undertaken using an individual-level, time-to-event simulation approach to simulate disease pathways, and treatment effects and outcomes using predictive modelling for patients until they reached 20 years of age. This was conducted using Microsoft Excel, from the perspective of a third-party payer in Canada. One hundred bootstrap samples were run for 10 replications for a total of 1,000 patients per treatment.

Treatment response was measured with the American College of Rheumatology Pediatric (ACR Pedi) score and the Child Health Assessment Questionnaire (CHAQ) score, which illustrate the patient's level of disability. Continuation of treatment was based on an ACR Pedi response of 30% (ACR Pedi 30) at the week 12 assessment. This denotes at least a 30% improvement in three of the six variables in the core set (physician global assessment of disease activity [visual analogue scale; VAS], parent/patient global assessment of overall well-being [VAS], functional ability, number of joints with active arthritis, number of joints with limited range of motion, and erythrocyte sedimentation rate [ESR]), while no more than one of the remaining variables can worsen by more than 30%. ACR Pedi response is linked to all other health outcomes simulated in the model; that is, ACR Pedi response was determined to influence whether a patient has inactive disease, is steroid-free, or discontinues treatment. Patients could discontinue treatment due to a lack of treatment response, loss of efficacy, or occurrence of macrophage activation syndrome (MAS).[3]

Baseline patient characteristics were derived from individual patient-level data from the open-label run-in stage of the G2301 trial.[3] Efficacy data (including ACR Pedi response, CHAQ score, steroid-use, inactive disease) were derived from a manufacturer-submitted indirect treatment comparison (ITC)[5] comparing data from the G2305 and TENDER trials for the comparison of canakinumab with tocilizumab; and by pooling data from patients enrolled in the two phase III trials (G2301 and G2305) and the extension phase (G2301E1) for the second-line comparison of canakinumab with BSC.[3] A mapping algorithm was developed for deriving utility values; its development was informed by EuroQoL five dimensions (EQ-5D) data collected in the G2301, G2305, and G2301E1 trials. This mapping algorithm was developed to correlate CHAQ scores to utility values; the CHAQ score correlating with patient's quality of life and the ACR Pedi score,[6] the latter being used as primary efficacy data in the model. Treatment effect was modelled through predictive equations. Only an ACR Pedi response of 90% (ACR Pedi 90) was found to be a statistically significant predictor of future factors, such as attaining steroid-free status, the time to attain steroid-free status, achievement of inactive disease (both at and after the week 12 assessment),

and treatment discontinuation. The base case assumes an excess risk of mortality associated with sJIA, by applying a standardized mortality ratio of 1.8 obtained from the literature.[6] Patients who achieve remission (defined by inactive disease for 52 weeks) remain on treatment until the end of the model time horizon.

Three types of events were costed in the model: steroid-related adverse events (AEs), MAS, and infection. The cost of steroid-related AEs was obtained from a United Kingdom study (Manson 2009);[7] the cost associated with MAS was obtained from the Ontario Case Costing Initiative (OCCI),[8] and infection costs were derived based expert opinion and OCCI data.[8] Treatment monitoring was based on ACR JIA 2011 treatment recommendations[9] and input from experts. Associated costs were sourced from the Ontario Schedule of Benefits — general[10] and laboratory services;[11] as well as the OCCI, Ontario Podiatry Schedule,[12] and Ontario Physical Therapy Schedule.[12] The cost of canakinumab was based on manufacturer information; comparator and concurrent treatment costs were sourced from the Ontario Drug Benefit Formulary.[13,14]

2. MANUFACTURER'S BASE CASE

In the first-line biologic setting, the ICUR for canakinumab compared with tocilizumab was $3,273,360 per QALY. In the second-line biologic setting, the ICUR for canakinumab compared with tocilizumab was $824,830 per QALY. The manufacturer also put forward a risk-sharing arrangement [redacted]. The results of the analyses are presented in Table 2.

TABLE 2: SUMMARY OF RESULTS OF THE MANUFACTURER'S BASE CASE.

Setting and Analysis	Cost of CAN / Cost of Comparator	Incremental Cost of CAN	QALYs for CAN/ QALYs for Comparator	Incremental QALYs of CAN	Incremental Cost per QALY
First-line (canakinumab vs. tocilizumab)					
Full price	$893,764 / $114,890	$785,943	5.03 / 4.78	0.24	$3,273,360
Risk-sharing arrangement[a]	$356,629 / $114,890	$248,808	5.03 / 4.78		$1,036,258
Second-line (canakinumab vs. BSC)					
Full price	$684,289 / $34,892	$649,396	4.67 / 3.89	0.79	$824,830
Risk-sharing arrangement[a]	$277,369 / $34,892	$242,476	4.67 / 3.89		$307,981

BSC = best supportive care; CAN = canakinumab; QALY = quality-adjusted life-year.
[a] [redacted]

3. SUMMARY OF MANUFACTURER'S SENSITIVITY ANALYSES

The manufacturer's one-way deterministic sensitivity analyses were reported on the secondary analysis, including the manufacturer's risk-sharing arrangement (ICUR = $307,981). The manufacturer concluded that the model results were stable relative to variations in the model parameters; aside from amendments to the treatment discontinuation rate, which resulted in an ICUR of $1,036,042 per QALY (base case: $307,981 per QALY). The results from the one-way deterministic sensitivity analyses ranged from $282,283 to $384,151 per QALY.

The manufacturer's probabilistic sensitivity analysis found there were no simulations in which canakinumab was cost-effective as a second-line treatment (compared with BSC) at a willingness-to-pay threshold of $200,000 per QALY.

4. LIMITATIONS OF MANUFACTURER'S SUBMISSION

CDR identified the following limitations with the manufacturer's economic analysis:

- **Uncertainty regarding the modelled patient populations for both the primary and secondary analyses:** The data used to populate the manufacturer's analyses do not appear to have been based on patient populations that are suggested as having been assessed. The data for the first-line comparison of canakinumab versus tocilizumab were based on an ITC that did not stratify patients to those that had not received prior biologic treatment and those that had received biologic treatment, while the data for the second-line comparison of canakinumab versus BSC were based on pooling data from the three canakinumab studies (G2301, G2305 and G2301E1). Although no stratification to look at only patients who had previously received biologic treatment for sJIA was evident in the manufacturer's pharmacoeconomic report, the manufacturer provided clarification that the pooled trial data for canakinumab were only from patients who had previously received biologic treatment, but acknowledged that there was no stratification in the BSC treatment group. CDR was unable to test revised estimates as subgroup data were not presented by the manufacturer or provided in the Clinical Study Reports.
- **Uncertainty regarding the patient characteristics at baseline:** Patient characteristics used for predictive equations are based on part 1 (open-label phase) of Study G2301 and are applied to all treatments in both the primary and secondary analyses; yet clinical efficacy data for canakinumab are based on G2305 (ITC versus tocilizumab) or from pooling data from studies G2301, G2305, and G2301E1 (versus BSC). CDR tested the potential impact of the patient characteristics by altering the values using the standard deviation around the mean from G2301 for all baseline patient characteristics except age, gender, weight, height, and individual utility value.
- **Uncertainty regarding the definition of treatment response:** The manufacturer used the ACR Pedi 30 in their base-case analysis at the threshold for treatment response; however, the only statistically significant predictive variable of future health outcomes was the ACR Pedi 90. Additionally, the CDR clinical expert noted that an ACR Pedi 50 is generally considered to define response in Canadian clinical practice. CDR tested the results using higher definitions of response; ACR Pedi 50 (based on feedback from the CDR clinical expert) and ACR Pedi 90 (based on the predictive equations).

