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CADTH Reimbursement Review

Belimumab (Benlysta)

Sponsor: GlaxoSmithKline Inc.

Therapeutic area: Lupus nephritis

Clinical Review
Pharmacoeconomic Review
Stakeholder Input

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Abbreviations

AE	adverse event
CI	confidence interval
CRR	complete renal response
C-SSRS	Columbia – Suicide Severity Rating Scale
dsDNA	double-stranded DNA
eGFR	estimated glomerular filtration rate
ERA-EDTA	European Renal Association–European Dialysis and Transplant Association
ESRD	end-stage renal disease
EULAR	European League Against Rheumatism
GFR	glomerular filtration rate
HR	hazard ratio
HRQoL	health-related quality of life
IP	investigational product
ITC	indirect treatment comparison
KDIGO	Kidney Disease: Improving Global Outcomes
LN	lupus nephritis
LS	least squares
MID	minimal important difference
mITT	modified intention to treat
OLE	open-label extension
OR	odds ratio
ORR	ordinal renal response
PERR	primary efficacy renal response
PGA	physician global assessment
SAE	serious adverse event
SD	standard deviation
SDI	Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index
SELENA	Safety of Estrogens in Lupus Erythematosus – National Assessment
SFI	SELENA SLEDAI Flare Index
SLE	systemic lupus erythematosus
SLEDAI-2K	Systemic Lupus Erythematosus Disease Activity Index 2000

SLEDAI-S2K	Systemic Lupus Erythematosus Disease Activity Index 2000 with modified scoring for proteinuria
uPCR	urine protein-creatinine ratio
UTI	urinary tract infection

Executive Summary

An overview of the submission details for the drug under review is provided in Table 1.

Introduction

Lupus is an autoimmune disease characterized by inflammatory processes that can occur in various tissues and organs of the body.[1] A common form of lupus is systemic lupus erythematosus (SLE)[2] with an estimated prevalence of about 1 in 2,000 individuals in Canada.[3,4] The age of onset is primarily between 16 and 55 years,[5] with females more commonly affected than males (9:1).[4] The median ages at diagnosis for white females range from 37 to 50 years, in white males from 50 to 59, in Black females from 15 to 44, and in Black males from 45 to 64.[5] Kidney injury is common in SLE, with lupus nephritis (LN) occurring in about 50% of patients with SLE,[6] usually within 5 years of SLE diagnosis.[7] Kidney involvement can remain silent or asymptomatic for a significant period of time;[8] however, patients may experience fatigue, joint and muscle pain, edema, rash, and a variety of other symptoms.[9] The disease is associated with substantial morbidity[6] as serious complications include progression to end-stage renal disease (ESRD),[10] in which patients require dialysis or kidney transplant.[8]

Initial treatment options for induction of class III, IV, and/or V active LN include a high-dose corticosteroid taper as well as immunosuppressive drugs such as mycophenolate mofetil (or mycophenolic acid) or cyclophosphamide.[8,11] The clinical expert consulted by CADTH for this review noted that other treatments in addition to standard of care for patients with an inadequate response to first-line induction therapy may include off-label use of rituximab, cyclosporin, or tacrolimus. The clinical expert for this review stated that in all cases of class III, IV, and/or V active LN, use of antimalarials (i.e., hydroxychloroquine), bone protection (vitamin D, calcium, possibly antiresorptive drugs), immunizations with nonlive vaccines, and adjunct treatment with renin-angiotensin blockade and statins should be considered.

Belimumab inhibits the B lymphocyte stimulator protein and thus reduces B-cell activity.[12] The IV administration is 10 mg/kg, administered over an hour, at 2-week intervals for the first 3 doses and at 4-week intervals thereafter in addition to standard of care therapy for patients with active LN. The recommended dose for subcutaneous injection, in addition to standard of care therapy, is 400 mg (two 200 mg injections) once weekly for 4 doses, then 200 mg once weekly thereafter for the treatment of adult patients with active LN.

The objective of this report is to perform a systematic review of the beneficial and harmful effects of belimumab IV infusion or subcutaneous injection in addition to standard of care therapy for the treatment of active LN in adults.

Stakeholder Perspectives

The information in this section is a summary of input provided by the patient groups who responded to CADTH's call for patient input and from the clinical expert consulted by CADTH for the purpose of this review.

Table 1: Submitted for Review

Item	Description
Drug product	Belimumab 400 mg per 20 mL vial and 120 mg in 5 mL vial lyophilized powder for IV infusion
Indication	Indicated in addition to standard therapy for the treatment of active LN in adult patients
Reimbursement request	In addition to standard therapy, for treatment of active LN in adult patients with all the following criteria: • adult patients ≥ 18 years • in addition to receiving standard therapy • in class III, class IV, and/or class V of active LN • if no improvements of disease activity and/or symptoms are observed after 6 months, use should be discontinued.
Health Canada approval status	NOC
Health Canada review pathway	Standard
NOC date	July 29, 2021
Sponsor	GlaxoSmithKline Inc.

LN = lupus nephritis; NOC = Notice of Compliance.

Patient Input

Four responses to CADTH's call for patient input for the belimumab submission were received. These consisted of submissions from Arthritis Consumer Experts, Lupus Ontario, a joint submission from the Kidney Foundation of Canada and Lupus Canada, and a cooperative submission from the Canadian Arthritis Patient Alliance, the Arthritis Society, the Canadian Skin Patient Alliance, and CreakyJoints. Patient input was gathered from surveys, video interviews, and focus group discussions among lupus patients across Canada: 34 respondents (88% female) from Arthritis Consumer Experts, 10 respondents (90% female) with SLE from Lupus Ontario, and 38 respondents (73% with LN and approximately 15% caregivers) from the Kidney Foundation of Canada and Lupus Canada. The cooperative submission conducted a focus group of 3 patients with LN as well as a video interview with 1 patient. The submission from Arthritis Consumer Experts also included an in-depth interview with 1 patient. Seventeen patients (6 from a previous survey) in the included submissions had experience with the treatment under review.

Patients reported managing SLE was difficult given the severity of the physical symptoms, such as debilitating fatigue, joint pain, flares, skin rashes, nausea, loss of appetite, bruising, back pain, brain fog, mobility issues, and mental health issues. Respondents reported that currently available treatments are difficult to tolerate because of the many side effects. While describing their experiences with the drug under review, patients reported both positive and negative outcomes. Some patients described experiencing side effects such as severe allergic reaction, extreme nausea, sleep deprivation, frequent urinary tract infections (UTIs), depression, and psychosis. Other patients reported an overall decrease in their disease symptoms and improvement in physical ability, leading to improvement in their health-related quality of life (HRQoL).

The key outcomes patients would like addressed by a new therapy are reduction of side effects and number of medications used; reduction in fatigue, flares, pain, and rash and skin irritations; increased mobility and participation in physical activities; overall improvement in HRQoL; improved engagement in social activities; and better affordability of medication.

Clinician Input

Input From the Clinical Expert Consulted by CADTH

According to the clinical expert consulted by CADTH for this review, response to current standard of care induction therapy is suboptimal (only 20% to 35% of patients achieve a complete renal response [CRR] within 6 months to 12 months after initiation of induction therapy; of those who do respond, 20% to 35% relapse within 3 years to 5 years), indicating a major unmet need as up to 40% of patients with LN can develop chronic kidney disease and progress to ESRD, requiring dialysis or transplant. Other unmet needs include lack of adherence, side effects (e.g., with prednisone), and recurrent flares that cause progressive organ damage, and only a few treatments are safe in pregnancy in a disease that largely affects those who can become pregnant. Currently, no treatments provide a long-term cure or long-term medication-free survival. According to the clinical expert, the current place in therapy for belimumab would be as add-on therapy to existing standard of care (i.e., corticosteroids and mycophenolate mofetil/mycophenolic acid or cyclophosphamide) in patients with class III or IV (with or without class V) or pure class V active LN who have not attained an adequate renal response after 2 months to 3 months of induction therapy; however, the clinical expert noted that the time to initiate belimumab may vary from start of induction therapy to 3 months to 6 months after initiation of induction therapy, dependent on disease severity, patient response, and expert physician judgment. Other factors that may identify active patients most likely to respond to belimumab include those with previous episodes of class III or IV (with or without class V) or class V LN in whom another flare may cause a serious decline in renal function; patients with active class III or IV (with or without class V) or class V LN with chronically impaired renal function or who still have prednisone use greater than 7.5 mg/day after 3 to 6 months of induction; or who have extrarenal manifestations in addition to LN. The clinical expert identified those least likely to benefit from belimumab as including patients with active LN who are not currently receiving standard of care induction therapy, patients for whom induction with both mycophenolate mofetil/mycophenolic acid and cyclophosphamide drugs has failed, and patients with an estimated glomerular filtration rate (eGFR) less than or equal to 30 mL/min/1.73 m^2. (It is unknown if belimumab would be efficacious in these patients as they were excluded from the BLISS-LN trial.) Further, patients who have attained a CRR after 6 months to 12 months of induction therapy will probably derive little incremental benefit from belimumab as add-on to standard of care and should not be considered as candidates for belimumab.

In the opinion of the clinical expert, a clinically meaningful response to belimumab would include, sequentially, at least a 25% reduction in proteinuria (as defined by a urine protein-creatinine ratio [uPCR]) after 2 to 3 months of induction therapy, at least a 50% reduction in proteinuria after 6 months of therapy, reduction in corticosteroids to less than or equal to 7.5 mg/day after 6 months to 12 months of therapy, proteinuria no greater than 0.5 g per 24 hours to 0.7 g per 24 hours after 12 months of therapy (the response time can be delayed to 18 months to 24 months if baseline proteinuria is in the nephrotic range [i.e., > 3.5 g

per 24 hours]), and an eGFR no worse than 10% to 20% of pre-flare value and greater than or equal to 60 mL/min/1.73 m^2 after 12 months of therapy.

Clinician Group Input

The Canadian Network for Improved Outcomes for Systemic Lupus Erythematosus and 31 associated physicians provided input for this review.

The clinician group and physicians agreed that there are some treatment gaps and unmet needs in the current LN therapeutics. These unmet needs include inability to achieve complete remission from existing treatment options (e.g., mycophenolate mofetil and cyclophosphamide); increased risk of multiple complications from moderate or high doses of corticosteroids; subsequent ESRD and renal replacement therapy associated with disease flares; and difficulty in maintaining adherence.

The clinician group and physicians indicated that a clinically meaningful response to treatment would include any of the following: complete remission (proteinuria less than 0.5 g per 24 hours) within 12 months of starting treatment, reduction in daily prednisone dose to levels lower than 7.5 mg, or reduction in the frequency and intensity of flares. According to the clinician group, sufficient time (at least 12 months) should be allowed for these outcomes to be observed and treatment should be discontinued after 12 months in cases where no response can be demonstrated. The input stated that belimumab is expected to cause a shift in the current treatment paradigm for LN by addressing the disease mechanism. Its ability to modulate the maturation and functional differentiation of B cells, which produce autoantibodies that are central in SLE pathogenesis and tissue damage, renders it most suitable for patients whose LN has not reached at least partial remission, patients experiencing early and frequent flares, patients with steroid-dependent disease, and patients with adherence issues.

Drug Program Input

The drug programs provide input on each drug being reviewed through CADTH's reimbursement review processes by identifying issues that may impact their ability to implement a recommendation. The drug plans identified implementation issues related to considerations for initiation, renewal, discontinuation, and prescription of therapy, as well as generalizability and system and economic issues. The clinical expert consulted by CADTH weighed evidence from the BLISS-LN trial and other clinical considerations to provide responses to the drug programs' implementation questions. Refer to Table 4 for more details.

Clinical Evidence

Pivotal Studies and Protocol-Selected Studies

Description of Studies

One double-blind, placebo-controlled, randomized controlled trial (BLISS-LN) was included in this review (107 sites in 21 countries; N = 448) evaluating the efficacy, safety, and tolerability of an IV treatment regimen of belimumab 10 mg/kg in adult patients with class III or IV (with or without the presence of class V) or pure class V active LN while receiving standard of care. The primary objective was to evaluate the effect of belimumab 10 mg/kg compared to placebo in renal response as measured by the difference in the

proportion of patients who achieve a primary efficacy renal response (PERR) at week 104. The key secondary objectives were to evaluate the effect of belimumab 10 mg/kg compared to placebo on CRR at week 104, PERR at week 52, time to renal-related event or death, and ordinal renal response (ORR) at week 104. Patients were defined as having treatment failure if they did not follow the corticosteroid rules (i.e., failed to taper corticosteroids to ≤ 10 mg/day by week 24 and to not exceed this dose of 10 mg/day through week 104); if they received additional immunosuppressive drugs (except topical drugs) beyond the induction and maintenance regimens; if the use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or antimalarial drugs was initiated after week 24; or if the patient's standard therapy (cyclophosphamide followed by azathioprine or mycophenolate mofetil) exceeded permitted doses. Baseline patient characteristics, including age, sex, and race, were balanced between groups. Patients were predominantly female (88.3% in the belimumab group and 87.9% in the placebo group) and predominantly Asian (51.1% in the belimumab group and 48.9% in the placebo group), and 84% of patients in both the belimumab and placebo groups were categorized as being in renal biopsy class III or IV (with or without class V) according to the local reader. Disease characteristics such as SLE and LN disease duration, mean score for the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) with modified scoring for proteinuria (SLEDAI-S2K), mean eGFR, and mean uPCR were balanced between treatment groups at baseline. There were some baseline differences in use of concomitant medications between groups, including of antimalarials (74.4% and 69.1%) and of prednisone (steroids were converted to prednisone equivalent), with a mean dose of 66.5 (standard deviation [SD] = 99.6) mg/day and 72.5 (SD = 133.2) mg/day for the belimumab and placebo groups, respectively. Patients also used immunosuppressants (88.8% in the belimumab group and 86.1% in the placebo group) and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (65.9% in the belimumab group and 67.3% in the placebo group) at baseline.

Efficacy Results

In BLISS-LN, the primary end point, PERR at week 104, was statistically significant in favour of the belimumab group (43.0% versus 32.3%), with an adjusted between-group difference of 10.66% (95% confidence interval [CI], 1.89 to 19.42; P = 0.0311). In addition, statistically significant differences in favour of the belimumab group were reported for all key secondary end points of CRR at week 104 (30.0% versus 19.7%), with an adjusted between-group difference of 10.27% (95% CI, 2.40 to 18.14; P = 0.0167); PERR at week 52 (46.6% versus 35.4%), with an adjusted between-group difference of 11.12% (95% CI, 2.25 to 19.99; P = 0.0245); ORR at week 104 (30.0% belimumab versus 19.7% placebo achieving a complete response), with an adjusted between-group difference of 10.27% (95% CI, 2.40 to 18.14; P = 0.0167); and time to renal-related event or death (15.7% belimumab versus 28.3% placebo experiencing an event), with a hazard ratio (HR) of 0.51 (95% CI, 0.34 to 0.77; P = 0.0014).

Subgroup analyses based on baseline renal biopsy class (class III or class IV, versus class III and V or class IV and V, versus class V) and the induction regimen (cyclophosphamide versus mycophenolate mofetil) for the primary and the key secondary end points were generally consistent with the overall results for all subgroups except for the baseline renal biopsy class V subgroup and the cyclophosphamide followed by azathioprine subgroup, the results of which were not statistically significantly different between treatment groups. However, the study was not designed or powered to evaluate efficacy in subgroups, and the small

number of patients in the class V and the cyclophosphamide followed by azathioprine subgroups might have led to the lack of statistical significance between treatment groups.

In terms of secondary outcomes, a higher proportion of patients in the belimumab group compared with the placebo group received an average daily prednisone dose of less than or equal to 7.5 mg at week 104 since the previous 4-week visit (40.8% versus 29.6%), with an odds ratio (OR) of 1.65 (95% CI, 1.11 to 2.45). In terms of disease activity, the least squares (LS) mean change from baseline in SLEDAI-S2K at week 104 was −7.7 (standard error [SE] = 0.46) in the belimumab group and −6.1 (SE = 0.47) in the placebo group, with an LS mean difference of −1.5 (95% CI, −2.4 to −0.6). The proportion of patients with a SLEDAI-S2K score less than 4 at week 104 was higher in the belimumab group compared to the placebo group (27.8% versus 18.4%), with an OR of 1.76 (95% CI, 1.11 to 2.78). A higher proportion of patients experienced a severe flare postbaseline through to week 104 in the placebo group (31.4%) than in the belimumab group (18.8%), and the risk of experiencing a severe flare at any time, based on the Safety of Estrogens in Lupus Erythematosus – National Assessment (SELENA) SLEDAI Flare Index (SFI), was lower in patients in the belimumab group compared with patients in the placebo group (HR = 0.57; 95% CI, 0.39 to 0.84).

No HRQoL data were assessed in the BLISS-LN trial.

Harms Results

The key harms reported in the BLISS-LN trial are summarized in Table 2.

Table 2: Summary of Key Results From the BLISS-LN Trial

Characteristic	Placebo group (N = 224)	Belimumab group 10 mg/kg N = 224
PERR at week 104		
N (%)	223 (99.6)	223 (99.6)
Response, n (%)	72 (32.3)	96 (43.0)
CMH adjusted difference (95% CI)[a] vs. placebo	10.66 (1.89 to 19.42)	
OR (95% CI)[b] vs. placebo	1.55 (1.04 to 2.32)	
P value[b]	0.0311	
PERR at week 52		
N (%)	223 (99.6)	223 (99.6)
Response, n (%)	79 (35.4)	104 (46.6)
CMH adjusted difference (95% CI)[a] vs. placebo	11.12 (2.25 to 19.99)	
OR (95% CI)[b] vs. placebo	1.59 (1.06 to 2.38)	
P value[b]	0.0245	
CRR at week 104		
N (%)	223 (99.6)	223 (99.6)
Response, n (%)	44 (19.7)	67 (30.0)

Characteristic	Placebo group (N = 224)	Belimumab group 10 mg/kg N = 224
CMH adjusted difference (95% CI)[a] vs. placebo	10.27 (2.40 to 18.14)	
OR (95% CI)[b] vs. placebo	1.74 (1.11 to 2.74)	
P value[b]	0.0167	
ORR at week 104[c]		
N (%)	223 (99.6)	223 (99.6)
CRR,[c] n (%)	44 (19.7)	67 (30.0)
Partial renal response,[c] n (%)	38 (17.0)	39 (17.5)
No response, n (%)	141 (63.2)	117 (52.5)
P value[b]	0.0096	
Time to renal-related event or death[d]		
N (%)	223 (99.6)	223 (99.6)
Patients with an event, n (%)	63 (28.3)	35 (15.7)
Days to event, median (range)	188 (28 to 675)	170 (25 to 651)
HR (95% CI)[e]	0.51 (0.34 to 0.77)	
P value[e]	0.0014	
SLEDAI-S2K		
Baseline, N (%)	222 (99.1)	223 (99.6)
Mean (SD) at baseline	12.1 (4.82)	12.3 (5.33)
Week 104, N (%)	128 (57.1)	138 (61.6)
LS mean change from baseline to week 104 (SE)[f]	−6.1 (0.47)	−7.7 (0.46)
LS mean difference vs. placebo (95% CI)[f]	−1.5 (−2.4 to −0.6)	
P value[f]	0.0009[g]	
SLEDAI-S2K score < 4 at week 104		
Baseline, N (%)	223 (99.6)	223 (99.6)
Response, n (%)	41 (18.4)	62 (27.8)
OR (95% CI)[h]	1.76 (1.11 to 2.78)	
P value[h]	0.0164[g]	
Prednisone use[i]		
Baseline, N (%)	223 (99.6)	223 (99.6)
Average daily prednisone dose at baseline (mg/day), mean (SD)	72.52 (133.16)	66.50 (99.59)
Proportion with average daily prednisone dose of ≤ 7.5 mg/day since the previous visit at week 104, n (%)[i]	66 (29.6)	91 (40.8)
OR (95% CI) vs. placebo[j]	1.65 (1.11 to 2.45)	
P value[j]	0.0139[g]	

Characteristic	Placebo group (N = 224)	Belimumab group 10 mg/kg N = 224
Severe SFI flares[k]		
Baseline, N (%)	223 (99.6)	223 (99.6)
Patients with a severe flare, n (%)[l]	70 (31.4)	42 (18.8)
Days to event, median (range)	263 (176 to 391)	204 (169 to 452)
HR (95% CI)[m]	0.57 (0.39 to 0.84)	
P value[m]	0.0042[g]	
Harms (safety population), n (%)		
Any adverse event	211 (94.2)	214 (95.5)
SAEs	67 (29.9)	58 (25.9)
Patients who stopped treatment due to adverse events	29 (12.9)	29 (12.9)
Deaths[n]	5 (2.2)	6 (2.7)
Notable harms		
Any postinfusion-related systemic reactions, n (%)	29 (12.9)	26 (11.6)
Serious infections, n (%)		
Herpes zoster	2 (0.9)	5 (2.2)
Active tuberculosis	1 (0.4)	2 (0.9)
Sepsis	1 (0.4)	0
Malignancies (including NMSC), n (%)	0	3 (1.3)
Basal cell carcinoma	0	1 (0.4)
Papillary thyroid cancer	0	1 (0.4)
Thymoma	0	1 (0.4)
Serious suicidal behaviour, n (%)	0	1 (0.4)

CI = confidence interval; CMH = Cochran-Mantel-Haenszel; CRR = complete renal response; eGFR = estimated glomerular filtration rate; GFR = glomerular filtration rate; HR = hazard ratio; LS = least squares; NMSC = nonmelanoma skin cancer; OR = odds ratio; ORR = ordinal renal response; PERR = primary efficacy renal response; SAE = serious adverse event; SD = standard deviation; SE = standard error; SFI = SELENA SLEDAI Flare Index; SLEDAI-S2K = Systemic Lupus Erythematosus Disease Activity Index 2000 with modified scoring for proteinuria; uPCR = urine protein-creatinine ratio.

[a]CMH estimates are adjusted for induction regimen (cyclophosphamide vs. mycophenolate mofetil) and race (Black vs. non-Black).

[b]OR (95% CI) and P value are from a logistic regression model for comparison between belimumab and placebo, with covariates treatment group, induction regimen (cyclophosphamide vs. mycophenolate mofetil), race (Black vs. non-Black), baseline uPCR, and baseline eGFR.

[c]Study withdrawal, treatment failures, and investigational product discontinuation imputed as "no response." Investigational product discontinuation and treatment failure not related to renal disease or study withdrawal were censored in the time-to-event analysis. A CRR: uPCR was < 0.5 g/g; eGFR no more than 10% below pre-flare GFR or within normal range; no treatment failure. A partial renal response: ≥ 50% decrease from baseline in uPCR and 1 of the following: uPCR value < 1 g/g if baseline value was ≤ 3 g/g, or uPCR value < 3 g/g if the baseline value was > 3 g/g; eGFR no more than 10% below baseline GFR or within normal range; and no treatment failure.

[d]Events are defined as the first event experienced among the following: death, progression to end-stage renal disease, doubling of serum creatinine from baseline, renal worsening, or renal-related treatment failure. Patients who discontinue randomized treatment, withdraw from the study, or are lost to follow-up are censored on that date. Patients who completed the 104-week treatment period are censored at the week 104 visit. Time to event is defined as (event date – treatment start date + 1).

[e]From a Cox proportional hazards model for comparison between belimumab and placebo, adjusting for induction regimen (cyclophosphamide vs. mycophenolate mofetil), race (Black vs. non-Black), baseline uPCR, and baseline eGFR.

[f]Week 104 statistics are from an analysis of covariance model comparing belimumab and placebo, with covariates for treatment group, baseline SLEDAI-S2K score, induction regimen (cyclophosphamide vs. mycophenolate mofetil), and race (Black vs. non-Black).

[g]P value has not been adjusted for multiple testing (i.e., the type I error rate has not been controlled).

[h]OR (95% CI) and P value are from a logistic regression model for comparison between belimumab and placebo, with covariates treatment group, baseline SLEDAI-S2K score, induction regimen (cyclophosphamide vs. mycophenolate mofetil), and race (Black vs. non-Black).

[i]Steroids were converted to prednisone equivalent. The prednisone average daily dose since previous visit was calculated at every 4-week visit after baseline. All prednisone doses since the visit 4 weeks prior, up to and including the current visit, were summed and divided by the number of days in the period. Days where a patient did not have a prednisone dose recorded were considered as 0 mg for the day in the calculation for average daily prednisone dose.

[j]OR (95% CI) and P value are from a logistic regression model for comparison between belimumab and placebo, with covariates treatment group, baseline prednisone dose, induction regimen (cyclophosphamide vs. mycophenolate mofetil), and race (Black vs. non-Black).

[k]Analysis excludes severe flares that were triggered only by an increase in SELENA SLEDAI score to more than 12. Treatment failure is considered an event. Patients who discontinue randomized treatment, withdraw from study, are lost to follow-up, die, or complete week 104 are censored at the last flare assessment date, death date, or the week 104 study visit. Time to first severe flare is defined as (event date – treatment start date + 1) .

[l]Only includes postbaseline severe flares.

[m]From a Cox proportional hazards model for comparison between belimumab and placebo, adjusting for induction regimen (cyclophosphamide vs. mycophenolate mofetil) and race (Black vs. non-Black).

[n]Includes all deaths that occurred during the double-blind phase including off treatment.

Source: Clinical Study Report for BLISS-LN.[13]

Rates of adverse events (AEs) were similar across treatment groups (95.5% belimumab versus 94.25% placebo). Frequent AEs that occurred more commonly in the belimumab group than in the placebo group were UTI (19.2% versus 15.6%), cough (12.5% versus 8.5%), and upper abdominal pain (6.3% versus 2.7%). The proportion of patients experiencing at least 1 serious AE (SAE) was similar between treatment groups (25.9% belimumab versus 29.9% placebo). The most common SAEs were pneumonia (4.0% versus 3.1%), herpes zoster (1.8% versus 0.9%), gastroenteritis (0% versus 2.2%), lung infection (0.9% versus 1.3%), LN (0.4% versus 1.8%), and UTI (1.3% versus 0.9%). A similar number of withdrawals due to AEs occurred in the belimumab group and the placebo group (12.9% versus 12.9%), with the most common reason for withdrawal in both groups being pneumonia (4.0% versus 3.1%).

Eleven deaths occurred during the double-blind phase of the BLISS-LN trial, mainly due to infections, with 6 deaths in the belimumab group (2.7%) and 5 deaths the placebo group (2.2%).

Common notable harms in the BLISS-LN trial included postinfusion-related systemic reactions (11.6% belimumab versus 12.9% placebo); serious infections of herpes zoster (2.2% versus 0.9%), active tuberculosis (0.9% versus 0.4%), and sepsis (0% versus 0.4%); malignancies (including nonmelanoma skin cancer) (1.3% versus 0%), and serious suicidal behaviour (0.4% versus 0%).

Critical Appraisal

In terms of limitations, a greater proportion of patients discontinued from the placebo group than the belimumab group, which may have led to bias in the results in favour of belimumab. However, the sensitivity analyses that assessed the impact of missing data generally showed results supportive of the primary analysis. Regarding calculations of patients' average daily prednisone dose in the BLISS-LN trial, days where a patient did not have a prednisone dose recorded were considered as 0 mg for the day in the calculation, which would likely have underestimated the average dose of prednisone used in the study and may also have led to bias, although the direction of bias is unknown. Improvements in HRQoL were identified as important outcomes by the patient groups providing input for this review. However, no HRQoL data were collected in the BLISS-LN trial; hence, it is unknown what impact belimumab would have on HRQoL.

The product monograph for belimumab authorized both IV and subcutaneous formulations for LN.[12] However, the approval of subcutaneous formulations was based on extrapolated data, and there is no clinical evidence regarding the subcutaneous formulation for patients with active LN.

Overall, the clinical expert consulted felt the characteristics of the patient population enrolled in the trials was a good representation of the target population and did not identify any issues with the use of concurrent treatments or conduct of the trial that could substantially affect the generalizability of the findings.

Indirect Comparisons

No indirect evidence was available.

Other Relevant Evidence

Data from 1 open-label extension (OLE) study were summarized in this report.

Description of Studies

The OLE study provided supplemental safety and efficacy data for patients who received IV belimumab 10 mg/kg plus standard of care for up to 28 weeks (N = 254) among eligible patients who completed all assessments at week 104 in the BLISS-LN trial. Patients received the first dose at week 104 of the double-blind phase of the BLISS-LN trial (marked as day 0 for the open-label phase). There were 2 groups in the extension phase: the placebo-to-belimumab group (patients switching from placebo to belimumab) and the belimumab-to-belimumab group (patients remaining on belimumab). Criteria for the open-label phase allowed for the use of concomitant medications including immunosuppressants and corticosteroids, which were prohibited in the BLISS-LN trial. Also, PERR and CRR were evaluated based on observed data at open-label weeks 12, 24, and 28, and criteria were required to be met at a single time point only, meaning criteria did not have to be met on consecutive visits as was required for the double-blind phase of the BLISS-LN trial.

Efficacy Results

In the OLE study, results found that the proportion of patients achieving the PERR increased from baseline to week 28 in both the belimumab-to-belimumab group (from 71% to 75%) and the placebo-to-belimumab group (from 60% to 67%) when using the open-label phase criteria. Post hoc analyses found that when using the pivotal trial-defined criteria for a PERR, the proportion of patients achieving a PERR from baseline to week 28 decreased in the belimumab-to-belimumab group (from 66% to 52%) and remained stable in the placebo-to-belimumab group (from 54% to 53%). Similar results were found for the proportion of patients who had a CRR. Reductions in PERR and CRR rates at open-label week 28 in the belimumab-to-belimumab group were mainly due to discontinuations (n = 8) or intake of concomitant medications (n = 9) allowed during the OLE phase but counted as treatment failures for the post hoc statistical analysis. Median uPCR and eGFR remained similar at baseline and at week 28 in both groups. There were no marked changes in the proportion of patients with SLEDAI-S2K scores less than 4 or in the proportion of patients receiving an average daily prednisone-equivalent dose of less than or equal to 7.5 mg in either group from baseline to week 28.

Harms Results

The proportion of patients experiencing at least 1 AE in the open-label phase was higher in the belimumab-to-belimumab group (70%) than in the placebo-to-belimumab group (62%). The most common AEs

occurring in at least 5% of patients in either group included infections and infestations (49% versus 42%), musculoskeletal and connective tissue disorders (12% versus 13%), skin and subcutaneous tissue disorders (13% versus 8%), gastrointestinal disorders (10% versus 9%), and respiratory, thoracic, and mediastinal disorders (11% versus 4%) in the belimumab-to-belimumab versus placebo-to-belimumab groups, respectively. The number of patients experiencing at least 1 SAE during the open-label phase was low (8% in the belimumab-to-belimumab group and 4% in the placebo-to-belimumab group). The number of withdrawals due to AEs was also very low in both groups (3% versus 0.8%). Common notable harms included postinfusion systemic reactions (4% versus 3%) and infections of special interest (opportunistic infections, herpes zoster, tuberculosis, sepsis) (5% versus 2%) in the belimumab-to-belimumab versus placebo-to-belimumab groups, respectively. Two serious infections of special interest were reported in the belimumab-to-belimumab group, 1 for serious tuberculosis and another for serious disseminated herpes zoster. One case of suicidal behaviour occurred in a patient diagnosed with an adjustment disorder. This patient recovered and completed the treatment throughout the open-label phase. One death, deemed SLE related, occurred during the open-label phase in the placebo-to-belimumab group.

Critical Appraisal

The extension study allowed for the investigation of the long-term efficacy and harms associated with belimumab for an additional 28 weeks for eligible patients who completed the BLISS-LN trial. As there was no active comparator and all outcomes were descriptive in nature, it is difficult to make any inferences regarding the results. Furthermore, extension studies are often limited by selection bias, as only patients who are tolerant to treatment and complete the parent studies are eligible to enrol in the OLE study. An additional limitation is the open-label nature of treatment, which can bias the reporting of subjective end points (i.e., harms). Lastly, the relatively short duration of the OLE study is insufficient to observe appreciable benefit among those who had transitioned from placebo to belimumab.

Conclusions

In adult patients with class III, IV, and/or V active LN, treatment with belimumab 10 mg/kg in addition to standard of care statistically significantly improved renal response as measured by the primary outcome PERR, relative to placebo, based on 104-week data from the BLISS-LN trial, the results of which were deemed to be clinically meaningful by the clinical expert consulted for this review. All key secondary outcomes, including CRR at week 104, PERR at week 52, ORR at week 104, and time to renal-related event or death, showed statistically significant differences in favour of belimumab. The trial showed that a greater proportion of patients in the belimumab group than in the placebo group had reductions in average daily prednisone use to less than 7.5 mg since the previous 4-week visit and showed improvements in mean SLEDAI-S2K score. Also, fewer patients in the belimumab group experienced severe flares than those in the placebo group. HRQoL was not assessed in the trial, and therefore the impact of belimumab on HRQoL in patients with LN is unknown. In addition, the long-term efficacy of belimumab on reducing flare rates is unknown. AEs, including infections, occurred with similar frequency in the 2 treatment groups. Data from the pivotal trial and the OLE study do not suggest issues of tolerability or safety, although the extension study was limited by lack of a control group.

