CADTH

CADTH COMMON DRUG REVIEW

Pharmacoeconomic Review Report

BELIMUMAB (BENLYSTA)

(GlaxoSmithKline Inc.)

Indication: Indicated in addition to standard therapy for reducing disease activity in adult patients with active, autoantibody-positive systemic lupus erythematosus.

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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

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Abbreviations

AMS	adjusted mean Systemic Lupus Erythematosus Disease Activity Index
CDEC	CADTH Canadian Drug Expert Committee
CDR	CADTH Common Drug Review
CV	cardiovascular
HDA	high disease activity
ICER	incremental cost-effectiveness ratio
NSAID	nonsteroidal anti-inflammatory drug
QALY	quality-adjusted life-year
SC	subcutaneous
SDI	Systemic Lupus Erythematosus International Collaborating Clinics Damage Index
SELENA	Safety of Estrogens in Lupus Erythematosus National Assessment
SLE	systemic lupus erythematosus
SLEDAI	Systemic Lupus Erythematosus Disease Activity Index
SoC	standard of care
SRI	Systemic Lupus Erythematosus Responder Index
TLC	Toronto Lupus Cohort

Table 1: Summary of the Sponsor's Economic Submission

Drug product	belimumab (Benlysta)
Study question	What is the cost-effectiveness of belimumab administered subcutaneously (SC) for the treatment of active, autoantibody-positive systemic lupus erythematosus (SLE) in adults in addition to standard of care (SoC) compared to SoC alone?
Type of economic evaluation	Cost-utility analysis
Target population	Adult patients who have autoantibody-positive SLE and who are receiving SoC
Treatment	Belimumab SC 200 mg weekly added to SoC
Outcome	QALYs
Comparators	SoC alone (e.g., naproxen, prednisone, azathioprine, and hydroxychloroquine)
Perspective	Canadian health care system perspective
Time horizon	50 years (assumed to be close to lifetime)
Results for base case	ICER = $147,695 per QALY (or $147,754 in a submitted revised analysis) At a threshold of $50,000 per QALY, the probability that belimumab is cost-effective is 0%.
Key limitations	• The regression analysis for costs and utilities lacks face validity in that it suggests both utility values increasing with age (potentially greater than 1) and costs decreasing with age (potentially less than 0). • The sponsor used a different utility model from that used for the base model in its report. This biased results in favour of belimumab + SoC. • Analysis fails to accurately consider the incremental effect of belimumab + SoC in terms of response, and, as a result, biases the results in favour of belimumab + SoC. CADTH Common Drug Review (CDR) requested that the sponsor revise the model and analysis to fully distinguish between responders and nonresponders for both belimumab + SoC and SoC alone — the sponsor declined to provide this. • The basis for determining survival benefit with belimumab + SoC is unclear. • The sponsor assumed that patients receiving belimumab + SoC could stay on treatment for up to 10 years but assumed no waning of treatment effect.
CADTH estimate(s)	• CADTH accounted for the choice of utility function and the incorrect modelling of nonresponders in reanalyses. • Based on the revision, CADTH estimated the ICER = $646,983 per QALY. • As the potential for waning of treatment effect could not be considered within the analysis and the survival benefits from belimumab are unsubstantiated, the true value of the ICER may be much higher.

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; SC = subcutaneous; SLE = systemic lupus erythematosus; SoC = standard of care.

Drug	belimumab (Benlysta)
Indication	Indicated in addition to standard therapy for reducing disease activity in adult patients with active, autoantibody-positive systemic lupus erythematosus (SLE).
Reimbursement request	For the treatment of patients with SLE who meet the following eligibility criteria: • adult patients age 18 years or older; and • patients with active, antibody-positive SLE; and • currently receiving standard therapy; and • has a disease activity SELENA-SLEDAI score ≥ 8. If no improvements are observed in a patient's SLE disease activity and/or symptoms after 6 months, use should be discontinued.
Dosage form	Solution for subcutaneous injection, 200 mg/mL, in pre-filled syringe or autoinjector
NOC date	December 7, 2017
Sponsor	GlaxoSmithKline Inc.

Executive Summary

Background

Belimumab (Benlysta) inhibits the B-lymphocyte simulator, and thus inhibits B cells, which are believed to play an important role in the pathophysiology of systematic lupus erythematosus (SLE). It is indicated, in addition to standard therapy, for reducing disease activity in adult patients with active, autoantibody-positive SLE.[1] This submission relates to belimumab subcutaneous (SC) injection, 200 mg/mL weekly formulation.[2] The submitted price is $421.79 per 200 mg. At the recommended dosage of 200 mg weekly, the average annual cost is $21,933 per patient.

Belimumab was previously reviewed by CADTH for the IV infusion.[3] CADTH Canadian Drug Expert Committee (CDEC) recommended belimumab IV not be reimbursed because its clinical benefit was uncertain and its cost-effectiveness could not be adequately assessed.

The sponsor submitted a cost-utility analysis over a 50-year time horizon (referred to as a lifetime horizon).[4] The analysis was conducted from the perspective of a Canadian public health care payer. Primary analysis was conducted for a population based on the BLISS SC trial population: patients with moderate-to-severe SLE (score of ≥ 8 on the Safety of Estrogens in Lupus Erythematosus National Assessment [SELENA]).[5,6] A secondary analysis was based on a subgroup analysis of the BLISS SC population with high disease activity (HDA): [redacted]. This comprised [redacted]% of the BLISS SC population (within this subgroup the response rates were [redacted]% with belimumab + SoC versus [redacted]% for placebo + SoC). Analyses for both populations compared belimumab in addition to standard of care (SoC) versus SoC alone. SoC was consisted of corticosteroids, immunosuppressants, antimalarial drugs, and nonsteroidal anti-inflammatory drugs (NSAIDs). All components of SoC (excluding NSAIDs) were assumed to vary by comparator.

A Markov model was used to predict the proportion of patients in different states relating to score on the Systemic Lupus International Collaborating Clinics/American College of

Rheumatology Damage Index (SDI; 0 to 5+) and the presence of cardiovascular (CV) damage. Patients were assumed to progress only (i.e., they could not improve in terms of SDI nor could they recover from CV damage). Thus, patients could transition in terms of disease progression (higher SDI), new CV damage, discontinuation of therapy (for belimumab + SoC only), or death. Transitions for progression of SDI were estimated as follows. For belimumab + SoC responders, the probabilities of staying in the current SDI state or progressing by one or by two points were obtained from one-year data from the BLISS SC study for this subgroup of patients receiving belimumab + SoC. For SoC, the probabilities of staying in the current SDI state or progressing by one or by two points were obtained from the Toronto Lupus Cohort (TLC) study for all patients on placebo + SoC, regardless of whether or not they were responders. For nonresponders with belimumab + SoC, the probabilities of staying in the current SDI state or progressing by one or by two points were assumed to be the same as for all patients on placebo + SoC (including the [redacted]% who were responders). Mortality was a function of age-specific all-cause mortality, the relative mortality of patients with SLE versus the general population, and the impact of SLE characteristics on mortality based on Cox regression and some form of calibration. The Cox regression model adopted includes steroid dosage, adjusted mean Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) (AMS), and SDI as predictors of mortality.[4]