- **Uncertainty associated with the utility values**: There is uncertainty associated with the utility values used in the manufacturer's base case. Direct values are preferred to values that are mapped from disease-specific quality of life questionnaires. Although the manufacturer used a mapping algorithm that weighted directly collected utility values and CHAQ scores from the canakinumab trials to derive a utility score to use in the model, the directly collected EQ-5D values were not presented by the manufacturer. CDR noted that the manufacturer tested their results based on the mapping algorithm used in the tocilizumab submission to the National Institute for Health and Care Excellence (NICE), which resulted in a higher ICUR. CDR tested the sensitivity of the model using two times the 95% confidence intervals around the values presented in the manufacturer's mapping algorithm.
- Data used to inform comparative efficacy of canakinumab and tocilizumab: Though CDR clinical reviewers indicated the [redacted], the reviewers noted mixed findings with regard to health-related quality of life and functional outcomes. CDR clinical reviewers also noted that there is a high degree of uncertainty surrounding the findings of the indirect comparisons. However, the manufacturer's CUA demonstrated additional health benefits from canakinumab compared with tocilizumab. CDR tested the assumption of equal efficacy of the two drugs.

5. CADTH COMMON DRUG REVIEW REANALYSES

CDR undertook one-way analyses on the manufacturer's model to test the limitations identified above:

- As patient characteristics were based on an at least partially combined population (treatment experienced and treatment naive), CDR tested the lower and upper bounds (based on standard deviation from the mean) of the patient characteristics from the G2301 trial to determine whether perceived treatment severity have an impact on the results; the ICURs for canakinumab were $2,273,719 and $5,904,314 per QALY versus tocilizumab as first-line biologic therapy, and $545,923 and $1,404,631 per QALY versus BSC for second-line biologic therapy. When including the manufacturer's risk-sharing arrangement, the ICURs for canakinumab as first-line biologic compared with tocilizumab were $706,261 and $1,833,177 per QALY, while as second-line biologic compared with BSC, the ICURs were $203,684 and $524,923 per QALY.
- As feedback from the clinical expert suggested that an ACR Pedi 30 may not be used in clinical practice to define response, CDR tested the results assuming response rates of ACR Pedi 50 and ACR Pedi 90. Using the revised response rates decreases the ICURs for canakinumab as first-line biologic compared with tocilizumab ($2,392,153 and $3,035,904 per QALY) and as second-line biologic compared with BSC ($697,997and $796,687 per QALY). When including the manufacturer's risk-sharing arrangement, the ICURs for canakinumab as first-line biologic compared with tocilizumab were $750,645 and $946,873 per QALY, while as second-line biologic compared with BSC, the ICURs were $260,594 and $296,594 per QALY. CDR notes there is still uncertainty with the predictive equations.

- Given the uncertainty associated with the utility values, CDR tested utility scores based on the mapping algorithm values revised by twice the 95% confidence intervals. Altering the upper and lower bounds resulted in ICURs for canakinumab as first-line biologic compared with tocilizumab of $2,827,052 and $3,806,858 per QALY, while as second-line biologic compared with BSC, the ICURs were $719,986 and $966,152 per QALY. When including the risk-sharing arrangement, the ICURs were $877,433 and $1,181,536 per QALY compared with tocilizumab and $268,833 and $360,749 per QALY compared with BSC.
- CDR assumed equivalent efficacy for canakinumab and tocilizumab, which found there is no difference in QALYs, but canakinumab has substantially higher incremental costs as compared with tocilizumab ($766,000; $[redacted] considering the risk-sharing arrangement).

Although CDR identified substantial uncertainty with regard to the data used to represent the patient populations for the analyses presented, as stratified data were not presented, CDR undertook a multi-way analysis to determine a range for CDR's best estimates, testing upper and lower bounds for baseline patient characteristics, upper and lower bounds for utility values, and considering an ACR Pedi 50 as definition of response. The results indicated the ICUR for canakinumab as second-line biologic therapy compared with BSC ranged from $459,000 to $1,584,000 per QALY; while the ICUR for canakinumab as first-line biologic therapy compared with tocilizumab ranged from $1,846,000 to $6,521,000 per QALY. When considering the risk-sharing arrangement, the incremental cost-effectiveness ratio (ICER) for first-line biologic treatment ranged from $576,249 and $2,034,598 per QALY (versus tocilizumab), while for second-line biologic treatment, the ICER ranged from $171,111 to $591,272 per QALY (versus BSC).

CDR undertook price reduction analyses based on the CDR base case for both the first-line biologic and second-line biologic comparisons. The results are reported in Table 3 for canakinumab as first-line biologic compared with tocilizumab and Table 4 as second-line biologic compared with BSC.

Further information on the CADTH CDR analyses (including price reduction scenarios for the risk-sharing arrangement) is available in APPENDIX 5: REVIEWER WORKSHEETS.

TABLE 3: CDR PRICE REDUCTION SCENARIO ANALYSES: FIRST-LINE BIOLOGIC

ICURs for canakinumab compared with tocilizumab			
Price	**Base-case analysis submitted by manufacturer**	**CDR best estimate (less severe)**	**CDR best estimate (more severe)**
Submitted ($16,000)	$3,273,360	$6,521,275	$1,846,134
25% reduction ($12,000)	$2,347,614	$4,724,164	$1,337,282
50% reduction ($8,000)	$1,451,309	$2,927,053	$828,430
75% reduction ($4,000)	$555,003	$1,129,942	$319,577
90% reduction ($1,600)	$17,220	$51,676	$14,266

CDR = CADTH Common Drug Review; ICUR = incremental cost-effectiveness ratio.

To achieve an ICUR of $100,000 per QALY based on the CDR best estimates, the price of canakinumab would have to be reduced by 90% (less severe) or 86% (more severe).

TABLE 4: CDR PRICE REDUCTION SCENARIO ANALYSES: SECOND-LINE BIOLOGIC

ICURs for canakinumab compared with BSC			
Price	**Base-case analysis submitted by manufacturer**	**CDR best estimate (less severe)**	**CDR best estimate (more severe)**
Submitted ($16,000)	$824,830	$1,584,896	$459,068
25% reduction ($12,000)	$618,206	$1,188,536	$344,075
50% reduction ($8,000)	$411,582	$791,376	$229,081
75% reduction ($4,000)	$204,958	$394,615	$114,081
90% reduction ($1,600)	$80,984	$156,559	$45,091

BSC = best Supportive Care; CDR = CADTH Common Drug Review; ICUR = incremental cost-effectiveness ratio.

To achieve an ICUR of $100,000 per QALY based on the CDR best estimates, the price of canakinumab would have to be reduced by 94% (less severe) or 79% (more severe).

6. ISSUES FOR CONSIDERATION

- To optimize the cost-effective use of canakinumab, it is important to assure the appropriate population is identified. The manufacturer indicated in their pharmacoeconomic report that there is currently no screening tool to identify patients with sJIA; therefore, diagnosis is based on symptoms using the International League of Associations of Rheumatology (ILAR) classification and on the elimination of possible alternative diseases, which is complex given some symptoms are common to other similar conditions.
- Canakinumab is a subcutaneous injection administered every four weeks, which may be preferable to patients compared with the administration of tocilizumab as an intravenous infusion over one-hour, every two weeks. Nevertheless, this preference should be weighted with the comparative cost and cost-effectiveness of the two drugs.
- The manufacturer's proposed a risk-sharing arrangement [redacted]. However, this may be difficult for some participating plans to implement. Also, feedback from the CDR clinical expert indicated that over time, treatments may be given at longer intervals than the proposed four weeks by the product monograph, which should be noted by the drug plans.

7. PATIENT INPUT

Input was received from two patient groups: the Canadian Arthritis Patient Alliance (CAPA), and the Arthritis Society (Canada). Both groups are primarily funded through grants and donations, from individuals, other professional organizations, and industry.

Patients with sJIA (or their caregivers, on their behalf) reported experiencing intense pain and fatigue associated with inflammation, which can lead them to feel isolated, depressed, and angry; this in turn has an impact on day-to-day activities. The limitations associated with the inability to perform daily routine activities can cause severe psychological burden to the child and to their families and caregivers. Caregivers are affected both psychologically and financially; requiring time off work. The main concern

highlighted by caregivers was cost; in terms of treatment, medical appointments, and time associated with each of these.