Introduction

Disease Background

Lupus is an autoimmune disease characterized by inflammatory processes that can occur in various tissues and organs of the body.[1] A common form of lupus is SLE,[2] with an estimated prevalence of about 1 in 2,000 individuals in Canada.[3,4] The age of onset is primarily between 16 years and 55 years, with females more commonly affected than males (9:1).[5] Kidney involvement is common in SLE, and LN occurs in about 50% of lupus patients,[6] usually within 5 years of SLE diagnosis.[7] Kidney involvement can remain silent or asymptomatic for a significant period of time;[8] however, patients may experience fatigue, joint and muscle pain, edema, rash, and a variety of other symptoms.[9] The typical disease course of LN is characterized by episodes of flares in between periods of disease inactivity.[14] LN flares and uncontrolled disease activity between flares contribute to accumulating nephron loss and progressive decline in renal function.[15] It is estimated that about 5% to 20% of patients with LN will progress to ESRD within 10 years of an initial SLE diagnosis,[10] eventually requiring dialysis or kidney transplant.[8] Those with proliferative LN have a significantly higher rate of mortality than those without LN, with about 5% to 25% of patients dying due to kidney disease within 5 years of onset.[6] Patients with SLE who develop LN usually present at a younger age than those without LN,[6] and evidence suggests that there is a slightly higher prevalence of LN in males with SLE than females with SLE (1.1:1 to 1.7:1).[10] Various cohort studies, including those with Canadian data,[16] suggest that the prevalence of LN is higher in Black, Hispanic, and Asian individuals than in white individuals[10] and that Hispanic and Black patients are more likely to progress to kidney failure than white patients.[6] Guidelines state the importance of early therapy to prevent progressive kidney damage while reducing medication-associated toxicities.[8] According to the clinical expert consulted for this review, diagnosis, treatment, and monitoring of patients with LN should be by a specialist physician, such as a rheumatologist or nephrologist.

Standards of Therapy

According to the clinical expert consulted for this review, the International Society of Nephrology/Renal Pathology Society classification represents the gold standard for histological classification of a renal biopsy[17] and is widely used throughout Canada. Immunosuppressive treatment is recommended in active class III (focal proliferative), IV (diffuse proliferative), and V (membranous) disease or mixed class III plus V or class IV plus V disease. According to the expert consulted, the current treatment paradigm for active class III to V LN consists of 2 phases: induction therapy with aggressive immunosuppression, usually lasting 3 months to 12 months; long-term maintenance with less intensive immunosuppression for at least 3 years to 5 years to prevent renal relapses. Guidelines from the European League Against Rheumatism and the European Renal Association–European Dialysis and Transplant Association (EULAR/ERA-EDTA) and Kidney Disease: Improving Global Outcomes (KDIGO) recommended that first-line induction treatment options include a high-dose corticosteroid taper and either mycophenolate mofetil or mycophenolic acid or cyclophosphamide,[8,11] which are used off label in Canada. After a satisfactory response has been achieved with induction therapy, patients are switched to a subsequent maintenance treatment, which — according to the clinical expert — most often consists of mycophenolate mofetil or mycophenolic acid at a lower dose than is used in the induction phase, with azathioprine (off label) generally reserved for when the patient

is considering pregnancy.[8] The use of corticosteroids should be gradually tapered in the maintenance phase[8] due to their substantial long-term toxicity and, according to the clinical expert, if continued, should not exceed a dose of 5 mg/day to 7.5 mg/day after 6 months to 12 months of therapy. The clinical expert suggested that multitarget therapy can be considered in patients with an inadequate response to first-line induction therapy (i.e., refractory cases), which may include off-label use of rituximab, cyclosporin, or tacrolimus in addition to standard induction therapy. As the single randomized trial comparing rituximab as add-on therapy to standard of care versus standard of care alone in LN (the LUNAR trial) did not achieve its primary outcome[18] and as supportive data for the use of calcineurin inhibitors (i.e., cyclosporin or tacrolimus) combined with mycophenolate mofetil (or other forms of mycophenolate) in patients of race or ethnicity other than Asian are scarce,[19,20] these approaches are not recommended as standard of care by the most recent versions of either the EULAR/ERA-EDTA or KDIGO guidelines.[8,11] The clinical expert suggested that in all cases of active class III to V LN, the use of antimalarials (i.e., hydroxychloroquine), bone protection (vitamin D, calcium, possibly antiresorptive drugs), immunizations with nonlive vaccines, and lifestyle modifications to reduce cardiovascular risk are recommended, and adjunct treatment with renin-angiotensin blockade and statins should be considered.

According to the clinical expert, important treatment goals include the optimization of kidney function (i.e., preservation or improvement in eGFR) accompanied by reduction in proteinuria, reduction of glucocorticoid use, prevention of relapse of LN, achievement of SLE remission or low disease activity, minimization of treatment-related AEs and accumulation of damage in the kidney and other organs, and decreased mortality. Secondary treatment goals can include improvement in urinary sediment, clinical parameters (serum hemoglobin, serum albumin), serological markers (i.e., anti–double-stranded DNA [anti-dsDNA], complement C3 and C4), HRQoL, and ability to maintain employment.

Drug

B cells are believed to play an important role in the pathophysiology of LN, which may lead to damage affecting multiple organ systems.[12] Belimumab reduces the survivability of B cells by limiting the activity of B lymphocyte stimulator protein. Belimumab is indicated in addition to standard therapy for reducing disease activity in adult patients with active LN. The Health Canada–recommended dose for IV administration is 10 mg/kg, administered over an hour, at 2-week intervals for the first 3 doses and at 4-week intervals thereafter. The product monograph indicates that the infusion rate may be slowed or interrupted if the patient develops an infusion reaction. In the event of a serious infusion-related or hypersensitivity reaction (e.g., anaphylaxis), treatment should be discontinued immediately and appropriate therapy should be administered. The Health Canada–recommended dose for subcutaneous injection is 400 mg (two 200 mg injections) once weekly for 4 doses, then 200 mg once weekly thereafter. For adult patients with LN transitioning from belimumab IV therapy to subcutaneous therapy, the first subcutaneous dose is to be administered 1 week to 2 weeks after the last IV dose. This transition can occur anytime after the patient completes the first 2 IV doses. The product monograph further states that belimumab should be used in combination with corticosteroids and mycophenolate or cyclophosphamide for induction, or mycophenolate or azathioprine for maintenance, and that the patient's condition should be evaluated continuously.[12]

The sponsor-requested reimbursement indication of belimumab differs from the Health Canada–approved indication. The sponsor reimbursement request is for belimumab in addition to standard therapy for treatment of active LN in adult patients who have class III, class IV, and/or class V active LN, and if no improvements in disease activity or symptoms are observed after 6 months, use should be discontinued.

Belimumab has been approved for use in Europe and the US for the treatment of adult patients with active LN who are receiving standard therapy. The subcutaneous formulation of belimumab was previously reviewed by CADTH in 2020 for SLE.

Key characteristics of biologic drugs used in the treatment of LN are presented in Table 3.

Table 3: Key Characteristics of Belimumab, Rituximab, Antimalarials, Corticosteroids, and Immune Suppressants

Parameter	Belimumab	Rituximab	Antimalarials	Corticosteroids	Immune suppressants
Mechanism of action	B lymphocyte stimulator–specific inhibitor	Monoclonal antibody	Mechanism in treating SLE unknown	Possess both and anti-inflammatory and immune-modulating effect through various mechanisms	By various mechanisms, suppress immune responses
Indication[a]	In addition to standard therapy for reducing disease activity in adult patients with active, autoantibody-positive, SLE, as well as for treatment of active LN in adult patients	• Non-Hodgkin lymphoma • Chronic lymphocytic leukemia • Rheumatoid arthritis • Granulomatosis with polyangiitis • Microscopic polyangiitis	Indicated for malaria prophylaxis and SLE	Many indications	Most are indicated for preventing organ transplant rejection
Route of administration	IV and subcutaneous injection	IV	Oral	Oral, parenteral	Oral, parenteral
Recommended dose	10 mg/kg at 2-week intervals for the first 3 doses and at 4-week intervals thereafter	Off-label use	Various doses depending on drug	Various doses depending on drug	Various doses depending on drug
Serious adverse events or safety issues	• Infusion-related systemic reactions and hypersensitivities • Infections • PML	• Infusion-related systemic reactions and hypersensitivities • Infections • PML • Tumour lysis	• Heart rhythm disorders • Retinopathy	• Osteoporosis • Infections • Cataracts • Glaucoma • Mood disturbances	• Heart rhythm disorders • Infections • Gastrointestinal adverse effects • Fetal harm in pregnancy

Parameter	Belimumab	Rituximab	Antimalarials	Corticosteroids	Immune suppressants
	• Psychiatric disorders	syndrome • Hepatitis B reactivation • Mucocutaneous reactions • Cardiovascular events		• Hypertension • Cushing syndrome • Hyperglycemia • Ulcer	• Infertility • Cardiac toxicity • Hepatotoxicity

LN = lupus nephritis; PML = progressive multifocal leukoencephalopathy; SLE = systemic lupus erythematosus.

[a]Health Canada–approved indication.

Sources: Product monographs for Benlysta,[12] Rituxan,[21] hydroxychloroquine,[22] prednisone,[23] Procytox,[24] and CellCept.[25]

Stakeholder Perspectives

Patient Group Input

This section was prepared by CADTH staff based on the input provided by patient groups. The full original patient input(s) received by CADTH have been included in the stakeholder section at the end of this report.

Four responses to CADTH's call for patient input for the belimumab submission were received. These consisted of submissions from Arthritis Consumer Experts, Lupus Ontario, a joint submission from the Kidney Foundation of Canada and Lupus Canada, and a cooperative submission from the Canadian Arthritis Patient Alliance, the Arthritis Society, the Canadian Skin Patient Alliance, and CreakyJoints. Patient input was gathered from surveys, video interviews, and focus group discussions among lupus patients across Canada: 34 respondents (88% female) from Arthritis Consumer Experts, 10 respondents (90% female) with SLE from Lupus Ontario, and 38 respondents (73% with LN and approximately 15% caregivers) from the Kidney Foundation of Canada and Lupus Canada. The cooperative submission conducted a focus group of 3 patients with LN as well as a video interview with 1 patient. The submission from Arthritis Consumer Experts also included an in-depth interview with 1 patient. Seventeen patients (6 from a previous survey) in the included submissions had experience with the treatment under review.

Patients reported managing SLE was difficult given the severity of the physical symptoms, such as debilitating fatigue, joint pain, flares, skin rashes, nausea, loss of appetite, bruising, back pain, brain fog, mobility issues, and mental health issues. Respondents reported that currently available treatments are difficult to tolerate because of the many side effects, such as headaches, brain fog, additional fatigue, frequent infections, eye issues, osteoporosis, upset stomach, gastric issues, insomnia, hair loss, weight gain or loss, mood swings, changes in kidney function, skin changes, heart disease, acne, nausea, vomiting, decrease in white blood count, bone marrow toxicity, liver toxicity, and bladder-related problems. While describing their experiences with the drug under review, patients reported both positive and negative outcomes. Some patients described experiencing side effects, such as severe allergic reaction, extreme nausea, sleep deprivation, frequent UTIs, depression, and psychosis. Other patients reported an overall

decrease in their disease symptoms and improvement in physical ability, leading to improvement in their HRQoL.

The key outcomes patients would like addressed by a new therapy are reduction of side effects and number of medications used; reduction in fatigue, flares, pain, and rash and skin irritations; increased mobility and participation in physical activities; overall improvement in HRQoL; improved engagement in social activities; and better affordability of medication. Patients identified financial barriers and difficulty in receiving reimbursement from private insurance and provinces while accessing belimumab a major concern, as costs to patients without drug coverage can be upward of $2,500 per month.

Clinician Input

Input From Clinical Expert Consulted by CADTH

All CADTH review teams include at least 1 clinical specialist with expertise in the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process (e.g., providing guidance on the development of the review protocol; assisting in the critical appraisal of clinical evidence; interpreting the clinical relevance of the results; and providing guidance on the potential place in therapy). The following input was provided by 1 clinical specialist with expertise in the diagnosis and management of LN.

Unmet Needs

According to the clinical expert consulted, response to current standard of care induction therapy is suboptimal, with only 20% to 35% of patients achieving a CRR within 6 months to 12 months from onset of LN, indicating a major unmet need. Of those that do achieve adequate disease control, 20% to 35% relapse within 3 years to 5 years. At least 20% of patients with LN develop chronic kidney disease within 10 years of LN onset, and up to 40% (in the most aggressive forms of proliferative LN) develop ESRD after 15 years and require dialysis or transplant. The expert noted that current treatments cause substantial short- and long-term side effects (i.e., mycophenolate mofetil mofetil or other forms of mycophenolate, cyclophosphamide, and azathioprine are associated with gastrointestinal intolerance and increased risk of infection; cyclophosphamide is associated with premature ovarian failure, infertility, and hematologic and bladder cancer; azathioprine is associated with hepatotoxicity; cyclosporin and tacrolimus require frequent monitoring of blood levels and can cause long-term reduction in kidney function; rituximab is associated with increased risk of infection; and corticosteroids are associated with premature cardiovascular and cerebrovascular disease, osteoporosis, avascular necrosis, cataracts, and diabetes). The expert also noted that there is a high rate of noncompliance with oral medications and only a few treatments are safe in pregnancy, which include hydroxychloroquine, corticosteroids, azathioprine, and tacrolimus.

Place in Therapy

The clinical expert noted that belimumab would be implemented as an add-on therapy to existing standard of care (i.e., corticosteroids and mycophenolate mofetil or other forms of mycophenolate or cyclophosphamide) for active LN class III or class IV (with or without class V) or pure class V if there is an inadequate response after 2 months to 3 months of induction therapy. In cases where there is no response

whatsoever or a worsening of symptoms after 2 weeks to 4 weeks of induction therapy, consideration could be given to initiating belimumab as add-on therapy at an earlier stage of induction. In the clinical expert's opinion, the efficacy and safety of initiating belimumab anytime within the 60-day window after initiation of standard of care induction therapy has been demonstrated in the BLISS-LN trial. In the trial, in 82.5% of patients, belimumab was initiated within 4 weeks after initiation of induction therapy and in 57.6% of patients, belimumab was initiated within 2 weeks after initiation of induction therapy.[26] However, given that 20% to 35% of patients will respond adequately to standard of care induction therapy alone and given the significant medication burden associated with standard of care induction therapy, the clinical expert noted that it would be prudent in patients who are gradually improving to wait for a maximum of 2 months to 3 months to assess response to standard of care before initiating belimumab. This should be sufficient time to allow for a response to be seen but should not prolong an ineffective treatment and risk increasing renal damage. If the response is deemed inadequate, belimumab could be added to standard of care. However, should the patient worsen or demonstrate no improvement whatsoever within 2 weeks to 4 weeks after initiation of induction therapy, the clinical expert believed it would be appropriate to initiate belimumab earlier in the induction course, either at the time of initiation of standard of care induction or within 1 month after initiation of standard of care induction (as was the case for most patients in BLISS-LN).

The clinical expert noted that BLISS-LN did not assess the efficacy of administering belimumab later in the induction phase (i.e., after > 60 days of induction therapy). The expert noted that for patients who show some initial response within the first 2 months to 3 months of induction therapy and then plateau or deteriorate or are unable to decrease steroids between months 3 to 6, there may be benefit in adding belimumab to standard of care at 3 months to 6 months after induction therapy (although there are no data from the trial addressing this use of belimumab). Hence, the clinical expert noted that it may be appropriate to provide the prescriber the flexibility to initiate belimumab anytime from start of standard of care induction to within the first 3 months to 6 months after initiation of standard of care induction therapy, based on clinician expert judgment.

Addition of belimumab to standard of care would represent a shift in the LN treatment paradigm. Currently, induction therapy is sequential, with a single immunosuppressive drug followed by maintenance, again with a single drug. Integration of belimumab into the induction regimen would represent a multitarget or combination approach.

Patient Population

According to the clinical expert, the patients best suited for treatment with belimumab in addition to standard of care are those with active class III or IV (with or without class V) or active class V LN. Other patients who may be most likely to respond to belimumab include patients with active class III or IV (with or without class V) or class V LN who are experiencing chronically impaired renal function, or patients for whom prednisone is unable to be decreased to less than or equal to 7.5 mg/day after 3 months to 6 months of induction, or patients who have extrarenal manifestations in addition to LN. Also, patients with previous episodes of class III or IV (with or without class V) or class V LN in whom another flare may cause a serious decline in renal function may respond to belimumab. The patients least suited for treatment with belimumab

include those with active LN who are not currently receiving standard of care induction therapy; patients for whom induction with both mycophenolate mofetil (or other forms of mycophenolate) and cyclophosphamide has failed, as the efficacy of belimumab has only been demonstrated when added to induction with either of these drugs; patients with an eGFR less than or equal to 30 mL/min/1.73 m^2 as these patients were excluded from the BLISS-LN trial; and patients who have attained a CRR after 6 months to 12 months of induction therapy, as these patients are less likely to derive additional benefit from belimumab. According to the clinical expert, LN should be suspected in any patient with SLE with an unexplained decline in renal function or a urine protein exceeding 500 mg/day. Such patients should undergo a prompt renal biopsy (providing there are no contraindications, such as increased risk of bleeding), which is the gold standard for diagnosis of LN. Based on renal biopsy findings, a decision would be made regarding the need to initiate induction therapy for LN. Several other laboratory parameters, (i.e., serum hemoglobin, serum albumin, urinalysis, anti-dsDNA, anti-C1q, complement C3 and C4) are also measured, and expert physician clinical examination is performed before confirming a diagnosis of LN and initiating induction therapy. The clinical expert states that kidney biopsy is indispensable and cannot be replaced by laboratory variables.

Assessing Response to Treatment

The clinical expert noted that a clinically meaningful response to standard of care would include, sequentially:

- at least a 25% reduction in proteinuria (as defined by a uPCR) after 3 months of therapy
- at least a 50% reduction in proteinuria after 6 months of therapy
- reduction in corticosteroids to less than or equal to 7.5 mg/day after 6 months to 12 months of therapy
- proteinuria no greater than 0.5 g per 24 hours to 0.7 g per 24 hours after 12 months of therapy (the response time can be delayed to 18 months to 24 months if baseline proteinuria is in the nephrotic range [i.e., > 3.5 g per 24 hours])
- an eGFR no worse than 10% to 20% of pre-flare value and greater than or equal to 60 mL/min/1.73 m^2 after 12 months of therapy.

Key secondary indicators of renal response according to the clinical expert would include increased time to renal-related event or death, prevention of relapse of LN, decreased disease activity in extrarenal domains, minimization of treatment-related AEs and accumulation of damage in the kidney and other organs, and decreased mortality. Other treatment goals can include improvement in clinical parameters (serum hemoglobin, serum albumin), urinalysis, serological markers (i.e., anti-dsDNA, complement C3 and C4), HRQoL, and ability to maintain employment.

Discontinuing Treatment

The clinical expert recommended discontinuing treatment with belimumab immediately if the patient experienced a severe adverse reaction to belimumab (e.g., anaphylaxis) or became pregnant (the Health Canada product monograph indicates that belimumab should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus). According to the clinical expert, it would be reasonable to discontinue treatment with belimumab after 6 months to 12 months of therapy if there was no

improvement or a worsening in renal function or proteinuria. The clinical expert noted that in BLISS-LN, the percentage of patients achieving the primary outcome (i.e., PERR) over time was identical through to week 20 after randomization and started to diverge at week 24 through to week 104 (with a greater percentage achieving PERR in the belimumab group). Hence, it would be appropriate to wait at least 6 months to assess response to belimumab, and in patients with higher levels of proteinuria the clinical expert believed it would be appropriate to wait up to 12 months to determine if the response is sufficient to warrant continuation. Hence, the clinical expert stated that it would be optimal to provide physicians the flexibility to prescribe belimumab for up to 12 months before assessing response. The expert would also discontinue treatment if there was a lack of steroid-sparing effect within 6 months to 12 months of therapy. If a CRR was achieved (as defined by stabilization or normalization of renal function and improvement in proteinuria to less than 700 mg/day) and maintained for at least 3 years to 5 years, it may be reasonable to discontinue therapy with belimumab with the expectation that remission will be maintained. However, there are currently no data to support duration of maintenance therapy, and EULAR/ERA-EDTA guidelines recommend at least 3 years to 5 years with current standard of care maintenance therapy with mycophenolate mofetil (or other forms of mycophenolate) or azathioprine before attempting gradual tapering.

Prescribing Conditions

According to the clinical expert, IV belimumab should be administered in a hospital outpatient or community infusion centre. Diagnosis, treatment, and monitoring of patients with LN who might receive belimumab should be by a specialist, typically a rheumatologist or nephrologist experienced in the management of LN.

Clinician Group Input

This section was prepared by CADTH staff based on the input provided by clinician groups. The full original clinician group input(s) received by CADTH have been included in the stakeholder section at the end of this report.

The Canadian Network for Improved Outcomes for Systemic Lupus Erythematosus and 31 associated physicians provided input for this review.

The clinician group and physicians agreed that there are some treatment gaps and unmet needs in the current LN therapeutics. These unmet needs include inability to achieve complete remission from existing treatment options (e.g., mycophenolate mofetil (or other forms of mycophenolate) and cyclophosphamide); increased risk of multiple complications from moderate or high doses of corticosteroids; subsequent ESRD and renal replacement therapy associated with disease flares; and difficulty in maintaining adherence.

The clinician group and physicians indicated that a clinically meaningful response to treatment would include any of the following: complete remission (proteinuria < 0.5 g per 24 hours) within 12 months of starting treatment, reduction in daily prednisone dose to levels less than or equal to 7.5 mg, or reduction in the frequency and intensity of flares. According to the clinician group, sufficient time (at least 12 months) should be allowed for these outcomes to be observed and treatment should be discontinued after 12 months in cases where no response can be demonstrated. The input stated that belimumab is expected to cause a shift in the current treatment paradigm for LN by addressing the disease mechanism. Its ability to modulate

the maturation and functional differentiation of B cells, which produce autoantibodies that are central in SLE pathogenesis and tissue damage, renders it most suitable for patients not achieving at least partial remission, patients experiencing early and frequent flares, patients with steroid-dependent disease, and patients with adherence issues.

Drug Program Input

The drug programs provide input on each drug being reviewed through CADTH's reimbursement review processes by identifying issues that may impact their ability to implement a recommendation. The implementation questions and corresponding responses from the clinical experts consulted by CADTH are summarized in Table 4.

Table 4: Summary of Drug Plan Input and Clinical Expert Response

Drug program implementation questions	Clinical expert response
Relevant comparators	
The clinical trial BLISS-LN looked at belimumab in combination with standard of care vs. placebo. Is placebo an appropriate comparator?	The clinical expert noted that placebo in addition to standard of care is an appropriate comparator for the indicated population, as there are no other applicable comparators.
Initiation of therapy	
In BLISS-LN, standard of care induction was initiated at any time within the 60 days before the day 1 baseline visit. Would this be an appropriate duration of time to assess response to standard of care?	The clinical expert noted that the efficacy and safety of initiating belimumab anytime within the 60-day window after initiation of standard of care induction therapy has been demonstrated in the BLISS-LN trial. In the trial, in 82.5% of patients, belimumab was initiated within 4 weeks after initiation of induction therapy, and in 57.6% of patients, belimumab was initiated within 2 weeks after initiation of induction therapy.[26] However, given that 20% to 35% of patients will respond adequately to standard of care induction therapy alone and given the significant medication burden associated with standard of care induction therapy, the clinical expert noted that it would be prudent in patients who are gradually improving to wait for a maximum of 2 months to 3 months to assess response to standard of care before initiating belimumab. This should be sufficient time to allow for a response to be seen but should not prolong an ineffective treatment and risk increasing renal damage. If response is deemed inadequate after 2 months to 3 months, belimumab can be initiated. However, should the patient worsen or demonstrate no improvement whatsoever within 2 weeks to 4 weeks after initiation of standard of care induction therapy, it would be appropriate to initiate belimumab earlier in the induction course, either at the time of initiation of induction or within 1 month after initiation of induction (as was the case for most patients in BLISS-LN). The clinical expert noted that BLISS-LN did not assess the efficacy of administering belimumab later in the induction phase (i.e., after > 60 days of induction therapy). The expert noted that for patients who show some initial response within the first 2 months to 3 months of induction therapy and then plateau or deteriorate or are unable to decrease steroids between months 3 to 6, there may be benefit in adding belimumab to standard of care at 3 months to 6 months after induction therapy (although there are no data from the trial addressing this use of

Drug program implementation questions	Clinical expert response
	belimumab). Hence, the clinical expert noted that it may be appropriate to provide the prescriber the flexibility to initiate belimumab anytime from the start of standard of care induction therapy to within the first 3 months to 6 months after initiation of standard of care induction therapy, based on clinician expert judgment.
How is it determined if patients are not responding or are refractory to standard of care?	The clinical expert noted that a clinically meaningful response to standard of care would include, sequentially, at least a 25% reduction in proteinuria (as defined by a uPCR) after 2 months to 3 months of therapy; at least a 50% reduction in proteinuria after 6 months of therapy; reduction in corticosteroids to ≤ 7.5 mg/day after 6 months to 12 months of therapy; proteinuria no greater than 0.5 g per 24 hours to 0.7 g per 24 hours after 12 months of therapy (the response time can be delayed to 18 months to 24 months if baseline proteinuria is in the nephrotic range [i.e., > 3.5 g per 24 hours]); an eGFR no worse than 10% to 20% of pre-flare value and ≥ 60 mL/min/1.73 m^2 after 12 months of therapy. These response criteria would also apply to treatment with belimumab in addition to standard of care.
What is an appropriate trial of standard of care before the addition of belimumab?	The clinical expert stated that standard of care should be trialled for a maximum of 2 months to 3 months to determine if the patient is responding and is able to tolerate the medication burden. The clinical expert noted that it would also be appropriate to initiate treatment with belimumab at the same time as initiation of standard of care if the patient is rapidly worsening or showing no improvement whatsoever.
How should standard of care be defined? In other words, what daily dose corticosteroid would be considered appropriate for induction therapy? Maintenance therapy?	The clinical expert noted that the appropriate daily dose of corticosteroid for induction therapy would be 500 mg/day to 1,000 mg/day of IV methylprednisolone for 3 days, followed by daily oral prednisone (0.5 mg/kg to 1 mg/kg). It is recommended that corticosteroids be gradually tapered and discontinued over 1 year to 2 years; however, if corticosteroids are continued, the dose should not exceed 5 mg/day to 7.5 mg/day (prednisone equivalent) due to their substantial long-term toxicity. The optimal duration of maintenance therapy is unknown, but it should be continued for at least 3 years to 5 years in those achieving a complete response and potentially indefinitely in cases of partial response.
The product monograph notes that in active LN, belimumab should be used in combination with corticosteroids and mycophenolate mofetil or cyclophosphamide for induction, or mycophenolate mofetil or azathioprine for maintenance. For patients refractory or not responding to standard of care as defined above, should additional drugs (i.e., alternate mycophenolate mofetil, cyclophosphamide and azathioprine combination and/or calcineurin inhibitors, or rituximab) be trialled? Should any of these alternatives be trialled before belimumab is added on to standard of care? What is an appropriate trial period for these medications?	The clinical expert stated that if a patient is refractory or not responding to standard of care induction therapy after 2 months to 3 months, options include switching to an alternative induction therapy (i.e., mycophenolate mofetil (or other forms of mycophenolate) to cyclophosphamide or cyclophosphamide to mycophenolate mofetil). Cyclophosphamide is associated with infertility, and the clinical expert stated that if belimumab were available to the prescriber, addition of belimumab to mycophenolate mofetil would be preferred to switching from mycophenolate mofetil to cyclophosphamide. A calcineurin inhibitor (i.e., cyclosporin or tacrolimus) or rituximab can also be used with mycophenolate mofetil, but usage is off label and there is limited evidence supporting this approach; guidelines recommend these drugs as add-on therapy only in refractory cases. Rarely, rituximab can be combined with cyclophosphamide for induction. Azathioprine would very rarely be used as induction therapy as it is less efficacious than

Drug program implementation questions	Clinical expert response
For patients for whom these therapies are not appropriate, is monotherapy with belimumab an option?	mycophenolate mofetil or cyclophosphamide. In summary, if a patient does not respond rapidly to induction with mycophenolate mofetil, addition of belimumab to mycophenolate mofetil would be the preferred option. The clinical expert noted that monotherapy with belimumab is not an appropriate therapy for induction or maintenance therapy for LN. In the BLISS-LN trial, belimumab was administered with standard of care and has never been studied as monotherapy for LN.
What is the appropriate place in therapy for belimumab (i.e., after 6 to 12 months of standard of care, before calcineurin inhibitors and/or rituximab)?	The clinical expert noted that standard of care (i.e., corticosteroids and mycophenolate mofetil or other forms of mycophenolate, or cyclophosphamide) for induction therapy should be trialled for a maximum of 3 months to 6 months to determine if the patient is responding to treatment before adding on belimumab (refer to previous discussion regarding why adding on belimumab up to 6 months after initiation of standard of care induction therapy may be appropriate). The clinical expert also noted that it would also be appropriate to initiate treatment with belimumab immediately alongside existing standard of care for patients with worsening renal parameters or no improvement within 2 weeks to 4 weeks after initiating induction.
Renewal of therapy	
Are the composite end points of PERR in the BLISS-LN trial appropriate to assess response to therapy?	The clinical expert noted that the outcomes used in clinical practice align with those used in the trial and these indicators would not vary much across physicians.
The sponsor notes that eGFR and proteinuria changes are predictive of renal survival. Does this outcome appropriately measure response to drug therapy over time, given the waxing and waning nature of the condition?	The clinical expert stated that these outcomes are appropriate measures of response to therapy over time. Treatment goals include attaining proteinuria levels ≤ 0.7 g per 24 hours and eGFR levels ≥ 60 mL/min/1.73 m^2. Not attaining or maintaining these levels over time suggests the patient is not responding to therapy and this therapy should not be renewed and another therapy should be tried.
It may be difficult for jurisdictions to assess response to therapy at a given point in time. Is there any point in time at which disease control could be appropriately measured?	The clinical expert commented that renewal should be on an annual basis, with treatment discontinued if the patient is not responding after the first 6 months to 12 months (the response time can be delayed to 18 months to 24 months if baseline proteinuria is in the nephrotic range [i.e., > 3.5 g per 24 hours]). The clinical expert noted that in BLISS-LN, the percentage of patients achieving the primary outcome over time were identical through to week 20 after randomization and started to diverge at week 24 through to week 104 (with a greater percentage achieving PERR in the belimumab group). Hence, it would be appropriate to wait at least 6 months to assess response to belimumab, and in patients with higher levels of proteinuria the clinical expert believed it would be appropriate to wait up to 12 months to determine if the response is sufficient to warrant continuation.
Is a corticosteroid dose less than or equal to 10 mg/day clinically meaningful for these patients?	The clinical expert indicated that during maintenance therapy it is recommended that corticosteroids be gradually tapered and discontinued; however, if corticosteroids are continued, the dose should not exceed 5 mg/day to 7.5 mg/day (prednisone equivalent) due to their substantial long-term toxicity.

Drug program implementation questions	Clinical expert response
Discontinuation of therapy	
BLISS-LN evaluated the PERR at week 104 (2 years). What is the appropriate time frame to assess patients for treatment response?	The clinical expert stated that initial approval should be for 2 years. Treatment with belimumab should be discontinued after the first 6 months to 12 months if there is inadequate response or improvement based on clinician judgment. The clinical expert also noted that it would be appropriate to wait at least 6 months to assess response to belimumab, and in patients with higher levels of proteinuria the clinical expert believed it would be appropriate to wait up to 12 months to determine if the response is sufficient to warrant continuation.
The sponsor is recommending that treatment with belimumab plus standard of care be discontinued if no improvements in disease activity and/or symptoms are observed after 6 months. What would be appropriate clinical markers of disease activity to demonstrate improvements in disease activity or symptoms at 6 months?	The clinical expert indicated that a partial renal response is a reasonable clinical marker of disease activity to demonstrate improvement at 6 months and is defined as reduction in proteinuria to at least 50% and to < 3 g per 24 hours if baseline > 3 g per 24 hours, and stabilization or improvement in eGFR within 20% of baseline (i.e., before onset of LN).
Prescribing	
Who would be most appropriate to prescribe belimumab for this indication? Would it be rheumatologists or nephrologists?	The clinical expert noted that the diagnosis, treatment, and monitoring of patients with LN who might receive belimumab should be by a specialist, either a rheumatologist or a nephrologist experienced in the management of LN.
Is there a difference in clinical benefit between the IV and subcutaneous treatments?	The clinical expert stated that it is currently unknown if there is a different clinical benefit between the IV and subcutaneous treatment for the indicated population.
Generalizability	
For patients for whom mycophenolate mofetil, or mycophenolic acid, or cyclophosphamide are not appropriate, is monotherapy with belimumab an option?	The clinical expert stated that monotherapy with belimumab is not an option for the indicated population as belimumab was only assessed as add-on therapy to standard of care with either mycophenolate mofetil (or other forms of mycophenolate) or cyclophosphamide in BLISS-LN.
Would belimumab be used to treat patients who are younger than 18 years?	The clinical expert stated that there are no current clinical data to support the use of belimumab to treat patients with LN who are younger than 18 years.
Would patients with class I, II, and VI LN be treated with belimumab?	The clinical expert noted that patients with class I (minimal mesangial), II (mesangial proliferative), and VI (advanced sclerotic) LN generally do not require immunosuppressive therapy and would not be treated with belimumab.
Patients with severe active renal lupus were excluded from the clinical trial. Would such patients be treated with belimumab? Are there additional treatment options used to control the disease in these patients?	The clinical expert stated that patients with severe impairment in eGFR (< 30 mL/min) were excluded from BLISS-LN and that there are no data to suggest whether belimumab might be effective in these patients. In such patients with refractory disease, there is no evidence supporting alternative therapies. Rituximab may be combined with mycophenolate mofetil (or other forms of mycophenolate) or cyclophosphamide as salvage therapy.
There are no Canadian-specific guidelines for management of LN. Is the international system, which stratifies LN into 6 classes (I to VI), used routinely in	The clinical expert stated that the 2003 ISN/RPS classification of LN, which stratifies LN into 6 classes (I to VI), is routinely used in

Drug program implementation questions	Clinical expert response
Canada? Would it be practical to incorporate this staging classification system into the reimbursement criteria (i.e., is this used in clinical practice)?	Canadian clinical practice and would be practical to incorporate into the reimbursement criteria.
System and economic issues	
Rituximab biosimilars have undergone pricing negotiations through pCPA.	For CDEC consideration.
There may be potential savings if the drug prevents or delays patients accessing dialysis.	For CDEC consideration.