For each health state within the model, a range of disease characteristics and treatment uptakes were modelled based on regression equations.[4,7] Variables tracked were AMS, mean steroid dosage (mg/day), mean number of mild/moderate flares, mean number of severe flares, proportion of patients using immunosuppressants, and proportion of patients using antimalarial drugs. For the first year (cycle) of the model, the data for these parameters were obtained from the BLISS SC trial; however, nonresponders with belimumab were not given their actual values but the values for all patients receiving SoC. For subsequent years, an approach similar to that adopted for SDI progression was used: separate regression equations were estimated for the subgroup of patients on belimumab + SoC who were responders and for all patients receiving placebo + SoC.[4] Nonresponders with belimumab + SoC were again assumed to have the same values as all patients on placebo + SoC (including the [redacted]% who were responders).

For the all patients with SLE (primary analysis), the sponsor reported that the incremental cost-effectiveness ratio (ICER) per quality-adjusted life-year (QALY) gained for belimumab + SoC versus SoC alone was $147,695 per QALY, with 0% chance that the ICER was less than $50,000. For the secondary analysis in the HDA subgroup, the ICER was $131,490 per QALY. Based on CADTH's initial comments relating to issues with costs and utilities, the sponsor provided a revised model with similar results (ICER = $147,754 for SLE population and $131,424 for the HDA subgroup).[8]

Summary of Identified Limitations and Key Results

There were a number of major limitations identified with the sponsor's analyses.

The most significant issue was the sponsor's assumption that a nonresponder receiving belimumab + SoC has the same outcomes as patients receiving SoC. This relates to both SDI transition probabilities and the predictive models relating to AMS, steroid dosage, flares, immunosuppressants, and antimalarial drugs. These have direct impact on estimates of costs and QALYs. In the BLISS SC study, [redacted]% of patients receiving SoC had a response at 24 weeks (the outcome used in the economic analysis) compared to [redacted]% with belimumab + SoC. Thus, the incremental effect of belimumab on response is only 10.4%

(i.e., 82.5% of patients who respond with belimumab would have responded with SoC alone).[5] Significant bias is therefore introduced by assuming that nonresponders with belimumab + SoC have the same outcomes as patients receiving SoC. CADTH requested that the sponsor provide a revised model that considers nonresponders and responders separately, allowing for differential outcomes in patients receiving SoC who respond versus those receiving belimumab + SoC who do not respond; however, this was not provided. To attempt to address this, CADTH revised the analysis by deriving transition probabilities with respect to SDI for nonresponders versus responders, using the same predictive equations (placebo + SoC) for all outcomes, and differentiating between responders and nonresponders for both SoC and belimumab.

Also, the sponsor assumed that patients receiving belimumab + SoC could stay on treatment for up to 10 years but assumed no waning of treatment effect. It was not possible to consider an alternative assumption in the model; as a result, the implications of this assumption are unknown and biased in favour of belimumab.

Further limitations are related to the cost and utility values used in the model. The sponsor did not use the actual cost models reported in its submitted appendix.[9] Instead, the sponsor assumed that costs decline with age and, as a result, the model required the use of an artificial lower cut-off for health care costs of $0 to avoid negative values. This suggests both a lack of face validity and an invalid statistical approach. The sponsor responded to this criticism by capping the age of patients at 77 in the regression model to avoid negative cost values, which does not address the lack of face validity with the approach.

Also, the sponsor used a different utility model than the core model identified in its submitted appendix.[7] The adoption of the new model provides more favourable results with respect to belimumab. To reflect the approach outlined by the sponsor in its report, CADTH adopted the original approach described by the sponsor. It should be noted that the impact of age on utility values within the model is curious: utility values decline with age up to age 77 , and then increase. The sponsor adopts an upper cut-off for utility values of 1. Utility values for patients with SLE approaching 1 again suggest a lack of face validity , and the approach adopted can be considered statistically invalid. The sponsor responded to this criticism by capping the age of patients at 77 in the regression model to avoid unrealistic utility values, which does not address the lack of face validity with the approach.

The sponsor assumes that mortality is a function of SDI, AMS, and steroid dosage. However, there is no evidence of a direct survival benefit with belimumab + SoC based on the submitted clinical studies, and the evidentiary basis from which to estimate any indirect survival benefit is limited. Also, the model employed in the analysis is not in the submitted appendix, despite being referred to in the primary report. Furthermore, if the assumption that increased mortality with SLE was consistent across disease severity, this would greatly increase the ICER associated with belimumab + SoC.

Analysis for the subgroup identified as HDA used the response rate and clinical outcomes for year 1 for this subgroup based on the BLISS SC trial but adopted the disease models applicable to the wider patient population and the impact of treatment on SDI progression for the total trial population. Results of the analysis for HDA patients paradoxically reported higher estimated QALYs and life expectancy for patients on both belimumab + SoC and SoC alone when compared to the estimates for the total trial population. The approach adopted is not valid; the results lack face validity and provide a basis to question the validity of the results for total trial population. Therefore, the analysis for the HDA group was not considered by CADTH.

Given the above limitations, CADTH conducted a revised analysis with modifications. It was not possible to reprogram the model to allow probabilistic analysis, so the CADTH-revised analysis is based on a deterministic analysis. Also, the waning of treatment effect over the 10-year treatment period and the assumed mortality effect could not be addressed. CADTH estimated a revised ICER of $646,893 for belimumab + SoC compared to SoC, for the entire SLE population.

Conclusions

The sponsor's analysis suggests that belimumab + SoC is not cost-effective in either the patient population studied in the BLISS SC (ICER of $147,695) or the subgroup of patients with HDA (ICER of $131,490).

However, CADTH identified a number of limitations with the submitted analysis. CADTH reanalysis suggests a much higher ICER for the total population ($646,893 per QALY), requiring a price reduction of 88.3% for belimumab + SoC to be considered cost-effective at a willingness-to-pay per QALY of $50,000.

CADTH notes that this is likely an underestimate of the true ICER, given that the analysis does not consider the potential for waning of treatment effect and assumes a mortality effect with belimumab + SoC that has not been demonstrated in clinical studies.

Information on the Pharmacoeconomic Submission

Summary of the Sponsor's Pharmacoeconomic Submission

The sponsor submitted a cost-utility analysis over a 50-year time horizon (referred to as a lifetime horizon).[4] The analysis was conducted from the perspective of a Canadian public health care payer. Primary analysis was conducted for a population based on the BLISS SC trial population: patients with moderate-to-severe SLE (score of ≥ 8 on the SELENA).[5,6] The primary outcome was the percentage of patients with an SLE Responder Index (SRI) response at 52 weeks. The economic model was based on a secondary outcome, SDI response at 52 weeks. More patients in the belimumab than placebo group (61% versus 48%) achieved the secondary outcome. For the economic submission, response rates from the studies were based on outcomes at 24 weeks ([redacted]% response with belimumab + SoC and [redacted]% response with placebo + SoC).[5]

A secondary analysis was based on a subgroup analysis of the BLISS SC population with HDA: [redacted]. This consisted of [redacted]% of the BLISS SC population (within this subgroup the response rates at 24 weeks were [redacted]% with belimumab + SoC versus [redacted]% for placebo + SoC).