It was noted that regardless of treatment, patients' response could differ substantially. Patients often have to switch medications to find the one that they will respond to. Side effects associated with treatments can be important. Patients and caregivers noted specifically that the daily injections of anakinra make it a very painful drug to receive, and that the biologic disease-modifying antirheumatic drugs (DMARDs) (canakinumab and tocilizumab) seem to them more effective. Parents, caregivers, and patients believe that there is a need for new treatment options to improve quality of life for patients suffering from sJIA. Finally, it was mentioned that canakinumab was seen to have an advantage in terms of frequency of administration: canakinumab is administered every four weeks versus every two weeks for tocilizumab, and daily for anakinra. Nevertheless, this preference should be weighted with the comparative cost and cost-effectiveness of the drugs.

8. CONCLUSIONS

The limitation regarding the true population assessed by the primary (biologic-naive) and secondary (biologic-experienced) analyses — both analyses actually assessed a population comprising a mixture of biologic-naive and biologic-experienced patients — is critical; and the true cost-effectiveness of canakinumab compared with tocilizumab (first-line biologic) and BSC (second-line biologic) is thus highly uncertain. This uncertainty also questions the results of the CDR reanalyses. Nevertheless, the variation of patients' baseline characteristics and utility scores by CDR may provide some indications of the cost-effectiveness of canakinumab with regard to disease severity. The CDR results represent a range of disease severity; the lower ICURs indicating higher disease severity.

APPENDIX 1: COST COMPARISON

The treatment options presented in the tables below have been deemed to be appropriate by clinical experts for the treatment of patients with sJIA. Comparators may be recommended (appropriate) practice, versus actual practice. Comparators are not restricted to drugs, but may be devices or procedures. Existing product reimbursement agreements are not reflected in the table and as such may not represent the actual costs to public drug plans.

TABLE 5: COST COMPARISON TABLE FOR SYSTEMIC JUVENILE IDIOPATHIC ARTHRITIS (BIOLOGIC DRUGS)

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Average Annual Drug Cost ($)
Drugs indicated for the treatment of sJIA					
Canakinumab (Ilaris)	150 mg	Vial of powder for sol. for SC injection	16,000.00[a]	Body weight > 9 kg, 4 mg/kg (max 300 mg) every 4 weeks 37 kg or below: 208,000 38 kg or above: 416,000	
Tocilizumab (Actemra)	80 mg/4mL 200 mg/10mL 400 mg/20mL	Vials (concentrate sol. for IV infusion)	180.8100 452.0300 904.0600	Patients < 30 kg: 12 mg/kg Patients ≥ 30 kg: 8 mg/kg every 2 weeks	12 to 29 kg:[b] 9,402 to 23,506 30 kg or above:[b] 14,103 to 28,207[c]
Off-label drugs[d]					
Anakinra (Kineret)	100 mg	Prefilled syringe for SC injection	47.5814	100 mg daily	17,367

IV = intravenous; SC = subcutaneous; sJIA = systemic juvenile idiopathic; sol = solution.
All prices are from the Ontario Drug Benefit Formulary and Exceptional Access Program (both accessed March 2016) unless otherwise indicated, but do not include dispensing fees.[15]
All vials are single-use. Wastage was assumed when calculating annual costs. The cost of intravenous infusion is not included.
[a] Manufacturer's submitted price.[3]
[b] Tocilizumab is listed for patients 2 years or older. The average weight of 2 year olds in Canada is 12 kg, and the average weight of 17 year olds in Canada is 60 kg.[16]
[c] The upper bound limit assumes a maximum patient weight of 60 kg; whereby, a 1 x 400 mg vial and 1 x 80 mg vial will be used.
[d] Anakinra is not indicated for patients with sJIA. However, as noted by the clinical expert, it is often prescribed to patients with sJIA. Additionally, it is reimbursed for sJIA by the Ontario Drug Benefit Formulary.[14]

TABLE 6: OTHER POTENTIAL TREATMENTS FOR SYSTEMIC JUVENILE IDIOPATHIC ARTHRITIS (TNF INHIBITORS) — NOT INDICATED

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Average Annual Drug Cost ($)
Adalimumab (Humira)	40 mg/0.8 mL	Vial of sterile solution for SC injection	740.3600	Age 2 to < 4: 20 mg every 2 weeks Age 4 to 17: 40 mg every 2 weeks	19,249
Abatacept (Orencia)	250 mg/15 mL	Vial for IV infusion	490.0470	Patients < 75 kg: 10 mg/kg (Patients ≥ 75 kg max 1,000 mg) every 4 weeks[a]	20 kg to 60 kg:[b] 6,371 to 19,112
Etanercept (Enbrel)	50 mg/mL 25 mg/vial	Prefilled syringe Powder for reconstitution	395.3900 197.6350	0.8 mg/kg (max 50 mg) per week[c]	16 kg to 60 kg:[d] 10,277 to 20,554
Infliximab (Remicade)	100 mg/vial	Injection for IV infusion	987.5600	3 mg/kg every 8 weeks[e]	33 kg or below: 6,419 34 kg to 60 kg: 12,838

IV = intravenous; SC = subcutaneous; TNF = tumour necrosis factor.
All prices are from the Ontario Drug Benefit Formulary and Exceptional Access Program (both accessed March 2016) unless otherwise indicated, but do not include dispensing fees.[15]
[a] Patients receive doses at weeks 2 and 4 to start, and then every 4 weeks. In the first year of treatment, abatacept would cost an extra $490 to $1,470 compared with subsequent years.
[b] Abatacept is listed for patients aged 6 years or older. The average weight of 6 year olds in Canada is 20 kg, and the average weight of 17 year olds in Canada is 60 kg.[16]
[c] The 50-mg prefilled syringe should only be used for pediatric patients weighing 63 kg or more. All other patients receive the 25 mg vial of powder for reconstitution.
[d] Etanercept is listed for patients aged 4 years or older. The average weight of 4 year olds in Canada is 16 kg, and the average weight of 17 year olds in Canada is 60 kg.[16] For the calculation of the annual cost, it was assumed all patients received the 25 mg vial of etanercept.
[e] Patients receive doses at week 0, 2, and 6 to start and then every 8 weeks thereafter. In the first year of treatment, infliximab would cost an extra $2,469 to $7,407 compared with subsequent years. Additionally, for patients who have an incomplete response, the dose of infliximab may be increased to 10 mg/kg and or/ treated every 4 weeks.

TABLE 7: TREATMENTS USED IN SUPPORTIVE CARE FOR SYSTEMIC JUVENILE IDIOPATHIC ARTHRITIS — NOT INDICATED

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Average Annual Drug Cost[a] ($)
Non-biologic DMARDs					
Methotrexate (generics)	2.5 mg 10 mg 10 mg/mL 25 mg/mL	Tablet Single-use vial	0.6325 2.7000[b] 12.5000/2 mL 8.9200/2 mL	1 mg/kg weekly	Oral: 173-842[c] Injection: 650-1,114[d]
Corticosteroids					
Prednisone[e] (generics)	1 mg 5 mg 50 mg	Tablet	0.1066 0.0220 0.1735	1 mg/kg weekly	11-13[f]

DMARD = disease-modifying antirheumatic drug.
All prices are from the Ontario Drug Benefit Formulary (accessed March 2016) unless otherwise indicated and do not include dispensing fees.[17]
[a] Based on a patient weight of 12 kg to 60 kg.
[b] Saskatchewan drug benefit formulary (accessed March 2016).
[c] Range is based on a 12 kg (1 x 10 mg tab + 1 x 2.5 mg tab weekly) to 60 kg (6 x 10 mg tab weekly) patient.
[d] Range is based on a 12 kg (1 x 25 mg/mL vial weekly) to 60 kg (1 x 25 mg/mL vial + 1 x 10 mg/mL vial weekly). The price of vials is based on a
2 mL solution package. Wastage assumed.
[e] Prednisone suspension might be used in younger patients, as noted by the CDR clinical expert.
[f] Range is based on a 60 kg patient (1 x 50 mg tablet + 2 x 5 mg tablet weekly) to 12 kg patient (2 x 5 mg tablet + 2 x 1 mg tablet weekly).