CDEC = CADTH Canadian Drug Expert Committee; eGFR = estimated glomerular filtration rate; ISN = International Society of Nephrology; LN = lupus nephritis; pCPA = pan-Canadian Pharmaceutical Alliance; PERR = primary efficacy renal response; RPS = Renal Pathology Society; uPCR = urine protein-creatinine ratio.

Clinical Evidence

The clinical evidence included in the review of belimumab is presented in 3 sections. The first section, the Systematic Review, includes pivotal studies provided in the sponsor's submission to CADTH and Health Canada, as well as those studies that were selected according to an a priori protocol. The second section includes indirect evidence selected from the literature that met the selection criteria specified in the review. The third section includes a sponsor-submitted long-term extension study that was considered to address important gaps in the evidence included in the systematic review.

Systematic Review (Pivotal and Protocol-Selected Studies)

Objectives

To perform a systematic review of the beneficial and harmful effects of belimumab IV infusion or subcutaneous injection in addition to standard of care therapy for the treatment of active LN in adults.

Methods

Studies selected for inclusion in the systematic review will include pivotal studies provided in the sponsor's submission to CADTH and Health Canada, as well as those meeting the selection criteria presented in Table 5. Outcomes included in the CADTH review protocol reflect outcomes considered to be important to patients, clinicians, and drug plans.

Table 5: Inclusion Criteria for the Systematic Review

Criteria	Description
Patient population	Adults with active LN Subgroups: Baseline renal biopsy showing active class (e.g., class III or class IV; class III plus class V or class IV plus class V; class V)[a]

Criteria	Description
Intervention	Belimumab: • IV infusion: 10 mg/kg at 2-week intervals for the first 3 doses and at 4-week intervals thereafter • Subcutaneous: 400 mg dose (two 200 mg injections) once weekly for 4 doses, then 200 mg once weekly thereafter
Comparators	Standard of care, including the following treatments in combination for induction or maintenance treatment phases: • Hydroxychloroquine or chloroquine • Oral corticosteroids • Immunosuppressants or immune modulators (e.g., azathioprine, mycophenolate mofetil, mycophenolic acid, cyclophosphamide, tacrolimus, cyclosporin) Standard of care plus rituximab
Outcomes	Efficacy outcomes: • Renal response activity (e.g., primary efficacy renal response, complete renal response, ordinal renal response) • Reduction in proteinuria • Increase or stabilization of eGFR • Reduction in corticosteroid use • Time to renal-related event or death • Reduction in chronic kidney disease stage • Disease activity (e.g., SLEDAI-S2K) • Organ damage (e.g., SDI) • Disease flare frequency and severity • HRQoL (e.g., SF-36; Lupus QoL; Lupus-Pro; FACIT-F) • Reduction in symptoms (e.g., fatigue, joint and muscle pain, rash and skin irritations, infections) • Serological outcomes: ◦ Decrease in anti–double-stranded DNA antibodies ◦ Increase in complement C3 and C4 Harms outcomes: AEs, SAEs, WDAEs, notable harms (serious infusion- or injection-related systemic reactions and hypersensitivity, serious infections [e.g., progressive multifocal leukoencephalopathy, pneumonia, herpes zoster, gastroenteritis, lung infection, UTI, anemia, febrile neutropenia], psychiatric disorders [e.g., serious depression, suicidal ideation or behaviour, self-injury], malignancy)
Study design	Published and unpublished phase III and IV RCTs

AE = adverse event; eGFR = estimated glomerular filtration rate; FACIT-F = Functional Assessment of Chronic Illness Therapy – Fatigue; HRQoL = health-related quality of life; LN = lupus nephritis; Lupus QoL = Lupus Quality of Life questionnaire; RCT = randomized controlled trial; SAE = serious adverse event; SDI = Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SF-36 = Short Form (36) Health Survey; SLEDAI-S2K = Systemic Lupus Erythematosus Disease Activity Index 2000 with modified scoring for proteinuria; UTI = urinary tract infection; WDAE = withdrawal due to adverse event.

[a]Classes according to the International Society of Nephrology/Renal Pathology Society 2003 classification of LN: class III = focal LN; class IV = diffuse LN; class V = membranous LN.

The literature search for clinical studies was performed by an information specialist using a peer-reviewed search strategy according to the PRESS Peer Review of Electronic Search Strategies checklist.[27] Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) via Ovid and Embase (1974–) via Ovid. All Ovid searches were run simultaneously as a multifile search. Duplicates were removed using Ovid deduplication for multifile searches, followed by manual deduplication in Endnote.

The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were belimumab and LN. Clinical trial registries were searched: the US National Institutes of Health's clinicaltrials.gov, WHO's International Clinical Trials Registry Platform search portal, Health Canada's Clinical Trials Database, and the European Union Clinical Trials Register.

No filters were applied to limit retrieval by study type. Retrieval was not limited by publication date or by language. Conference abstracts were excluded from the search results. Refer to Appendix 1 for the detailed search strategies.

The initial search was completed on August 4, 2022. Regular alerts updated the search until the meeting of the CADTH Canadian Drug Expert Committee on November 23, 2022.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the Grey Matters: A Practical Tool for Searching Health-Related Grey Literature checklist.[28] Included in this search were the websites of regulatory agencies (FDA and the European Medicines Agency). Google was used to search for additional internet-based materials. Refer to Appendix 1 for more information on the grey literature search strategy.

In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Two CADTH clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least 1 reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion.

Findings From the Literature

A total of 299 studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 6. A list of excluded studies is presented in Appendix 2.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

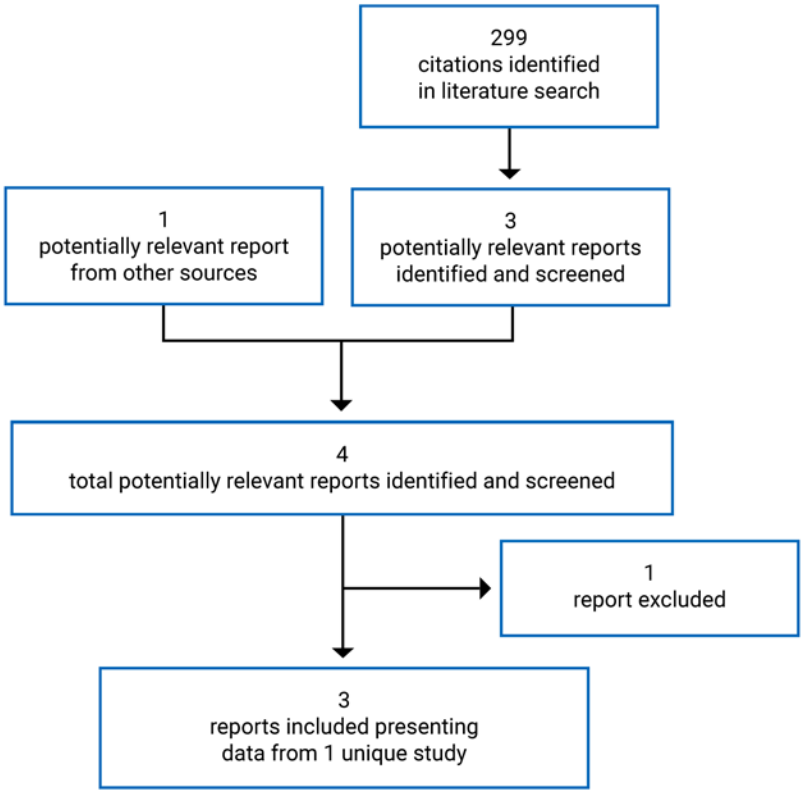


Table 6: Details of Included Studies

Parameter	BLISS-LN Trial
Study design	DB RCT
Locations	107 sites across 21 countries (e.g., China, US, Philippines, Korea)
Patient enrolment dates	July 2012 to July 2017
Randomized (N)	448
Inclusion criteria	• Patients 18 years or older with active, biopsy-proven proliferative LN class III or IV [excluding class III(C), IV-S(C), and IV-G(C)], with or without the presence of class V, or pure class V membranous LN using the 2003 ISN/RPS criteria • Unequivocally positive antinuclear antibody test results, defined as an antinuclear antibody titre ≥ 1:80 (based on HEp-2 immunofluorescence assay or equivalence by enzyme immunoassay assay), and/or a positive anti-dsDNA (≥ 30 IU/mL based on ELISA) serum antibody test at the screening visit based on the study's central laboratory results • Documentation of active renal disease at screening requiring induction therapy with high-dose corticosteroids with either IV cyclophosphamide or mycophenolate mofetil or other oral forms of mycophenolate within 60 days before baseline The following factors were used to define active renal disease at screening:

Parameter	BLISS-LN Trial

	• uPCR of ≥ 1.0 g/g AND active urinary sediment, as defined by at least 1 of the following (in absence of menses and genitourinary tract infection):
	  ◦ > 5 RBC per high-power field or above the laboratory reference range
	  ◦ > 5 WBC per high-power field or above the laboratory reference range
	  ◦ Presence of cellular casts (RBC or WBC)
	• Patients without active urinary sediment were eligible if they met at least 1 of the following criteria:
	  ◦ A confirmatory biopsy performed within 3 months before the screening visit or during the screening period meeting the biopsy criteria previously outlined
	  ◦ Proteinuria ≥ 3.5 g per day (or uPCR ratio ≥ 3.5 g/g)

Exclusion criteria	• Patients for whom both cyclophosphamide and mycophenolate mofetil (or other forms of mycophenolate) induction therapies have previously failed, based on the investigator's opinion • Patients with severe active central nervous system lupus • History of malignant neoplasm within the past 5 years, except for adequately treated cancers of the skin (basal or squamous cell) or carcinoma in situ of the uterine cervix • Required management of acute or chronic infections within 60 days of day 1 • Receipt of specific treatments or therapy (e.g., B cell–targeted therapy, any biologic drug other than B cell–targeted therapy, plasmapheresis, nonbiologic investigational drug, a live vaccine) within protocol-defined time frames before day 1 • Patients who have been on dialysis within 364 days of baseline • Patients who have an estimated glomerular filtration rate < 30 mL/min/1.73 m^2 at the screening visit
Intervention	Belimumab: 10 mg/kg IV infusion at 2-week intervals for the first 3 doses and at 4-week intervals thereafter in addition to standard of care
Comparator(s)	Placebo IV infusion at 2-week intervals for the first 3 doses and at 4-week intervals thereafter in addition to standard of care
Phase	
Screening	Up to 35 days
DB	104 weeks
OLE	28 weeks
Primary end point	PERR at week 104

Secondary and exploratory end points	**Key secondary:**
	• CRR at week 104
	• PERR at week 52
	• Time to renal-related event or death
	• ORR (complete, partial, or no response) at week 104
	Other secondary:
	• PERR:
	  ◦ individual components of PERR
	  ◦ proportion of patients with PERR by visit
	  ◦ time to PERR that is maintained through week 52

Parameter	BLISS-LN Trial
	◦ time to PERR that is maintained through week 104 • CRR: ◦ individual components of CRR ◦ proportion of patients with CRR by visit ◦ time to CRR that is maintained through week 52 ◦ time to CRR that is maintained through week 104 • Renal-specific measures: ◦ proportion of patients with a doubling of serum creatinine or progression to end-stage renal disease • Proteinuria: ◦ Percent change in proteinuria by visit ◦ Change in proteinuria by visit • Disease activity: ◦ proportion of patients with SLEDAI-S2K < 4 by visit ◦ proportion of patients with improvement in SLEDAI-S2K organ systems by visit among patients with organ system involvement at baseline ◦ proportion of patients with worsening in SLEDAI-S2K organ systems by visit among patients with no organ system involvement at baseline ◦ change from baseline in SLEDAI-S2K score by visit ◦ change from baseline in SLEDAI-S2K score without renal items by visit • Corticosteroid use: ◦ proportion of patients receiving prednisone ≤ 5 mg average daily dose since previous visit ◦ proportion of patients receiving prednisone ≤ 7.5 mg average daily dose since previous visit • SFI flares: ◦ Time to first severe SFI flare ◦ Time to first severe SFI flare after week 24 • SDI: ◦ SDI change from baseline at week 104 ◦ percentage of patients with any SDI worsening (change > 0) compared with baseline by visit **Safety:** AEs (including AESIs), vital signs, physical examination, immunogenicity, assessed for suicidality: C-SSRS
Publications	Furie et al. (2020)[29] Rovin et al. (2021)[26]

AE = adverse event; AESI = adverse event of special interest; anti-dsDNA = anti-double-stranded DNA; CRR = complete renal response; C-SSRS = Columbia – Suicide Severity Rating Scale; DB = double-blind; ELISA = enzyme-linked immunosorbent assay; ISN = International Society of Nephrology; LN = lupus nephritis; OLE = open-label extension; ORR = ordinal renal response; PERR = primary efficacy renal response; RBC = red blood cell; RCT = randomized controlled trial; RPS = Renal Pathology Society; SDI = Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SFI = SELENA SLEDAI Flare Index; SLEDAI-S2K = Systemic Lupus Erythematosus Disease Activity Index 2000 with modified scoring for proteinuria; uPCR = urine protein-creatinine ratio; WBC = white blood cell.

Source: Clinical Study Report for BLISS-LN;[13] Furie et al. (2020);[29] Rovin et al. (2021).[26]

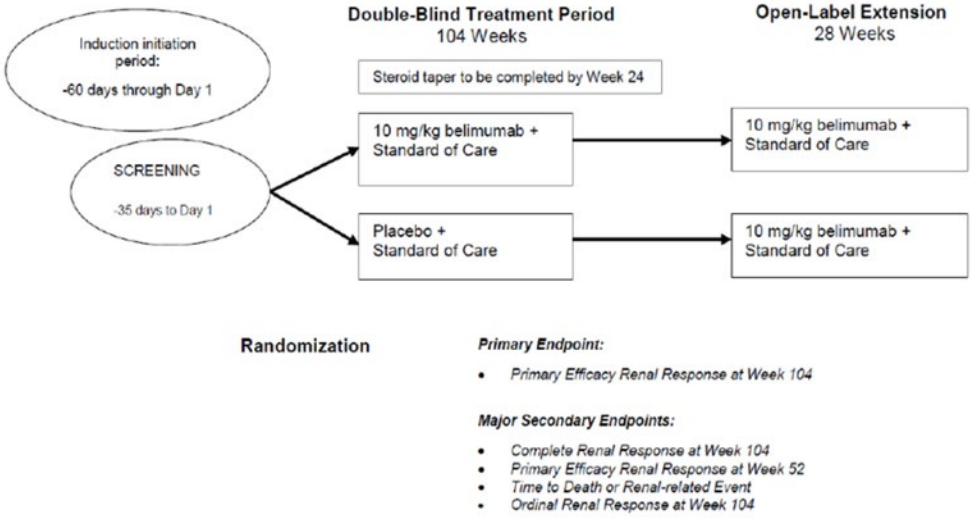
Description of Studies

One double-blind, placebo-controlled randomized controlled trial met the inclusion criteria for the systematic review (BLISS-LN).

The objective of the BLISS-LN study was to determine the efficacy, safety, and tolerability of belimumab in adult patients with active LN (classes III, IV, V, or V in combination with III or IV). The trial took place in 107 sites across 21 countries including China, the US, and the Philippines, with 1 site in Canada. A total of 448 patients who met the eligibility criteria during screening were randomized to 1 of 2 treatment groups — 10 mg/kg IV belimumab plus standard of care or placebo plus standard of care — in a 1:1 ratio (Figure 2). In addition to the investigational product (IP), all patients received standard of care regimens chosen by the investigators, which were initiated within 60 days before receiving the IP and which included high-dose corticosteroids and either IV cyclophosphamide for induction therapy followed by azathioprine for maintenance therapy or oral mycophenolate mofetil for induction and maintenance therapy. The randomization of all eligible patients was stratified by their induction regimen (high-dose corticosteroids plus cyclophosphamide versus high-dose corticosteroids plus mycophenolate mofetil) and race (Black versus non-Black). The study recommended that the high-dose corticosteroid regimen included 0 to 3 IV pulses of methylprednisolone (500 mg/pulse to 1,000 mg/pulse) followed by an oral prednisone dose of up to 60 mg/day that had to be tapered to less than or equal to 10 mg/day by week 24. The recommended taper regimen suggested reducing corticosteroids by approximately 5 mg/week. In addition to standard of care, patients received IV belimumab or placebo on days 1 (baseline), 15, and 29 and every 28 days thereafter to week 100, with final assessments at week 104. Hydroxychloroquine as well as angiotensin-converting enzyme inhibitors or angiotensin receptor blockers were encouraged for all patients. Patients who received treatment with the IP through week 100 and completed week 104 assessments in the double-blind period could enter into a 6-month OLE study.

Patients were defined as having treatment failure if they did not follow the corticosteroid rules (i.e., failed to taper corticosteroids to ≤ 10 mg/day by week 24 and not exceed this dose through week 104); if they received additional immunosuppressive drugs (except topical drugs) beyond the induction and maintenance regimens; if the use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or antimalarial drugs was initiated after week 24; or if the patient's standard therapy (i.e., cyclophosphamide, azathioprine, or mycophenolate mofetil) exceeded permitted doses. Patients were to be withdrawn from the study treatment if they missed 3 or more consecutive IP doses, took prohibited medication or a prohibited dose of concurrent medication, experienced unacceptable toxicity, became pregnant, withdrew consent, or tested positive for hepatitis B at screening.

Figure 2: Flow Chart of BLISS-LN Study Design



Source: Clinical Study Report for BLISS-LN.[13]

Populations

Inclusion and Exclusion Criteria

The BLISS-LN trial enrolled adult patients aged 18 years and older with active, biopsy-proven LN class III or IV, with or without class V, or pure class V membranous LN. In addition, patients had to have an antinuclear antibody titre greater than or equal to 1:80 and/or anti-dsDNA greater than or equal to 30 IU/mL and active renal disease requiring induction therapy with high-dose corticosteroids with either cyclophosphamide or mycophenolate mofetil or oral forms of mycophenolate. Patients were excluded if both cyclophosphamide and mycophenolate mofetil induction therapy had previously failed, if they had received cyclophosphamide induction therapy within 3 months of the trial, if they had an eGFR less than 30 mL/min/1.73 m^2, if they were pregnant or breastfeeding, or if they had been on dialysis, been treated with belimumab, or received any B cell–targeted therapy (e.g., rituximab) in the past year.

Baseline Characteristics

Baseline characteristics were generally well balanced between treatment groups in the BLISS-LN trial (Table 7). The mean (SD) age of patients enrolled in the BLISS-LN trial was 33.7 (10.74) years and 33.4 (10.6) years in the belimumab and placebo groups, respectively. Patients were predominantly female (88.3% and 87.9%) and predominantly Asian (51.1% and 48.9%), and 84% of patients in both the belimumab and placebo groups had renal biopsy class III or IV (with or without class V) according to the local reader. The mean of LN disease duration was 2.3 years (SD = 4.3 years) and 2.4 years (SD = 4.1 years) in the belimumab and placebo groups, respectively. The mean uPCR levels were 3.2 g/g (SD = 2.7 g/g) and 3.5 g/g (SD = 3.6 g/g), and the mean eGFR levels were 100.0 mL/min/1.73 m^2 (SD = 37.7 mL/min/1.73 m^2) and 101.0 mL/min/1.73 m^2 (SD = 42.7 mL/min/1.73 m^2) in the belimumab and placebo groups, respectively. A total of 73.5% of patients in both groups received mycophenolate mofetil as induction therapy. Patients in both the belimumab and

placebo groups had previous cyclophosphamide therapy (19.3% and 21.1%) and previous mycophenolate mofetil therapy (13.9% and 15.2%).

There were some baseline differences in use of concomitant medications between groups (Table 8), with slightly more patients using antimalarials in the belimumab group than in the placebo group (74.4% and 69.1%). A total of 96.9% and 94.2% of patients used steroids at baseline in the belimumab and placebo groups, respectively. The mean dose of prednisone at baseline (steroids were converted to prednisone equivalent) was slightly lower in the belimumab group, at 66.5 mg/day (SD = 99.6 mg/day), than in the placebo group, at 72.5 mg/day (SD = 133.2 mg/day). Patients also used immunosuppressants (88.8% and 86.1%) and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (65.9% and 67.3%) at baseline in the belimumab and placebo groups, respectively, the proportions of which were comparable between groups.

Table 7: Summary of Baseline Characteristics of Patients in the BLISS-LN Trial

Characteristic	Placebo group N = 223	Belimumab group 10 mg/kg N = 223
Region, n (%)		
Asia	105 (47.1)	106 (47.5)
Europe	45 (20.2)	41 (18.4)
US and Canada	38 (17.0)	38 (17.0)
North and South America (excluding US and Canada)	35 (15.7)	38 (17.0)
Sex, n (%)		
Female	196 (87.9)	197 (88.3)
Male	27 (12.1)	26 (11.7)
Ethnicity, n (%)		
Hispanic or Latino	43 (19.3)	50 (22.4)
Other	180 (80.7)	173 (77.6)
Age (years)		
Mean (SD)	33.1 (10.6)	33.7 (10.7)
Median (range)	31.0 (18 to 77)	31.0 (18 to 63)
Age group (years), n (%)		
≤ 45	190 (85.2)	191 (85.7)
> 45 to < 65	31 (13.9)	32 (14.3)
≥ 65	2 (0.9)	0
Race,[a] n (%)		
American Indian or Alaskan Native	6 (2.7)	4 (1.8)

Characteristic	Placebo group N = 223	Belimumab group 10 mg/kg N = 223
Asian	109 (48.9)	114 (51.1)
Black or African American	31 (13.9)	30 (13.5)
White or Caucasian	75 (33.6)	73 (32.7)
Multiple	2 (0.9)	2 (0.9)
BMI (kg/m^2), mean (SD)	24.5 (5.6)	23.8 (4.7)
Previous cyclophosphamide therapy, n (%)	47 (21.1)	43 (19.3)
Failed therapy, n (%)	6 (2.7)	11 (4.9)
Previous mycophenolate[b] therapy, n (%)	34 (15.2)	31 (13.9)
Failed therapy, n (%)	8 (3.6)	12 (5.4)
Induction and maintenance therapy, n (%)		
Cyclophosphamide and azathioprine	59 (26.5)	59 (26.5)
Mycophenolate mofetil	164 (73.5)	164 (73.5)
Disease characteristics		
SLE disease duration (years), mean (SD)	5.1 (5.8)	5.5 (6.4)
LN disease duration (years), mean (SD)	2.4 (4.1)	2.3 (4.3)
Renal biopsy class category[c] per local reader, n (%)		
N (%)	223 (100)	223 (100)
Class III or IV	132 (59.2)	126 (56.5)
Class III + V or class IV + V	55 (24.7)	61 (27.4)
Class V	36 (16.1)	36 (16.1)
Renal biopsy class category[c] per central reader,[d] n (%)		
N (%)	160 (71.7)	155 (69.5)
Class III or IV	113 (70.6)	102 (65.8)
Class III + V or class IV + V	30 (18.8)	33 (21.3)
Class V	13 (8.1)	18 (11.6)
Other	4 (2.5)	2 (1.3)
uPCR (g/g), n (%)		
< 0.5	8 (3.6)	9 (4.0)
0.5 to < 3	123 (55.2)	123 (55.2)
≥ 3	92 (41.3)	91 (40.8)
uPCR level (g/g), mean (SD)	3.5 (3.6)	3.2 (2.7)
eGFR (mL/min/1.73 m^2) category, n (%)		

Characteristic	Placebo group N = 223	Belimumab group 10 mg/kg N = 223
< 30	6 (2.7)	3 (1.3)
30 to < 60	35 (15.7)	30 (13.5)
60 to < 90	49 (22.0)	59 (26.5)
≥ 90	133 (59.6)	131 (58.7)
eGFR (mL/min/1.73 m^2), mean (SD)	101.0 (42.7)	100.0 (37.7)
SLEDAI-S2K category, n (%)		
N (%)	222 (99.6)	223 (100)
< 8	36 (16.1)	37 (16.6)
8 to < 12	60 (26.9)	55 (24.7)
12 to < 16	59 (26.5)	63 (28.3)
≥ 16	67 (30.0)	68 (30.5)
SLEDAI-S2K score		
N (%)	222 (99.6)	223 (100)
Mean (SD)	12.2 (4.8)	12.5 (5.3)
PGA		
N (%)	221 (99.1)	215 (96.4)
Mean (SD)	1.8 (0.6)	1.8 (0.6)
SDI score		
N	223 (100)	222 (99.6)
Mean (SD)	0.4 (0.8)	0.4 (1.1)
Pre-flare[e] serum creatinine level (µmol/L)		
N (%)	113 (50.7)	125 (56.1)
Mean (SD)	71.2 (22.8)	71.2 (31.8)
Pre-flare[e] eGFR (mL/min/1.73 m^2)[f]		
N (%)	113 (50.7)	125 (56.1)
Mean (SD)	98.6 (30.5)	99.6 (33.4)
Immunoglobulin G (g/L)		
N (%)	223 (100)	223 (100)
Mean (SD)	9.6 (4.7)	10.1 (5.0)
Anti-dsDNA (IU/mL)		
N (%)	223 (100)	223 (100)
Positive (≥ 30 IU/mL), n (%)	169 (75.8)	173 (77.6)
Antinuclear antibody (titre)		

Characteristic	Placebo group N = 223	Belimumab group 10 mg/kg N = 223
N (%)	223 (100)	223 (100)
Positive (≥ 1:80 titre), n (%)	197 (88.3)	194 (87.0)
Anti-C1q antibody (IU/mL)		
N (%)	221 (99.1)	223 (100)
Positive (≥ 22.2 IU/mL), n (%)	172 (77.8)	181 (81.2)
Anti-Smith antibody (kU/L)		
N (%)	219 (98.2)	223 (100)
Positive (≥ 15 kU/L), n (%)	72 (32.9)	73 (32.7)
BLyS[g]		
N (%)	222 (99.6)	223 (100)
Mean (SD)	0.7 (0.6)	0.8 (1.2)
Complement C3 (g/dL)		
N (%)	223 (100)	223 (100)
Mean (SD)	84.4 (29.6)	81.4 (27.3)
Complement C4 (g/dL)		
N (%)	223 (100)	223 (100)
Mean (SD)	16.1 (9.1)	15.7 (8.6)

anti-dsDNA = anti–double-stranded DNA; BLyS = B lymphocyte stimulator; BMI = body mass index; eGFR = estimated glomerular filtration rate; LN = lupus nephritis; PGA = physician global assessment; SD = standard deviation; SDI = Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SLE = systemic lupus erythematosus; SLEDAI-S2K = Systemic Lupus Erythematosus Disease Activity Index 2000 with modified scoring for proteinuria; uPCR = urine protein-creatinine ratio.

[a]Patients are only counted in 1 category.

[b]Mycophenolate mofetil or any other form of mycophenolate.

[c]Based on the presence of class III, IV, and V results, although other classes may be present also.

[d]Not all patients had an assessment by the central reader.

[e]Pre-flare is defined as the most recent values obtained before screening and before first manifestations of the current renal flare, as reported by investigator if available.

[f]Derived from pre-flare serum creatinine.

[g]Two different laboratory assays were used for BLyS protein: 366 samples were analyzed with 1 assay, and 79 samples were analyzed with the other.

Source: Clinical Study Report for BLISS-LN.[13]

Table 8: Summary of Systemic Lupus Erythematosus and Lupus Nephritis Treatments Patients Receiving at Baseline

Treatment	Placebo group N = 223	Belimumab group N = 223
Daily prednisone[a] dose (mg/day), mean (SD)	72.5 (133.2)	66.5 (99.6)
Use of steroids, n (%)	210 (94.2)	216 (96.9)
Use of antimalarials, n (%)	154 (69.1)	166 (74.4)
Use of immunosuppressants, n (%)	192 (86.1)	198 (88.8)
Use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, n (%)	150 (67.3)	147 (65.9)

SD = standard deviation.

[a]Steroids were converted to prednisone equivalent.

Source: Clinical Study Report for BLISS-LN.[13]

Interventions

In the BLISS-LN trial, eligible patients were randomized in a 1:1 ratio to receive IV belimumab 10 mg/kg or matching placebo administered over at least 1 hour. Patients were dosed on days 0 (baseline), 14, and 28 and then every 28 days thereafter through 100 weeks, with a final evaluation for the double-blind treatment period at 104 weeks. Patients who received treatment with the IP through week 100 and completed week 104 assessments in the double-blind period could enrol in a 28-week OLE study. Belimumab and placebo were supplied as open-label vials, and the IP was reconstituted and diluted by an unblinded qualified person (i.e., site pharmacist or designee), independent of the study. The infusion rate of the IP could be slowed or interrupted if a patient developed an infusion reaction, but the dose could not be altered. If a clinically significant AE possibly related to the IP was suspected, doses could be delayed by up to 2 weeks or 1 dose could be withheld at the investigators' discretion.

In addition to the IP, all patients received standard of care, which included high-dose corticosteroids and either:

- cyclophosphamide for induction therapy (500 mg by IV infusion every 2 weeks for 6 infusions) followed by azathioprine for maintenance therapy (target dose of 2 mg/kg/day)
- mycophenolate mofetil for induction and maintenance therapy with recommended oral dosing of 0.5 g twice daily for the first week, increasing to 1 g twice daily for the second week, and then 1.5 g twice daily for the third and subsequent weeks (mycophenolate sodium was permitted in lieu of mycophenolate mofetil for induction and/or maintenance therapy with a recommended oral dose from 720 mg/day to 2,160 mg/day).

The induction therapy was chosen by the investigator and initiated within 60 days before patients received the IP. Patients were able to switch maintenance regimens if certain tolerability or toxicity issues occurred. Patients were to be withdrawn from the study treatment if they missed 3 or more consecutive IP doses, took prohibited medication or a prohibited dose of concurrent medication, experienced unacceptable toxicity, became pregnant, withdrew consent, or tested positive for hepatitis B at screening.

High-Dose Corticosteroids

All patients were on a daily corticosteroid regimen as part of the induction therapy. The study-recommended corticosteroid regimen included 0 to 3 IV pulses of methylprednisolone followed by oral prednisone for a total daily dose up to 60 mg. Corticosteroids had to be tapered over time to less than or equal to 10 mg/day by week 24. Short-term rescue treatment was permitted between weeks 24 and 76 for reasons other than LN. No corticosteroid rescue treatment was allowed from week 76 to week 104.

Concomitant Medications

Concomitant medications, including LN-related treatments, were recommended and used by most patients in the BLISS-LN trial as shown in Table 8. Most patients in both the belimumab and placebo groups received antimalarials (74.4% versus 69.1%) and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (65.9% versus 67.3%). Other immunosuppressives (e.g., methotrexate) were allowed provided these were started before baseline and met eligibility criteria. Starting a new angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, or antimalarial treatment after the week 24 visit would be considered treatment failure.

Prohibited medications included new immunosuppressant drugs (other than as part of the induction and maintenance regimens), corticosteroid use outside of the limits, other investigational drugs (biologic or nonbiologic), anti–tumour necrosis factor therapy (e.g., adalimumab, etanercept, infliximab), other biologics (e.g., rituximab, abatacept, IV immunoglobulin), or plasmapheresis.

Outcomes

A list of efficacy outcomes identified in the CADTH review protocol and assessed in the clinical trials included in this review is provided in Table 9. These outcomes are further summarized below. A detailed discussion and critical appraisal of the outcome measures is provided in Appendix 4.

Table 9: Summary of Outcomes of Interest Identified in the CADTH Review Protocol

Outcome measure	Type of outcome in BLISS-LN trial
PERR at week 104	Primary
CRR at week 104	Key secondary
PERR at week 52	Key secondary
ORR at week 104	Key secondary
Reduction in proteinuria	Secondary
Increase or stabilization of eGFR	Secondary and post hoc analysis
Reduction in corticosteroid use	Secondary
Time to renal-related event or death	Key secondary
Reduction in chronic kidney disease stage	NR
Disease activity: SLEDAI-S2K	Secondary
Organ damage: SDI	Secondary

Outcome measure	Type of outcome in BLISS-LN trial
Disease flare frequency and severity: SFI flares	Secondary
HRQoL	NR
Reduction in symptoms	NR
Decrease in anti-dsDNA antibodies	Assessed biomarker
Increase in complement C3 and C4 levels	Assessed biomarker

anti-dsDNA = anti–double-stranded DNA; CRR = complete renal response; eGFR = estimated glomerular filtration rate; HRQoL = health-related quality of life; NR = not reported; ORR = ordinal renal response; PERR = primary efficacy renal response; SDI = Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SFI = SELENA SLEDAI Flare Index; SLEDAI-S2K = Systemic Lupus Erythematosus Disease Activity Index 2000 with modified scoring for proteinuria.