Analysis for both populations compared belimumab + SoC with SoC alone. SoC consists of corticosteroids, immunosuppressants, antimalarial drugs, and NSAIDs. All components of SoC (excluding NSAIDs) were assumed to vary by comparator.

The base of the analysis is a Markov model that predicts the proportion of patients in different states related to SDI score (0 to 5+) and the presence of cardiovascular (CV) damage. Patients are assumed to progress (i.e., they cannot improve in terms of SDI nor can they recover from CV damage). There are a total of 23 states in the model:

SDI 0 no CV damage on treatment		SDI 0 no CV damage off treatment	
SDI 1 no CV damage on treatment	SDI 1 CV damage on treatment	SDI 1 no CV damage off treatment	SDI 1 CV damage off treatment
SDI 2 no CV damage on treatment	SDI 2 CV damage on treatment	SDI 2 no CV damage off treatment	SDI 2 CV damage off treatment
SDI 3 no CV damage on treatment	SDI 3 CV damage on treatment	SDI 3 no CV damage off treatment	SDI 3 CV damage off treatment
SDI 4 no CV damage on treatment	SDI 4 CV damage on treatment	SDI 4 no CV damage off treatment	SDI 4 CV damage off treatment
SDI 5+ no CV damage on treatment	SDI 5+ CV damage on treatment	SDI 5+ no CV damage off treatment	SDI 5+ CV damage off treatment
Death			

Thus, patients can transition in terms of disease progression (change in SDI), can develop CV damage, can discontinue therapy (relates to belimumab + SoC only), and can die. Transitions can occur every year, based on the model cycle length. Patients can either stay in the same SDI category or can have an increase of 1 or 2 in their SDI score.

The model has additional features, in that, for each cycle, a range of disease characteristics and the use of additional treatments are estimated. Variables tracked are AMS, mean steroid dosage (mg/day), mean number of mild/moderate flares, mean number of severe flares, proportion of patients using immunosuppressants and proportion of patients using antimalarial drugs. Estimates for these variables are based primarily on regression equations, which were a function of a variety of factors, including age and SDI score, but are

also interrelated, in that the estimate for one characteristic is a function of the estimate of another — for example, estimated AMS predicts the estimated mean number of flares.[4,7]

Transitions for progression of SDI were estimated as follows. For belimumab + SoC responders, the probabilities of staying in the current SDI state or progressing by one or by two points were obtained from one-year data from the BLISS SC study for this subgroup of patients receiving belimumab + SoC.[6] Note that probabilities were the same, regardless of current SDI status. Probabilities were 96.5% for staying in the current SDI, 3.3% for progressing by one point, and 0.2% for progressing by two points. For placebo + SoC, the probabilities of staying in the current SDI state or progressing by one or by two points were obtained from the TLC study for all patients on placebo + SoC, regardless of whether they were responders. Probabilities were 91.3% for staying in the current SDI, 6.0% for progressing by one point, and 2.7% for progressing by two points. For nonresponders with belimumab + SoC, the probabilities of staying in the current SDI state or progressing by one or by two points were assumed to be the same as for all patients on placebo + SoC (including the [redacted]% who were responders).

Discontinuation for belimumab + SoC for the first year is based on the rate of nonresponse in the clinical trial at 24 weeks: [redacted]%. For years 2 to 5, discontinuation is assumed to be 6.83% per year and, for years 6 to 10, 7.38% per year. After 10 years, all patients will stop therapy.

The methods for incorporating mortality in the model are poorly described. The report suggests that mortality is a function of age-specific all-cause mortality, relative mortality of patients with SLE versus the general population, and impact of SLE characteristics on mortality based on Cox regression and some form of calibration, which is unclear. The Cox regression model adopted includes steroid dosage, AMS, and SDI as predictors of mortality.[7]

For the additional patient characteristics modelled, for the first year (cycle) of the model, the data for these parameters were obtained from the BLISS SC trial, adopting a similar approach to SDI progression in that separate regression equations were estimated for the subgroup of patients on belimumab + SoC who were responders and for all patients receiving placebo + SoC. Variables tracked were AMS, mean steroid dosage (mg/day), mean number of mild/moderate flares, mean number of severe flares, proportion of patients using immunosuppressants, and proportion of patients using antimalarial drugs. For the first year (cycle) of the model, the data for these parameters were obtained from the BLISS SC trial; however, nonresponders with belimumab were not given their actual values but the values for all patients receiving SoC. For subsequent years, an approach similar to that adopted for SDI progression is used, in that separate regression equations were estimated for the subgroup of patients on belimumab + SoC who were responders and for all patients receiving placebo + SoC.[4] Nonresponders with belimumab + SoC were again assumed to have the same values as all patients on placebo + SoC (including the [redacted]% who were responders).

The model incorporated the costs of treatment, which are obtained from reliable sources. The model also included the costs of managing SLE through a regression model adapted from the LUCIC study.[9] Costs are assumed to increase with disease severity (SDI), decrease with age, and increase with flares.

The BLISS SC study did not include utility data. Thus, utility values were modelled based on data from the extension study of the BLISS-76 study and the TLC data.[4] In addition, analysis

assumed an incremental effect of belimumab + SoC on treatment in year 1 based on the BLISS-76 study. The "core" utility model reported in Appendix A of the submission includes the following covariates: age, age squared, AMS, obesity, baseline SLEDAI ≥ 12, number of flares, steroid dosage in previous year, and SDI score.[7] The regression model used in the analysis ("detailed" or "expanded" model) includes an additional term not identified within the original analysis (presence of CV damage).

Analysis for the subgroup identified as HDA used the response rate and clinical outcomes for year 1 for this subgroup, based on the BLISS SC trial, but adopted the disease models applicable to the wider patient population and the impact of treatment on SDI progression for the total trial population.

For the primary analysis population, the sponsor reported that the incremental cost per QALY gained (ICER) for belimumab + SoC versus placebo + SoC was $147,695, with 0% chance that the ICER was less than $50,000. For the secondary analysis in the HDA subgroup, the ICER was $131,490.

Relevant input parameters were assumed to be uncertain. Expected values of outcomes for each treatment were obtained from randomly sampling parameter values 5,000 times.

Based on initial comments relating to the handling of costs and utilities, the sponsor submitted a revised analysis with a reported ICER for belimumab + SoC versus placebo + SoC of $147,754 for the total population and $131,424 for the HDA subgroup.