APPENDIX 2: SUMMARY OF KEY OUTCOMES

The following tables are presented based on the CDR best estimate (excluding the risk-sharing agreement).

TABLE 8: WHEN CONSIDERING ONLY COSTS, OUTCOMES & QUALITY OF LIFE, HOW ATTRACTIVE IS CANAKINUMAB RELATIVE TO TOCILIZUMAB FOR FIRST-LINE BIOLOGIC TREATMENT OF SJIA?

Canakinumab Vs. Tocilizumab	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	Range: $1,846,134 to $6,521,275 per QALY					

CE = cost-effectiveness; NA = not applicable; QALY = quality-adjusted life-year; sJIA = systemic juvenile idiopathic arthritis.

TABLE 9: WHEN CONSIDERING ONLY COSTS, OUTCOMES & QUALITY OF LIFE, HOW ATTRACTIVE IS CANAKINUMAB RELATIVE TO BSC FOR SECOND-LINE BIOLOGIC TREATMENT OF SJIA?

Canakinumab Vs. Best Supportive Care	Attractive	Slightly attractive	Equally attractive	Slightly unattractive	Unattractive	NA
Costs (total)					X	
Drug treatment costs alone					X	
Clinical Outcomes	X[a]					
Quality of life		X				
Incremental CE ratio or net benefit calculation	Range: $459,068 to $1,584,896 per QALY					

BSC = best supportive care; CE = cost-effectiveness; NA = not applicable; QALY = quality-adjusted life-year; sJIA = systemic juvenile idiopathic arthritis.

[a]This was based on the results of Study G2305 demonstrating that canakinumab is superior to placebo in achieving a treatment response as reflected by the significantly greater proportion of patients treated with canakinumab who achieved adapted ACR Pedi 50 responses at day 15; treatment response judged by the CDR clinical expert to be clinically meaningful.

APPENDIX 3: ADDITIONAL INFORMATION

TABLE 10: SUBMISSION QUALITY

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?			X
Comments	The submitted micro-simulation model lacks transparency and flexibility.		
Was the material included (content) sufficient?			X
Comments	Sufficient information was not provided regarding the efficacy data, predictive modelling equations, and there is substantial uncertainty based on the lack of transparency of the model. CDR also notes that there are some errors in reporting, and not all relevant information is provided in the report.		
Was the submission well organized and was information easy to locate?			X
Comments	As noted above, the model lacked transparency and was not sufficiency described in the report		

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

APPENDIX 4: SUMMARY OF OTHER HEALTH TECHNOLOGY ASSESSMENT REVIEWS OF CANAKINUMAB

Two health technology assessments that appraised canakinumab were identified. These included appraisals from the Pharmaceutical Benefits Advisory Committee (PBAC, Australia) and the Haute Autorité de Santé (HAS, France). The submission to HAS did not include economic evidence, but based on the submitted evidence, the committee considered that the actual benefit of canakinumab is sufficient and recommended it to be available as a second-line treatment for patients two years and older with active systemic juvenile idiopathic arthritis (sJIA) who have inadequately responded to previous therapy with NSAIDs and systemic corticosteroids; though HAS will re-assess this drug reimbursement listing after one year based on new data captured by a risk-management registry.[18] Table 12 provides a summary of the submission and recommendation from Australia (PBAC) and a comparison to the current submission to CDR.

TABLE 12: SUMMARY OF OTHER HEALTH TECHNOLOGY ASSESSMENT FINDINGS

	PBAC (March 2015)[19]
Drug	Canakinumab; 150 mg vial for subcutaneous injection
Price	Not available (redacted)
Treatment	4 mg/kg every four weeks
Comparator	Tocilizumab, 8 mg/kg (patients weighing > 30 kg) or 12 mg/kg (patients weighing < 30 kg) every 2 weeks Etanercept and adalimumab were also considered (secondary comparisons)
Population	Patients with a diagnosis of sJIA, without a polyarticular presentation, who have failed to respond to previous treatment with methotrexate, nonsteroidal anti-inflammatories or glucocorticoids
Type of model	Cost-minimization analysis, based on the assumption that canakinumab was likely to be non-inferior to tocilizumab (based on a manufacturer-conducted indirect comparison)
Results	Not available (redacted)
Key sources of uncertainty	Uncertainty in the determination of equi-effective doses between canakinumab and tocilizumab due to tocilizumab's variable dosing by weight, dependent on whether a patient is lighter or heavier than 30 kg. The submission assumed a normal distribution of body weight in its calculation of equi-effective doses; however, weight was not normally distributed in the trials.
Recommendation	Recommended
CDR assessment	The economic evaluation submitted to CDR was a cost-utility analysis, which is different to that submitted to PBAC (i.e., a cost-minimization analysis, based on non-inferiority versus tocilizumab). For the PBAC submission, the manufacturer only looked at first-line use of canakinumab; whereas, in the submission to CDR, both first and second-line use were considered. In the submission to CDR, canakinumab was noted to be superior in terms of efficacy (based on the ACR Pedi response) as compared with tocilizumab.

ACR Pedi = American College of Rheumatology Pediatric score; CDR = CADTH Common Drug Review; PBAC = Pharmaceutical Benefits Advisory Committee; sJIA = systemic juvenile idiopathic arthritis.

APPENDIX 5: REVIEWER WORKSHEETS

Manufacturer's Model Structure

The manufacturer undertook two cost-utility analyses to assess the cost-effectiveness of canakinumab in Canada:

- Primary analysis: to compare canakinumab and tocilizumab for first-line biologic treatment for patients two years and older with active systemic juvenile idiopathic arthritis (sJIA) who have responded inadequately to previous therapy with one or more NSAIDs and corticosteroids.
- Secondary analysis: to compare canakinumab and best supportive care (BSC) for second-line biologic treatment for patients two years and older with active sJIA who are contraindicated to or have discontinued any biologic therapy for lack of efficacy or intolerance (as per the manufacturer's drug reimbursement request).