Source: Clinical Study Report for BLISS-LN.[13]

Primary Efficacy Renal Response

PERR at week 104 was the primary outcome and PERR at week 52 was a key secondary outcome in the BLISS-LN trial. PERR was a dichotomous composite outcome ("responder" versus "nonresponder" [from original source, referred to as "response" versus "no response" hereafter) that was considered achieved when all 3 of the following components were met: uPCR was less than or equal to 0.7 g/g, eGFR was no more than 20% below pre-flare value or at least 60 mL/min/1.73 m^2, and there was no treatment failure (i.e., patients did not take a protocol-prohibited or -restricted medication or dose). "Response" was defined as a response at the week 48 or week 100 visit that was confirmed by a repeat measure at the week 52 or week 104 visit, respectively. Patients who met treatment failure criteria were to continue in the study.

Complete Renal Response

CRR at week 104 was a key secondary outcome in the pivotal trial. CRR was a composite outcome that was considered achieved when all 3 of the following components were met: uPCR was less than or equal to 0.5, eGFR was no more than 10% below pre-flare value or within the normal range of at least 90 mL/min/1.73 m^2, and there was no treatment failure (i.e., patients did not take a protocol-prohibited or -restricted medication or dose). A response was defined as a response at the week 100 visit confirmed by a repeat measurement at the week 104 visit.

Ordinal Renal Response

ORR at week 104 was a key secondary outcome in the BLISS-LN trial in which patients achieved a CRR, partial renal response, or no response. A CRR was achieved if a patient had all of the following:

- uPCR less than 0.5 g/g
- eGFR no more than 10% below pre-flare glomerular filtration rate (GFR) or within normal range
- no treatment failure (i.e., did not take a protocol-prohibited or -restricted medication or dose).

A partial renal response was achieved if a patient had all of the following:

- 50% or greater decrease from baseline in uPCR and either:
  - uPCR value less than 1 g/g if baseline value was less than or equal to 3 g/g
  - uPCR value less than 3 g/g if the baseline value was greater than 3 g/g

- eGFR no more than 10% below baseline GFR or within normal range
- no treatment failure (i.e., did not take a protocol-prohibited or -restricted medication or dose).

The complete and partial renal responses required a response at the week 100 visit that was confirmed by a repeat measurement at the week 104 visit. Patients not meeting criteria for either a complete or partial renal response were classified as "no response."

Reduction in Proteinuria

Secondary outcomes in the BLISS-LN trial included the proportion of patients with a uPCR less than or equal to 0.7 g/g or a uPCR less than 0.5 g/g by visit, as well as the absolute and percent change in proteinuria over time as measured by the uPCR change from baseline by visit while on treatment.

Increase or Stabilization of eGFR

Secondary outcomes in the BLISS-LN trial included the proportion of patients with an eGFR no more than 20% below pre-flare value or at least 60 mL/min/1.73 m^2 by visit and the proportion of patients with an eGFR no more than 10% below the pre-flare value or within the normal range (≥ 90 mL/min/1.73 m^2) by visit. Post hoc analyses of the BLISS-LN trial included outcomes of time to 30% and 40% decline in eGFR from baseline using either only on-treatment data or all on-study data. Post hoc analyses also included sustained 30% and 40% decline in eGFR, which was defined as a 30% or 40% decrease in eGFR from baseline and was confirmed by the last 2 eGFR values in the trial.

Reduction in Corticosteroid Use

In the BLISS-LN trial, corticosteroid use was converted to a prednisone-equivalent dose. Secondary outcomes include the proportion of patients who received an average daily prednisone dose of less than or equal to 5 mg or less than or equal to 7.5 mg since the previous visit. The prednisone average daily dose since previous visit was calculated at every 4-week visit after baseline. All prednisone doses since the previous 4-week visit were summed and divided by the number of days in the period. Days where a patient did not have a prednisone dose recorded were considered as 0 mg for the day in the calculation for average prednisone dose.

Time to Renal-Related Event or Death

Time to renal-related event or death was a key secondary outcome in the trial, defined as the first event occurring after day 1 among the following: death by any cause; ESRD (defined as the need for chronic dialysis or renal transplant); doubling of serum creatinine (compared with baseline, confirmed with a second measurement at least 3 weeks later); renal worsening as evidenced by increased proteinuria and/or impaired renal function; or renal disease–related treatment failure (based on adjudication of treatment failures). Renal worsening was defined in the trial as a reproducible increase in 24-hour urine protein levels (as measured in uPCR) to more than 1 g if the baseline value was less than 0.2 g, or more than 2 g if the baseline value was between 0.2 g and 1 g, or more than twice the value at baseline if the baseline value was more than 1 g. Impaired renal function was defined as a reproducible decrease in GFR of more than 20% accompanied by at least 1 of the following: proteinuria (> 1), red blood cell casts, or white blood cell casts.

Reduction in Chronic Kidney Disease Stage

This outcome was not reported in the BLISS-LN trial.

Disease Activity: SLEDAI-S2K

In the trial, disease activity was assessed with the SELENA SLEDAI, a measure of disease activity consisting of 24 items across 9 organ systems that are scored based on the time of visit or preceding 10 days (Appendix 4).[30] The items are answered yes or no (presence or absence), and answers are weighted to arrive at a total score (range, 0 to 105), with higher scores indicating greater disease activity. The items include the following: seizure, psychosis, organic brain syndrome, visual disturbance, cranial nerve disorder, lupus headache, cerebrovascular attack, vasculitis, arthritis, myositis, urinary casts, hematuria, proteinuria, pyuria, rash, alopecia, mucosal ulcers, pleurisy, pericarditis, low complement, increased DNA binding, fever, thrombocytopenia, and leukopenia.[30] As noted in Appendix 4, a minimal important difference (MID) was not found for the SLEDAI-2K in patients with LN; however, the SLE literature suggests a minimal clinically meaningful increase of 3 or 4 points in the SLEDAI-2K for prediction of worsening and suggests a minimal clinically meaningful decrease in score of 1 to 2 points for improvement.[31] In the BLISS-LN trial, the proteinuria component of the SELENA SLEDAI was modified with the SLEDAI-2K, which considers new as well as persistent proteinuria of more than 0.5 g per 24 hours, to create the SLEDAI-S2K. Assessed end points included SLEDAI-S2K change from baseline by visit and SLEDAI-S2K score less than 4 by visit.

Organ Damage: Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index

In the pivotal trial, organ damage was assessed using the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI) as a secondary outcome. Assessed end points included SDI change from baseline by visit and the percent of patients with any SDI worsening (change > 0) compared with baseline by visit. The SDI was developed to assess irreversible damage in patients with SLE independently of its cause (SLE activity, therapy, comorbidities) but occurring after disease onset. Damage is usually defined as a clinical feature that must be continuously present for at least 6 months to score. The SDI consists of 42 items in 12 domains, with a maximum score of 46 (higher scores denote more damage). The SDI is defined for 12 organ systems (possible scores): peripheral vascular (0 to 5), ocular (0 to 2), neuropsychiatric (0 to 6), renal (0 to 3), pulmonary (0 to 5), cardiovascular (0 to 6), gastrointestinal (0 to 6), musculoskeletal (0 to 7), skin (0 to 3), endocrine (diabetes) (0 to 1), gonadal (0 to 1), and malignancies (0 to 2). The SDI global score is the sum of the damage scores for all 12 organ systems. An SDI greater than or equal to 1 indicates worsening.[32] The SDI has been found to be a predictor of mortality, and SDI scores have been shown to increase with disease duration.[33] No formal MID has been estimated for patients with SLE or LN. An SDI greater than or equal to 1 indicates damage, which may remain stable or increase over time.[32]

Disease Flare Frequency and Severity: SFI Flares

In the pivotal trial, a modified version of SFI was used to assess flares. The SFI is a disease-specific composite measure that classifies flares as mild/moderate or severe, based on criteria of clinical activity,

need for additional treatment, or physician global assessment (PGA) score.[33] In the pivotal trials, mild or moderate flares and severe flares were defined according to the following criteria:

- Mild or moderate flare (any of the following):
  - Change in SLEDAI-2K score of at least 3 points but no more than 12 points compared to previous visit
  - New or worse discoid, photosensitivity, profundus, cutaneous vasculitis, bullous lupus, nasopharyngeal ulcers, pleuritis, pericarditis, arthritis, or SLE fever
  - Increase in prednisone, but not exceeding 0.5 mg/kg/day
  - Addition of nonsteroidal anti-inflammatory drug or hydroxychloroquine for SLE activity
  - A 1.0 or greater increase in PGA score, but not to more than 2.5.
- Severe flare (any of the following):
  - Change in SLEDAI-2K score of more than 12 points compared to previous visit
  - New or worse central nervous system SLE, vasculitis, nephritis, myositis, hemolytic anemia (hemoglobin < 70 g/L or decrease in hemoglobin > 30 g/L) requiring doubling of prednisone or prednisone increase to more than 0.5 mg/kg/day or hospitalization
  - Increase in prednisone to more than 0.5 mg/kg/day
  - New cyclophosphamide, azathioprine, methotrexate, or mycophenolate for SLE activity
  - Hospitalization for SLE
  - Increase in PGA score to more than 2.5.

In the BLISS-LN trial, flares originally marked severe were downgraded if the only reason they had been marked as such was a change in SELENA SLEDAI score to greater than 12, because this may indicate only a modest increase in disease activity.

Health-Related Quality of Life

This outcome was not reported in the BLISS-LN trial.

Reduction in Symptoms

This outcome was not reported in the BLISS-LN trial.

Serological Outcomes: Decrease in Anti-dsDNA Antibodies

Anti-dsDNA serum levels usually increase as the clinical activity of the disease increases, most often before the clinical deterioration of kidney function.[10] In the BLISS-LN trial, the mean change from baseline in anti-dsDNA through to week 104 was calculated, as was the proportion of patients who shifted from a positive anti-dsDNA (≥ 30 IU/mL) at baseline to a negative anti-dsDNA (< 30 IU/mL) at week 104.

Serological Outcomes: Increase in Complement C3 and C4 Levels

Complement C3 and C4 typically decrease as the clinical activity of the disease increases, most often before the clinical deterioration of kidney function.[10] Decrease in circulating complement levels are associated with LN and may also be diagnostic markers in this disease.[10] In the BLISS-LN trial, the mean change from

baseline in complement C3 and C4 levels through to week 104 was calculated, as was the proportion of patients who shifted from a low level in each complement (C3 < 90 mg/dL; C4 < 10 mg/dL) at baseline to a normal or high level (C3 ≥ 90 mg/dL; C4 ≥ 10 mg/dL) at week 104.

Safety Assessments

AEs were any untoward medical occurrence that may or may not have been related to the study drug. The criteria for SAEs included death; events that were life threatening, required hospitalization or prolongation of hospitalization, or resulted in persistent or significant disability or incapacity; congenital anomalies or birth defects; events of possible drug-induced liver injury with hyperbilirubinemia; or events that may have required medical or surgical intervention to prevent 1 of the other outcomes listed.

In addition, the Columbia – Suicide Severity Rating Scale (C-SSRS) was utilized as a safety assessment for suicidality. The C-SSRS is an assessment tool that evaluates suicidal ideation and behaviour and was completed at every visit during the double-blind phase in the BLISS-LN trial. It is made up of 10 categories, all of which maintain binary responses (yes or no) to indicate a presence or absence of behaviours that are significantly predictive of completed suicide.[34] The outcome of the C-SSRS is a numerical score obtained from the aforementioned categories.

Statistical Analysis

Sample Size Determination and Power Calculation

In the BLISS-LN trial, the original sample size calculations using ORR as the primary outcome resulted in a target sample size of N = 464 patients (232 per arm) to achieve at least 85% power to detect a treatment difference for the initial primary outcome. The primary outcome was revised to PERR with a final sample size of N = 448, with 80% power (2-sided test; significance level of 0.05) to detect a 13.6% between-group difference and a minimum detectable difference of 9.7%, assuming response rates of 40% and 53.6% for placebo and belimumab, respectively.

Efficacy outcomes were analyzed in the modified intention-to-treat (mITT) population, which included all the patients who underwent randomization and received at least 1 dose of belimumab or placebo.

Statistical Test or Model

The main components of the statistical test and model for the BLISS-LN trial are discussed in Table 10. The primary outcome, PERR at week 104, as well as 2 of the key secondary outcomes — CRR at week 104 and PERR at week 52 — were compared between belimumab and placebo using logistic regression. All statistical tests were 2-sided and performed at an overall significance level of alpha = 0.05. The key secondary outcome of time to renal-related event or death was assessed using a Cox proportional hazards model, and ORR was analyzed using rank analysis of covariance (ANCOVA). The primary and all key secondary outcomes controlled for induction regimen (cyclophosphamide versus mycophenolate mofetil), race (Black versus non-Black), baseline proteinuria, and baseline eGFR.

Proportion outcomes as defined in Table 10 were compared between belimumab and placebo using logistic regression. For continuous outcomes, ANCOVA was used to evaluate change from baseline in SLEDAI-S2K,

and rank ANCOVA was used to evaluate change from baseline in proteinuria and SDI. All analyses for these proportion outcomes and continuous outcomes controlled for baseline value, induction regimen (cyclophosphamide versus mycophenolate mofetil), and race (Black versus non-Black).

Other time-to-event outcomes, including time to first PERR, time to first CRR that is maintained through week 52 or week 104, and time to first severe SFI flare, were assessed using a Cox proportional hazards model controlling for induction regimen (cyclophosphamide versus mycophenolate mofetil) and race (Black versus non-Black).

Post hoc analyses of the BLISS-LN trial by Rovin et al. (2022)[26] included end points of time to 30% and 40% decline in eGFR from baseline and sustained 30% and 40% decline in eGFR, which were analyzed with a Cox proportional hazards model and logistic regression models, respectively. Analyses were adjusted for induction regimen, race, baseline uPCR, and baseline eGFR.

Data Imputation Methods

Patients who discontinued treatment or withdrew from the study were imputed as no response from the visit after the first missed IP dose for the primary and major secondary efficacy outcomes other than time to renal-related event or death; the latter had data censored from the first missed treatment dose.

For the primary outcome (PERR at week 104), both the week 100 and week 104 visits were used to derive the outcome. If a patient missed the week 100 or week 104 visit, the week 96 renal response was used in place of the missing visit. If the patient was missing both week 100 and week 104 visits or had only 1 nonmissing visit among weeks 96, 100, and 104, the patient was imputed as no response. Imputation for missing visits was limited to the current visit and 2 previous visits, thereby limiting reproducibility to 3 visits. This 3-visit rule was used for determining renal response at all visits in which renal response is derived. The same rules were applied if either lab components (eGFR or uPCR) were missing for the week 100 or week 104 visits.

For end points for renal-specific measures, including SLEDAI-S2K organ improvement or worsening, serum creatinine doubling, or progression to ESRD, a last observation carried forward strategy was used in which the last observed value on or before the intercurrent event was carried forward for all subsequent time points through week 104. The secondary outcome of SDI used a worst observation carried forward imputation method and was presented for data for both on-treatment and on-study analyses.

Censoring Rules for Time-to-Event Analyses

For the key secondary outcome of time to renal-related event or death, intercurrent events of IP discontinuation, treatment failure not related to renal event, loss to follow-up, and study withdrawal resulted in censoring unless they occurred after a renal-related event. Death and treatment failure related to renal event were counted as an event if they occurred on or before the events that resulted in censoring. For the secondary outcome of time to first maintained PERR and CRR, IP discontinuation, treatment failure, or withdrawal were imputed as no response. For the secondary outcome of time to severe SFI flares, a treatment failure was imputed as an event, while IP discontinuation and study withdrawal were censoring events.

Subgroup Analyses

Of the subgroups of interest to this review, the BLISS-LN study conducted preplanned analyses based on baseline renal biopsy class (class III or class IV, versus class III + V or class IV + V, versus class V) and induction regimen (cyclophosphamide versus mycophenolate mofetil).

Sensitivity Analyses

In the BLISS-LN trial, various preplanned sensitivity analyses were conducted to investigate the impact of imputing intercurrent events as no response for the primary and key secondary outcomes. Prespecified tipping point analyses were conducted on the outcomes of PERR at week 104, CRR at week 104, and time to renal-related event or death to evaluate the robustness of the results of the conclusions when the intercurrent event assumptions are changed. Additional sensitivity analyses were conducted as shown in Table 10.

Table 10: Statistical Analysis of Efficacy Outcomes in the BLISS-LN Trial

Outcome	Statistical model	Adjustment factors	Sensitivity analyses
PERR at week 104 (primary outcome): defined by a response at the week 100 visit that is confirmed by a repeat measurement at the week 104 visit Response: uPCR ≤ 0.7 g/g, and eGFR no more than 20% below pre-flare value or ≥ 60 mL/min/1.73 m^2, and not a treatment failure	Logistic regression	Adjustment for covariates: induction regimen, race, baseline uPCR, and baseline eGFR	Sensitivity analyses: • included data collected post–treatment discontinuation and treatment failures • included only patients who completed IP • included per-protocol population[a] • were unadjusted for covariates Tipping point analyses were performed to assess the impact of premature discontinuation of IP (e.g., Cochran-Mantel-Haenszel chi-square test)
CRR at week 104 (key secondary outcome) Defined by a response at the week 100 visit that is confirmed by a repeat measurement at the week 104 visit. Response: uPCR < 0.5 g/g, and eGFR no more than 10% below pre-flare value or ≥ 90 mL/min/1.73 m^2, and not a treatment failure	Same as primary outcome	Same as primary outcome	Same as primary outcome
PERR at week 52 (key secondary outcome) Defined in the same manner as primary outcome only using a response at the week 48 visit that was confirmed by a repeat measurement at the week 52 visit.	Same as primary outcome	Same as primary outcome	NR

Outcome	Statistical model	Adjustment factors	Sensitivity analyses
Time to renal-related event or death (key secondary outcome) Defined as first of the following: death, ESRD, doubling of serum creatinine, renal worsening as evidenced by increased proteinuria and/or impaired renal function, or renal disease–related treatment failure.	Cox proportional hazards	Same as primary outcome	Sensitivity analysis: renal event–related treatment failure was removed Tipping point analysis: assess the sensitivity to the censoring-at-random assumption
ORR at week 104 (key secondary outcome) Patients achieved a complete response, a partial response, or no response. A complete response is defined as uPCR < 0.5 g/g, eGFR no more than 10% below pre-flare GFR or within normal range, and not a treatment failure. A partial response was defined as a ≥ 50% decrease from baseline in uPCR and 1 of the following: uPCR < 1 g/g if baseline ≤ 3 g/g, or uPCR < 3 g/g if the baseline was > 3 g/g; eGFR no more than 10% below baseline GFR or within normal range; and no treatment failure.	Rank ANCOVA	Same as primary outcome	Sensitivity analysis:[b] ORR including urinary sediment at week 104 and ORR including urinary sediment using calculated GFR at week 104
Other secondary variables: Proportion outcomes — individual components of PERR and CRR, renal-specific measures, SLEDAI-S2K, corticosteroids, SDI	Same as primary outcome	Same as primary outcome	Sensitivity analysis: based on observed data ignoring intercurrent events
Other secondary variables: Continuous outcomes — renal outcomes, SLEDAI-S2K, SDI	ANCOVA used to evaluate SLEDAI-S2K change from baseline outcomes Rank ANCOVA used to evaluate proteinuria and SDI change from baseline outcomes	Same as primary outcome	For renal outcomes and SLEDAI-S2K: sensitivity analysis is based on observed data, ignoring treatment failure, and does not impute values for unobserved data For SDI: sensitivity analysis uses all observed data while on study and applies worst observation carried forward on the observed visits only
Other secondary variables: time-to-event outcomes — PERR, CRR, SFI flares	Cox proportional hazards model	Same as primary outcome	None

ANCOVA = analysis of covariance; CRR = complete renal response; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; GFR = glomerular filtration rate; IP = investigational product; NR = not reported; ORR = ordinal renal response; PERR = primary efficacy renal response; SDI = Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SFI = SELENA SLEDAI Flare Index; SLEDAI-S2K = Systemic Lupus Erythematosus Disease Activity Index 2000 with modified scoring for proteinuria; uPCR = urine protein-creatinine ratio.

[a]To be performed only if ≥ 15% of patients were excluded from the modified intention-to-treat population.

[b]Performed if PERR at week 52 is statistically significant per the testing hierarchy.

Sources: Clinical Study Report for BLISS-LN;[13] Rovin et al. (2022).[26]

Multiplicity Testing

The primary and the 4 major secondary efficacy outcomes were evaluated based on a prespecified stepdown sequential testing procedure to control the overall type I error rate. If the prior end point was statistically significant ($P < 0.05$), then testing of the next sequential end point would proceed. The primary and 4 major secondary outcomes were evaluated for statistical significance in this prespecified approach, as follows:

- PERR at week 104
- CRR at week 104
- PERR at week 52
- Time to renal-related event or death
- ORR at week 104

Analyses of other efficacy outcomes, including the individual components of these composite outcomes, were not subject to any multiplicity adjustment.

Results

Patient Disposition

A summary of the patient disposition in the pivotal trial is available in Table 11. In BLISS-LN, 797 patients were screened for eligibility into the trial, 43.8% of whom either did not meet the trial's inclusion criteria or did meet the exclusion criteria. A total of 224 patients were randomized into each of the belimumab and placebo groups. There were fewer study discontinuations in the belimumab group (16.6%) than in the placebo group (24.2%). The major reason for study discontinuation was withdrawal by patient (8.5% belimumab and 11.7% placebo), followed by AEs (3.1% and 4.5%) and investigator discretion (2.2% and 4.9%). A total of 34.5% of patients in the belimumab group and 40.8% in the placebo group prematurely discontinued the IP, with the main reasons including an AE (13.5% belimumab and 13.5% placebo), lack of efficacy (8.1% and 9.0%), or patient meeting protocol-defined stopping criteria (5.4% and 9.9%).

Table 11: Patient Disposition in the BLISS-LN Trial

Disposition	Placebo group	Belimumab group
Screened, N	797	
Randomized, N	224	224
Completed study, N (%)	169 (75.8)	186 (83.4)
Discontinued study, N (%)	54 (24.2)	37 (16.6)
Reason for study discontinuation, N (%)		
Adverse event	10 (4.5)	7 (3.1)
Lack of efficacy	2 (0.9)	1 (0.4)
Withdrew consent	26 (11.7)	19 (8.5)
Investigator discretion	11 (4.9)	5 (2.2)

Disposition	Placebo group	Belimumab group
Lost to follow-up	5 (2.2)	3 (1.3)
Protocol deviation	0	2 (0.9)
Discontinued from IP prematurely, N (%)	91 (40.8)	77 (34.5)
Reason for IP discontinuation, N (%)		
Adverse event	30 (13.5)	30 (13.5)
Lack of efficacy	20 (9.0)	18 (8.1)
Patient met protocol-defined stopping criteria	22 (9.9)	12 (5.4)
Patient decision	13 (5.8)	11 (4.9)
Investigator discretion	5 (2.2)	2 (0.9)
Lost to follow-up	1 (0.4)	4 (1.8)
mITT, N (%)	223 (99.6)	223 (99.6)
PP, N (%)	217 (96.9)	218 (97.3)
Safety, N (%)	224 (100)	224 (100)

IP = investigational product; mITT = modified intention to treat; PP = per protocol.

Source: Clinical Study Report for BLISS-LN.[13]

Table 12: Duration of Treatment Exposure Through Week 104 (mITT)

Time points	Placebo group (N = 223)	Belimumab group (N = 223)
Duration of exposure (days),[a] mean (SD)	546.4 (251.29)	577.3 (243.50)
Duration of exposure (weeks),[b] n (%)		
< 24	31 (13.9)	33 (14.8)
24 to 52	38 (17.0)	16 (7.2)
> 52 to 76	12 (5.4)	19 (8.5)
> 76	142 (63.7)	155 (69.5)
Total number of infusions, n (%)		
1 to 9	47(21.1)	38 (17.0)
10 to 18	30 (13.5)	25 (11.2)
19 to 27	146 (65.5)	160 (71.7)
Mean (SD)	20.0 (9.0)	21.0 (8.6)

mITT = modified intention to treat; SD = standard deviation.

[a]Duration of exposure (days) = (last infusion date – first infusion date + 28). Only complete dates were used when calculating duration of exposure. First and last infusion dates were used, regardless of any missed doses.

[b]Based on the visit week of the last infusion received.

Source: Clinical Study Report for BLISS-LN.[13]

Exposure to Study Treatments

Exposure data from the BLISS-LN trial are summarized in Table 12. The mean (SD) treatment duration was 577 (243.5) days in the belimumab group and 546 (251.3) days in the placebo group. Most patients in both treatment groups had a duration of exposure > 76 weeks (69.5% belimumab versus 63.7% placebo), and most received 19 to 27 infusions (71.7% versus 65.5%).

Efficacy

Only those efficacy outcomes and analyses of subgroups identified in the review protocol are reported below. Results of the subgroup analyses were available for certain outcomes and will be presented under each respective efficacy outcome. Detailed efficacy data are available in Appendix 3.

Renal Response Activity

Primary Efficacy Renal Response

Key results of the primary outcome, PERR at week 104, are summarized in Table 13. There was a statistically significant difference in the number of patients who achieved a PERR in the belimumab group versus the placebo group (43.0% versus 32.3%), with an adjusted between-group difference of 10.66% (95% CI, 1.89 to 19.42; P = 0.0311). A larger proportion of patients in the treatment group met each component of the composite outcome than in the placebo group; however, the difference was not statistically significant for the eGFR component, with an adjusted between-group difference of 7.10%, (95% CI, −1.84 to 16.04; P = 0.1599). A greater percentage of patients in the belimumab group achieved a PERR as of week 24, and this difference was maintained through week 104 (Figure 3). A total of 43.0% of patients in the belimumab group and 32.3% in the placebo group achieved a PERR that was maintained through to week 104. The HR for time to first PERR that was maintained through week 104 was 1.46 (95% CI, 1.07 to 1.98).

Table 13: Summary of Key Response Variables in the BLISS-LN Trial (mITT)

Characteristic	Placebo group N = 223	Belimumab group N = 223
PERR at week 104		
N (%)	223 (100)	223 (100)
Response, n (%)	72 (32.3)	96 (43.0)
CMH adjusted difference (95% CI)[a] vs. placebo	10.66 (1.89 to 19.42)	
OR (95% CI)[b] vs. placebo	1.55 (1.04 to 2.32)	
P value[b]	0.0311	
Time to first PERR that is maintained through week 104, HR (95% CI)[c]	1.46 (1.07 to 1.98)	
Individual components of PERR at week 104		
uPCR < 0.7 g/g		
N (%)	223 (100)	223 (100)
Response, n (%)	75 (33.6)	99 (44.4)

Characteristic	Placebo group N = 223	Belimumab group N = 223
CMH adjusted difference (95% CI)[a] vs. placebo	10.70 (1.79 to 19.61)	
OR (95% CI)[b] vs. placebo	1.54 (1.04 to 2.29)	
P value[b]	0.0320[d]	
eGFR no more than 20% below pre-flare value or ≥ 60 mL/min/1.73 m²		
N (%)	223 (100)	223 (100)
Response, n (%)	112 (50.2)	128 (57.4)
CMH adjusted difference (95% CI)[a] vs. placebo	7.10 (−1.84 to 16.04)	
OR (95% CI)[b] vs. placebo	1.32 (0.90 to 1.94)	
P value[b]	0.1599[d]	
Not a treatment failure[e]		
N (%)	223 (100)	223 (100)
Response, n (%)	166 (74.4)	185 (83.0)
CMH adjusted difference (95% CI)[a] vs. placebo	8.49 (1.06 to 15.93)	
OR (95% CI)[b] vs. placebo	1.65 (1.03 to 2.63)	
P value[b]	0.0364[d]	
PERR at week 52		
N (%)	223 (100)	223 (100)
Response, n (%)	79 (35.4)	104 (46.6)
CMH adjusted difference (95% CI)[a] vs. placebo	11.12 (2.25 to 19.99)	
OR (95% CI)[b] vs. placebo	1.59 (1.06 to 2.38)	
P value[b]	0.0245	
CRR at week 104		
N (%)	223 (100)	223 (100)
Response, n (%)	44 (19.7)	67 (30.0)
CMH adjusted difference (95% CI)[a] vs. placebo	10.27 (2.40 to 18.14)	
OR (95% CI)[b] vs. placebo	1.74 (1.11 to 2.74)	
P value[b]	0.0167	
Time to first CRR that is maintained through week 104, HR (95% CI)[c]	1.58 (1.08 to 2.31)	
Individual components of CRR at week 104		
uPCR < 0.5 g/g		
N (%)	223 (100)	223 (100)
Response, n (%)	64 (28.7)	88 (39.5)
CMH adjusted difference (95% CI)[a] vs. placebo	10.72 (2.04 to 19.40)	

Characteristic	Placebo group N = 223	Belimumab group N = 223
OR (95% CI)[b] vs. placebo	1.58 (1.05 to 2.38)	
P value[b]	0.0268[d]	
eGFR no more than 10% below pre-flare value or within the normal range (≥ 90 mL/min/1.73 m^2)		
N (%)	223 (100)	223 (100)
Response, n (%)	89 (39.9)	104 (46.6)
CMH adjusted difference (95% CI)[a] vs. placebo	6.68 (−2.31 to 15.67)	
OR (95% CI)[b] vs. placebo	1.33 (0.90 to 1.96)	
P value[b]	0.1539[d]	
Not a treatment failure[e]		
N (%)	223 (100)	223 (100)
Response, n (%)	166 (74.4)	185 (83.0)
CMH adjusted difference (95% CI)[a] vs. placebo	8.49 (1.06 to 15.93)	
OR (95% CI)[b] vs. placebo	1.65 (1.03 to 2.63)	
P value[b]	0.0364[d]	
ORR at week 104[f]		
N (%)	223 (100)	223 (100)
Complete renal response, n (%)	44 (19.7)	67 (30.0)
Partial renal response, n (%)	38 (17.0)	39 (17.5)
No response, n (%)	141 (63.2)	117 (52.5)
P value[b]	0.0096	
Time to renal-related event or death[g]		
N (%)	223 (100)	223 (100)
Patients with an event, n (%)	63 (28.3)	35 (15.7)
Days to event, median (range)	188 (28 to 675)	170 (25 to 651)
HR (95% CI)[c]	0.51 (0.34 to 0.77)	
P value[c]	0.0014	

CI = confidence interval; CMH = Cochran-Mantel-Haenszel; CRR = complete renal response; eGFR = estimated glomerular filtration rate; HR = hazard ratio; mITT = modified intention to treat; OR = odds ratio; ORR = ordinal renal response; PERR = primary efficacy renal response; uPCR = urine protein-creatinine ratio.

[a]CMH estimates are adjusted for induction regimen (cyclophosphamide vs. mycophenolate mofetil) and race (Black vs. non-Black).

[b]OR (95% CI) and P value are from a logistic regression model for comparison between belimumab and placebo, with covariates treatment group, induction regimen (cyclophosphamide vs. mycophenolate mofetil), race (Black vs. non-Black), baseline uPCR, and baseline eGFR.

[c]From Cox proportional hazards model for comparison between belimumab and placebo, adjusting for induction regimen (cyclophosphamide vs. mycophenolate mofetil), race (Black vs. non-Black), baseline uPCR, and baseline eGFR.

[d]P value has not been adjusted for multiple testing (i.e., the type I error rate has not been controlled).

[e]Patients did not take a protocol-prohibited or -restricted medication or dose. The same treatment failure rules apply for PERR and CRR.

[f]Study withdrawal, treatment failures, and investigational product discontinuation imputed as "no response." Investigational product discontinuation or treatment failure not related to renal disease or study withdrawal are censored in the time-to-event analysis.

[9]Events are defined as the first event experienced among the following: death, progression to end-stage renal disease, doubling of serum creatinine from baseline, renal worsening, or renal-related treatment failure. Patients who discontinue randomized treatment, withdraw from the study, or are lost to follow-up are censored on the date. Patients who complete the 104-week treatment period are censored at the week 104 visit. Time to event is defined as (event date – treatment start date + 1).
Source: Clinical Study Report for BLISS-LN.[13]

In BLISS-LN, a statistically significant difference was observed in the belimumab group in the proportion of patients who achieved the key secondary outcome of PERR at week 52 (46.6% versus 35.4%), with an adjusted between-group difference of 11.12% (95% CI, 2.25 to 19.99; P = 0.0245).

Various sensitivity analyses were conducted on the primary outcome, all of which were consistent with the result of the primary efficacy analysis. For the primary outcome, the tipping point analysis varying the no response assumption for all withdrawn patients regardless of treatment found that 21.2% of those in the placebo group considered no response needed to be altered to response to tip the conclusion from statistical significance to nonsignificance, assuming no additional patients on belimumab were considered response; however, this was deemed highly implausible.