Sponsor's Base Case

Original Submission

The sponsor reported that, for the reference case population (the BLISS SC trial population), belimumab + SoC was more costly ($229,270 versus $146,117) and more effective (12.96 QALYs versus 12.40 QALYs), leading to an ICER per QALY gained for belimumab + SoC versus SoC alone of $147.695 (Table 19). At a willingness-to-pay for QALY of $50,000, the probability that belimumab + SoC is optimal was 0%.

For the HDA population, the sponsor reported that belimumab + SoC was more costly ($242,740 versus $153,663) and more effective (13.57 QALYs versus 12.89 QALYs), leading to an ICER for belimumab + SoC versus SoC alone of $131,490 per QALY (Table 19). At a willingness-to-pay of $50,000 per QALY, the probability that belimumab + SoC is optimal was 0%.

Revised Submission

Based on initial comments relating to the handling of costs and utilities, the sponsor submitted a revised analysis with a reported ICER for belimumab + SoC versus placebo + SoC of $147,754 for the total population and $131,424 for the HDA subgroup.[7]

Table 2: Summary of Results of the Sponsor's Revised Analyses

	Total costs ($)	Total QALYs	ICER versus SoC alone
Total population			
SoC alone	138,792	12.396	–
Belimumab + SoC	221,978	12.959	$147,754
HDA population			
SoC alone	146,489	12.889	–
Belimumab + SoC	235,501	13.567	$131,424

HDA = high disease activity; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; SoC = standard of care.

Source: Sponsor's revised analysis.[8]

Summary of Sponsor's Sensitivity Analyses

The sponsor provided a range of scenario analyses for both the total trial population and the HDA subgroup. Scenario analyses involved changing parameter values related to time horizon, discount rate, maximum years on treatment, age, medical costs, corticosteroid usage, proportion of population who are male, probability of SDI progression, response rates, and utility values. Results were generally consistent across all scenarios; in all scenarios for both populations, belimumab would not be considered cost-effective.

Limitations of Sponsor's Submission

There were a number of major limitations identified with the sponsor's analyses.

Clinical data — estimation of response. The most serious limitation of the analysis was the assumption relating to nonresponders with belimumab + SoC. The sponsor assumed that a nonresponder with belimumab + SoC has the same outcomes as a patient receiving SoC. This relates to SDI transition probabilities, one-year clinical effect data, and the predictive models relating to AMS, steroid dosage, flares, immunosuppressants, and antimalarial drugs. These have a direct impact on estimates of costs and QALYs. In the BLISS SC study, [redacted]% of patients receiving SoC had a response at 24 weeks (the outcome used in the pharmacoeconomic analysis) compared to [redacted]% with belimumab + SoC. Thus, the incremental effect of belimumab on response is only 10.4% (i.e., 82.5% of patients who respond with belimumab would have responded with SoC alone).[5,6] Significant bias is therefore introduced by assuming that nonresponders receiving belimumab + SoC have the same outcomes as all patients receiving SoC. CADTH requested that the sponsor supply a revised model that considers nonresponders and responders separately, thus allowing for differential outcomes in patients receiving SoC who respond versus those receiving belimumab + SoC who do not respond. The sponsor declined to provide this analysis.

The effect of the problem can be illustrated by the model predictions. At 52 weeks, the clinical study reports that there was no difference (0.00) in the change in SDI score between those receiving placebo + SoC and belimumab + SoC. The sponsor's model forecasted a difference in change in SDI score at 52 weeks of 0.04 in favour of belimumab + SoC.

CADTH approached the sponsor to make this correction; however, the sponsor declined. As a result, to account for this, CADTH revised the model to allow for differential transition probabilities and initial clinical outcomes for SDI for nonresponders versus responders and to use the same predictive equations (placebo + SoC) for all outcomes. CADTH assumed,

based on input from clinical experts, that responders would have the same outcomes regardless of whether they had received belimumab or not. By adopting the revised approach, the CADTH-revised model forecasted a difference in change in SDI score at 52 weeks of 0.016, still potentially biased in favour of belimumab + SoC based on the trial results.

Mortality. The methods for incorporating mortality within the model were poorly described. The Cox regression model used includes steroid dosage, AMS, and SDI as predictors of mortality.[4] It is not, however, the Cox regression model reported in Appendix A of the sponsor's report, as referenced by the sponsor.[7] The sponsor's submitted analysis estimates an increase in undiscounted life-years of 0.99 with belimumab. It should be noted that no direct survival benefit with belimumab has been demonstrated in the clinical literature. Furthermore, the evidentiary basis to accurately measure the extent of any indirect mortality benefit is insufficient, due to the uncertainty inherent in the clinical studies, which demonstrate a link between disease activity and mortality and, more importantly, due to the uncertainty over the long-term relative impacts of belimumab on disease activity.

Treatment waning. A further limitation of the analysis is the assumption that patients receiving belimumab + SoC could stay on treatment for up to 10 years without any waning of treatment effect. It was not possible to consider an alternative assumption in the current model.

Costs and utility inputs. The sponsor did not use the cost models reported in its submitted appendix.[4,7] Pharmaceutical costs are "subtracted out" based on average costs and not by allowing variation by patient characteristics; this is likely an invalid approach. It is unclear why the data were not reanalyzed. The cost models appear to use a simple linear regression model, which is inappropriate, given the nature of cost data. In this case, the cost models lead to highly unlikely results, in that costs decline with age and, for older patients. the regression model would predict negative values. This is avoided by using a lower cut-off for health care costs of 0. Having costs for patients with SLE decline with age and approach $0 suggests a lack of face validity. The approach adopted can be considered statistically invalid. The sponsor responded to this by capping the age of patients at 77 in the regression model. This approach still lacks face validity because costs are decreasing by patient age.

The sponsor used a different utility model than the one cited in the appendix of its economic report.[4,7] Adoption of the "expanded" model gives more favourable results for belimumab. Thus, CADTH adopted the original "core" model that had been identified as the preferred model in the submitted report. The impact of age on utility values in the model is curious: utility values decline with age up to age 77 and then increase. There is the potential for utility values greater than 1, which is avoided in the model by using a cut-off for utility values of 1. Utility values for patients with SLE approaching 1 again suggests a lack of face validity, and the approach adopted can be considered statistically invalid. The sponsor responded to this criticism by capping the age of patients at 77 in the regression model. This approach still lacks face validity.

HDA subgroup. Analysis for the subgroup identified as HDA used the response rate and clinical outcomes for year 1 for this subgroup based on the BLISS SC trial, but adopted the disease models applicable to the wider patient population and the impact of treatment on SDI progression for the total trial population. Results of the analysis for patients with HDA paradoxically reported higher estimated QALYs and life expectancy for patients on both belimumab + SoC and SoC alone when compared to the estimates for the total trial population. The approach adopted is invalid, and the results lack face validity (and provide a

basis to question the validity of the results for total trial population). Therefore, the analysis for the HDA group was not considered in CADTH reanalyses, as it is unlikely to reflect an actual HDA population.