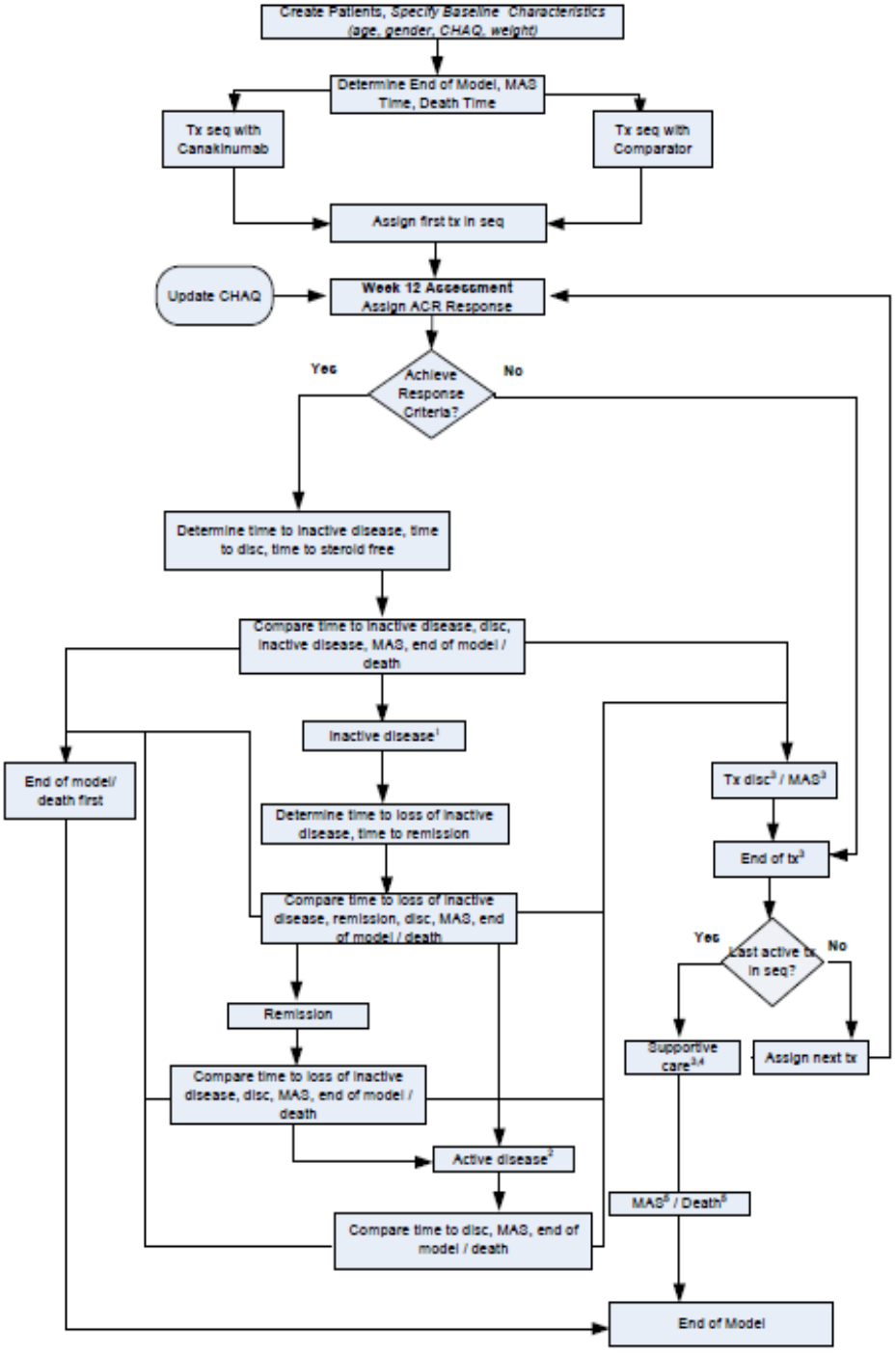
The manufacturer used an individual-level, time-to-event simulation approach to simulate disease progression, treatment effects, and outcomes for patients up to 20 years of age, using Microsoft Excel, from the perspective of a third-party payer in Canada. One hundred bootstrap samples were run for 10 replications for a total of 1,000 patients per treatment.

Treatment effect was measured through the American College of Rheumatology Pediatric (ACR Pedi) and the Childhood Health Assessment Questionnaire (CHAQ) scores. Continuation of treatment was based on an ACR Pedi response of 30% (referred to as ACR Pedi 30) at the week 12 assessment. CHAQ scores represent patients' disability status and illustrate the impact on quality of life. CHAQ scores were used to estimate utility scores used in the model. ACR Pedi responses are linked to all other health outcomes simulated in the model; that is, an ACR Pedi response was determined to influence whether a patient has inactive disease, is steroid-free, or discontinued treatment. Patients could discontinue treatment due to lack of treatment response, loss of efficacy, occurrence of macrophage activation syndrome (MAS), protocol deviation, or withdrawal of consent.[20-22]

A set of baseline patient characteristics were derived from individual data from patients enrolled in part 1 of the Study G2301.[3] From this, predictive equations were used to determine the occurrence and timing of future events, also using ACR Pedi response score. The manufacturer found that an ACR Pedi response of 90% (referred to as ACR Pedi 90) was a significant predictor of future factors, such as attaining steroid-free status, the time to attain steroid-free status, achievement of inactive disease (both before and after the week 12 assessment), and treatment discontinuation. Though utility values were captured directly in the canakinumab trials through the EuroQoL 5-dimensions (EQ-5D), CHAQ scores were used to estimate utility scores employed in the model based on published literature indicating a correlation between ACR Pedi score and quality of life. Therefore utility values were derived using a mapping algorithm, estimating a regression equation that predicted a utility score based on CHAQ score and EQ-5D data from patients in the G2301 and G2305 studies: $EQ\text{-}5D\ utility = 0.9555 - 0.3347*CHAQ$.[3] The manufacturer tested the model results using an alternative mapping algorithm, which was used in the National Institute for Health and Care Excellence (NICE) submission for tocilizumab: $EQ\text{-}5D = 0.8229 - 0.1125*HAQ - 0.06874*HAQ^2$.[23]

The model structure is shown in Figure 1.

FIGURE 1: MANUFACTURER'S MODEL STRUCTURE



MAS – macrophage activation syndrome; Tx – treatment; Seq – sequence; Disc – discontinuation
1 – CHAQ is updated for patients who achieve inactive disease post Week 12 at the time of their achievement of inactive disease as seen in G2301 trial
2 – Patients return to their CHAQ at the Week 12 Assessment when they lose their inactive disease
3 – Patients' CHAQ returns to their baseline levels
4 – Patients remain at their baseline CHAQ for the remainder of the model with no possibility of improvement
5 – Patients are still at risk of MAS and/or death while they remain on supportive care for the remainder of the model. For MAS, since patients are not on a treatment, they will only accrue the event cost but will not be discontinued from a treatment

The manufacturer used an individual time-to-event simulation approach, claiming it provides more flexibility than a Markov approach in dealing with the heterogeneity of the sJIA population, various outcome measurements, and individualized treatment patterns. Additionally, the manufacturer noted that duration of time in certain health states are important clinician and payer outcomes, and the use of individual patient simulations can facilitate applying the interrelationships between outcomes, avoiding a large number of Markovian health states. Also, the manufacturer claimed the use of a patient-level simulation allowed them to account for different treatments and resource use for different health states; increasing transparency, facilitating model validation and potential future modifications to the model. Furthermore, the use of an individual patient simulation model facilitated the inclusion of treatment sequencing and allowed a better representation of the cohort.

Relevant data sources are reported in Table 13. The information in the table specifies whether the data sources differ between the use of canakinumab as a first-line biologic treatment (versus tocilizumab) and the use of canakinumab as a second-line biologic treatment (versus BSC); where it is not specified, the data source is the same for both analyses.

TABLE 13: DATA SOURCES

Data Input	Description of Data Source	Comment
Efficacy	For the use of canakinumab as first-line biologic, data from an ITC comparing canakinumab (Study G2305) and tocilizumab (TENDER trial)[5] was used to generate the efficacy inputs. For the use of canakinumab as a second-line biologic, pooled data from the phase 3 canakinumab studies (G2305, G2301) and extension Study (G2301E1) were used to generate efficacy inputs.[3] This information was employed to determine predictive values to use for modelling.	There is some uncertainty in the comparability of the studies used for the ITC, which lead to uncertainty in the results of the primary analysis. A major limitation is that the data used for the primary (first-line biologic and secondary (second-line biologic) analyses are not systematically reflective of the assessed populations; the data were from populations including a combination of patients using treatment as first and second line.
Baseline characteristics	Individual patient characteristics from G2301 trial (part 1); a 29-day, double-blind, placebo-controlled RCT.[20] These data were employed to determine predictive values to use for modelling. The same patient set was used for all treatments in the model, including BSC.	Baseline characteristics from a canakinumab trial population of patients that includes a combination of patients using treatment as first and second line were used for all analyses for all treatments. This is inappropriate.
Discontinuation	Reported to be based on data from G2301 trial for patients who responded based on ACR Pedi 30 (post 12 weeks) Beyond 12 weeks, a constant rate was assumed. Before week 12, no patients discontinued.	The discontinuation rate was the same for all treatments in the model, including BSC, which is highly questionable. Values reported in the Pharmacoeconomic report could not be verified in the Clinical Study Report.