Subgroup analysis: A summary of PERR at week 104 stratified by baseline renal biopsy class and induction regimen subgroups is presented in Appendix 3. Results numerically favoured the belimumab group for all subgroups except for the baseline renal biopsy class V and the cyclophosphamide followed by azathioprine subgroups, the results of which were not statistically significantly different between treatment groups. However, the study was not designed or powered to evaluate efficacy in subgroups, and the small number of patients in the class V and the cyclophosphamide followed by azathioprine subgroups might have led to the lack of statistical significance between treatment groups.

Complete Renal Response

In BLISS-LN, as shown in Table 13, the key secondary outcome of CRR at week 104 was statistically significant in favour of belimumab (30.0% versus 19.7%; adjusted between-group difference of 10.27% [95% CI, 2.40 to 18.14; P = 0.0167]). A total of 30.0% of patients in the belimumab group and 19.7% in the placebo group had achieved a CRR that was maintained through to week 104. The HR for time to first CRR that was maintained through week 104 was 1.58 (95% CI, 1.08 to 2.31).

As shown in Figure 5, a greater proportion of patients in the belimumab group than in the placebo group achieved a CRR at each visit; however, CIs overlapped until approximately week 72, after which a separation was maintained through week 104.

Various sensitivity analyses and tipping point analyses were conducted on the outcome of CRR at week 104, all of which were consistent with the result of the primary efficacy analysis.

Subgroup analysis: A summary of CRR at week 104 stratified by baseline renal biopsy class and induction regimen subgroups is presented in Appendix 3. Results numerically favoured the belimumab group for all subgroups except for the baseline renal biopsy class V and the cyclophosphamide followed by azathioprine subgroups, the results of which were not statistically significantly different between treatment groups. However, the study was not designed or powered to evaluate efficacy in subgroups, and the small number of patients in the class V and the cyclophosphamide followed by azathioprine subgroups might have led to the lack of statistical significance between treatment groups.

Ordinal Renal Response

For the key secondary outcome of ORR at week 104, there was a statistically significant treatment difference between the belimumab and placebo groups in the composite outcome of patients with complete response, partial response, and no response (P = 0.0096), as shown in Table 13. The proportion of patients with complete response was higher in the belimumab group than in the placebo group (30.0% versus 19.7%), and the proportion of patients with partial response was similar between the belimumab group and the placebo group (17.5% versus 17.0%). A higher proportion of patients in the placebo group were had no response (63.2%) than in the belimumab group (52.5%).

The results of sensitivity analyses of ORR including urinary sediment at week 104 and ORR including urinary sediment using calculated GFR at week 104 were supportive of the primary analysis.

Reduction in Proteinuria

A secondary outcome in the BLISS-LN trial was the proportion of patients achieving uPCR less than or equal to 0.7 g/g at week 104, the results of which, as shown in Table 13, were higher for patients in the belimumab group compared with the placebo group (44.4% versus 33.6%), with an OR of 1.54 (95% CI, 1.04 to 2.29). Also, a higher proportion of patients in the belimumab group than in the placebo group achieved a uPCR less than 0.5 g/g at week 104 (39.5% versus 28.7%), with an OR of 1.58 (95% CI, 1.05 to 2.38).

As shown in Table 15, the mean absolute change from baseline to week 104 in uPCR was −2.33 (SD = 2.88) for the belimumab group (n = 138) and −2.43 (SD = 2.65) in the placebo group (n = 128). The mean percent change from baseline to week 104 in uPCR was −70.66% (SD = 43.98%) and −62.36% (SD = 49.43%) for the belimumab and placebo groups, respectively.

Increase or Stabilization of eGFR

As shown in Table 13, at week 104 in the BLISS-LN trial, a higher proportion of patients in the belimumab group than in in the placebo group achieved an eGFR no more than 20% below pre-flare value or at least 60 mL/min/1.73 m^2 (57.4% versus 50.2%); however, no statistically significant difference was detected between groups, with an adjusted difference of 7.10 (95% CI, −1.84 to 16.04; P = 0.1599). Similarly, a higher proportion of patients in the belimumab group than in the placebo group achieved an eGFR at week 104 that was no more than 10% below pre-flare value or within the normal range (≥ 90 mL/min/1.73 m^2) (46.6% versus 39.9%); however, no statistically significant difference was detected between groups, with an adjusted difference of 6.68 (95% CI, −2.31 to 15.67; P = 0.1539).

As shown in Table 15, there was a numerical increase in the mean (SD) observed GFR values from baseline to week 104 for the belimumab group, which increased from 100.2 (37.68) mL/min/1.73 m^2 to 111.3 (35.75) mL/min/1.73 m^2 and decreased in the placebo group from 101.0 (42.61) mL/min/1.73 m^2 to 100.8 (29.18) mL/min/1.73 m^2.

In a post hoc analysis of on-study patients in the BLISS-LN trial, fewer patients in the belimumab group than in the placebo group experienced a 30% decline in eGFR (8.5% versus 17.0%) between baseline and week 104, with an HR of 0.47 (95% CI, 0.27 to 0.83), and fewer patients in the belimumab group than in the placebo

group experienced a 40% decrease in eGFR (4.5% versus 11.7%) between baseline and week 104, with an HR of 0.35 (95% CI, 0.17 to 0.74).

In a post hoc analysis, a sustained 30% decline in eGFR by the end of the study (as confirmed by the last 2 observed eGFR measurements) was reported by fewer patients in the belimumab group than in the placebo group (3.6% versus 11.2%), with a OR of 0.29 (95% CI, 0.13 to 0.68). A sustained 40% decline in eGFR was reported by 1.8% and 6.7% of patients in the belimumab and placebo groups, respectively, with an OR of 0.25 (95% CI, 0.08 to 0.78).

Reduction in Corticosteroid Use

In BLISS-LN, corticosteroid use was converted to a prednisone-equivalent dose. As shown in Table 15, a higher proportion of patients in the belimumab group compared with the placebo group received an average daily prednisone dose of less than or equal to 7.5 mg since the previous visit (40.8% versus 29.6%), with an OR of 1.65 (95% CI, 1.11 to 2.45). A total of 82 patients (36.8%) in the belimumab group received an average daily prednisone dose less than or equal to 5 mg since the previous visit, compared to 62 (27.8%) in the placebo group, with an OR of 1.51 (95% CI, 1.01 to 2.27) as of week 104.

Time to Renal-Related Event or Death

As shown in Table 13, there was a statistically significant difference in the key secondary outcome of risk of a renal-related event or death through to week 104 between patients in the belimumab and placebo groups (15.7% versus 28.3%), with an HR of 0.51 (95% CI, 0.34 to 0.77; P = 0.0014). As shown in Table 14, most events that contributed to this composite end point were renal worsening (7.6% belimumab versus 17.5% placebo) and renal-related treatment failures (7.2% belimumab versus 9.0% placebo).

Table 14: Number of Renal-Related Events or Deaths by Group in the BLISS-LN Trial (mITT)

Event,[a] n (%)	Placebo N = 223	Belimumab 10 mg/kg N = 223
Death for any reason	2 (0.9)	1 (0.4)
Progression to ESRD[b]	1 (0.4)	0 (0.4)
Doubling of serum creatinine[c]	1 (0.4)	1 (0.4)
Renal worsening[d]	39 (17.5)	17 (7.6)
Treatment failure related to renal event[e]	20 (9.0)	16 (7.2)

ESRD = end-stage renal disease; mITT = modified intention to treat.

[a]Represents first event for each patient with an event. A patient who died following a renal-related event will be included in this analysis as a renal-related event, not a death.

[b]Progression to ESRD is defined as the need for chronic dialysis or renal transplant.

[c]Doubling of serum creatinine compared with baseline, confirmed with a second measurement at least 3 weeks later.

[d]Renal worsening is defined by increased proteinuria (a reproducible increase in urine protein-creatinine ratio to > 1 g if the baseline value was < 0.2 g, to > 2 g if the baseline value was between 0.2 g and 1 g, or more than twice the value at baseline if the baseline value was > 1 g) or impaired renal function (a reproducible decrease in glomerular filtration rate of > 20%, accompanied by proteinuria [> 1] and/or cellular [red blood cell and/or white blood cell] casts).

[e]Based on adjudication of treatment failures.

Source: Clinical Study Report for BLISS-LN.[13]

Reduction in Chronic Kidney Disease Staging

This outcome was not reported in the BLISS-LN trial.

Disease Activity

Systemic Lupus Erythematosus Disease Activity Index 2000 With Modified Scoring for Proteinuria

As shown in Table 15, the LS mean change from baseline in SLEDAI-S2K at week 104 was −7.7 (SE = 0.46) in the belimumab group and −6.1 (SE = 0.47) in the placebo group, with an LS mean difference of −1.5 (95% CI, −2.4 to −0.6). The proportion of patients with a SLEDAI-S2K score less than 4 at week 104 was higher in the belimumab group compared with the placebo group (27.8% versus 18.4%), with an OR of 1.76 (95% CI, 1.11 to 2.78).

Table 15: Summary of Other Secondary Response Variables in the BLISS-LN Trial (mITT)

Characteristic	Placebo group N = 223	Belimumab group N = 223
SLEDAI-S2K		
Patients at baseline, N (%)	222 (99.6)	223 (100)
SLEDAI-S2K score at baseline, mean (SD)	12.1 (4.82)	12.3 (5.33)
Patients at week 104, N (%)	128 (57.4)	138 (61.9)
SLEDAI-S2K score change from baseline to week 104,[a] LS mean (SE)	−6.1 (0.47)	−7.7 (0.46)
LS mean difference vs. placebo (95% CI)[a]	−1.5 (−2.4 to −0.6)	
P value[a]	0.0009[b]	
SLEDAI-S2K score < 4 at week 104		
Patients at baseline, N (%)	223 (100)	223 (100)
Response, n (%)	41 (18.4)	62 (27.8)
OR (95% CI)[c]	1.76 (1.11 to 2.78)	
P value[c]	0.0164[b]	
SDI		
Patients at baseline, N (%)	223 (100)	222 (99.6)
SDI score at baseline, mean (SD)	0.4 (0.82)	0.4 (1.11)
Patients at week 104, N (%)	129 (57.8)	138 (61.9)
SDI score at week 104, mean (SD)	0.1 (0.27)	0.1 (0.29)
P value[d]	0.8825[b]	
uPCR		
Patients at baseline, N (%)	223 (100)	223 (100)
uPCR (g/g) at baseline, mean (SD)	3.53 (3.56)	3.20 (2.75)
Patients at week 104, N (%)	128 (57.4)	138 (61.9)
uPCR (g/g) absolute change from baseline to week 104, mean (SD)	−2.43 (2.65)	−2.33 (2.88)

Characteristic	Placebo group N = 223	Belimumab group N = 223
P value[e]	0.1750[b]	
uPCR percent change from baseline to week 104, mean (SD)	−62.36 (49.43)	−70.66 (43.98)
P value[e]	0.0244[b]	
GFR from creatinine adjusted for BSA, safety population		
Patients at baseline, N (%)	224 (100)	224 (100)
GFR at baseline (mL/min/1.73 m^2), mean (SD)	101.0 (42.61)	100.2 (37.68)
Patients at week 104, N (%)	130 (58.0)	140 (62.5)
GFR at week 104 (mL/min/1.73 m^2), mean (SD)	100.8 (29.18)	111.3 (35.75)
P value	NR	
Prednisone use[f]		
Patients at baseline, N (%)	223 (100)	223 (100)
Average daily prednisone dose at baseline (mg/day), mean (SD)	72.52 (133.16)	66.50 (99.59)
Patients at week 104, N (%)	223 (100)	223 (100)
Patients with average daily prednisone dose of ≤ 5 mg since the previous visit at week 104, n (%)[f]	62 (27.8)	82 (36.8)
OR (95% CI) vs. placebo[g]	1.51 (1.01 to 2.27)	
P value[g]	0.0444[b]	
Patients with average daily prednisone dose of ≤ 7.5 mg since the previous visit at week 104, n (%)[f]	66 (29.6)	91 (40.8)
OR (95% CI) vs. placebo[g]	1.65 (1.11 to 2.45)	
P value[g]	0.0139[b]	
Severe SFI flares[h]		
Patients at baseline, N (%)	223 (100)	223 (100)
Patients with a severe flare, N (%)[i]	70 (31.4)	42 (18.8)
Days to event, median (range)	263 (176 to 391)	204 (169 to 452)
HR (95% CI)[i]	0.57 (0.39 to 0.84)	
P value [j]	0.0042[b]	

ANCOVA = analysis of covariance; BSA = body surface area; CI = confidence interval; GFR = glomerular filtration rate; HR = hazard ratio; LS = least squares; mITT = modified intention to treat; NR = not reported; OR = odds ratio; SD = standard deviation; SDI = Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SE = standard error; SFI = SELENA SLEDAI Flare Index; SLEDAI-S2K = Systemic Lupus Erythematosus Disease Activity Index 2000 with modified scoring for proteinuria; uPCR = urine protein-creatinine ratio.

[a]Week 104 statistics are from an ANCOVA model comparing belimumab and placebo, with covariates for treatment group, baseline SLEDAI-S2K score, induction regimen (cyclophosphamide vs. mycophenolate mofetil), and race (Black vs. non-Black).

[b]P value has not been adjusted for multiple testing (i.e., the type I error rate has not been controlled).

[c]OR (95% CI) and P value are from a logistic regression model for comparison between belimumab and placebo, with covariates treatment group, baseline SLEDAI-S2K score, induction regimen (cyclophosphamide vs. mycophenolate mofetil), and race (Black vs. non-Black).

[d]Week 104 P value is from a rank ANCOVA model comparing belimumab and placebo, with covariates for treatment group, baseline SDI score, induction regimen (cyclophosphamide vs. mycophenolate mofetil), and race (Black vs. non-Black).

[e]P value is from a rank ANCOVA model comparing belimumab and placebo, with covariates for treatment group, baseline uPCR value, induction regimen (cyclophosphamide vs. mycophenolate mofetil), and race (Black vs. non-Black).

[f]Steroids were converted to prednisone equivalent. The prednisone average daily dose since previous visit was calculated at every 4-week visit after baseline. All prednisone doses since the visit 4 weeks prior, up to and including the current visit, were summed and divided by the number of days in the period. Days where a patient did not have a prednisone dose recorded were considered as 0 mg for the day in the calculation for average daily prednisone dose.

[g]OR (95% CI) and P value are from a logistic regression model for comparison between belimumab and placebo, with covariates treatment group, baseline prednisone dose, induction regimen (cyclophosphamide vs. mycophenolate mofetil), and race (Black vs. non-Black).

[h]Analysis excludes severe flares triggered only by an increase in SELENA SLEDAI score to > 12. Treatment failure is considered an event. Patients who discontinue randomized treatment, withdraw from study, are lost to follow-up, die, or complete week 104 are censored at the last flare assessment date, the death date, or the week 104 study visit. Time to first severe flare is defined as (event date – treatment start date + 1).

[i]Only includes postbaseline severe flares.

[j]From Cox proportional hazards model for the comparison between belimumab and placebo adjusting for induction regimen (cyclophosphamide vs. mycophenolate mofetil) and race (Black vs. non-Black).

Source: Clinical Study Report for BLISS-LN.[13]

Organ Damage

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

In the pivotal trial, a similar proportion of patients in the belimumab group (n = 138) and the placebo group (n = 129) experienced SDI worsening (change > 0) at week 104 compared with baseline (7.8% versus 6.5%), with an OR of 0.85 (95% CI, 0.33 to 2.18) (Table 15).

Disease Flare Frequency and Severity

SELENA SLEDAI Flare Index As shown in Table 15, in the BLISS-LN trial, the percentage of patients who experienced a severe SFI flare postbaseline through to week 104 was 18.8% in the belimumab group and 31.4% in the placebo group. The risk of experiencing a severe flare at any time, based on the SFI, was lower in patients in the belimumab group than in the placebo group, with an HR of 0.57 (95% CI, 0.39 to 0.84). Of the patients experiencing a severe flare, the median study day to first severe flare was 204 for the belimumab group and 262.5 for the placebo group.

Health-Related Quality of Life

This outcome was not reported in the BLISS-LN trial.

Reduction in Symptoms

This outcome was not reported in the BLISS-LN trial.

Serological Outcomes

Decrease in Anti-dsDNA Antibodies

As shown in Table 16, in the BLISS-LN trial, the mean change in anti-dsDNA antibody levels from baseline to week 104 was greater for the belimumab group than the placebo group, with an LS mean change from baseline of −188.6 IU/mL (SD = 629.3 IU/mL) in the belimumab group and −30.6 IU/mL (SD = 682.0 IU/mL) in the placebo group. Among the patients who were anti-dsDNA antibody positive (≥ 30 IU/mL) at baseline (n = 38 belimumab; n = 14 placebo), a greater proportion of patients in the belimumab group shifted to negative (< 30 IU/L) at week 104 than in the placebo group (35.5% versus 14.4%).

Table 16: Summary of Serological Outcomes of Interest in BLISS-LN (mITT)

Characteristic	Placebo N = 223	Belimumab 10 mg/kg N = 223
Anti-dsDNA antibody		
Patients at baseline, N (%)	169 (75.8)	173 (77.6)
Value at baseline (IU/mL), mean (SD)	284.5 (794.4)	266.3 (623.3)
Patients at week 104, N (%)	129 (57.8)	142 (63.7)
Change from baseline value to week 104 (IU/mL), LS mean (SD)	−30.6 (682.0)	−188.6 (629.3)
P value[a]	< 0.0001[b]	
Patients anti-dsDNA positive at baseline,[c] N (%)	97 (43.5)	107 (48.0)
Positive at baseline to negative anti-dsDNA (< 30 IU/mL) at week 104,[c] N (%)	14 (14.4)	38 (35.5)
Complement C3		
Patients at baseline, N (%)	223 (100)	223 (100)
Value at baseline (mg/dL), mean (SD)	84.4 (29.6)	81.4 (27.3)
Patients at week 104, N (%)	129 (57.8)	142 (63.7)
Change from baseline value to week 104 (mg/dL), LS mean (SE)[a]	11.1 (3.1)	17.2 (3.0)
LS mean difference vs. placebo (mg/dL) (95% CI)[a]	6.1 (0.2 to 12.0)	
P value[a]	0.0415[b]	
Patients with low C3 at baseline,[d] N (%)	69 (30.9)	82 (36.8)
Low C3 at baseline to normal or high C3 at week 104,[c] N (%)	32 (46.4)	48 (58.5)
Complement C4		
Patients at baseline, N (%)	223 (100)	223 (100)
Value at baseline (mg/dL), mean (SD)	16.1 (9.1)	15.7 (8.6)
Patients at week 104, N (%)	129 (57.8)	142 (63.7)
Change from baseline value to week 104 (mg/dL), LS mean (SE)[a]	1.3 (0.9)	4.3 (0.9)
LS mean difference vs. placebo (mg/dL) (95% CI)[a]	3.0 (1.3 to 4.7)	
P value[a]	0.0006[b]	
Patients with low C4 at baseline,[d] N (%)	34 (15.2)	42 (18.8)
Low C4 at baseline to normal or high C4 at week 104,[c] N (%)	21 (61.8)	34 (81.0)

anti-dsDNA = anti–double-stranded DNA; CI = confidence interval; LS = least squares; mITT = modified intention to treat; SD = standard deviation; SE = standard error.

[a]Only on-treatment data are displayed. Week 104 statistics are from an analysis of covariance model comparing belimumab and placebo, with covariates for treatment group, baseline complement value, induction regimen (cyclophosphamide vs. mycophenolate mofetil), and race (Black vs. non-Black).

[b]P value has not been adjusted for multiple testing (i.e., the type I error rate has not been controlled).

[c]Anti-dsDNA positive (≥ 30 IU/mL); anti-dsDNA negative (< 30 IU/mL).

[d]Baseline status is defined as low (C3 < 90 mg/dL; C4 < 10 mg/dL) or normal or high (C3 ≥ 90 mg/dL; C4 ≥ 10 mg/dL).

Source: Clinical Study Report for BLISS-LN.[13]

Increase in Complement C3 and C4 Levels

As shown in Table 16, for both complement C3 and C4, the mean change from baseline to week 104 was greater for the belimumab group than the placebo group, with an LS mean difference of 6.1 (95% CI, 0.2 to 12.0) in complement C3 and 3.0 (95% CI, 1.3 to 4.7) in complement C4. Among patients with low C3 at baseline (n = 82 belimumab; n = 69 placebo), the percentage of patients who shifted to normal or high at week 104 was 58.5% in the belimumab group and 46.4% in the placebo group. Among patients with a low C4 at baseline (n = 42 belimumab; n = 34 placebo), the percentage of patients who shifted to normal or high at week 104 was 81.0% in the belimumab group and 61.8% in the placebo group.

Harms

Only those harms identified in the review protocol are reported below. Refer to Table 17 for detailed harms data.

Table 17: Summary of Harms (Safety Population) in the BLISS-LN Trial

Harms	Placebo group (N = 224)	Belimumab group (N = 224)
Patients with ≥ 1 adverse event		
Any adverse event, n (%)	211 (94.2)	214 (95.5)
Most common events,[a] n (%)		
Upper respiratory tract infection	70 (31.3)	72 (32.1)
Diarrhea	45 (20.1)	42 (18.8)
UTI	35 (15.6)	43 (19.2)
Headache	35 (15.6)	30 (13.4)
Nasopharyngitis	29 (12.9)	31 (13.8)
Arthralgia	33 (14.7)	23 (10.3)
Cough	19 (8.5)	28 (12.5)
Nausea	24 (10.7)	22 (9.8)
Gastroenteritis	25 (11.2)	17 (7.6)
Hypokalemia	20 (8.9)	22 (9.8)
Herpes zoster	19 (8.5)	19 (8.5)
Rash	17 (7.6)	20 (8.9)
Anemia	23 (10.3)	12 (5.4)
Leukopenia	19 (8.5)	16 (7.1)
Bronchitis	17 (7.6)	16 (7.1)
Vomiting	16 (7.1)	16 (7.1)
Back pain	16 (7.1)	15 (6.7)
Dizziness	18 (8.0)	13 (5.8)
Pyrexia	17 (7.6)	11 (4.9)

Harms	Placebo group (N = 224)	Belimumab group (N = 224)
Hypertension	14 (6.3)	13 (5.8)
Muscle spasms	12 (5.4)	15 (6.7)
Fatigue	15 (6.7)	11 (4.9)
Edema peripheral	12 (5.4)	13 (5.8)
Abdominal pain	13 (5.8)	11 (4.9)
Pneumonia	13 (5.8)	11 (4.9)
Insomnia	13 (5.8)	10 (4.5)
Dyspepsia	14 (6.3)	8 (3.6)
Abdominal pain upper	6 (2.7)	14 (6.3)
Acne	8 (3.6)	12 (5.4)
Edema	12 (5.4)	8 (3.6)
Pain in extremity	8 (3.6)	12 (5.4)
Systemic lupus erythematosus	12 (5.4)	2 (0.9)
Patients with ≥ 1 SAE		
Any SAE, n (%)	67 (29.9)	58 (25.9)
Most common SAEs,[b] n (%)		
Pneumonia	7 (3.1)	9 (4.0)
Herpes zoster	2 (0.9)	4 (1.8)
Gastroenteritis	5 (2.2)	0
Lung infection	3 (1.3)	2 (0.9)
Lupus nephritis	4 (1.8)	1 (0.4)
UTI	2 (0.9)	3 (1.3)
Anemia	3 (1.3)	1 (0.4)
Acute kidney injury	2 (0.9)	1 (0.4)
Arthralgia	2 (0.9)	1 (0.4)
Febrile neutropenia	0	3 (1.3)
Gastritis	2 (0.9)	1 (0.4)
Noncardiac chest pain	2 (0.9)	1 (0.4)
Pleural effusion	2 (0.9)	1 (0.4)
Systemic lupus erythematosus	3 (1.3)	0
Vomiting	2 (0.9)	1 (0.4)
Cellulitis	2 (0.9)	0
Flank pain	2 (0.9)	0
Hypertension	0	2 (0.9)

Harms	Placebo group (N = 224)	Belimumab group (N = 224)
Pancytopenia	0	2 (0.9)
Skin laceration	0	2 (0.9)
Subcutaneous abscess	0	2 (0.9)
Upper respiratory tract infection	2 (0.9)	0
Patients who stopped treatment due to adverse events		
Any, n (%)	29 (12.9)	29 (12.9)
Most common events,[b] n (%)		
Lupus nephritis	3 (1.3)	4 (1.8)
Pneumonia	1 (0.4)	5 (2.2)
Blood immunoglobulin G decrease	1 (0.4)	2 (0.9)
Hypertension	0	2 (0.9)
Pulmonary tuberculosis	0	2 (0.9)
Systemic lupus erythematosus	2 (0.9)	0
Deaths[c]		
Total, n (%)	5 (2.2)	6 (2.7)
On-treatment fatal SAE,[d] n (%)	3 (1.3)	4 (1.8)
Pneumonia	1 (0.4)	3 (1.3)
Sepsis	1 (0.4)	0
Dyspnea (hypertension)	0	1 (0.4)
Encephalopathy	1 (0.4)	0
Posttreatment fatal SAE,[e] n (%)	2 (0.9)	2 (0.9)
Hemorrhage intracranial	1 (0.4)	0
Seizure	1 (0.4)	0
Septic shock	0	1 (0.4)
Cardiac failure	0	1 (0.4)
Notable harms		
Any postinfusion-related systemic reactions, n (%)	29 (12.9)	26 (11.6)
Serious acute postinfusion systemic reactions or hypersensitivity	0	1 (0.4)
Serious infections, n (%)		
Herpes zoster	2 (0.9)	5 (2.2)
Active tuberculosis	1 (0.4)	2 (0.9)
Sepsis	1 (0.4)	0
Malignancies (including NMSC), n (%)	0	3 (1.3)
Basal cell carcinoma	0	1 (0.4)

Harms	Placebo group (N = 224)	Belimumab group (N = 224)
Papillary thyroid cancer	0	1 (0.4)
Thymoma	0	1 (0.4)
Serious suicidal behaviour, n (%)	0	1 (0.4)

NMSC = nonmelanoma skin cancer; SAE = serious adverse event; UTI = urinary tract infection.

[a]Frequency > 5%.

[b]Frequency ≥ 2 patients.

[c]Includes all deaths that occurred during the double-blind phase, including off treatment.

[d]Developed fatal SAEs while on study treatment; death may have occurred anytime thereafter.

[e]Fatal SAEs occurred after the on-treatment period.

Source: Clinical Study Report for BLISS-LN.[13]

Adverse Events

The proportion of patients experiencing at least 1 AE in the BLISS-LN trial was similar between the belimumab group (95.5%) and the placebo group (94.2%). The most common AEs were upper respiratory tract infection (32.1% belimumab versus 31.3% placebo), diarrhea (18.8% versus 20.1%), UTI (19.2% versus 15.6%), headache (13.4% versus 15.6%), nasopharyngitis (13.8% versus 12.9%), and arthralgia (10.3% versus 14.7%).

Frequent AEs that occurred more commonly in the belimumab group than in the placebo group were UTI (19.2% versus 15.6%), cough (12.5% versus 8.5%), and upper abdominal pain (6.3% versus 2.7%).

Serious AEs

The proportion of patients experiencing at least 1 SAE was similar between treatment groups (25.9% belimumab versus 29.9% placebo). The most common SAEs were pneumonia (4.0% versus 3.1%), herpes zoster (1.8% versus 0.9%), gastroenteritis (0% versus 2.2%), lung infection (0.9% versus 1.3%), LN (0.4% versus 1.8%), and UTI (1.3% versus 0.9%).

IP Discontinuations Due to AEs

There was a similar proportion of IP discontinuation due to AEs in the belimumab group and the placebo group (12.9% versus 12.9%), with the most common reason for withdrawal for both groups being pneumonia (2.2% versus 0.4%) and lupus nephritis (1.8% versus 1.3%),

Mortality

Eleven deaths occurred during the double-blind phase of the BLISS-LN trial, mainly due to infections, with 6 deaths (2.7% of patients) in the belimumab group and 5 deaths (2.2% of patients) in the placebo group (Table 17). In 7 patients (4 belimumab; 3 placebo), the deaths occurred while on study treatment, 5 of which were deemed related to the IP by the investigator. In the remaining 4 patients (2 belimumab; 2 placebo), the deaths occurred posttreatment,1 of which was deemed related to the IP.

Notable Harms

Common notable harms (as outlined in the CADTH protocol) included postinfusion-related systemic reactions (11.6% belimumab versus 12.9% placebo); serious infections of herpes zoster (2.2% versus 0.9%),

active tuberculosis (0.9% versus 0.4%), and sepsis (0% versus 0.4%); malignancies (including nonmelanoma skin cancer) (1.3% versus 0%); and serious suicidal behaviour (0.4% versus 0%).

Critical Appraisal

Internal Validity

In the BLISS-LN trial, patients were allocated to treatment groups with randomization stratified by relevant prognostic factors of patient induction and maintenance regimen (high-dose corticosteroids plus cyclophosphamide followed by azathioprine versus high-dose corticosteroids plus mycophenolate mofetil followed by mycophenolate mofetil) and race (Black versus non-Black) to reduce the risk of confounding. The primary and key secondary end points were controlled for multiplicity, but all other end points — as well as all post hoc analyses — were not. As a result, outcomes assessed other than the primary and key secondary end points may be at risk of a type I error and should be viewed as supportive evidence for the overall effects of belimumab. The primary outcome for BLISS-LN was PERR at week 104, which was changed after initiating patient recruitment from the original primary end point of ORR (complete, partial, no response) at week 104, where renal response was determined by changes in urinary sediment, proteinuria, and renal function. The changes to the primary end point were made before unblinding of the study results; therefore, the risk of operational bias is low. An mITT population was used that included all patients who received at least 1 dose of the IP. Given that the vast majority of patients were included in the mITT population (99.6%), this analysis population would be unlikely to introduce bias into the study.

Overall, baseline demographics (e.g., sex, race, age, and gender) and disease characteristics (e.g., mean eGFR and uPCR) were generally similar and balanced between groups in the BLISS-LN trial. There was, however, a greater percentage of patients in the belimumab group than in the placebo group taking antimalarials (74.4% versus 69.1%) and steroids (96.9% versus 94.2%) at baseline. The belimumab group had a slightly lower mean dosage of prednisone than the placebo group (mean = 66.5 mg/day [SD = 99.6 mg/day] mg/day versus mean = 72.5 mg/day [SD = 133.2 mg/day]). The clinical expert consulted for this review stated that these differences were minimal and not likely to bias results. Overall, it is unclear how this may have affected the results as the differences may have underestimated or overestimated the effects of belimumab relative to placebo.

The BLISS-LN trial reported power calculations for the primary end point and detected a statistically significant difference between the belimumab group and the placebo group for the primary outcome and key secondary outcomes, while adhering to their statistical testing hierarchy for the multiplicity adjustment. The primary efficacy outcome was a composite outcome, which was considered to be appropriate and clinically relevant by the clinical expert consulted. Other outcomes of interest to this review (e.g., increase or stabilization of eGFR and change in SLEDAI-S2K scores from baseline) were not controlled for multiplicity. Moreover, analyses for time to 30% and 40% decline in eGFR from baseline and sustained 30% and 40% decline in eGFR were conducted post hoc. Furthermore, as discussed in Appendix 4, the SLEDAI-S2K, as it uses a single weighted score to summarize disease activity, on the one hand standardizes the judgment of disease activities, while on the other it could mask the underlying importance of organ systems that are contributing to the total score (i.e., the same score could represent multiple mild disease in many organs or

severe disease in a single organ, or an unchanged score may occur despite worsening in 1 organ system if there is also improvement in another system).

A relatively high percentage of patients withdrew from the BLISS-LN study in each of the belimumab (16.6%) and placebo (24.2%) groups, with the primary reasons for study discontinuation being withdrawal of consent, AE, and investigator discretion. A slightly higher proportion of patients in the placebo group than in the belimumab group discontinued due to withdrawal of consent (11.7% versus 8.5%) and due to investigator discretion (4.9% versus 2.2%). Patients who discontinued the study were classified as no response, and when more patients discontinued in the placebo group, this may have biased the results in favour of belimumab as these patients were considered no response whether they were responding at the time of discontinuation or not. However, sensitivity and tipping point analyses performed by the sponsor, which examined the extent to which results were affected by response assumptions for intercurrent events, were generally supportive of the findings of the primary analyses.

Patient HRQoL was identified as an important outcome by the patient groups providing input for this review, specifically symptoms such reduction in fatigue, flares, pain, rash, and skin irritations. However, HRQoL was not assessed in the BLISS-LN trial; hence, it is unknown what impact belimumab would have on HRQoL.

Regarding calculations of patients' average daily prednisone dose in the BLISS-LN trial, days where a patient did not have a prednisone dose recorded were considered as 0 mg for the day in the calculation. This assumption may have led to lower estimates of average prednisone doses in both the belimumab and placebo groups. It is unclear in which direction this may have biased results as the number of missing doses in each treatment group is unknown.

For the subgroups identified as important to this review (i.e., baseline renal biopsy class and induction regimen), the analyses were exploratory; the study was not designed or powered to evaluate efficacy in subgroups, and results were limited by the small number of patients in these subgroups. With these limitations in mind, overall subgroup analyses should be viewed as supportive evidence for the overall effects of belimumab.