CADTH Common Drug Review Reanalyses

CADTH conducted a reanalysis of the sponsor's model, adopting the following changes:

1. Probability of SDI progression varies by responders and nonresponders; probability of SDI progression for responders is the same regardless of treatment; and probability of SDI progression for nonresponders is the same regardless of treatment.

This was facilitated by adopting the following approach. For belimumab + SoC responders ([redacted]%), the probability of SDI progression of 1 was 3.3% and of 2 was 0.3%. Assume that, for responder to SoC, the same probabilities apply as recommended by the clinical experts: 3.3% for 1 and 0.3% for 2. Derive the probabilities for all nonresponders based on the response rate for SoC ([redacted]%) and the probabilities for all patients receiving SoC (6% for 1 and 2.7% for 2).

i.e.,

$$\text{Probability of progression of 1 SDI for a nonresponder} = \frac{0.06 - 0.033*0.495}{1-0.495} = 0.087$$

$$\text{Probability of progression of 2 SDI for a nonresponder} = \frac{0.027 - 0.003*0.495}{1-0.495} = 0.051$$

To control for the effect of discontinuation and avoid introducing a bias against belimumab + SoC, patients on SoC alone were assumed to move from being a responder to nonresponder at the same rate as for belimumab + SoC.

After year 1, [redacted]% of patients receiving belimumab + SoC and [redacted]% of patients receiving SoC alone are responders. After year 2, the proportion who are responders are 55.8% (0.599 × [1 – 0.0683]) for belimumab + SoC and 46.1% (0.495 × [1 – 0.0683]) for SoC alone. Thus, the analysis assumes no waning of treatment effect, as the relative proportions of patients who are responders between the two treatment alternatives remains constant.

Ideally, the actual probabilities for responders and nonresponders would have been used, but these were not available from the sponsor.

2. One-year clinical outcomes (e.g., AMS and utility values) vary by responders and nonresponders; outcomes for responders are the same regardless of treatment; and outcomes for nonresponders are the same regardless of treatment. This was facilitated by adopting an approach mathematically similar to that adopted for SDI progression.
3. Adopt the same regression models to predict disease characteristics for all patients. The analysis adopted the equations for SoC alone for all comparators.
4. Adopt the utility regression model identified as core in the submitted Appendix A of the sponsor's economic report.

A reanalysis that focused only on handling the approach to modelling nonresponders with belimumab + SoC, addressing points 1 to 3, led to an estimated ICER of $464,061 (Table 21). A reanalysis that adopted the core utility model (alone) led to an estimated ICER of $155,283 (ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; SoC = standard of care.

Table 22).

It was not possible, however, to reprogram the model to conduct probabilistic analysis, so the CADTH-revised analysis is based on a deterministic analysis. Furthermore, caution must be taken with respect to the interpretation of the results, as it was not possible to obtain the reanalysis requested from the sponsor, which would have more accurately reflected the true ICER in this context.

Under the approach adopted, the estimated ICER was $646,893 for the full population (Table 3), with additional details provided in Table 23.

Table 3: Summary of Results for CADTH Reanalysis – Full Trial Population (Deterministic)

	Total costs ($)	Total QALYs	ICER versus SoC alone ($/QALY)
SoC alone	126,292	14.996	–
Belimumab + SoC	219,504	15.110	$646,893

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; SoC = standard of care.

As noted above, due to the lack of validity of the original sponsor's analysis, no analysis was conducted for the HDA subgroup. Furthermore, the CADTH pharmacoeconomic reviewer was not able to address concerns relating to the potential waning of treatment effect or the unsubstantiated survival benefits.

CADTH undertook a price-reduction analysis based on the sponsor's revised submission and the CADTH reanalyses, assuming proportional price reductions for belimumab and based on the full trial population (Table 4). Given the inability to run the probabilistic analysis with the CADTH reanalysis, the required price reductions were obtained using deterministic analysis.

Price-reduction analyses were conducted for both the sponsor's received base case and the CADTH reanalyses. Using the sponsor's revised base-case analysis, the price reduction required for belimumab to have an incremental cost per QALY gained of $100,000, compared to SoC, was 22.8%. For an incremental cost per QALY gained of $50,000, the required price reduction was 56.4%. Based on the CADTH reanalysis, the price reduction required for belimumab to have an incremental cost per QALY gained of $100,000, compared to SoC, was 80.9%. For an incremental cost per QALY gained of $50,000, the required price reduction was 88.3%.

Table 4: CADTH Reanalysis Price-Reduction Scenarios

ICER ($/QALY) for belimumab + SoC versus SoC alone		
Price	**Sponsor's deterministic base case**	**CADTH reanalysis**
Submitted price	$133,850	$646,893
10% reduction	$118,973	$579,314
20% reduction	$104,095	$511,735
30% reduction	$89,217	$444,156
40% reduction	$74,339	$376,577
50% reduction	$59,461	$308,999
60% reduction	$**44,583**	$241,420
70% reduction	$29,705	$173,841

ICER ($/QALY) for belimumab + SoC versus SoC alone		
Price	**Sponsor's deterministic base case**	**CADTH reanalysis**
80% reduction	$14,827	$106,262
90% reduction	Dominant	**$38,683**

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; SoC = standard of care.

Source: Reanalysis of the sponsor's model based on deterministic results.[4] Thus, minor difference from estimates are presented.

Patient Input

Patient input was received from the Canadian Arthritis Patient Alliance (CAPA) and The Arthritis Society (TAS) through a joint submission. The CAPA and TAS developed a survey that was distributed to patients with SLE. Reponses were received from 14 people.

Patients noted that SLE results in muscle pain, which can lead to issues with mobility. They also noted that the condition tends to affect a number of systems (including respiratory, musculoskeletal, and vision). They also cited concerns regarding the unpredictability and duration of flares as being challenging to manage. Patients also indicated that the disease has a significant impact on quality of life: it limits patients' abilities to perform daily household chores, work, participate in leisure activities, and care for children and loved ones. Spouses, partners, or children often must take on additional responsibilities, such as household chores and taking patients to medical appointments, to support patients with SLE. The sponsor has captured some of these outcomes by using clinical outcomes from its clinical studies SLEDAI and SDI; however, impact on informal caregivers was not captured in the sponsor's clinical studies.

Patients seek treatments to prevent long-term organ damage. Clinical studies were not of sufficient duration to capture this information. Patients also indicate that currently available treatments for SLE have many side effects that are often difficult for patients to tolerate. Adverse events for comparators and belimumab were included in the sponsor's economic evaluation. The administration of belimumab by a three-hour infusion was mentioned as a concern, especially for those who are currently employed. While the self-injector alleviates this concern, the drug requires refrigeration, which may restrict travel for some patients; this was not considered by the sponsor in its economic evaluation.

Conclusions

The sponsor's analysis suggests that belimumab + SoC is not cost-effective in either the patient population studied in the BLISS SC (ICER of $147,695 per QALY) or the subgroup of patients with HDA (ICER of $131,490 per QALY).