Data Input	Description of Data Source	Comment
Adverse events	Safety profile of canakinumab was assumed similar for use as both a first-line and second-line biologic treatment.	CDR clinical expert accepted as appropriate.
- MAS	Annual hazard rate estimated from G2301 trial data.[20] It was assumed applicable to all treatments in the model, including BSC.	Feedback from the CDR clinical expert indicated MAS rate may be reduced with biologic treatment.
- Infection	Based on data from G2301 trial (part 2)[20] for canakinumab and BSC, and an adjusted rate from the TENDER trial[24] for tocilizumab.	
All-cause mortality	Canadian Life Tables for 2009 to 2011.[25]	Appropriate
sJIA specific mortality	Indianapolis Pediatric Rheumatology Disease Registry.[26] The same mortality values were applicable to all treatments in the model.	The CDR clinical expert indicated that sJIA specific mortality was mainly due to MAS. This was tested by the manufacturer sensitivity analysis; it did not significantly impact the results from the analysis.
sJIA specific mortality (MAS only)	The acute mortality associated with MAS of 22% was obtained from a study conducted by Sawhney and Agarwal.[27]	See above comment re sJIA specific mortality.
Utilities	Derived from CHAQ scores from the canakinumab trials,[20-22] using mapping algorithms.	Use of directly derived utility values from EQ-5D data is preferred. Some uncertainty with mapping procedure used.
Resource use	Different resource use for canakinumab, tocilizumab, and BSC was assumed based on data from the canakinumab clinical trials (treatment use, AE rates), product monographs (treatment dosing), and clinical expert opinion (monitoring and administration).	Resource use may be underestimated based on feedback from CDR clinical expert. Altering assumption doesn't significantly impact results.
Costs		
Biologic treatments	Canakinumab: Novartis List Price Tocilizumab: Ontario Drug Benefit Formulary (December 2015)[13]	Appropriate
BSC (prednisone and methotrexate)	Ontario Drug Benefit Formulary (December 2015)[14]	Appropriate
Administration	Ontario Case Costing Initiative[8a]	Appropriate
Monitoring	Hospitalization: Ontario Case Costing Initiative[8a] GP/specialist visits: Ontario Schedule of Benefits[10] MRI/bone scan: Ontario Schedule of Benefits[10] Lab tests and X-ray: Ontario Schedule of Benefits Laboratory Schedule[11] Allied health professional: Ontario Podiatry Schedule of Fees,[12] Ontario Physical Therapy Schedule of Fees[12]	Appropriate
Event: steroid-related AE	Manson et al. 2009 (UK cost).[7] Inflated to 2015 prices through the Office of National Statistics[28] and adjusted to Canadian dollars through	The use of a UK cost for a Canadian assessment is questionable. However, altering

Data Input	Description of Data Source	Comment
	www.exchangerates.org.uk	this estimate does not significantly impact the results.
Event: MAS	Ontario Case Costing Initiative[8a]	Appropriate
Event: Infection	Ontario Case Costing Initiative[8a]	Appropriate

ACR Pedi = American College of Rheumatology Pediatric score; AE = adverse event; BSC = best supportive care; CDR = CADTH Common Drug Review; CHAQ = Childhood Health Assessment Questionnaire; CPI = consumer price index; EQ-5D = EuroQoL 5-Dimension; GP = general practitioner; ITC = indirect treatment comparison; MAS = macrophage activation syndrome; RCT = randomized controlled trial; sJIA = systemic juvenile idiopathic arthritis; UK = United Kingdom.
[a] Inflated to 2015 prices with the Statistics Canada CPI.[29]

The manufacturer's key assumptions are reported in Table 14. The information in the table specifies whether the key assumptions differ between the use of canakinumab as a first-line biologic treatment (versus tocilizumab) and the use of canakinumab as a second-line biologic treatment (versus BSC); where it is not specified, the key assumption is the same for both analyses.

TABLE 14: MANUFACTURER'S KEY ASSUMPTIONS

Assumption	Comment
For the assessment of canakinumab as second-line biologic treatment compared to BSC (secondary analysis) efficacy data from the G2305 trial was used for canakinumab, but from the ITC for BSC.	It is not clear why the manufacturer used the pooled placebo arm data from the ITC to inform the BSC treatment arm in the secondary analysis. This is questionable in the context. Given the differences in the trial durations and information available in the CSRs and published studies, CDR was unable to undertake revised analyses using BSC data from the canakinumab trials.
Treatment response rate was set at ACR Pedi 30.	Only ACR Pedi 90 was found to be a significant predictor of event parameters (e.g., steroid-free, discontinuation, etc.), though responders were classified as those reaching an ACR Pedi 30 score. The clinical expert mentioned that a score of ACR Pedi 50 is usually considered a response in clinical practice, which drives treatment continuation.
Correlation between ACR Pedi scores and QoL has been previously demonstrated;[6] thus the use of CHAQ scores to derive utility scores with a mapping algorithm is appropriate.	The paper that demonstrated a correlation between ACR Pedi score and QoL noted significant concordance between patients who were ACR responders (20% and 50%) and those who demonstrated 20% and 50% improvement in the disease-specific and generic measures of function and health-related QoL.[6] The QoL measurements used were the HAQ, MHAQ, PET, and SF-36. There is some uncertainty as to whether the correlation would exist with other ACR scores and other QoL measures such as the CHAQ.
The ITC appropriately used available and relevant trials, and the results suggest that canakinumab is associated with a non-significant benefit compared to tocilizumab for the first-line biologic treatment comparison.	CDR clinical reviewers identified an additional ITC to the one submitted by the manufacturer.[30] This ITC had broader inclusion criteria, and included an additional study (assessing anakinra versus placebo) compared to the manufacturer ITC. CDR considered the [redacted]. A high degree of uncertainty surrounding the findings of the ITCs was identified. CDR pharmacoeconomic reviewers noted that the data used to

Assumption	Comment
	populate the model that was indicated to have been sourced from the ITC (i.e., ACR response at 12 weeks) were not located within the manufacturer ITC report, resulting in increased uncertainty with the ITC data used in the model.
Infection rate for tocilizumab was based on the TENDER trial, but placebo-adjusted based on part 2 of Study G2301.	There is no information provided regarding the adjustment applied to the tocilizumab infection rate. Feedback from the CDR clinical expert was that infection rate was likely to be similar for both canakinumab and tocilizumab. Varying this estimate does not significantly impact the results.
The use of a micro-simulation model is appropriate and represents the best way to model the disease.	The manufacturer indicated using a time-to-event simulation provides more flexibility than a Markov model approach in dealing with population heterogeneity; allowing an optimal prediction of patient disease course and treatment pathway. However, the submitted model lacks of transparency and flexibility.
Discontinuation only applied after patient's initial 12 weeks on treatment.	May not be appropriate; discontinuation data before 12 weeks from canakinumab trials are not available.
The treatments for BSC were steroids, conventional DMARDs and NSAIDs. NSAIDs were not costed due to their low cost, while prednisone and methotrexate were chosen to represent their respective classes.	These assumptions are appropriate and were supported by the CDR clinical expert.
Resource use associated with monitoring of biologics and BSC based on expert opinion.	Feedback from the CDR clinical expert indicated that other tests such as CRP, ESR, ferritin, fibrinogen, and lipids (cholesterol and triglycerides) may be undertaken, and children receiving steroids may also be monitored for blood glucose. The clinical expert indicated that the frequency of monitoring may underestimate the number of specialist visits and overestimate GP visits in patients with severe (active) disease. CDR assessed this, but determined that reasonable revisions in cost and resource use do not have a significant impact on the ICUR.