External Validity

Although there was only 1 site in Canada in the BLISS-LN trial, the clinical expert consulted by CADTH agreed that the baseline patient characteristics in regard to age, gender, race, and disease activity in the BLISS-LN trial were reflective of patients they see in Canadian clinical practice for the present indication. At baseline, a greater proportion of patients were assigned to mycophenolate mofetil induction therapy (73.5%) than to cyclophosphamide as per the investigator's choice. The clinical expert consulted for this review stated that this is reflective of Canadian clinical practice and many patients with LN may be considering pregnancy and cyclophosphamide is associated with premature ovarian failure and infertility. Overall, the clinical expert consulted felt the characteristics of the patient population enrolled in the trials were a good representation of the target population and did not identify any issues with the use of concurrent treatments or conduct of the trials that could substantially affect the generalizability of the findings.

The product monograph for belimumab authorized both IV and subcutaneous formulations for LN. However, this recommendation was based on extrapolated data, and there is no clinical evidence regarding the subcutaneous formulation for patients with active LN.

The BLISS-LN trial did not include rituximab as a comparator; therefore, the efficacy and harms of belimumab in addition to standard of care compared to the addition of rituximab to standard of care in the treatment of LN is unknown. However, rituximab is used as a salvage therapy for refractory cases of LN, therefore it may not be appropriate to include it as a comparator in addition to standard of care.

Indirect Evidence

Objectives and Methods for the Summary of Indirect Evidence

No direct comparative data for the use of belimumab in the adult LN population were identified in the systematic review; thus, a search for indirect evidence was conducted.

A focused literature search for indirect treatment comparisons (ITCs) dealing with LN was run in MEDLINE All (1946–) on August 4, 2022. No limits were applied to the search. The search results were screened by 1 researcher to identify ITCs that met the patient, intervention, comparator, and outcome criteria in the review protocol (Table 5). No ITC was submitted by the sponsor; however, the indirect comparison feasibility assessment included in the sponsor's submission was reviewed.

No relevant ITCs were found in the literature search. CADTH's review of the sponsor's feasibility assessment is provided subsequently.

Appraisal of the Feasibility Assessment

The sponsor conducted a feasibility assessment to determine if the clinical trials for belimumab and rituximab in patients with LN were sufficiently similar to permit valid comparison in an ITC. Four studies were evaluated: the BLISS-LN[13] trial (belimumab plus mycophenolate mofetil or cyclophosphamide versus mycophenolate mofetil or cyclophosphamide), an open-label pilot study by Li et al. (2009)[35] (rituximab versus rituximab plus cyclophosphamide), the LUNAR trial[18] (rituximab plus mycophenolate mofetil versus mycophenolate mofetil), and a study by Zhang et al. (2015)[36] (rituximab plus cyclophosphamide versus cyclophosphamide).

The authors of the feasibility assessment determined that it was possible to construct 2 stratified evidence networks, which essentially splits BLISS-LN into 2 studies to conduct separate network meta-analyses for cyclophosphamide and for mycophenolate mofetil while preserving randomization. However, the feasibility assessment identified several important differences in baseline characteristics and potential effect modifiers — including dosing regimens, gender, ethnicity, geography, duration of LN, mean complement C3, mean complement C4, and LN class — between studies and concluded it was not possible to generate robust estimates of the comparative treatment effects due to between-study heterogeneity.

Based on the information presented in the sponsor's feasibility assessment, the CADTH reviewer agrees that the heterogeneity between the studies is significant; thus, any ITC is unlikely to produce robust estimates of comparative efficacy or safety. There were differences in enrolment criteria related to baseline renal biopsy

class as Zhang et al. only enrolled patients with severe refractory LN. The mean age was generally consistent across studies: between 29 years and 40 years. However, sex and racial distributions were not consistent across trials. The mycophenolate mofetil doses were consistent across trials. However, cyclophosphamide doses varied between 500 mg and 800 mg across trials, and cyclophosphamide dosing regimens varied. In Zhang et al., the cyclophosphamide dosing regimen was 800 mg at weeks 1 and 3 in the treatment group and 800 mg monthly for 48 weeks in the comparator group, as opposed to 500 mg biweekly for 12 weeks total in both treatment groups in the BLISS-LN trial. Furthermore, trials had inconsistent definitions for the end point of CRR as only the BLISS-LN trial used eGFR in its criteria for CRR, while only the LUNAR trial incorporated serum creatinine levels, and only the Zhang et al. trial included serum albumin levels in its criteria. Other key end points such as uPCR, eGFR, and harms-related data were not reported in the Zhang et al. study,[36] which would disconnect the cyclophosphamide network, preventing the conduct of network meta-analysis. Furthermore, the sample size of the study population in Li et al.[37] (n = 16) was limited and unlikely to be a representative population of patients with LN, which may limit the ability to use methods such as unanchored matching-adjusted indirect comparison with Zhang et al.

Other Relevant Evidence

This section includes submitted long-term extension studies and additional relevant studies included in the sponsor's submission to CADTH that were considered to address important gaps in the evidence included in the systematic review.

Long-Term Extension Studies

Description of Study

The OLE phase of the BLISS-LN trial was a 28-week study that took place between February 2015 and March 2000. During the extension phase, all eligible patients received 10 mg/kg IV belimumab plus standard of care every 28 days, continued until week 24. A final evaluation was done at week 28, 4 weeks after receiving the last dose. Patients receiving belimumab or placebo through week 100 and completing all assessments of week 104 of the double-blind phase were considered eligible for participation in the extension study. Patients received the first dose at week 104 of the double-blind phase (marked as day 0 for the OLE phase) after completing all assessments of week 104. There were 2 groups in the extension phase: the placebo-to-belimumab group (patients switching from placebo to belimumab) (n = 122) and the belimumab-to-belimumab group (patients remaining on belimumab) (n = 132). Prohibited medications applicable during the double-blind phase (e.g., immunosuppressants and corticosteroids) were not applicable in the OLE phase (exceptions were live vaccines, biologics, and other investigational drugs).

Populations

Baseline characteristics showed a similar trend in both the placebo-to-belimumab and belimumab-to-belimumab groups. The characteristics were also similar to the baseline patient characteristics during the double-blind phase. The mean (SD) age of patients in the open-label phase was 36 (10) years in both the placebo-to-belimumab and belimumab-to-belimumab groups. Patients were predominantly female (90% and 89%) and predominantly Asian (55% and 54%) in the placebo-to-belimumab and belimumab-to-belimumab

groups, respectively. Moreover, 82% and 86% of patients in the placebo-to-belimumab and belimumab-to-belimumab groups, respectively, had LN class III or IV (with or without class V).

At OLE baseline, patients in the belimumab-to-belimumab group compared with the placebo-to-belimumab group had lower median uPCR values (0.3 g/g versus 0.4 g/g), a higher proportion of patients with SLEDAI-S2K scores less than 8 (n = 103 [78%] versus n = 84 [69%]), a lower average daily prednisone-equivalent dose (median = 5.0 mg/day versus median = 7.5 mg/day), a lower proportion of patients with positive biomarkers (anti-dsDNA: n = 64 [49%] versus n = 85 [70%]; anti-C1q: n = 60 [55%] versus n = 60 [68%]), and fewer patients with low C3 or C4 levels (C3: n = 37 [28%] versus n = 45 [37%]; C4: n = 12 [9%] versus n = 18 [15%]).

Statistical Analysis

For the open-label phase of the BLISS-LN study, no hypothesis testing of treatment differences was conducted. The last available value before the first dose of treatment on day 0 was defined as the open-label baseline value. Descriptive statistics were used to summarize safety and efficacy end points, assessed only for the duration of the open-label phase, unless otherwise specified. Analyses on end points were conducted based on observed data with no imputation for withdrawal. All enrolled patients receiving 1 or more doses of open-label belimumab treatment were defined as the open-label safety population. While safety end points for the open-label phase were assessed in the safety population, 1 patient was excluded from efficacy analysis for issues related to good clinical practice nonadherence. The efficacy population was defined as the mITT population for the open-label phase. For the post hoc analyses of PERR and CRR using the double-blind criteria, withdrawal from the trial, treatment failure, and discontinuation of study treatment were imputed as nonresponse.

Patient Disposition

A total of 257 of 448 patients (57.4%) from the double-blind phase enrolled in the open-label phase. Of these, 255 were included in the safety population and 254 in the open-label mITT population, receiving 1 or more doses of 10 mg/kg IV belimumab. In total, 122 and 132 patients were placed in the placebo-to-belimumab group and the belimumab-to-belimumab group, respectively. Of these 254 patients, 9 withdrew from the study, leaving 245 (96.5%) completing the open-label phase through week 28. Among the patients who withdrew, more than half did so due to AEs (55.6%), following withdrawal of consent (22.2%), protocol deviation (11.1%), and loss to follow-up (11.1%).

Exposure to Study Treatments

The median (range) duration of exposure to belimumab 10 mg/kg during the OLE study was 196 (56 to 214) days in the belimumab-to-belimumab group and 196 (85 to 207) days in the placebo-to-belimumab group (following approximately 2 years of blinded exposure to belimumab).

Efficacy

The efficacy end points (assessed as secondary end points after safety assessments) for the OLE study were to evaluate the proportions of patients with PERR and the proportions of patients with CRR at week 28. During the open-label phase, PERR was defined as follows: uPCR less than or equal to 0.7, eGFR no more than 20% below the open-label baseline eGFR or greater than or equal to 60 mL/min/1.73 m^2, and no

prohibited medications. CRR was defined as follows: uPCR less than 0.5, eGFR no more than 10% below the open-label baseline eGFR or greater than or equal to 90 mL/min/1.73 m^2, and no prohibited medications. PERR and CRR were evaluated based on observed data at open-label weeks 12, 24, and 28, and criteria were required to be met at a single time point only, meaning criteria did not have to be met on consecutive visits as was required for the double-blind phase.

The post hoc analyses of PERR and CRR at open-label week 28 were performed according to the double-blind phase criteria to assess the maintenance of response over time; in other words, the eGFR component was relative to the pre-flare value, and the PERR and CRR criteria were required to be met on 2 consecutive visits (at week 100 and week 104 in the double-blind phase and at week 24 and week 28 in the open-label phase).

Using the OLE criteria, the number of patients with PERR and CRR increased from baseline to week 28 in both groups (PERR: 93 [71%] to 91 [75%] in the belimumab-to-belimumab group and 73 [60%] to 79 [67%] in the placebo-to-belimumab group; CRR: 63 [48%] to 76 [62%] in the belimumab-to-belimumab group and 44 [36%] to 57 [48%] in the placebo-to-belimumab group). In the post hoc analyses, the number of patients in the belimumab-to-belimumab group with double-blind criteria of PERR and CRR at baseline was 87 (66%) and 60 (46%), respectively, and 69 (52%) and 54 (41%), respectively, at week 28, showing a reduction from the baseline. In the placebo-to-belimumab group, the number of patients with double-blind criteria of PERR and CRR at baseline was 66 (54%) and 41 (34%), respectively; the number of patients was maintained through to week 28, with 64 (53%) and 43 (35%) achieving PERR and CRR, respectively.

In addition to PERR and CRR, other efficacy end points assessed during the open-label phase were proportions of patients with a uPCR less than 0.5 g/g from double-blind week 4 through open-label week 28 by visit; mean eGFR levels from double-blind baseline to open-label week 28 by visit; proportions of patients with SLEDAI-S2K score less than 4 at open-label week 28; proportions of patients with average daily prednisone-equivalent dose less than or equal to 5 mg, less than or equal to 7.5 mg, or less than or equal to 10 mg at open-label week 28; time to a sustained PERR and CRR from double-blind baseline through to open-label week 28 (using double-blind phase criteria; post hoc analyses); proportion of patients with a doubling of serum creatinine (compared with open-label baseline) and/or progression to kidney failure (defined as the need for chronic dialysis or renal transplant); and percentage changes from open-label baseline in biomarker levels (anti-dsDNA, complement C3 andC4) to open-label week 28 among patients who were anti-dsDNA positive and or had low C3 or C4 at open-label baseline.

In terms of efficacy end points, the median uPCR values remained stable both in the belimumab-to-belimumab group, from 0.3 g/g (interquartile range [IQR], 0.1 to 0.7 g/g) at OLE baseline to 0.2 g/g (IQR, 0.1 to 0.5 g/g) at week 28, and in the placebo-to-belimumab group, from 0.4 g/g (0.1 to 1.0 g/g) at OLE baseline to 0.4 g/g (0.1 to 0.9 g/g) at week 28. The number of patients with a uPCR less than 0.5 g/g increased in the belimumab-to-belimumab group from 89 (67%) at OLE baseline to 91 (75%) at week 28 and remained stable in the placebo-to-belimumab group, from 71 of 122 patients (58%) at OLE baseline to 68 of 118 patients (58%) at week 28. The median (interquartile range) eGFR values remained stable in the belimumab-to-belimumab group, from 108 mL/min/1.73 m^2 (IQR, 88 to 130 mL/min/1.73 m^2) at OLE baseline to 106 mL/min/1.73 m^2 (88 to 127 mL/min/1.73 m^2) at week 28, and remained stable in the placebo-to-belimumab

group, from 105 mL/min/1.73 m^2 (IQR, 84 to 123 mL/min/1.73 m^2) at OLE baseline to 104 mL/min/1.73 m^2 (81 to 124 mL/min/1.73 m^2) at week 28. The number of patients who received an average daily prednisone dose of less than or equal to 7.5 mg remained stable in the belimumab-to-belimumab group, from 85 (64%) at OLE baseline to 83 (65%) at week 28 and remained stable in the placebo-to-belimumab group, from 62 (51%) at OLE baseline to 66 (55%) at week 28. There were no marked changes in the proportions of patients with SLEDAI-S2K scores less than 4 in either group, which ranged from 64 of 132 patients (49%) at OLE baseline to 64 of 122 patients (53%) at week 28 for the belimumab-to-belimumab group and from 44 of 122 patients (36%) at OLE baseline to 40 of 120 patients (33%) at week 28 for the placebo-to-belimumab group.

Harms

The primary objective of this OLE study was to evaluate the safety of belimumab for another 28 weeks. The proportion of patients experiencing at least 1 AE in the open-label phase was slightly higher in the belimumab-to-belimumab group (70%) than in the placebo-to-belimumab group (62%). The most common AEs by system organ class occurring in at least 5% of patients in either group included infections and infestations (49% versus 42%), musculoskeletal and connective tissue disorders (12% versus 13%), skin and subcutaneous tissue disorders (13% versus 8%), gastrointestinal disorders (10% versus 9%), and respiratory, thoracic, and mediastinal disorders (11% versus 4%) in the belimumab-to-belimumab and placebo-to-belimumab groups, respectively.

The proportion of patients with at least 1 treatment-related AE during the open-label phase was similar between the groups: 18% and 20% in the belimumab-to-belimumab and placebo-to-belimumab groups, respectively. The proportion of patients experiencing at least 1 SAE during the open-label phase was low (8% in the belimumab-to-belimumab group and 4% in the placebo-to-belimumab group) compared with the double-blind phase (25.9% belimumab versus 29.9% placebo). The proportion of withdrawals due to AEs was also very low in both groups (3% versus 0.8%).

Common notable harms included postinfusion systemic reactions (4% versus 3%) and infections of special interest (opportunistic infections, herpes zoster, tuberculosis, sepsis) (5% versus 2%) in the belimumab-to-belimumab versus placebo-to-belimumab groups, respectively. Two serious infections of special interest were reported in the belimumab-to-belimumab group, 1 for serious tuberculosis and another for serious disseminated herpes zoster. Among the 4 depression events reported in the belimumab-to-belimumab group, 1 case of suicidal behaviour occurred in a patient diagnosed with an adjustment disorder who took an overdose of lorazepam. This patient recovered and completed the treatment throughout the open-label phase. One death occurred during the open-label phase in the placebo-to-belimumab group. The death was reported to be associated with fatal serious AEs of multiple organ dysfunction syndrome, sepsis secondary to nosocomial pneumonia, and chronic kidney disease.

Critical Appraisal

Internal Validity

The baseline characteristics in the open-label patients were similar and balanced between the placebo-to-belimumab and belimumab-to-belimumab groups. Nonobjective end points like harms and SLEDAI-S2K can be biased because of the open-label nature of the trial. Moreover, patients who had required treatment

with prohibited medications due to their disease activity were withdrawn from treatment during the double-blind phase and were not enrolled in the open-label phase, which may have led to selection bias favouring belimumab, as patients who completed the double-blind phase were those who had better tolerance with belimumab or placebo with background immunosuppressants and were more willing to participate in the open-label phase and potentially more likely to respond well to belimumab over time. The same validity, reliability, and responsiveness concerns for the tools used to measure the outcomes described for the randomized phase also apply to the extension period.

Since no hypothesis testing of treatment differences was conducted for the active treatment period, it is not possible to draw causal conclusions based on the descriptive results. The lack of a comparator group also poses risk of confounding. Although between-group differences were observed in uPCR, proportions of patients with SLEDAI-S2K scores less than 8, average prednisone-equivalent doses, and proportions of autoantibody-positive patients and patients with low C3 or C4 levels, favouring the belimumab-to-belimumab group, it is not possible to draw causal conclusions (i.e., changes following the randomized phase cannot be attributed to the treatment with any certainty) without a randomized comparator. The safety results were consistent with those observed during the double-blind randomized phase. Since the OLE phase was a crossover study and not controlled, differences in safety profile between the belimumab-to-belimumab and placebo-to-belimumab groups should be viewed in light of this limitation. Since the treatment failure criterion regarding prohibited medications (e.g., immunosuppressants and corticosteroids) was less restrictive during the open-label phase than during the double-blind phase, these differences made it difficult to evaluate the rates of maintenance of PERR and CRR across the 2 phases of the study. Lastly, the relatively short duration of the open-label phase is not enough to observe appreciable benefit among those who had transitioned from placebo to belimumab.

External Validity

The external validity of the extension phase is equivalent to that reported for the randomized phase. As with the randomized phase, per the clinical expert there are no major concerns for the generalizability of the findings to Canadian clinical practice.

Discussion

Summary of Available Evidence

The systematic review included a double-blind randomized controlled trial that evaluated the efficacy and safety of IV belimumab 10 mg/kg plus standard of care compared to placebo plus standard of care in adult patients with active LN (histological classes III, IV, V, or V in combination with III or IV LN). The primary outcome in the BLISS-LN study was PERR at week 104, a dichotomous end point (response versus no response); "response" was defined by a uPCR less than or equal to 0.7 g/g, an eGFR no more than 20% below pre-flare value or greater than or equal to 60 mL/min/1.73 m^2, and no use of prohibited therapy for treatment failure.

One OLE study was also summarized in this report and provided supplemental safety and efficacy data for patients who received IV belimumab 10 mg/kg plus standard of care for up to 28 weeks (N = 254) among eligible patients who completed the BLISS-LN study. No indirect evidence comparing belimumab to other treatments for LN was submitted by the sponsor, and none was found in the literature.

Interpretation of Results

Efficacy

The clinical expert who consulted on this review suggested that the outcomes used in clinical practice align with those used in the BLISS-LN study, with the most recent KDIGO and EULAR/ERA-EDTA clinical practice guidelines for LN suggesting that a complete response to therapy should aim for proteinuria of less than 0.5 g per 24 hours to less than 0.7 g per 24 hours within 12 months of initiating therapy (but may require an additional 12 months in those with nephrotic range proteinuria) alongside stabilization or improvement in eGFR within 10% to 15% of baseline (i.e., pre-flare).[8,11] The BLISS-LN study met its primary end point of PERR at week 104 as well as key secondary end points including CRR at week 104, PERR at week 52, ORR at week 104, and time to renal-related event or death. About 11% more patients in the belimumab group than in the placebo group achieved the primary outcome of PERR at week 104 and the key secondary outcome of CRR at week 104. Patients who received belimumab had a significantly lower risk of a renal-related event or death than those who received placebo. The clinical expert consulted deemed these primary and key secondary results to be clinically meaningful in favour of belimumab 10 mg/kg in a disease with limited therapeutic options and substantial morbidity and mortality.

The subgroup analyses based on baseline renal biopsy class and induction regimen for the primary and key secondary outcomes were generally consistent with the overall results for all subgroups except for the baseline renal biopsy class V and cyclophosphamide followed by azathioprine subgroups, the results of which were not statistically significantly different between treatment groups. However, the study was not designed or powered to evaluate efficacy in subgroups, and the small number of patients in the class V and the cyclophosphamide followed by azathioprine subgroups might have led to the lack of statistical significance between treatment groups.

Secondary analyses in the BLISS-LN trial were generally supportive of the results of the primary outcome. However, as some secondary outcomes were not included in the hierarchy, they were not controlled for the type I error rate; therefore, any results should be viewed as overall supportive evidence of the effects of belimumab relative to placebo. The clinical expert consulted on this review noted the importance of reducing the use of corticosteroids in the management of LN due to their substantial long-term toxicity. Results of the BLISS-LN trial found that at week 104 a greater proportion of patients in the belimumab group than in the placebo group had an average daily dose of prednisone less than or equal to 7.5 mg since their previous 4-week visit, with a between-group difference of 11.21%, which the clinical expert found to be clinically meaningful.

Regarding disease activity, the SLEDAI-S2K, which measures general disease activity, was modified in the BLISS-LN study to consider new as well as persistent proteinuria of more than 0.5 g per 24 hours. Secondary

analyses found a greater proportion of patients in the belimumab group than in the placebo group had a SLEDAI-S2K score less than 4 by week 104. As discussed in Appendix 4, the SLEDAI-S2K uses a single weighted score to summarize disease activity, and it could have the potential to mask the underlying importance of organ systems that are contributing to the total score (i.e., the same score could represent multiple mild disease in many organs or severe disease in a single organ, or an unchanged score may occur despite worsening in 1 organ system if there is also improvement in another system). The clinical expert noted that it is clinically meaningful that a greater proportion of patients in the belimumab group had a SLEDAI-S2K score less than 4 by week 104, but as only the global SLEDAI-S2K score was presented, it is not known whether the improvements were in renal versus extrarenal systems; it would have been of interest to present the SLEDAI-S2K results stratified by organ system.

The clinician and patient group input received for this review indicated that patients would like to experience fewer flares. In the BLISS-LN study, patients in the belimumab group experienced fewer severe SFI flares and had a lower risk of experiencing a severe SFI flare than those in the placebo group. According to the clinician group and clinical expert input, flares have been associated with worse outcomes, increasing the risk of progression to ESRD and dialysis among patients with LN; hence, these results were found to be clinically meaningful to the clinical expert consulted.

The clinician group input noted that HRQoL is significantly impaired in patients with LN. The patient group input received for this CADTH review indicated that patients would like new therapies that provide increased mobility, increase ability to participate in physical and social activities, and improve overall HRQoL. As the BLISS-LN study did not assess HRQoL, the impact of belimumab in addition to standard of care on HRQoL is unclear. The clinical expert stated that, while HRQoL outcomes would have been of interest, the renal-focused primary and key secondary outcomes included in BLISS-LN trial are the outcomes of greatest importance in an LN trial.

Other limitations include the fact that a greater proportion of patients discontinued from the placebo group than the belimumab group, which may have led to bias in favour of belimumab. However, the sensitivity analyses that assessed the impact of missing data generally showed results that were supportive of the primary analysis. Regarding calculations of patients' average daily prednisone dose in the BLISS-LN trial, days where a patient did not have a prednisone dose recorded were considered as 0 mg for the day in the calculation, which may also have led to bias, although the direction of bias is unknown.

The product monograph for belimumab authorized both IV and subcutaneous formulations for LN.[12] However, this recommendation was based on extrapolated data, and there is no clinical evidence regarding the subcutaneous formulation for patients with active LN. While the product monograph states that belimumab is indicated for adult patients in addition to standard of care for the treatment of active LN, the sponsor reimbursement request is for adult patients with class III, IV, and/or V active LN in addition to standard of care, and if no improvements in disease activity and/or symptoms are observed after 6 months, use of belimumab should be discontinued. Patients with class III, IV, and/or V active LN were enrolled and assessed for the end points in the BLISS-LN trial, and according to the clinical expert consulted, patients with class I, II, or VI LN should not be candidates for immunotherapy such as belimumab. The clinical expert

and clinician group input noted that treatment with belimumab should be discontinued after 6 months to 12 months of therapy if there was no improvement in renal functioning or proteinuria, suggesting the reimbursement request to discontinue treatment after 6 months may have been too conservative. In the opinion of the clinical expert, in the BLISS-LN trial, the percentage of patients achieving the primary outcome over time were identical through to week 20 after randomization and started to diverge at week 24 through to week 104 (with a greater percentage achieving PERR in the belimumab group). Hence, it would be appropriate to wait at least 6 months to assess response to belimumab, and in patients with higher levels of proteinuria the clinical expert believed it would be appropriate to wait up to 12 months to determine if the response is sufficient to warrant continuation.

There were no head-to-head studies comparing the efficacy and safety of belimumab relative to rituximab, and the clinical expert believed it would be inappropriate to include a comparator arm in BLISS-LN consisting of rituximab added to standard of care. Although rituximab is used as add-on therapy to mycophenolate in refractory cases of LN, neither the EULAR/ERA-EDTA nor KDIGO guidelines recognize it as standard of care. Both guidelines recommend either mycophenolate or cyclophosphamide as standard of care and advise that rituximab is reserved as salvage therapy for refractory cases. Hence, it would have been inappropriate to include a comparator arm consisting of rituximab added to standard of care. The sponsor did not conduct an ITC as the heterogeneity between studies is significant and any ITC is therefore unlikely to produce robust estimates of comparative efficacy or safety. Thus, the comparative efficacy and safety of belimumab relative to rituximab is unknown.

Harms

Based on its mechanism of action, targeting B cells, infection would be 1 of the notable harms that should be monitored with belimumab. The clinical expert consulted by CADTH felt that the safety profile of belimumab was in line with other treatments. There has been no indication from the pivotal trial that there is an increased risk of mortality due to AE while on belimumab. Eleven deaths occurred during the double-blind phase of the BLISS-LN trial (2.7% of patients in the belimumab group versus 2.2% in the placebo group), mainly due to infections, and 1 death (0.4% of patients) occurred in the OLE, which was deemed SLE related. Most patients reported 1 or more AEs during the BLISS-LN trial, with UTI, cough, and upper abdominal pain reported more frequently among patients who received belimumab versus placebo. SAEs were comparable across treatment groups (25.9% of patients in the belimumab group versus 29.9% in the placebo group). The OLE study confirmed these findings (N = 254; duration up to 28 weeks), although the conclusions that can be drawn are limited by the lack of control group. Concerns over infection risk with belimumab also need to be weighed against the risk of infection of current standard of care medications, including immunosuppressants and corticosteroids, which are known for their increased infection risk.

Psychiatric AEs were a notable harm of this review, and there was no indication of an increased risk of these events occurring with belimumab compared to placebo. Patients judged recently to be at high risk of suicide were excluded from BLISS-LN; thus, the safety of belimumab in these patients is unknown.

Conclusions

In adult patients with class III, IV, and/or V active LN, treatment with belimumab 10 mg/kg in addition to standard of care statistically significantly improved renal response as measured by the primary outcome PERR, relative to placebo, based on 104-week data from the BLISS-LN trial, the results of which were deemed to be clinically meaningful by the clinical expert consulted for this review. All key secondary outcomes, including CRR at week 104, PERR at week 52, ORR at week 104, and time to renal-related event or death, showed statistically significant differences in favour of belimumab. The trial showed that a greater proportion of patients in the belimumab group than in the placebo group had reductions in average daily prednisone use to less than 7.5 mg since the previous 4-week visit and showed improvements in mean SLEDAI-S2K score. Also, fewer patients in the belimumab group experienced severe flares than those in the placebo group. HRQoL was not assessed in the trial, and therefore the impact of belimumab on HRQoL in patients with LN is unknown. In addition, the long-term efficacy of belimumab on reducing flare rates is unknown. AEs, including infections, occurred with similar frequency in the 2 treatment groups. Data from the pivotal trial and the OLE study do not suggest issues of tolerability or safety, although the extension study was limited by a lack of a control group.

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Appendix 1: Literature Search Strategy

Note that this appendix has not been copy-edited.

Clinical Literature Search

Overview

Interface: Ovid

Databases:

- MEDLINE All (1946 to present)
- Embase (1974 to present)
- Note: Subject headings and search fields have been customized for each database. Duplicates between databases were removed in Ovid.

Date of search: August 4, 2022

Alerts: Biweekly search updates until project completion

Search filters applied: No filters were applied to limit the retrieval by study type.

Limits:

- Conference abstracts: excluded

Table 18: Syntax Guide

Syntax	Description
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
adj#	Requires terms to be adjacent to each other within # number of words (in any order)
.ti	Title
.ot	Original title
.ab	Abstract
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Keyword heading word
.dq	Candidate term word (Embase)
.pt	Publication type
.rn	Registry number

Syntax	Description
.nm	Name of substance word (MEDLINE)
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
oemezd	Ovid database code; Embase, 1974 to present, updated daily

Multi-Database Strategy

1. (benlysta* or belimumab* or benlista* or benlystia* or LimphoStat-B or LimphoStatB or LymphoStat-B or LymphoStatB or 73B0K5S26A or L04AA26 or HGS-1006 or HGS1006 or BEL-114333 or BEL114333 or GSK-1550188 or GSK1550188).ti,ab,kf,ot,hw,rn,nm.
2. Lupus Nephritis/
3. ((lupus or scleros* or lupoid* or SLE) adj5 (neph* or kidney or mesangial* or renal)).ti,ab,kf.
4. (glomeruloneph* or glomerulosclerosis).ti,ab,kf.
5. or/2-4
6. 1 and 5
7. 6 use medall
8. *belimumab/
9. (benlysta* or belimumab* or benlista* or benlystia* or LimphoStat-B or LimphoStatB or LymphoStat-B or LymphoStatB or L04AA26 or HGS-1006 or HGS1006 or BEL-114333 or BEL114333 or GSK-1550188 or GSK1550188).ti,ab,kf,dq.
10. 8 or 9
11. lupus erythematosus nephritis/
12. ((lupus or scleros* or lupoid* or SLE) adj5 (neph* or kidney or mesangial* or renal)).ti,ab,kf,dq.
13. (glomeruloneph* or glomerulosclerosis).ti,ab,kf,dq.
14. or/11-13
15. 10 and 14
16. 15 use oemezd
17. (conference abstract or conference review).pt.
18. 16 not 17
19. 7 or 18
20. remove duplicates from 19

Clinical Trials Registries

ClinicalTrials.gov

Produced by the US National Library of Medicine. Targeted search used to capture registered clinical trials.

[Search -- Studies with results | Benlysta or belimumab AND lupus nephritis]

WHO ICTRP

International Clinical Trials Registry Platform, produced by the World Health Organization. Targeted search used to capture registered clinical trials.

[Search terms -- Benlysta or belimumab AND lupus nephritis]

Health Canada's Clinical Trials Database

Produced by Health Canada. Targeted search used to capture registered clinical trials.

[Search terms -- Benlysta or belimumab AND lupus nephritis]

EU Clinical Trials Register

European Union Clinical Trials Register, produced by the European Union. Targeted search used to capture registered clinical trials.

[Search terms -- Benlysta or belimumab AND lupus nephritis]

Grey Literature

Search dates: July 24 to 27, 2022

Keywords: Benlysta, belimumab, lupus nephritis

Limits: none

Relevant websites from the following sections of the CADTH grey literature checklist Grey Matters: A Practical Tool for Searching Health-Related Grey Literature were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Clinical Trials Registries
- Databases (free)
- Health Statistics
- Internet Search
- Open Access Journals

Appendix 2: Excluded Studies

Note this appendix has not been copy-edited.

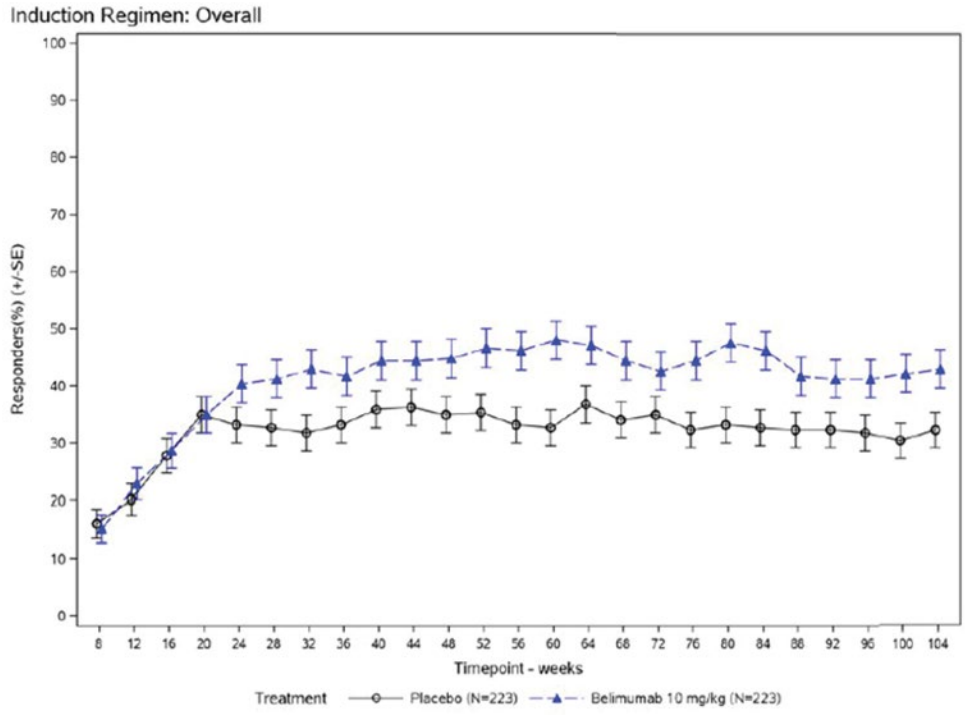
Table 19: Excluded Studies

Reference	Reason for exclusion
Atisha-Fregoso Y, Malkiel S, Harris KM, et al. Phase II randomized trial of rituximab plus cyclophosphamide followed by belimumab for the treatment of lupus nephritis. *Arthritis Rheumatol*. 2021;73(1):121-131.	Study design

Appendix 3: Detailed Outcome Data

Note this appendix has not been copy-edited.