CADTH identified a number of major limitations with the submitted analysis. When accounting for the limitations to the extent possible, CADTH reanalysis suggests a much higher ICER for the total population ($646,893 per QALY versus $147,695 as suggested by the sponsor). A price reduction of 88.3% would be required for belimumab + SoC to be considered cost-effective at a willingness-to-pay threshold of $50,000 per QALY.

However, given that the reanalysis could not account for the potential for waning of treatment effect and assumed a mortality effect with belimumab + SoC, which has not been demonstrated, caution should be exerted when interpreting the results.

Appendix 1: Cost Comparison

The comparators presented in Table 5 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 5: CDR Cost Comparison Table of Treatments for Adults With SLE

Drug/ comparator	Strength	Dosage form	Price ($)	Recommended dose	Average annual drug cost ($)
Belimumab (Benlysta)	**200 mg/mL**	**Solution for SC injection**	**421.7900[a]**	**200 mg once weekly**	**21,933**
	120 mg/5 mL 400 mg/20 mL Single-use vials	Lyophilized powder for IV infusion	293.5700[b] 978.5600[b]	10 mg per kg every 2 weeks for first 3 doses, then every 4 weeks	Year 1: 24,660 (14 doses) Year 2: 22,898 (13 doses)
Antimalarial drugs					
Hydroxychloroquine (Plaquenil, generic)	200 mg	Oral tablet	0.1576	200 mg to 400 mg daily	57 to 115
Corticosteroids					
Prednisolone (generic)	5 mg/5 mL	Oral solution	0.0900 per mL	≤ 7.5 mg daily[c]	Up to 246
Immunosuppressants — *Treatments used but not approved*					
Azathioprine (generic)	50 mg	Oral tablet	0.2405	50 mg to 100 mg daily[c]	88 to 175
Cyclosporine (generic)	10 mg 25 mg 50 mg 100 mg	Capsule	0.6520 0.9952 1.9400 3.8815	50 mg to 100 mg daily[c]	706 to 1,412
	100 mg/mL	Oral solution	3.7707 per mL		686 to 1,373
Methotrexate (generic)	2.5 mg 10 mg	Oral tablet	0.6325 2.7000[d]	10 mg weekly[c]	132
Mycophenolate mofetil (Cellcept, generic)	250 mg 500 mg	Capsule Oral tablet	0.3712 0.7423	1 g to 1.5 g daily[c]	540 to 811

SC = subcutaneous.

Note: Prices do not include costs of product dispensing, dose preparation, or administration. A patient weight of 70 kg was assumed. Annual period assumes 52 weeks, or 13 × 4 weeks per year (364 days for all comparators). The calculated annual doses are based on product monograph, where available. When multiple formulations were available, the least expensive type was used to calculate costs. All injected comparators are assumed to be used as single-use vials, with leftover product being wasted.

[a] Sponsor-submitted price.[2]

[b] Wholesale acquisition price based on IQVIA DeltaPA database (April 2019).[11]

[c] British Society for Rheumatology guideline for the management of SLE in adults.[10]

[d] Saskatchewan Online Formulary Database (August 2019).[12]

Table 6: CDR Cost Comparison Table of Other Treatments for Adults With SLE

Drug/ comparator	Strength	Dosage form	Price ($)	Recommended dose	Average drug cost per treatment ($)
Corticosteroids					
Methylprednisolone (Solu-Medrol, generic)	40 mg 125 mg 500 mg 1,000 mg	Sterile powder for IM injection or IV infusion	4.7801[a] 10.401[a] 24.696[a] 37.9336[a]	Three pulses of 100 mg to 750 mg infusions[b]	29 to 114 per 3 pulses
(Depo-Medrol, generic)	40 mg / mL 80 mg / mL 20 mg / mL	Injectable suspension for intra-articular, intra-synovial, intralesional, or IM injection	5.9955 11.5015 13.4259	80 mg to 120 mg per dose[b]	12 to 18 per dose
Immunosuppressants — *Treatments used but not approved*					
Cyclophosphamide (Procytox)	200 mg vial	Sterile powder for IV injection	70.0300[c]	≤ 2.5 mg/kg daily[b]	Up to 70 per day
Leflunomide (Arava, generic)	10 mg 20 mg	Film-coated tablet	2.6433	20 mg daily[b]	3 per day
Rituximab (Rituxan[d])	100 mg/10 mL 500 mg/50 mL single-use vials	Solution for injection	48.2305 per mL[e]	1,000 mg on day 1 and 15 of an infusion cycle. Re-treat responders when further disease flare develops.[b,f]	9,646 per infusion cycle

IM = intramuscular.

Note: Prices do not include costs of product dispensing, dose preparation, or administration. A patient weight of 70 kg was assumed. Annual period assumes 52 weeks, or 13 × 4 weeks per year (364 days for all comparators). The calculated annual doses are based on product monograph, where available. When multiple formulations were available, the least expensive type was used to calculate costs. All injected comparators are assumed to be used as single-use vials, with leftover product being wasted.

[a] Alberta Interactive Drug Benefit List (August 2019).[13]

[b] British Society for Rheumatology guideline for the management of SLE in adults.[10]

[c] Wholesale acquisition price based on IQVIA DeltaPA database (August 2019).[11]

[d] A biosimilar, Truxima, was also approved in Canada.[14]

[e] Saskatchewan Online Formulary Database (August 2019).[12]

[f] August 2013 National Health Service England interim clinical commissioning policy statement.[15]

Appendix 2: Additional Information

Table 7: Submission Quality

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?			X
Comments Reviewer to provide comments if checking "no"	The model is unduly complex, and there are discrepancies between the disease models used within the model and those in Appendix A.		
Was the material included (content) sufficient?			X
Comments Reviewer to provide comments if checking "poor"	The sponsor did not provide the revised analysis requested by CADTH.		
Was the submission well organized and was information easy to locate?		X	
Comments Reviewer to provide comments if checking "poor"			

Table 8: Authors Information

Authors of the pharmacoeconomic evaluation submitted to CADTH

☐ Adaptation of global model/Canadian model done by the sponsor

☒ Adaptation of global model/Canadian model done by a private consultant contracted by the sponsor

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

☐ Other (please specify)