ACR Pedi = American College of Rheumatology Pediatric score; BSC = best supportive care; CDR = CADTH Common Drug Review; CHAQ = Childhood Health Assessment Questionnaire; CRP = C-reactive protein; DMARD = disease-modifying antirheumatic drug; CSR = Clinical Study Report; ESR = erythrocyte sedimentation rate; GP = general practitioner; HAQ = Health Assessment Questionnaire; ICUR = incremental cost-utility ratio; ITC = indirect treatment comparison; MAS = macrophage activation syndrome; MHAQ = modified Health Assessment Questionnaire; NSAID = nonsteroidal anti-inflammatory; PET = Problem Elicitation Technique; QoL = quality of life; SF-36 = Medical Outcomes Study Short Form 36; sJIA = systemic juvenile idiopathic arthritis.

Manufacturer's Sensitivity Analyses

The manufacturer undertook a series of one-way deterministic sensitivity analyses based on set values and scenarios. The following parameters were tested: time horizon, perspective, minimum ACR Pedi score at week 12 to continue treatment, inclusion of wastage, discount rates, inclusion of sJIA mortality associated with MAS, efficacy of canakinumab compared with tocilizumab, CHAQ change, treatment discontinuation, daily rate of MAS, no excess risk of death, infection rates, biologic costs, event costs, management costs, and utility values.

The manufacturer also undertook a probabilistic sensitivity analysis that varied inputs from replication to replication by sampling from probability distributions. The probabilistic sensitivity analysis was run for 500 simulations.

Manufacturer's Results

As primary analysis, the manufacturer compared canakinumab and tocilizumab for first-line biologic treatment for patients two years and older with active sJIA who have responded inadequately to previous therapy with one or more NSAIDs and corticosteroids. In this setting, the ICUR for canakinumab compared with tocilizumab was reported to be $3,273,360 per QALY. The manufacturer also presented a scenario applying a risk-sharing arrangement [redacted]. When including the risk-sharing arrangement, the ICUR for canakinumab compared with tocilizumab was reported to be $1,036,258 per QALY. The incremental costs and QALYs associated with canakinumab compared with tocilizumab (including and excluding the confidential risk-sharing arrangement) are presented in Table 2.

As secondary analysis, the manufacturer compared canakinumab and BSC for second-line biologic treatment for patients two years and older with active sJIA who are contraindicated to or have discontinued any biologic therapy for lack of efficacy or intolerance, as per the manufacturer's requested drug reimbursement indication. In this setting, the ICUR for canakinumab compared with tocilizumab was $824,830 per QALY. When including the risk-sharing arrangement, the ICUR for canakinumab compared with tocilizumab was $307,981 per QALY. The incremental costs and QALYs associated with canakinumab compared to tocilizumab (including and excluding the confidential risk-sharing arrangement) are presented in Table 2.

Manufacturer's Sensitivity Analyses

The manufacturer's one-way deterministic sensitivity analyses were reported on the secondary analysis (as a second-line biologic treatment compared to BSC), including the manufacturer's risk-sharing arrangement. The manufacturer concluded that the model results were stable relative to variations in the model parameters; aside from amendments to the treatment discontinuation rate, which resulted in an ICUR of $1,036,042 per QALY (base case: $307,981 per QALY). The results from the one-way deterministic sensitivity analyses ranged from $282,283 to $384,151 per QALY.

The manufacturer's probabilistic sensitivity analysis was undertaken on the primary analysis, excluding the components of the risk-sharing arrangement, and found there were no simulations in which canakinumab was cost-effective as a second-line treatment (compared with BSC) at a willingness-to-pay threshold of $200,000 per QALY.

CADTH Common Drug Review Reanalyses

Uncertainty regarding the patient population modelled for both the primary and the secondary analyses.

As noted in the data sources table (Table 13), the manufacturer used efficacy data from the ITC to inform the comparison of canakinumab and tocilizumab as first-line biologic treatments, and from pooling efficacy data from studies G2301, G2305 and G2301E1 to inform the comparison of canakinumab as second-line biologic treatment compared withBSC.[3] The manufacturer's analysis in the ITC does not stratify the patients that had previously received biologic treatment and those who had not; noting that a greater proportion of patients in the included tocilizumab trial (TENDER) had received

prior biologic treatment for sJIA compared with patients in the canakinumab studies (~35% to 50%).[5] CDR also noted that the manufacturer does not specify in their pharmacoeconomic submission whether the data from the pooled analysis of studies G2301, G2305 and G2301E1 were stratified to include only patients who had failed a prior biologic treatment (as per the second-line biologic treatment comparison), thus creating greater uncertainty in the data used to inform the pharmacoeconomic model. However, the manufacturer later clarified that the pooled dataset included only canakinumab patients who had previously received biologic treatment; but still a mix population for the BSC comparator arm. Because of a lack of data and the model's flexibility, this limitation could not be tested by CDR.

Uncertainty in the patient characteristics at baseline.
Patient characteristics at baseline are based on the full patient set from part 1 of trial G2301 (177 patients). CDR noted that efficacy data for the primary analysis (first-line biologic) are informed by an ITC that does not include Study G2301 (it uses a different canakinumab study, G2305); and for the secondary analysis from a pooled population that includes data from Study G2305 and Study G2301E1, in addition to Study G2301. In addition, CDR noted that the manufacturer did not adjust the patient characteristics for the different analyses (first-line biologic use or second-line biologic use), assuming that the characteristics of the patients did not differ based upon prior biologic treatment. This is not appropriate as patients that have failed on a biologic are likely to have more severe disease than patients who had not yet received biologic therapy. To test the potential impact of patient characteristics at baseline, CDR altered all baseline characteristics except for age, gender, weight, height and individual utility value by the standard deviation from the base-case value to potentially estimate the impact of patients with more and less severe disease on the results. The results based on revised baseline characteristics are reported in Table 15.

TABLE 15: CADTH CDR ANALYSIS: REVISED BASELINE CHARACTERISTICS

Parameter: Response	Incremental Cost	Incremental QALYs	ICUR (cost per QALY)	ICUR (cost per QALY) Including RSA
First line: CAN vs. TOC				
Baseline characteristics from G2301 (base case)	$778,874	0.24	$3,243,919	$1,006,816
Baseline characteristics tested minus standard deviation	$778,999	0.13	$5,904,314	$1,833,177
Baseline characteristics tested plus standard deviation	$778,842	0.34	$2,273,719	$706,261
Second line: CAN vs. BSC				
Baseline characteristics from G2301 (base case)	$649,396	0.79	$824,830	$307,981
Baseline characteristics tested minus standard deviation	$649,730	0.46	$1,404,631	$524,923
Baseline characteristics tested plus standard deviation	$649,322	1.19	$545,923	$203,684

BSC = best supportive care; CAN = canakinumab; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; RSA = risk-sharing arrangement; TOC = tocilizumab.

Uncertainty regarding the definition of response.
CDR noted that the manufacturer found that only the ACR Pedi 90 score threshold for response was a significant predictor of the model outcomes. However, the manufacturer assumed the response threshold to be at ACR Pedi 30 score. Additionally, the clinical expert mentioned that a score of ACR Pedi 50 is usually considered a response in clinical practice. CDR undertook an analysis using revised response rates of ACR Pedi 90 and ACR Pedi 50. The level of ACR score used to determine response appears to slightly impact the ICUR — higher ACR scores used for response (i.e., ACR Pedi 50, ACR Pedi 90) result in lower ICURs (Table 16).