Figure 3: Proportion of Patients With PERR by Visit From Week 8 to Week 104 in BLISS-LN (mITT)



mITT = modified intention to treat.

Source: Clinical Study Report for BLISS-LN.[13]

Table 20: PERR Response by Subgroup — Baseline Renal Biopsy Class and Induction Regimen (mITT)

Characteristic	Placebo N = 223	Belimumab 10 mg/kg N = 223
Baseline renal biopsy class subgroup		
Class III or class IV, N (%)	132 (59.2)	126 (56.5)
Responders, n (%)	42 (31.8)	60 (47.6)
OR (95% CI) vs. placebo[a]	1.82 (1.08 to 3.08)	
P value[a]	0.0250[b]	
Class III plus V or class IV plus V, N (%)	55 (24.7)	61 (27.4)
Responders, n (%)	15 (27.3)	23 (37.7)

Characteristic	Placebo N = 223	Belimumab 10 mg/kg N = 223
OR (95% CI) vs. placebo[a]	1.76 (0.77 to 4.05)	
P value[a]	0.1796[b]	
Class V, N (%)	36 (16.1)	36 (16.1)
Responders, n (%)	15 (41.7)	13 (36.1)
OR (95% CI) vs. placebo[a]	0.65 (0.23 to 1.86)	
P value[a]	0.4196[b]	
Induction regimen subgroup		
Cyclophosphamide, N (%)	59 (26.5)	59 (26.5)
Responders, n (%)	16 (27.1)	20 (33.9)
OR (95% CI) vs. placebo[a]	1.52 (0.66 to 3.49)	
P value[a]	0.3272[b]	
Mycophenolate mofetil, N (%)	164 (73.5)	164 (73.5)
Responders, n (%)	56 (34.1)	76 (46.3)
OR (95% CI) vs. placebo[a]	1.58 (1.00 to 2.51)	
P value[a]	0.0501[b]	

CI = confidence interval; mITT = modified intention to treat; OR = odds ratio.

[a]Odds ratio (OR), 95% CI, and p value are from a logistic regression model run within the subgroup level for the comparison between belimumab and placebo with covariates treatment group, induction regimen (cyclophosphamide versus mycophenolate mofetil), race (Black versus Non-Black), baseline uPCR, and baseline eGFR.

[b]P value has not been adjusted for multiple testing (i.e., the type I error rate has not been controlled).

Source: Clinical Study Report for BLISS-LN.[13]

Table 21: CRR Response by Subgroup — Baseline Renal Biopsy Class and Induction Regimen (mITT)

Characteristic	Placebo N = 223	Belimumab 10 mg/kg N = 223
Baseline renal biopsy class subgroup		
Class III or class IV, N (%)	132 (59.2)	126 (56.5)
Responders, n (%)	25 (18.9)	39 (31.0)
OR (95% CI) vs. placebo[a]	1.78 (0.98 to 3.21)	
P value[a]	0.0563[b]	
Class III plus V or class IV plus V, N (%)	55 (24.7)	61 (27.4)
Responders, n (%)	8 (14.5)	16 (26.2)
OR (95% CI) vs. placebo[a]	2.76 (0.99 to 7.72)	
P value[a]	0.0522[b]	
Class V, N (%)	36 (16.1)	36 (16.1)

Characteristic	Placebo N = 223	Belimumab 10 mg/kg N = 223
Responders, n (%)	11 (30.6)	12 (33.3)
OR (95% CI) vs. placebo[a]	0.83 (0.27 to 2.62)	
P value[a]	0.4300[b]	
Induction regimen subgroup		
Cyclophosphamide, N (%)	59 (26.5)	59 (26.5)
Responders, n (%)	11 (18.6)	11 (18.6)
OR (95% CI) vs. placebo[a]	1.07 (0.41 to 2.78)	
P value[a]	0.8843[b]	
Mycophenolate mofetil, N (%)	164 (73.5)	164 (73.5)
Responders, n (%)	33 (20.1)	56 (34.1)
OR (95% CI) vs. placebo[a]	2.01 (1.19 to 3.38)	
P value[a]	0.0085[b]	

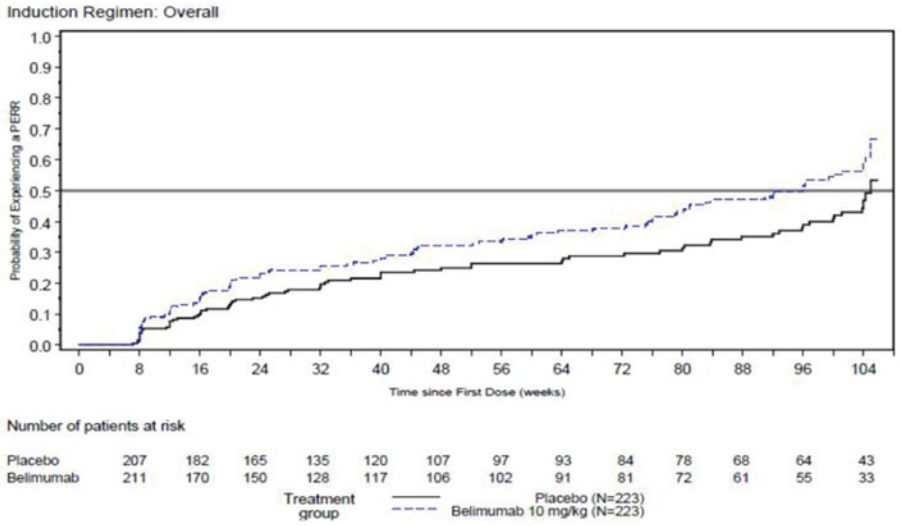
CI = confidence interval; mITT = modified intention to treat; OR = odds ratio.

[a]Odds ratio (OR), 95% CI, and p value are from a logistic regression model run within the subgroup level for the comparison between belimumab and placebo with covariates treatment group, induction regimen (cyclophosphamide versus mycophenolate mofetil), race (Black versus Non-Black), baseline uPCR, and baseline eGFR.

[b]P value has not been adjusted for multiple testing (i.e., the type I error rate has not been controlled).

Source: Clinical Study Report for BLISS-LN.[13]

Figure 4: Time to PERR That Is Maintained Through Week 104 (mITT)

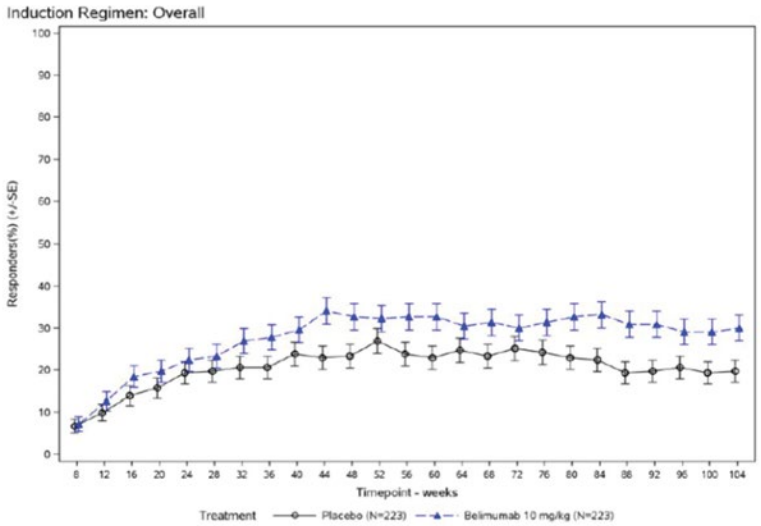


mITT = modified intention to treat.

Note: The at-risk numbers are the number of patients who have the potential to experience the event at that time point. Patients without PERR at week 104 are censored at the last available visit up through week 104. Patients with investigational product discontinuation, treatment failure, study withdrawal, lost to follow-up, or death are censored. Time to event is defined as (event date – treatment start date + 1).

Source: Clinical Study Report for BLISS-LN.[13]

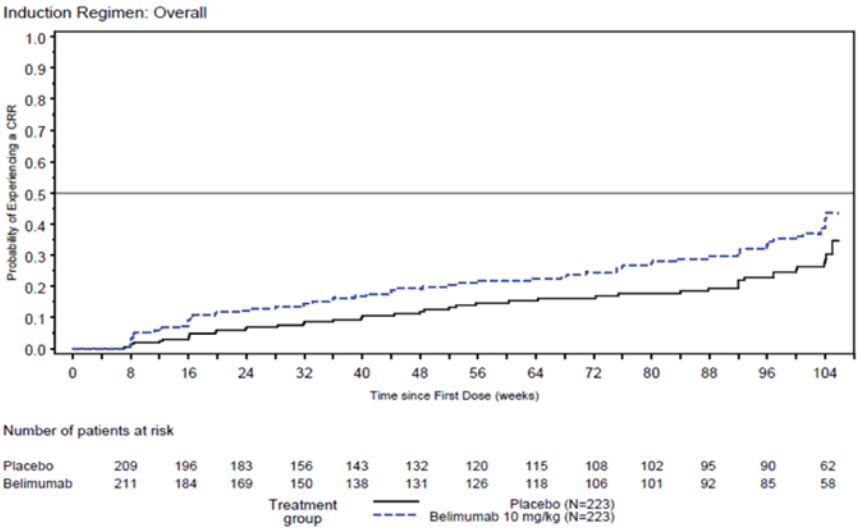
Figure 5: Proportion of Patients With CRR by Visit From Week 8 to Week 104 in BLISS-LN (mITT)



mITT = modified intention to treat.

Source: Clinical Study Report for BLISS-LN.[13]

Figure 6: Time to CRR That Is Maintained Through Week 104 (mITT)

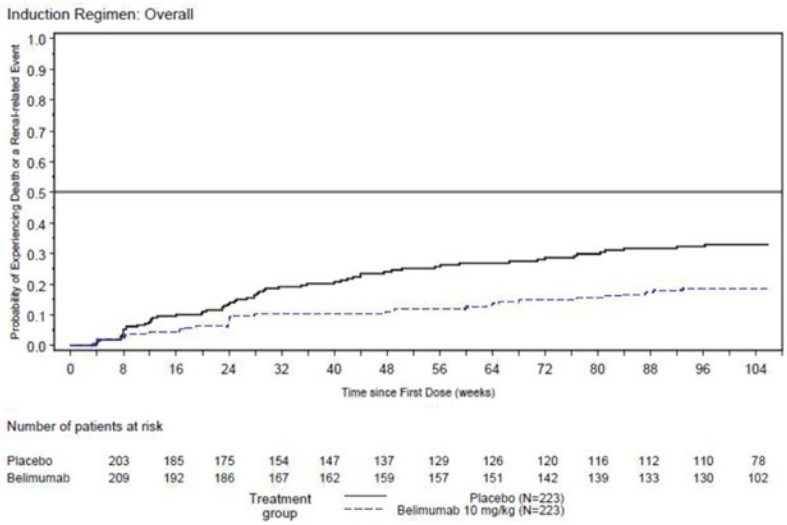


CRR = complete renal response; mITT = modified intention to treat.

Note: The at-risk numbers are the number of patients who have the potential to experience the event at that time point. Figure is truncated at day 742. Patients without CRR at week 104 are censored at the last available visit up through week 104. Patients with investigational product discontinuation, treatment failure, study withdrawal, lost to follow-up, or death are censored. Time to event is defined as (event date - treatment start date + 1).

Source: Clinical Study Report for BLISS-LN.[13]

Figure 7: Time to Renal-Related Event or Death Through Week 104 (mITT)

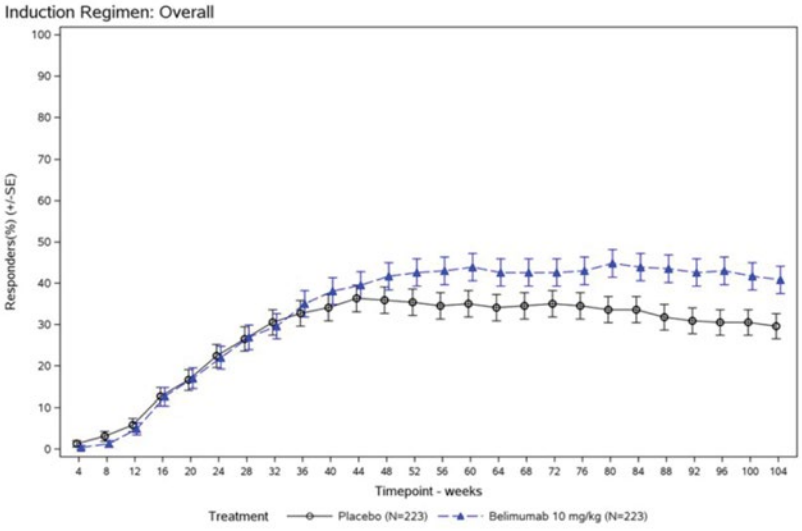


mITT = modified intention to treat.

Note: The at-risk numbers are the number of subjects who have the potential to experience the event at that time point. Figure is truncated at day 742.

Source: Clinical Study Report for BLISS-LN.[13]

Figure 8: Proportion of Patients in Response Group With an Average Daily Dose of Prednisone of 7.5 mg or Less Since Prior 4-Week Visit (mITT)

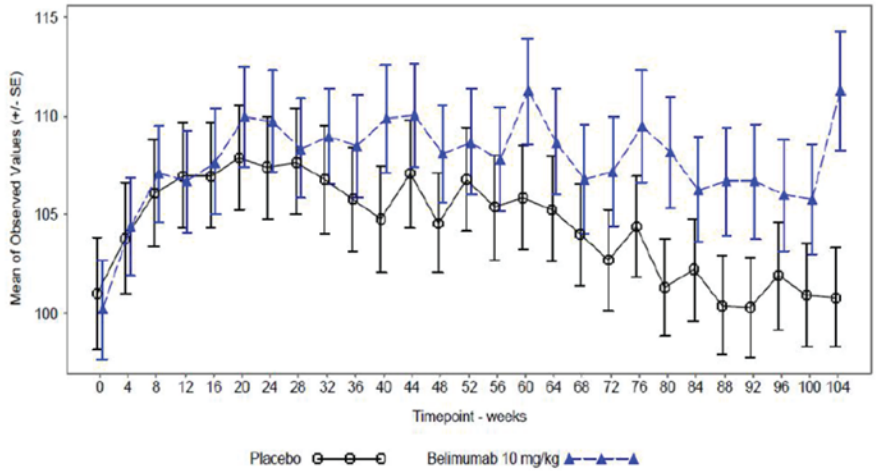


mITT= modified

Note: All prednisone doses since the previous 4-week visit were summed and divided by the number of days in the period. Days where a patient did not have a prednisone dose recorded were considered as 0 mg for the day in the calculation for average prednisone dose.

Source: Clinical Study Report for BLISS-LN.[13]

Figure 9: Mean Observed GFR[a] Values by Visit in BLISS-LN (Safety Population)



BSA = body surface area; GFR = glomerular filtration rate.

[a] From creatinine adjusted for BSA (mL/min/1.73 m^2).

Source: Clinical Study Report for BLISS-LN.[13]

Appendix 4: Description and Appraisal of Outcome Measures

Note this appendix has not been copy-edited.

Aim

To describe the following outcome measures and review their measurement properties (validity, reliability, responsiveness to change, and MID):

- SLEDAI-2K
- SDI
- SFI
- C-SSRS

Findings

Table 22: Summary of Outcome Measures and Their Measurement Properties

Outcome measure	Type	Conclusions about measurement properties	MID
SLEDAI-S2K	A measure of disease activity at time of visit or in the preceding 4 weeks. Consists of 24 weighted clinical and laboratory variables in 9 organ systems, with total possible score of 105 (higher scores represent greater disease activity).[38,39]	**For patients with SLE:** **Validity:** Strong Spearman rank correlation (0.824) was observed between the SLEDAI-2K and the PGA, supporting construct validity.[40] **Reliability:** Good reliability; agreement for each of the items between 81.7% and 100% in a study of 93 patients with SLE.[41] **Responsiveness:** Less responsive to change than the PGA[42] and the BILAG-2004.[41] The validity, reliability, and responsiveness were not assessed for patients with LN.	**For patients with SLE:** Clinically meaningful: +3 points for worsening; −1 point for improvement.[31] Associated with flare: +3 points.[43] MID not assessed in patients with LN.
SDI	Disease-specific score of organ damage defined as irreversible change in an organ system, regardless of cause, that has occurred since the onset of SLE, and present for at least 6 months. Consists of 42 items in 12 domains, with a maximum score of 46 (higher scores denote more damage). At SLE diagnosis, the SDI score is 0. Damage is considered if the score is ≥1.[32]	For patients with SLE: **Validity:** Higher scores found in patients with damage vs. stable disease and in patients with active vs. inactive disease. Predictor of mortality. Low correlation observed with SLEDAI and BILAG, although one study found strong correlation with SLEDAI.[44]	For patients with SLE: SDI ≥ 1 indicates worsening.[32]

Outcome measure	Type	Conclusions about measurement properties	MID
		Reliability: Moderate agreement among raters.[45] **Responsiveness:** Scores have been shown to increase with disease duration.[33] The validity, reliability, and responsiveness were not assessed for patients with LN.	
SFI	Disease-specific composite measure that classifies flares as mild/moderate or severe, based on criteria of clinical activity, need for additional treatment, or PGA score.[33] Pivotal trial used a modified version of SFI where the SLEDAI-2K was used instead of SELENA SLEDAI to identify flares.[13,28]	For patients with SLE: **Validity**: Associated with a significant change in the FACIT-F and all domains of the SF-36v2 except role emotional scores, indicating convergent validity.[46] **Reliability:** Fair agreement among raters.[47] The validity and reliability were not assessed for patients with LN. **Responsiveness:** Not assessed in patients with SLE or LN.	NA
C-SSRS	Assesses the lethality of attempts and other features of ideation (frequency, duration, controllability, reasons for ideation, and deterrents), all of which are significantly predictive of completed suicide.[34] Suicidal ideation: a "yes" response to any of 5 ideation questions ranging from "wish to be dead" to "active suicidal ideation with specific plan and intent." Suicidal behaviour defined as a "yes" response to any of 5 suicidal behaviour questions ranging from "preparatory acts or behaviour" to "completed suicide."[28,48]	**Validity:** Not assessed in patients with SLE or LN. **Reliability:** Not assessed in patients with SLE or LN. **Responsiveness:** Not assessed in patients SLE or LN.	Not assessed in patients with SLE or LN.

BILAG=British Isles Lupus Assessment Group; C-SSRS = Columbia – Suicide Severity Rating Scale; ESR = erythrocyte sedimentation rate; FACIT-F = Functional Assessment of Chronic Illness Therapy – Fatigue; LN = lupus nephritis; MID = minimal important difference; NA = not applicable; PGA = physician global assessment; SDI = Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SELENA SLEDAI = Safety of Estrogens in Lupus National Assessment-Systemic Lupus Erythematosus Disease Activity Index; SF-36 = 36-Item Short Form Survey; SFI = SELENA SLEDAI Flare Index; SLE= systemic lupus erythematosus; SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index 2000; v2= version 2.

SLEDAI-S2K

Description and Scoring

The SELENA SLEDAI is a measure of disease activity that was derived by consensus among experts in rheumatology, followed by regression models to assign relative weights to each parameter.[30] The SELENA SLEDAI assessment is based on the presence of 24 individual items in 9 organ systems which are given a

weighted score and summed if present at the time of the visit or in the preceding 10 days and incudes the use of signs and symptoms, laboratory tests, and physician's assessment for this purpose. Each descriptor has a weighted score and the sum of all 24 descriptor scores falls between 0 and 105, with higher scores representing higher disease activity, and 0 representing inactive disease. However, not many patients could achieve a score of > 45.[49,50] In the BLISS-LN trial, the SLEDAI-S2K is a modified version of the original SLEDAI. The proteinuria descriptor was modified with the use of the SLEDAI-2000 (SLEDAI-2K) version that captures new as well as persistent proteinuria of more than 0.5 g per 24 hours.

Validity

In a study of 334 patients with SLE in Portugal, a strong Spearman rank correlation (0.824) was observed between the SLEDAI-2K and the PGA at the 36-month follow-up, supporting the construct validity of the SLEDAI-2K in patients with SLE.[40] In another study of 92 patients with SLE, a good correlation coefficient of 0.677 between the SLEDAI-2K and PGA was identified, indicating construct validity.[51]

Reliability

The reliability of the SLEDAI-2K was demonstrated using interrater reliability between 2 raters in a study of 93 patients with SLE.[41] Results found agreement between the raters for each of the items ranging between 81.7% and 100%.[41]

Responsiveness

In terms of responsiveness, in one study, the SLEDAI-2K was unable to detect a clinically meaningful improvement or worsening in SLE disease activity; as it failed to identify more than 60% of cases with a worsening or improvement, which was defined as a change of 0.3 points in the patient global assessment PGA.[42] The BILAG-2004 has been found to be more responsive to change in disease activity than the SLEDAI-2K.[41] Using a summary score to describe disease activity as in the SLEDAI-2K can mask the underlying organ systems that are contributing to the score (i.e., the same score could indicate mild disease in multiple organs or severe disease in 1 organ; or an unchanged score may occur despite worsening in 1 organ system if there is also improvement in another system).[32]

The validity, reliability, and responsiveness were not assessed for patients with LN.

MID

One study identified a minimal clinically meaningful increase of 3 or 4 points for prediction of increase in therapy (worsening) and suggest a minimal clinically meaningful decrease in score of 1 to 2 points for improvement.[31] Another study found that the SLEDAI-2K score increased by > 3 points when the clinician assessed that the patient was experiencing a flare.[43]

MID not assessed for patients with LN.

Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI)

Description and Scoring

The SDI was developed by the international collaboration, Systemic Lupus International Collaborating Clinics.[32] The purpose of the assessment is to score irreversible damage, regardless of cause. Damage is defined as irreversible change in an organ system that has occurred since the onset of SLE, and is present for at least 6 months.[32] The tool is completed by a physician and consists of 42 items in 12 domains (peripheral vascular, ocular, neuropsychiatric, renal, pulmonary, cardiovascular, gastrointestinal, musculoskeletal, skin, endocrine (diabetes), gonadal, and malignancies) with a maximum score of 47 points (higher scores denote more damage).[32,45] The items are rated as present or absent and, in the case of recurring events, such as a stroke, there is a possibility of providing a rating of 2 or 3 points to an item.[32] At diagnosis of SLE, the SDI score is 0 by definition.[45] Damage is considered if the SDI score is ≥ 1 and damage can remain stable or increase over time, however points should not decrease.[45]

Validity

To assess the validity of the SDI, centres who treated patients with SLE submitted 2 assessments, 5 years apart, on 2 patients with active disease (one patient with increase in damage over the 5 years and one patient with stable damage) and 2 patients with inactive disease (one patient with increase in damage and one patient with stable damage).[44] The cases (14 cases in 3 separate packages) were written up in a uniform format and sent back out, in mixed order, to the centres where the SDI was completed by 20 physicians (2 assessments per patient at time 1 and time 2). The SDI scores of patients with damage after 5 years were increased by a greater degree compared with patients with stable disease (2.08 points versus 0.24 points).[44] The SDI scores of patients with active disease also increased more compared with patients with inactive disease (1.48 points versus 0.83 points).[44] A study of 71 patients found that the SDI was associated with SLEDAI-S2K (r=0.742) and the European Consensus Lupus Activity Measurement (ECLAM) (r=0.699).[52] The SDI and BILAG have been found to have weak correlation (Spearman correlation coefficient 0.19).[53]

Reliability

Among 20 SLICC members who completed the SDI on 42 SLE cases, there was moderate agreement between raters (ICC = 0.553).[45] Similarly, when the SDI was completed by another physician based on retrospective review of patient cases, interobserver reliability was moderate (kappa 0.47, 95% CI 0.28 to 0.66).[53]

Responsiveness

The SDI is a statistically significant predictor of clinically important outcomes. In a 10-year retrospective study of 80 patients with SLE, the mean SDI renal damage score at one year after diagnosis was a significant predictor of end-stage renal failure (at 1 year: renal failure versus no renal failure, SDI renal damage score 0.33 versus 0.03; at 5 years: SDI renal damage score 1.33 versus 0.14; at 10 years: SDI renal damage score 2.80 versus 0.35).[33] The total SDI score was also associated with end-stage renal failure at 5 and 10 years.[33] The SDI pulmonary damage score at 1 year after diagnosis was a significant predictor of death

within 10 years, however total SDI score was not associated with death.[33] More recent studies with larger cohorts of patients have shown that the SDI is a predictor of mortality. Patients with SLE (N=1,297) were identified within 2 years of a first clinical visit from 8 centres, and followed for 2, 5-10, and >10 years.[45] The SDI increased over time and was found to be higher among patients who died.[45] In the University of Toronto Lupus Clinic, 263 patients were followed for 10 years.[54] Within 10 years, 25% of patients who exhibited damage at the first SDI assessment (i.e., one year after diagnosis) died, compared with 7.3% of patients who had no early signs of damage.[54]

The validity, reliability, and responsiveness were not assessed for patients with LN.

MID

No formal MID has been assessed for patients with SLE or LN. An SDI ≥ 1 indicates damage which can remain stable or increase over time.[32]

SELENA SLEDAI Flare Index (SFI)

Description and Scoring

The SFI is used to identify and classify flares as mild/moderate or severe, based on clinical activity, need for additional treatment, or PGA score.[55] The original definitions of mild/moderate and severe flares were reached by consensus of the investigators of the SELENA trials.[56] In the BLISS-LN trial,[13,28] a modified version of the SFI was used, using the SLEDAI-2K instead of the SELENA SLEDAI. In this trial, mild/moderate flare and severe flare were defined according to the following criteria:

- Mild or moderate flare:
  - change in SLEDAI-2K score of ≥ 3 points but not > 12 points, or
  - new or worse discoid, photosensitive, profundus, cutaneous vasculitis, or bullous lupus, or
  - nasopharyngeal ulcers, pleuritis, pericarditis, arthritis, or SLE fever, or
  - increase in prednisone, but not > 0.5 mg/kg/day
  - added NSAID or hydroxychloroquine for SLE
  - ≥ 1.0 increase in PGA score (but not > 2.5).
- Severe flare:
  - change in SLEDAI-2K score > 12 points compared to previous visit, or
  - new or worse CNS-SLE, vasculitis, nephritis, myositis, Plt < 60,000, hemolytic anemia (Hb < 70 g/L or decrease in Hb > 30 g/L); requiring double prednisone, or prednisone increase to > 0.5 mg/kg/day, or hospitalization
  - increase in prednisone increase to > 0.5 mg/kg/day
  - new cyclophosphamide, azathioprine, methotrexate, or mycophenolate for SLE
  - hospitalization for SLE, or
  - increase in PGA score to > 2.5.[13,28]

Validity

In a post hoc analysis of BLISS-52 trial data with 867 patients with SLE, the occurrence of a new SFI flare using the SELENA SLEDAI was associated with a significant change in the FACIT-F and all domains of the SF-36v2 except role emotional scores, indicating convergent validity.[46] In a small study of 16 patients who were each evaluated by 4 physicians, there was 52% agreement between the SFI and BILAG-2004 flare index in classifying patients as having no flare, or mild, moderate or severe flare.[57] It was unclear, however, if this study used the SFI, or the modified SFI. The agreement among raters on the SFI was fair (ICC 0.21, 95% CI, 0.08 to 0.48), and lower than the BILAG 2004 assessment of flares.[57]

Reliability

A study evaluated the modified SFI using paper-based cases of patients with SLE.[47] Initially, 988 cases were assessed by 3 physicians for degree of flare or presence of disease activity and rated as severe, moderate, or mild flare, or persistent/ongoing disease. For those cases where there was agreement by the 3 physicians (N=451 cases), they were moved on the second part of the study and assessed by 18 pairs of physicians with 3 instruments, BILAG-2004 flare index, SFI, and modified SFI. The assessments based on these instruments were compared with the assessments conducted initially in the first stage of the study by the 3 physicians. For the modified SFI, assessments matched the conclusions of the thee physicians in 70% of cases (weighted kappa 0.74).[47] The discrepancies were concentrated in classifying moderate flares as severe flares, and identifying persistent activity as a flare.[47] There was also an issue of over-scoring due to classifying treatment change as a flare, even when there were no new or worsening clinical features.[47] The authors of this study indicate that "the problem of capturing lupus flare accurately" is not completely solved.[47]

The validity and reliability were not assessed for patients with LN. No literature was identified regarding the responsiveness of the instrument in patients with SLE or LN.

C-SSRS

Assesses the lethality of attempts and other features of ideation (frequency, duration, controllability, reasons for ideation, and deterrents), all of which are significantly predictive of completed suicide.[34] In the pivotal trials,[28,48] 2 different versions of the questionnaire were used: one assessing the last 12 months prior to the assessment and another assessing the time since last visit. Suicidal ideation was defined as a "yes" answer at any time in the respective study period to any one of the 5 (re-ordered) suicidal ideation questions ranging from category 1 "wish to be dead" to category 5 "active suicidal ideation with specific plan and intent" on the C-SSRS. Suicidal behaviour was defined as a "yes" answer at any time in the respective study period, to any one of the 5 (re-ordered) suicidal behaviour questions ranging from category 6: preparatory acts or behaviour" to category 10: "completed suicide" on the C-SSRS. Evidence related to the validity, reliability, responsiveness or MID of the instrument among patients with SLE or LN was not identified.

Appendix 5: Summary of Other Studies

Note this appendix has not been copy-edited.

Aim

The aim of this section was to summarize and appraise evidence from Coresh et al., 2014 that was used to inform the pharmacoeconomic model.

Findings

In a meta-analysis conducted by Coresh et al. (2014),[58] the associations of decline in eGFR with subsequent progression to ESRD as well as all-cause mortality risk have been characterized to evaluate lesser declines in eGFR as potential alternative end points for CKD progression. The prognostic contribution of change in eGFR over 1, 2 and 3 years to subsequent ESRD and mortality had been assessed in cohorts taken from the Chronic Kidney Disease Prognosis Consortium (CKD-PC), which consisted of up to 1.7 million participants with 12,344 ESRD events and 223,944 deaths. Among the included cohorts (from separate datasets), 22 cohorts presented with a repeated measure of serum creatinine over 1 to 3 years to assess the relationship of change in eGFR on subsequent ESRD, whereas 35 cohorts included mortality outcome data. Patient data transfer and a random-effects meta-analysis were conducted between July 2012 and September 2013, with baseline assessments done between 1975-2012.[58]

In this study, the CKD-EPI 2009 creatinine equation was used to calculate eGFR.[59,60] Since the doubling of serum creatinine corresponds to a change in eGFR of 57% or greater reduction with the CKD-EPI equation (for serum creatinine ≥ 0.9 mg/dL in males and ≥ 0.7 mg/dL in females), the primary data presentation used in this study was based on percent change in eGFR. ESRD was defined as an initiation of renal replacement therapy or death due to kidney disease other than acute kidney injury in this study. While the primary outcome of interest for this study was to measure ESRD cases after the baseline period, an analysis had been conducted for all-cause mortality as well as cardiovascular mortality and non-cardiovascular mortality, given that majority of CKD patients die before reaching ESRD. The covariates assessed in this study included – age, sex, race/ethnicity (Black versus non-Black), systolic blood pressure, total cholesterol, history of diabetes or CVD, and first eGFR.[58]

For statistical analyses, a 2-stage analytic approach had been applied, where in the first step, each study had been analyzed individually, followed by a random-effects meta-analysis in the second step. The adjusted HRs of ESRD and mortality after the end of the baseline period had been modelled as a spline function of percent change in eGFR including the covariates. Using the weighted average baseline risk, the meta-analyzed adjusted HRs for percent change in eGFR had been translated to absolute risk of ESRD and mortality at 1, 3, 5, and 10 years after the baseline period. One year baseline risk had been calculated for the following covariates: no change in eGFR, a first eGFR of 50 mL/min/1.73m^2, age 60 years, male, non-Black, a systolic blood pressure of 130 mm Hg, a total cholesterol of 5 mmol/L, no history of diabetes or CVD. Using a weighted average, risk had been scaled for longer follow-up and pooled across cohorts in the analyses.[58]

From the analyses, the adjusted HRs for ESRD were found to be 32.1 (95% CI: 22.3 to 46.3) and 5.4 (95% CI: 4.5 to 6.4) for −57% and −30% eGFR changes, respectively, for patients with a baseline eGFR <60 mL/min/1.73m^2, while corresponding adjusted HRs for mortality were 3.7 (95% CI: 3.2 to 4.4) and 1.8 (95% CI: 1.6 to 1.9) for −57% and −30% eGFR changes, respectively, showing exponentially higher adjusted HRs for ESRD and mortality with larger eGFR declines. Results compiled from the whole consortium indicated that changes of −30% or greater eGFR (6.9%, 95% CI: 6.4 to 7.4%) were more common than changes of −57% eGFR (0.79%, 95% CI: 0.52 to 1.06%), This association had been found to be strong and consistent across length of baseline (1 or 3 years), baseline eGFR, age, diabetes status, or albuminuria.[58]

The average adjusted 10-year risks of ESRD for eGFR changes of−57%, −40%, −30% and 0% were 99% (95% CI: 95-100%), 83% (95% CI: 71 to 93%), 64% (95% CI: 52 to 77%), versus 18% (95% CI: 1 to −22%) respectively, for a baseline eGFR of 35 mL/min/1.73m^2, adjusted for aforementioned covariates and competing mortality risk. The corresponding absolute all-cause mortality risks were 77% (95% CI: 71 to 82%), 60% (95% CI: 56 to 63%), 50% (95% CI: 47 to 52%), versus 32% (95% CI: 31 to 33%), showing a similar but weaker pattern. Results from this study indicated that eGFR decline starting at severely reduced eGFR was associated with very high rates of ESRD during the subsequent 1-5 years, whereas eGFR decline starting at moderately reduced or normal eGFR was associated with a lower risk with ESRD occurring after 10 or more years. Moreover, a consistently higher absolute all-cause mortality risk had been observed with larger eGFR declines for all levels of baseline eGFR and across different subsequent follow-up time. Results from this study demonstrated that the average absolute risk of ESRD was very strongly related to the first eGFR, the length of follow-up and the change in eGFR.[58]

This study provided some evidence in support of using lesser declines in eGFR as an alternative end point for CKD progression, rather than using the established CKD progression end points like ESRD or doubling of serum creatinine. Since these events occur at much later stage in CKD, and a 30% decline in eGFR was found to be approximately 10 times more common than a doubling of serum creatinine as well as associated with an approximately 5-fold increased risk of ESRD after adjusting for covariates including the first eGFR, consideration of lesser declines in eGFR as an alternative end point addresses the limiting feasibility issue of clinical nephrology trials. The study had excluded ESRD cases before baseline period from the relevant analyses, which may potentially lead to bias. Moreover, the authors had acknowledged that standardization of serum creatinine values might not be consistent across time and studies, as well as heterogeneity issues related to variation in design across cohorts.[58]

Pharmacoeconomic Review

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Abbreviations

AZA	azathioprine
BIA	budget impact analysis
CKD	chronic kidney disease
CYC	cyclophosphamide
eGFR	estimated glomerular filtration rate
ESRD	end-stage renal disease
ICER	incremental cost-effectiveness ratio
LN	lupus nephritis
MMF	mycophenolate mofetil
QALY	quality-adjusted life-year
SC	subcutaneous
SLE	systemic lupus erythematosus
ST	standard therapy

Executive Summary

The executive summary comprises 2 tables (Table 1 and Table 2) and a conclusion.