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

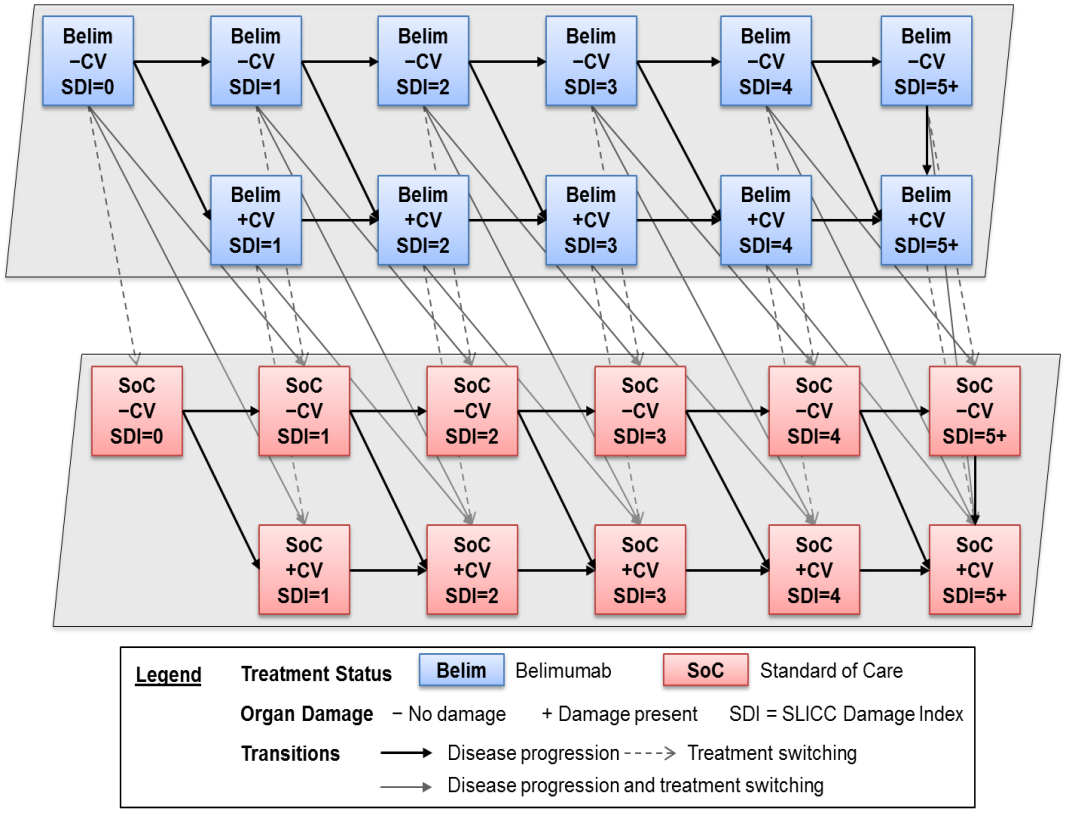
Appendix 3: Summary of Other Health Technology Assessment Reviews of Drug

The cost-effectiveness of belimumab (Benlysta) SC injection as an add-on therapy in adult patients with active, autoantibody-positive SLE with a high degree of disease activity despite standard therapy has been reviewed by the Haute Autorité de santé (HAS) in France.[16] Although HAS considered belimumab to have an important medical benefit (*service médical rendu important*), HAS found the SC formulation of belimumab to provide no improvement in medical benefit over the IV-injection formulations (*amélioration du service médical rendu* level V).

Although the UK National Institute for Health and Care Excellence (NICE) and the Scottish Medicines Consortium (SMC) did not specifically review the SC injection formulation of belimumab, their reviews of the IV-injection formulation considered the trial for the SC formulation (BLISS SC).[17,18] NICE noted that BLISS SC was an ongoing trial at the time of the review,[17] while the SMC could consider the trial's SRI primary outcome at week 52 as supportive data. NICE and the SMC recommended the IV-injection formulation of belimumab as an add-on treatment option for active autoantibody-positive SLE, but only in adults with HDA (low complement and anti-double-stranded DNA [dsDNA] and a SELENA-SLEDAI score of at least 10 despite standard treatment).[17,18] NICE further restricted the use of belimumab such that the treatment could continue beyond 24 weeks only if SELENA-SELDAI scores improved by at least four points. Both NICE and the SMC have considered belimumab and recommended funding based on patient access schemes. The details of the patient access schemes are unknown, and the related price reductions are not available.

Appendix 4: Reviewer Worksheets

Figure 1: Model Structure



Patients in any health state may remain in current health state (not shown)
Patients can transition to Death from any health state (not shown)

Belim = belimumab; CV = cardiovascular; SDI = Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SoC = standard of care.

Source: Sponsor's pharmacoeconomic submission.[4]

Model Inputs

Table 9: Annual Probability of Change in SDI Score

	Belimumab responders	Standard of care[a]
No SDI change	[redacted]	[redacted]
SDI increase by 1	[redacted]	[redacted]
SDI increase by 2+	[redacted]	[redacted]

SDI = Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index.

[a] Nonresponders with belimumab nonresponders were assumed to have same probabilities as standard of care patients (which includes [redacted]% of patients who responded). CADTH reanalysis derived probabilities for responders and nonresponders.

Source: Sponsor's pharmacoeconomic submission.[4]

Table 10: Population Characteristics at the End of Year 1

	Belimumab responders	Standard of care[a]
Mean SLEDAI	3.36	6.20
Mean steroid usage (mg)	8.56	10.70
Mean mild/moderate flares	1.23	1.77
Mean severe flares	0.04	0.27
Mean SF-6D	0.6600	0.6500
% on immunosuppressants	41.2%	51.4%
% on antimalarial drugs	71.5%	68.6%

SF-6D = Short Form Six-Dimensions Health Survey; SLEDAI = Systemic Lupus Erythematosus Disease Activity Index.

[a] Nonresponders with belimumab nonresponders were assumed to have same probabilities as standard of care patients (which includes [redacted]% of patients who responded). CADTH reanalysis derived probabilities for responders and nonresponders.

Source: Sponsor's pharmacoeconomic submission.[4]

Table 11: Beta Parameters for Predicted Adjusted Mean SLEDAI (AMS) Model

	Belimumab responders	Standard of care[a]
Intercept	0.7334	3.9628
Log(age)	0.0000	–0.8020
AMS in previous year	0.7501	0.6873
Total SDI	0.0000	0.0405

[a] Nonresponders with belimumab were assumed to have same coefficients as standard of care patients (which includes [redacted]% of patients who responded). CADTH reanalysis adopted the regression model for standard of care for all patients.

Source: Sponsor's pharmacoeconomic submission.[4]

Table 12: Predicted Number of Mild/Moderate Flares (Lognormal AFT Model)

	Belimumab responders	Standard of care[a]
Intercept	0.6970	0.4388
AMS in current year (inverse sine)	–0.4090	–0.4053
Log(model year)	0.0000	0.0752
Log(scale)	0.1640	–0.2033

AFT = accelerated time failure; AMS = adjusted mean Systemic Lupus Erythematosus Disease Activity Index.

[a] Nonresponders with belimumab were assumed to have same coefficients as standard of care patients (which includes [redacted]% of patients who responded). CADTH reanalysis adopted the regression model for standard of care for all patients.

Source: Sponsor's pharmacoeconomic submission.[4]

Table 13: Predicted Number of Severe Flares (Lognormal AFT Model)

	Belimumab responders	Standard of care[a]
Intercept	5.7038	1.3897
AMS in current year (inverse sine)	–1.1146	–0.5014
Log(model year)	0.0871	0.0759
% on immunosuppressants	–0.9852	–0.2935
Log(scale)	0.5286	–0.0885

AFT = accelerated time failure; AMS = adjusted mean Systemic Lupus Erythematosus Disease Activity Index.