TABLE 16: CADTH CDR ANALYSIS: REVISED ACR RESPONSE LEVEL

Parameter: ACR Score Used for Response	Incremental Cost	Incremental QALYs	ICUR (cost per QALY)	ICUR (cost per QALY) Including RSA
First line: CAN vs. TOC				
ACR 30 response (base case)	$778,874	0.24	$3,243,919	$1,006,816
ACR 50 response	$770,848	0.25	$3,035,904	$946,873
ACR 90 response	$656,397	0.27	$2,392,153	$750,645
Second line: CAN vs. BSC				
ACR 30 response (base case)	$649,396	0.79	$824,830	$307,981
ACR 50 response	$641,138	0.80	$796,687	$296,966
ACR 90 response	$551,682	0.79	$697,997	$260,594

ACR = American College of Rheumatology score; BSC = best supportive care; CAN = canakinumab; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; RSA = risk-sharing arrangement; TOC = tocilizumab.

Uncertainty associated with the utility values used in the model.
Although the manufacturer collected information using the EQ-5D in the canakinumab studies, these values have not been used or presented by the manufacturer. CHAQ scores were used to estimate utility scores for the model, based on published literature indicating a correlation between ACR Pedi score and quality of life.[6] Therefore utility values were derived using a mapping algorithm, which was reported to have an approach consistent with other mapping algorithms used for treating the assessed population.[31,32] The manufacturer's mapping algorithm used a mixed-effect model incorporating patient's EQ-5D and CHAQ score data from the G2305 and G2301 studies. The manufacturer tested the model results using an alternative mapping algorithm.[3] The use of directly derived utility values from EQ-5D data are preferred to mapped utility values; the latter being associated with more uncertainty. To test this uncertainty, CDR tested the results by altering the values of the mapping algorithm by two times the 95% confidence intervals (Table 17).

TABLE 17: CADTH CDR ANALYSIS: REVISED UTILITY VALUES

Parameter: Utility Value Mapping Algorithm	Incremental Cost	Incremental QALYs	ICUR (cost per QALY)	ICUR (cost per QALY) Including RSA
First line: CAN vs. TOC				
Utility values using mapping from the canakinumab studies (base case)	$778,874	0.24	$3,243,919	$1,006,816
Utility values using	$778,874	0.28	$2,827,052	$877,433

Parameter: Utility Value Mapping Algorithm	Incremental Cost	Incremental QALYs	ICUR (cost per QALY)	ICUR (cost per QALY) Including RSA
manufacturer's mapping — lower bound (95% CI)				
Utility values using manufacturer's mapping — upper bound (95% CI)[a]	$778,874	0.20	$3,806,858	$1,181,536
Utility values using mapping from an alternative mapping algorithm	$778,874	0.20	$3,871,281	$1,201,531
Second line: CAN vs. BSC				
Utility values using mapping from the canakinumab studies (base case)	$649,396	0.79	$824,830	$307,981
Utility values using manufacturer's mapping — lower bound (95% CI)	$649,396	0.90	$719,986	$268,833
Utility values using manufacturer's mapping — upper bound (95% CI)[a]	$649,396	0.67	$966,152	$360,749
Utility values using mapping from an alternative mapping algorithm	$649,396	0.66	$983,445	$367,206

BSC = best supportive care; CAN = canakinumab; CI = confidence interval; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; RSA = risk-sharing arrangement; TOC = tocilizumab.
[a] CDR capped the intercept at 1.

Uncertainty in the comparative effectiveness of canakinumab and tocilizumab based on the ITC. CDR clinical reviewers identified two ITCs[5,30] which were appraised. The CDR appraisal indicated the [redacted]. However, several limitations with the ITC were identified; leading the CDR clinical reviewers to report a high degree of uncertainty surrounding the findings of the indirect comparison. Thus, CDR undertook an analysis assuming no difference in efficacy between canakinumab and tocilizumab (using data from the canakinumab study for tocilizumab), which indicated that canakinumab was as effective, but associated with substantially higher costs than tocilizumab (Table 18).

TABLE 18: CADTH CDR ANALYSIS: REVISED COMPARATIVE EFFECTIVENESS ESTIMATES

Parameter: Comparative Effectiveness Estimates	Incremental Cost	Incremental QALYs	ICUR (cost per QALY)	ICUR (cost per QALY) Including RSA
First line: CAN vs. TOC				
Point estimates from the ITC used (base case)	$785,943	0.24	$3,273,360	$1,036,258
Assumption of equivalent efficacy between CAN and TOC	$776,024	0.00	NA	NA

BSC = best supportive care; CAN = canakinumab; ICUR = incremental cost-utility ratio; NA = not applicable; QALY = quality-adjusted life-year; TOC = tocilizumab.

Multi-Way analysis: CDR best estimate

Based on the above reanalyses, CDR undertook a multi-way analysis assessing two scenarios:

1. "Less severe" scenario: considered the lower confidence intervals on baseline characteristics (i.e., a population with less severe disease), ACR Pedi 50 as definition of response, and higher utility values (i.e., less severe patients).
2. "More severe" scenario: considered the upper confidence intervals on baseline characteristics (i.e., a population with more severe disease), ACR Pedi 50 as definition of response, and lower utility values (i.e., more severe patients).

These scenarios provided ranges of ICURs for the cost-effectiveness of canakinumab, considered to be CDR best estimates. The results are presented in Table 19, and are also presented for a supplementary analysis which considered a risk-sharing arrangement [redacted].

TABLE 19: CADTH CDR BEST ESTIMATES: MULTI-WAY ANALYSIS

	Incremental Cost Main Analysis/ Analysis with RSA	Incremental QALYs	ICUR (cost per QALY)	ICUR (cost per QALY) Including RSA
First line: CAN vs. TOC				
Manufacturer's base case	$785,943/$241,739	0.24	$3,273,360	$1,036,258
CDR best estimate (less severe)	$770,963/$240,536	0.12	$6,521,275	$2,034,598
CDR best estimate (more severe)	$770,810/$240,599	0.42	$1,846,134	$576,249
Second line: CAN vs. BSC				
Manufacturer's base case	$649,396/$242,476	0.79	$824,830	$307,987
CDR best estimate (less severe)	$641,461/$239,308	0.40	$1,584,896	$591,272
CDR best estimate (more severe)	$641,064/$238,948	1.40	$459,068	$171,111

BSC = best supportive care; CAN = canakinumab; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; RSA = risk-sharing agreement; TOC = tocilizumab.

CDR undertook price reduction scenarios, based on the manufacturer's risk-sharing arrangement (Table 20 and Table 21). However, it is uncertain as to whether the risk-sharing arrangement will be one that drug plans participating in the CDR process can put into operation.

TABLE 20: CDR PRICE REDUCTION SCENARIO ANALYSES (INCLUDING RSA): FIRST-LINE BIOLOGIC

ICURs for canakinumab compared to tocilizumab			
Price per vial	**Analysis submitted by manufacturer with RSA**	**CDR best estimate (less severe)**	**CDR best estimate (more severe)**
Submitted ($16,000)	$1,036,258	$2,034,598	$576,249
25% reduction ($12,000)	$669,787	$1,359,156	$384,868
50% reduction ($8,000)	$332,757	$683,715	$193,487
75% reduction ($4,000)	Dominant	$8,273	$2,106
90% reduction ($1,600)	Dominant	Dominant	Dominant

CDR = CADTH Common Drug Review; ICUR = incremental cost-effectiveness ratio; RSA = risk-sharing arrangement.

TABLE 21: CDR PRICE REDUCTION SCENARIO ANALYSES (INCLUDING RSA): SECOND-LINE BIOLOGIC

ICURs for canakinumab compared to BSC			
Price per vial	**Analysis submitted by manufacturer with RSA**	**CDR best estimate (less severe)**	**CDR best estimate (more severe)**
Submitted ($16,000)	$307,987	$591,272	$171,111
25% reduction ($12,000)	$230,569	$442,918	$128,107
50% reduction ($8,000)	$153,158	$294,564	$85,103
75% reduction ($4,000)	$75,746	$146,209	$42,098
90% reduction ($1,600)	$29,299	$57,197	$16,296

BSC = best Supportive Care; CDR = CADTH Common Drug Review; ICUR = incremental cost-effectiveness ratio; RSA = risk-sharing arrangement.

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