[a] Nonresponders with belimumab were assumed to have same coefficients as standard of care patients (which includes [redacted]% of patients who responded). CADTH reanalysis adopted the regression model for standard of care for all patients.

Source: Sponsor's pharmacoeconomic submission.[4]

Table 14: Predicted Mean Daily Steroid Dosage

	Dosage, mg/day	
	Belimumab responders	Standard of care[a]
Intercept	3.2055	4.9763
Log(year)	–0.8174	–1.0887
AMS in current year	0.4061	0.7022
% baseline age > 35	1.8037	–1.5812
AMS in current year and % baseline age > 35	–0.4603	0.0000

AMS = adjusted mean Systemic Lupus Erythematosus Disease Activity Index.

[a] Nonresponders with belimumab were assumed to have same coefficients as standard of care patients (which includes [redacted]% of patients who responded). CADTH reanalysis adopted the regression model for standard of care for all patients.

Source: Sponsor's pharmacoeconomic submission.[4]

Table 15: Predicted Annual Direct Medical Costs

	Coefficient
Baseline medical costs	$9,022.87
Per year of age	–$131.92
Per unit SDI	$1,424.21
Per mild/moderate flare	$105.24
Per severe flare	$2,523.88

SDI = Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index.

Note: The model used is not the model reported in the sponsor's submission Appendix A, in that the reported model included pharmacy costs.

Source: Sponsor's pharmacoeconomic submission.[4]

Table 16: Predicted Utility Values

	Model used in report	Model as per Appendix A[a]
Intercept	0.9112	0.9103
Age	–0.0077	–0.0077
Age^2	0.0001	0.0001
AMS	–0.0031	–0.0031
Obesity	–0.0326	–0.0340
Baseline SLEDAI ≥ 12	0.0288	–0.0064
Total flares	–0.0063	–0.0095
Steroid dosage in previous year	–0.0009	–0.0009
Total SDI score	–0.0078	0.0285
SDI cardiovascular damage	–0.0279	0.0000

AMS = adjusted mean Systemic Lupus Erythematosus Disease Activity Index; SDI = Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SLEDAI = Systemic Lupus Erythematosus Disease Activity Index.

[a] Model adopted in CADTH reanalysis.

Source: Sponsor's pharmacoeconomic submission.[4]

Summary of Sponsor Data Sources

Table 17: Model Data Sources

Data input	Description of data source	Comment
Baseline cohort characteristics	BLISS SC	Appropriate
Efficacy	BLISS SC	Likely appropriate in modelling short-term treatment effects, but appropriateness in the long term (up to 10 years) is unknown, given potential for waning of treatment effectiveness
Natural history	BLISS SC for disease progression with respect to SDI US data from BLISS-76 extension study and analysis of the Toronto Lupus Cohort used to determine disease models from disease characteristics.	Unclear how valid in the long term Unclear how valid disease models are in the long term
Utilities	Derived from regression models using US data from BLISS-76 extension study and analysis of the Toronto Lupus Cohort	Model allows for increased utility values in those older than 77. Validity of a retrospective approach of capping values at age 77 is unclear.
Adverse events	N/A	
Mortality	Data from general population — Statistics Canada adjusted by data on increased mortality based on post hoc analysis of the Toronto Lupus Cohort	Unclear if appropriate
Resource use and costs		
Drug	Sponsor and ODB formulary	Appropriate
Adverse events	N/A	
Health state	Data from 3 SLE clinics in Halifax, Montreal, and Toronto	Model suggests costs of management decrease with age. This lacks face validity.

Data input	Description of data source	Comment
		Validity of the approach to remove pharmaceutical costs from cost estimates is unclear.

N/A = not applicable; ODB = Ontario Drug Benefit; SDI = Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SLE = systemic lupus erythematosus.

Summary of Key Assumptions

Table 18: Sponsor's Key Assumptions

Assumption	Comment
Nonresponders with belimumab + SoC will have the same short- and long-term outcomes as all patients on SoC alone	Inappropriate. In the BLISS SC study, [redacted]% of patients receiving SoC had a response at 24 weeks (the outcome used in the pharmacoeconomic analysis) compared to [redacted]% with belimumab + SoC. Thus, the incremental effect of belimumab on response is only 10.4% (i.e., 82.5% of patients who respond with belimumab would have responded with SoC alone). Significant bias is therefore introduced by assuming that nonresponders with belimumab + SoC have the same outcomes as all patients receiving SoC.
Treatment with belimumab + SoC will increase life expectancy	Unclear whether appropriate, given lack of long-term clinical data to support proposition
Treatment effectiveness will continue for up to 10 years of re-treatment	Unclear whether appropriate, given lack of long-term clinical data to support proposition
Models to predict disease characteristics are appropriate to be used for lifetime	Unclear whether appropriate, given lack of long-term clinical data to support proposition
Adoption of revised utility model	Unclear whether appropriate, given that an alternative utility model is identified in the submitted appendix as the "core" model

Sponsor's Analyses

Sponsor's Original Analyses

Table 19: Summary of Results of the Sponsor's Base Case — Original Analyses

	Total costs ($)	Total QALYs	ICER versus SoC alone ($/QALY)
SoC alone	146,117	12.396	–
Belimumab + SoC	229,270	12.959	$147,695

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; SoC = standard of care.

Source: Sponsor's pharmacoeconomic submission.[4]

Table 20: Summary of Results of the Sponsor's Analysis for High Disease Activity Population

	Total costs ($)	Total QALYs	ICER versus SoC alone ($/QALY)
SoC alone	153,663	12.889	–
Belimumab + SoC	242,740	13.567	$131,490

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; SoC = standard of care.

Source: Sponsor's pharmacoeconomic submission.[4]

CADTH Reanalyses

Table 21: Summary of Results of CADTH Reanalysis for Total Population — Changes In Handling Nonresponders With Belimumab + SoC

	Total costs ($)	Total QALYs	ICER versus SoC alone ($/QALY)
SoC alone	126,292	13.631	–
Belimumab + SoC	219,504	13.832	$464,061

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; SoC = standard of care.

Table 22: Summary of Results of CADTH Reanalysis for Total Population — Using Base Utility Model

	Total costs ($)	Total QALYs	ICER versus SoC alone ($/QALY)
SoC alone	118,926	15.1220	–
Belimumab + SoC	206,836	15.6881	$155,283

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; SoC = standard of care.

Table 23: Disaggregated Results of CADTH Base Reanalysis for Total Population

	Standard of care	Belimumab
Pharmacy costs	$5,128	$100,815
Medical costs	$121,164	$118,690
Total costs	**$126,292**	**$219,504**
QALYs	14.9663	15.1104
Life-years	19.25	19.46

QALY = quality-adjusted life-year.

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