Table 1: Submitted for Review

Item	Description
Drug product	Belimumab (Benlysta) 120 mg per 5mL or 400 mg per 20 mL vial lyophilized powder for IV infusion, or 200 mg per 1 mL solution for subcutaneous injection.
Submitted price	Belimumab: 120 mg in 5 mL vial lyophilized powder for IV infusion, $305.71 400 mg in 20 mL vial lyophilized powder for IV infusion, $1,091.01 200 mg in 1 mL for subcutaneous injection, $1,581.59 (1 pack of 4)
Indication	In addition to standard therapy for the treatment of active lupus nephritis in adult patients
Health Canada approval status	NOC
Health Canada review pathway	Standard
NOC date	July 29, 2021
Reimbursement request	As per indication with all the following criteria: • adult patients ≥ 18 years • in addition to receiving standard therapy • in class III, class IV, and/or class V of active lupus nephritis • if no improvements of disease activity and/or symptoms are observed after 6 months, use should be discontinued.
Sponsor	GlaxoSmithKline Inc.
Submission history	Previously reviewed: Yes Indication: Systemic lupus erythematosus Recommendation date: April 22, 2020 Recommendation: Do not reimburse

NOC = Notice of Compliance.

Table 2: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	Adult patients with active LN
Treatment	Belimumab in combination with standard therapy (IV CYC for induction followed by AZA for maintenance, or MMF monotherapy): • Belimumab plus CYC followed by AZA • Belimumab plus MMF

Component	Description
Comparator	Standard therapy: • CYC followed by AZA • MMF
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (70 years)
Key data source	BLISS-LN: evaluated the efficacy and safety of belimumab (IV, 10 mg/kg) plus ST
Submitted results	• Compared to MMF, belimumab plus MMF was associated with an ICER of $345,269 per QALY gained (incremental costs = $196,902; incremental QALYs = 0.57). • Belimumab plus CYC followed by AZA was dominated (more costly, less effective) by belimumab plus MMF.
Key limitations	• The sponsor did not consider the reimbursement request as a scenario analysis, and the model was not sufficiently flexible to report the cost-effectiveness of belimumab plus ST in the reimbursement request population, specifically in relation to incorporating the criteria of patients who do not respond to treatment within 6 months. • Due to the small number of patients, clinical subgroup data on CYC followed by AZA were insignificant and imprecise. As the clinical subgroup data on CYC followed by AZA were used to derive the model transition probabilities, this propagated uncertainty into the modelled treatment effect of belimumab. Furthermore, modelling transitions between health states primarily based on levels of decline from baseline eGFR is likely an oversimplification of disease progression. • The model structure does not adequately reflect the management of active LN in Canadian clinical practice. Subsequent therapies after treatment discontinuation and/or having inadequate response to first-line therapy and long-term immunosuppressive therapy were not modelled. • The long-term efficacy of belimumab on reducing flare rates is unknown, and extrapolated data predicting long-term flare events for ST were underestimated. • Utility values were informed by CKD patients and may not be reflective of patients with active LN. • The cost-effectiveness model was overly complex and unstable. Vastly different ICERs were produced when the probabilistic analyses were run using the sponsor's suggested 1,000 iterations.
CADTH reanalysis results	• Due to the inappropriate model structure and the limitations and uncertainty in the clinical data, CADTH was unable to derive a base-case analysis. Instead, an exploratory reanalysis was conducted that utilized more appropriate assumptions, though CADTH notes the magnitude of clinical benefit estimated for belimumab plus ST in this reanalysis may be overestimated due to uncontrolled limitations. • In the CADTH exploratory reanalysis, the following changes were made: probabilistic analyses were run using 5,000 iterations, and a generalized gamma curve was used to inform the time to first renal flare for belimumab and the comparator arm. • The CADTH exploratory reanalysis estimated that belimumab plus MMF was associated with an ICER of $352,880 per QALY gained (incremental costs = $201,083; incremental QALYs = 0.57) vs. MMF alone. Belimumab plus CYC followed by AZA was dominated (more costly, less effective) by belimumab plus MMF. • At a willingness-to-pay threshold of $50,000 per QALY, belimumab would require a price reduction of at least 58%, whereas belimumab plus CYC followed by AZA required a price reduction of 73% and belimumab plus MMF required a price reduction of 58%. However, given the uncertainties in the reanalysis, higher price reductions may be required to ensure the cost-effectiveness of belimumab plus ST.

Component	Description
	• CADTH was unable to address the following: cost-effectiveness of add-on belimumab in the reimbursement population; uncertainties in the modelled disease progression; a model structure that failed to adequately reflect the management of active LN in clinical practice; and utility values for patients with LN. Therefore, the cost-effectiveness of add-on belimumab is uncertain.

AZA = azathioprine; CKD = chronic kidney disease; CYC = cyclophosphamide; eGFR = estimated glomerular filtration rate; ICER = incremental cost-effectiveness ratio; LN = lupus nephritis; LY = life-year; MMF = mycophenolate mofetil; QALY = quality-adjusted life-year; ST = standard therapy.

Conclusions

Evidence from the BLISS-LN trial suggested that compared to placebo, belimumab plus standard therapy (ST) significantly improved renal response as measured by the primary outcome — primary efficacy renal response — for adult patients with active class III, IV, and/or V lupus nephritis (LN). Time to renal-related events or death also showed statistically significant differences in favour of belimumab, with a greater proportion of patients in the belimumab group experiencing reductions in prednisone use and fewer severe flares than in the placebo group.

As a result of the inappropriate model structure and limitations or uncertainty in the clinical data, CADTH was unable to derive a base-case analysis. Instead, CADTH undertook exploratory reanalyses to address limitations related to flare data, where an alternative extrapolation was selected to inform the time to first renal flare event (and subsequently the annual probability of a renal flare) to better align with clinical expert feedback sought by CADTH.

Based on the CADTH exploratory reanalysis, belimumab plus mycophenolate mofetil (MMF) was associated with an incremental cost-effectiveness ratio (ICER) of $352,880 per quality-adjusted life-year (QALY) gained (incremental costs = $201,083; incremental QALYs = 0.57) versus MMF alone. Belimumab plus cyclophosphamide (CYC) followed by azathioprine (AZA) was dominated (more costly, less effective) by belimumab plus MMF. The CADTH exploratory reanalysis results were similar to those submitted by the sponsor, in that belimumab was not cost-effective at commonly used willingness-to-pay thresholds. At a willingness-to-pay threshold of $50,000 per QALY gained, belimumab plus CYC followed by AZA would require a price reduction of 73% and belimumab plus MMF would require a price reduction of 58% to be considered cost-effective versus CYC followed by AZA alone. However, given the uncertainty around the economic model, further price reductions may be necessary to ensure the cost-effectiveness of belimumab plus ST.

There remains a significant degree of uncertainty in the cost-effectiveness of belimumab plus ST (CYC followed by AZA or MMF monotherapy) compared to ST alone for adult patients with active LN. CADTH was unable to adjust for major limitations, including inability to model the reimbursement population, uncertainties in the modelled disease progression, model structure that failed to adequately reflect the management of active LN in clinical practice, and utility values for patients with LN. As such, the cost-effectiveness of belimumab plus ST should be interpreted with caution.

Stakeholder Input Relevant to the Economic Review

This section is a summary of the feedback received from the patient groups, registered clinicians, and drug plans that participated in the CADTH review process.

CADTH received patient input from Arthritis Consumer Experts, Lupus Ontario, the Kidney Foundation of Canada and Lupus Canada, as well as a jointly by Canadian Arthritis Patient Alliance, Arthritis Society, Canadian Skin Patient Alliance, and CreakyJoints. The joint group gathered patient input by recruiting 1 patient for a video interview and 3 patients for a focus group. Responses from a previously conducted 2019 survey for the use of belimumab for systemic lupus erythematosus (SLE) were also used to inform greater context around living with SLE (6 participants). Patients noted that SLE impacts all aspects of their lives, including difficulties in contributing and participating at school or work due to fatigue, pain, and other symptoms. Patients mentioned that there are many challenges in finding the right combination of drugs to help manage their SLE and LN as responses to medications can vary significantly. Many patients expressed a desire to reduce their use of steroids due to concerns of increased bone density loss. All 3 patients in the focus group and all 6 previous survey responders had experience with belimumab for treating their SLE symptoms. Broadly, 1 patient had negative side effects, another did not have any changes in symptoms or side effects, and all other remaining patients reported an overall decrease in their disease symptoms and increased ability to participate in activities of daily living.

Registered clinical input was received from the Canadian Network for Improved Outcomes in Systemic Lupus Erythematosus and associated physicians (rheumatologists and nephrologists). Clinical input noted that the current treatment strategies for LN are aimed at suppressing or modulating the autoimmune response and preserving renal function, without increasing the risk of adverse events, while minimizing the use of more harmful drugs. Clinician input recognized that belimumab is the first approved drug to address the disease mechanism of modulating the maturation and functional differentiation of the B cells and, therefore, is expected to cause a shift in the current treatment paradigm for LN. Specifically, clinical input believed that belimumab would be most beneficial to patients who do not achieve at least partial remission in a reasonable time period after commencing treatment with currently available therapies, patients who experience early flares and cannot reduce their daily prednisone dose, patients who have frequent flares, and patients for whom adherence is a major factor for treatment failure.

Feedback from drug plans noted uncertainty around the appropriateness of placebo as the comparator in the BLISS-LN trial, given available off-label therapies (e.g., calcineurin inhibitors or rituximab) currently used in practice. Additionally, the plans highlighted the waxing and waning nature of the condition and how it could negatively impact reporting response over time. Lastly, the drug plans highlighted the different modes of administration of belimumab (IV or subcutaneous [SC]) and how efficacy could be impacted.

Several of these concerns were addressed in the sponsor's model:

- The impact of LN on patients' quality of life was captured via utility values.
- Adverse events associated with belimumab and renal flares were included within the analysis.

CADTH was unable to address the following concerns raised from stakeholder input:

- cost-effectiveness of belimumab plus ST against available off-label therapies such as rituximab
- cost-effectiveness of SC belimumab.

Economic Review

The current review is for belimumab (Benlysta) for patients with active LN.

Economic Evaluation

Summary of Sponsor's Economic Evaluation

Overview

The sponsor submitted a cost-utility analysis to assess the cost-effectiveness of belimumab plus ST (defined as MMF monotherapy or CYC followed by AZA for induction and/or maintenance) against ST alone as a treatment for adult patients with active LN. This model population aligned with the BLISS-LN trial population and the Health Canada indication.[1] The reimbursement request had the following additional criteria: adult patients aged 18 years and older who are receiving ST and who have class III, class IV, and/or class V active LN, and if no improvement in disease activity and/or symptoms are observed after 6 months, use should be discontinued.[2]

Belimumab is a recombinant human immunoglobulin G1 lambda (IgG1λ) monoclonal antibody that is to be used alongside ST. Belimumab is available for both IV and SC administration, where IV belimumab is available in 120 mg and 400 mg strengths and SC belimumab is available in a 200 mg per unit strength, distributed in packs of 4.[1] The recommended IV dose for patients with LN is 10 mg/kg at weeks 0, 2, and 4, and every 4 weeks thereafter, whereas the SC regimen includes a 400 mg dose once weekly for the first 4 doses, then 200 mg once weekly thereafter.[1] The submitted price for belimumab is $305.7100 for the 120 mg per 5 mL vial lyophilized powder for IV infusion, $1,019.0100 for the 400 mg in 20 mL vial lyophilized powder for IV infusion, and $1,581.5900 for the 200 mg in 1 mL for SC injection (only available in packages of 4).[3] The comparators for this analysis were ST regimens of MMF monotherapy or CYC followed by AZA for induction and/or maintenance.[2]

Outcomes of the model included QALYs and life-years over a lifetime horizon of 70 years. Discounting (1.5% per annum) was applied for both costs and outcomes, and a cycle length of 1 year was used.

Model Structure

The sponsor submitted a Markov model consisting of 7 health states: estimated glomerular filtration rate (eGFR) greater than 60 mL/min, eGFR 30 mL/min to 59 mL/min, eGFR 15 mL/min to 29 mL/min, dialysis dependent, renal transplant, posttransplant dialysis dependent, and death (Figure 1).[2] Patients entered the model based on their baseline eGFR and the percent decline in eGFR at the end of the 2-year BLISS-LN trial period (i.e., stable eGFR or those with a 1% to 20%, 21% to 25%, 26% to 30%, 31% to 40%, and 41% to 57% decline). The proportion of patients experiencing varying degrees of eGFR decline during the BLISS-LN study

was also used to inform the rate of progression to end-stage kidney disease (hereby referred to as end-stage renal disease) or death.[2] Once a patient entered an ESRD health state (i.e., dialysis dependent, renal transplant, posttransplant dialysis dependent), they could no longer transition backward.[2] Patients could transition to the death health state from any health state in the model.[2]

It was assumed that patients would transition through the model at a rate relative to their baseline eGFR and percentage decline from baseline eGFR during the 2-year trial period versus having a treatment-specific efficacy.[2] Patients discontinued treatment at a rate relative to renal worsening, defined by BLISS-LN, for the first 2 years and at a rate reflective of renal flares thereafter.[2]

Model Inputs

The target population was informed by the BLISS-LN trial, which enrolled patients with LN. The mean age was 33.4 years, and the proportion of females was 88.1%.[4]

Model transition probabilities were sourced from the BLISS-LN trial and published literature. Transition probabilities between eGFR greater than 60 mL/min, 30 mL/min to 59 mL/min, 15 mL/min to 29 mL/min, and less than 15 mL/min health states for the first 2 years (i.e., cycles) of each treatment arm were informed by BLISS-LN, whereas the remaining transition probabilities between the eGFR health states were informed by an international study examining 700 patients with LN over a mean follow-up of 5.2 years.[5] The latter transition probabilities were adjusted so that the proportion experiencing ESRD and death at years 3, 5, and 10 aligned with the estimates reported by Coresh et al. (2014) per baseline eGFR and percent decline category.[2,6] Transition probabilities between ESRD health states (i.e., dialysis dependent, renal transplant, posttransplant dialysis dependent) were sourced from Nuijten et al. (2015).[7]

Discontinuation for the first 2 cycles in the model was based on the reported rate of renal worsening in the BLISS-LN trial, defined as increased proteinuria and/or impaired renal function.[2] From cycle 3 onward, it was assumed patients would discontinue at a rate equal to the probability of renal flares,[2] where time to first flare data were taken from the BLISS-LN trial and used to derive the annual flare probabilities fitted with a lognormal parametric function.

The annual probabilities of adverse events for both belimumab plus ST and ST alone were informed using data from the BLISS-LN trial and applied over the time horizon of the model as costs and disutilities.[2]

Health state utility values in the model were informed by 3-Level EQ-5D estimates for chronic kidney disease (CKD) health states, as reported by Jesky et al. (2016).[8] Estimates were reported by CKD stages, including G1/G2, G3a, G3b, G4, and G5, which corresponded to greater than or equal to 60 mL/min, 45 mL/min to 59 mL/min, 30 mL/min to 44 mL/min, 15 mL/min to 29 mL/min, and less than 15 mL/min eGFR health states, respectively.[2] It was assumed that the renal transplant health state had a utility value equivalent to the eGFR greater than or equal to 60 health state, and the posttransplant dialysis-dependent health state had the same utility value as the dialysis-dependent health state.[2] Renal flare and adverse event–related disutility values were informed by published literature.[9-12] In the sponsor's base case, a steroid sparing utility was also applied as reported by Bexelius et al. (2013).[13]

The drug acquisition cost of belimumab was provided by the sponsor, while the cost of all other therapies (i.e., AZA, CYC, MMF, prednisone) were informed by the Ontario Drug Benefit formulary or DeltaPA.[14,15] Treatment adherence was assumed to be 100%.[2] Drug administration, disease management, renal flare, and end-of-life costs were sourced from the Ontario Nurses' Association[16] and published literature.[17-21] All costs were expressed as 2021 Canadian dollars.[2]

Summary of Sponsor's Economic Evaluation Results

All analyses were run probabilistically (1,000 iterations). Submitted deterministic analyses were aligned with the probabilistic results. The probabilistic findings are presented in the Base-Case Results section.

Base-Case Results

Based on the sponsor's probabilistic sequential analysis, belimumab plus CYC followed by AZA was dominated (i.e., more costly and less effective) by belimumab plus MMF. The least costly nondominated therapy was CYC followed by AZA, with the second and third most expensive therapies being MMF and belimumab plus MMF. Belimumab plus MMF was associated with an additional 0.57 QALYs at an additional cost of $196,902 compared to MMF, resulting in an ICER of $345,269 per QALY gained. A disaggregated summary of the incremental analysis is presented in Appendix 3.

The results of the sponsor's probabilistic pairwise base-case analysis can be found in Appendix 3. It demonstrated that belimumab plus CYC followed by AZA was associated with an ICER of $515,277 per QALY gained versus CYC followed by AZA alone. For the comparison between belimumab plus MMF and MMF alone, the ICER was $345,269 per QALY gained.

Based on the deterministic results, the majority (94%) of the incremental QALYs for belimumab versus CYC followed by AZA or MMF were found to be accrued during the extrapolation period (i.e., after the approximately 2 years observed from BLISS-LN).

Table 3: Summary of the Sponsor's Economic Evaluation Results (Sequential Analysis)

Drug	Total costs ($)	Total QALYs	Sequential ICER ($/QALY)
CYC followed by AZA	661,474	24.3	Reference
MMF	672,151	24.5	65,390
Belimumab plus MMF	869,053	25.0	345,269
Belimumab plus CYC followed by AZA	875,054	24.7	Dominated

AZA = azathioprine; CYC = cyclophosphamide; ICER = incremental cost-effectiveness ratio; MMF = mycophenolate mofetil; QALY = quality-adjusted life-year.
Source: Sponsor's pharmacoeconomic submission.[2]

Sensitivity and Scenario Analysis Results

The sponsor conducted several scenario analyses pertaining to different discounting, maximum treatment duration, utility sources, inclusion of treatment waning, inclusion of proteinuria disutilities, exclusion of administration costs, reduced renal flare costs and disutilities, and perspective. No scenarios had an important effect on the ICER, with the following exceptions: when a 5-year maximum treatment duration was included, belimumab plus MMF had an ICER of $29,858 per QALY versus CYC followed by AZA; when

waning was included, belimumab plus MMF had an ICER of $315,434 per QALY versus CYC followed by AZA, and belimumab plus CYC followed by AZA was extendedly dominated through CYC followed by AZA and belimumab plus MMF.

CADTH Appraisal of the Sponsor's Economic Evaluation

CADTH identified several key limitations to the sponsor's analysis that have notable implications for the economic analysis:

- **The reimbursement request population cannot be modelled.** The modelled population in the sponsor's base-case analysis explores the cost-effectiveness of belimumab plus ST (i.e., either MMF alone or CYC followed by AZA) in the full Health Canada indication, which is not aligned with the reimbursement request, which includes the following criteria: adult patients aged 18 years and older who are receiving ST and who have class III, class IV, and/or class V active LN, and if no improvements in disease activity and/or symptoms are observed after 6 months, use should be discontinued. The sponsor's model was not sufficiently flexible to report the cost-effectiveness of belimumab plus ST in the reimbursement request population, incorporating the criteria that patients who do not respond to treatment within 6 months discontinue. It was noted by the sponsor that a half-cycle correction implemented within the sponsor's economic model may account for patients discontinuing at 6 months due to increased proteinuria and/or impaired renal function. However, the underlying data from BLISS-LN did not capture the sponsor's criteria; therefore, the sponsor's modelling practice may represent some form of discontinuation but is neither representative nor a direct substitute for the reimbursement request population criteria of patients who do not respond within 6 months.
    - CADTH was unable to address this limitation within the model. The cost-effectiveness of belimumab plus ST in the reimbursement request population is uncertain because the criteria specifying discontinuation in patients who did not respond to treatment within 6 months was not incorporated into the model's structure or clinical efficacy inputs.
- **Uncertainties in modelled disease progression.** In the sponsor-submitted model, the distribution of patients across health states for the first 2 years of the model was based on the baseline eGFR and percentage decline data from the BLISS-LN trial for both the CYC followed by AZA and the MMF regimens. Results from the sponsor's base-case analysis found a large difference between the life-years gained between ESRD health states (Appendix 3); this does not align with the clinical expert feedback received by CADTH, which stated that CYC followed by AZA or MMF alone were likely to have similar efficacy. Discrepancies between the ST regimen results is likely due to uncertainties from the CYC followed by AZA subgroup. As noted in the CADTH clinical report, subgroup data regarding CYC followed by AZA were insignificant and imprecise, as analyses were limited by the small number of patients. As a result, uncertainty is likely propagated into the reported transition probabilities between eGFR health states from the trial period, which has significant downstream implications as renal outcomes are primarily driven by eGFR improvements from the first 2 cycles (i.e., during the BLISS-LN trial period).

For transitions between eGFR health states (excluding ESRD health states) for year 2 onward, inputs are informed by values from Hanly et al. (2016) and adjusted to reflect the risk of ESRD and death for each baseline eGFR as a percentage decline category, as reported by Coresh et al. (2014).[5,6] According to the CADTH clinical report, Coresh et al. (2014) provided some evidence in support of using lesser declines in eGFR as an alternative end point for CKD progression, and clinical expert feedback further confirmed that transition probabilities from Hanly et al. (2016) would likely reflect Canadian clinical practice and that declining eGFR is predictive of development of ESRD; however, it was noted that this was likely an oversimplification as other factors not captured in the model, such as comorbidities and proteinuria levels, would also impact disease progression.

  - CADTH was unable to address this limitation within the model due to the model structure and data limitations. The direction and magnitude of the impact on the cost-effectiveness results for belimumab plus ST are unknown.

- **Model structure does not adequately reflect the management of active LN in clinical practice.** In the sponsor-submitted economic model, subsequent therapies were not considered, and it was assumed that once patients discontinued belimumab plus ST, they would continue to receive ST alone. However, clinical expert feedback received by CADTH noted that this modelled treatment pattern is not reflective of clinical practice, as patients who discontinue belimumab treatment and/or have inadequate response to first-line induction therapy (e.g., those who do not respond to CYC followed by AZA within 4 months to 6 months) would instead be initiated on additional or different therapies as their disease would still need to be treated (i.e., reintroducing high-dose corticosteroids, modifying ST, and/or putting patients on an alternative therapy such as calcineurin inhibitors [i.e., tacrolimus, cyclosporine] or rituximab in addition to ST). Costs and outcomes associated with subsequent therapies after belimumab discontinuation were not modelled.

  Additionally, clinical expert feedback noted that patients in remission for 3 years to 5 years would likely discontinue immunosuppressive therapy; however, long-term data informing how discontinuation would differ between treatments and patients' responses are limited. Although the sponsor incorporated functionality to discontinue a proportion of patients at a certain time (i.e., 5 years) in the model, this would not accurately capture patients in remission.

  - CADTH was unable to address this limitation due to the model structure and limited data informing comparative efficacy between belimumab plus ST versus other treatments for LN, such as calcineurin inhibitors and rituximab. The direction and magnitude of the impact on the cost-effectiveness results for belimumab plus ST are unknown.

- **Effect of belimumab on long-term flare rate is unknown.** In the sponsor's base-case analysis, the annual rate of renal flares (i.e., 5.8% and 13.0% for belimumab plus ST and ST alone, respectively) was determined using the probability of a flare observed at 2 years based on a lognormal curve fitted to the time to first flare Kaplan-Meier data from BLISS-LN. The lognormal curve was selected as it was associated with the lowest Akaike information criterion and Bayesian information criterion values.[2] The Akaike information criterion and Bayesian information criterion reflect statistical fit in the observed trial period (i.e., interpolation); selection based on Akaike information criterion or

Bayesian information criterion alone may not accurately predict long-term flare rates for treatments (i.e., extrapolation). Clinical expert feedback received by CADTH noted that the sponsor's use of lognormal curves may be conservative, as 20% to 35% of patients who experience adequate disease control are expected to show relapse within 5 years and 27% to 66% of patients with SLE in remission eventually have subsequent flares.[22-24] However, given the absence of evidence, the long-term efficacy of belimumab on reducing flare rates is unknown.

- CADTH was unable to fully address this limitation due to limitations in data availability regarding the effect of belimumab on long-term flare rate. Owing to this and other limitations that could not be addressed, CADTH was unable to derive a base-case analysis. Instead, an exploratory reanalysis using more appropriate assumptions was conducted. In the CADTH exploratory reanalysis, a generalized gamma curve was used to inform the time to first renal flare, and subsequently the annual probability of a renal flare, where an extrapolated 29.0% and 13.8% of patients in the ST alone arm and the belimumab plus ST arms, respectively, were expected to experience a renal flare by year 5.
- To examine the impact of the extrapolated benefit of flares, CADTH conducted a scenario analysis assuming no difference in annual renal flare probabilities between belimumab plus ST and ST alone for year 2 onward.

- **Utilities informed by CKD patients.** In the sponsor's base-case analysis, health state utility values were informed by a UK study examining the health-related quality of life associated with CKD.[8] Clinical expert feedback sought by CADTH noted that patients with active LN are likely to have worse quality of life than their CKD counterparts, and therefore Jesky et al. (2016) values may not accurately reflect the quality of life of patients with active LN.
  - Due to limitations in available data, CADTH was unable to address this limitation. The direction and magnitude of the impact of the cost-effectiveness results are unknown.
- **Cost-effectiveness model is overly complex.** The submitted model was found to be lacking transparency and to be highly inefficient. Coding of the model was spread over multiple sheets, including more than 126 sheets for individual Markov trace calculations.
  - CADTH was unable to address this limitation.

Additional limitations were identified but were not considered to be key limitations. These limitations are outlined subsequently:

- **Model ICERs were associated with variability.** The sponsor's probabilistic analyses were conducted using 1,000 iterations as it was estimated that ICER stabilization would occur at approximately 750 iterations onward. However, CADTH conducted multiple probabilistic analysis runs at 1,000 iterations and noted that the ICER was associated with some variability.
  - CADTH conducted the probabilistic exploratory reanalyses using 5,000 iterations.

Additionally, the following key assumptions were made by the sponsor and have been appraised by CADTH (refer to Table 4).

Table 4: Key Assumptions of the Submitted Economic Evaluation (Not Noted as Limitations to the Submission)

Sponsor's key assumption	CADTH comment
At baseline, patients are assumed to be distributed to the same eGFR health state, regardless of arm, based on the average distribution of patients from BLISS-LN at baseline.	Reasonable.
In year 2 onward, no treatment effect is assumed and patients are assumed to progress through health states based on their baseline eGFR and percentage decline from BLISS-LN.	Reasonable. Assuming no treatment effect between belimumab and comparators was a conservative assumption, confirmed by clinical expert feedback received by CADTH.
Discontinuation of belimumab in year 2 onward is consistent with the probability of renal flares informed by BLISS-LN.	Uncertain but reasonable. Clinical expert feedback sought by CADTH noted that it is reasonable to assume patients would discontinue belimumab treatment after experiencing a renal flare; however, additional reasons for discontinuation that were not captured in the sponsor's model include pregnancy. The effect of treatment discontinuation as a result of pregnancy on the cost-effectiveness of belimumab plus ST is unknown.
Health state utility values for renal transplant patients were assumed to be the same as those in eGFR ≥ 60 mL/min, and utility values for the posttransplant dialysis health state were equal to those on dialysis.	Reasonable. However, as indicated above, clinical expert feedback received by CADTH noted that Jesky et al. (2016) values may not accurately reflect the quality of life of patients with active LN.
Steroid reduction seen at week 104 from BLISS-LN is assumed to be reflective of a reduction seen at 1 year in the model, and patients would remain on their reduced dose for the duration of the model's time horizon.	Reasonable. Clinical expert feedback received by CADTH noted that generally only patients in remission (approximately 40%) would be subjected to a reduction in steroid use, and it would be reasonable to assume that those not in remission may stay on a high dose (or consequently be switched to a higher dose or undergo induction again) to control their disease.

eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; LN = lupus nephritis; ST = standard therapy.

CADTH Reanalyses of the Economic Evaluation

Base-Case Results

Due to limitations with the model design and efficacy data, CADTH was unable to determine a base-case estimate of the cost-effectiveness of belimumab plus ST compared to ST alone (CYC followed by AZA or MMF alone) in the modelled population. As such, the changes in Table 6 reflect a CADTH exploratory reanalysis, rather than a base-case estimate of cost-effectiveness. The CADTH exploratory reanalysis was derived by making changes in model parameter values and assumptions, in consultation with feedback from clinical experts.

The results of the CADTH exploratory reanalysis were consistent with those submitted by the sponsor. The exploratory reanalysis conducted by CADTH demonstrated that belimumab plus MMF compared to MMF was associated with 0.57 additional QALYs at an incremental cost of $201,083, resulting in an ICER of $352,880 per QALY gained. Belimumab plus CYC followed by AZA was dominated (more costly, less effective) by belimumab plus MMF. At a willingness-to-pay threshold of $50,000 per QALY, there was a 0.7% and 0.4% probability of, respectively, belimumab plus CYC followed by AZA and belimumab plus MMF being

cost-effective compared to their ST alone. A summary of the CADTH exploratory reanalysis is presented in Table 6.

Table 5: CADTH Revisions to the Submitted Economic Evaluation

Stepped analysis	Sponsor's value or assumption	CADTH value or assumption
Corrections to sponsor's base case		
None	—	—
Changes to derive the CADTH exploratory reanalysis		
1. Number of iterations for PSA analysis	1,000	5,000
2. Parametric distribution for time to first flare	Belimumab plus ST: Lognormal ST: Lognormal	Belimumab plus ST: Generalized gamma ST: Generalized gamma
CADTH exploratory reanalysis	—	1 + 2

PSA = probabilistic scenario analysis, ST = standard therapy.

Table 6: Summary of the CADTH Exploratory Reanalysis Sequential Results

Drug	Total costs ($)	Total QALYs	Sequential ICER ($/QALY)
CYC followed by AZA	659,831	24.3	Reference
MMF	670,851	24.4	64,701
Belimumab plus MMF	871,934	25.0	352,880
Belimumab plus CYC followed by AZA	878,391	24.7	Dominated

AZA = azathioprine; CYC = cyclophosphamide; ICER = incremental cost-effectiveness ratio; MMF = mycophenolate mofetil; QALY = quality-adjusted life-year.

Scenario Analysis Results

A scenario analysis was conducted assuming equal annual flare probabilities on the CADTH exploratory reanalysis. Results of this scenario are presented in Appendix 4 and resulted in an ICER of 426,779 per QALY gained for belimumab plus MMF compared to CYC followed by AZA only (belimumab plus CYC followed by AZA was dominated by belimumab plus MMF).

Additionally, CADTH undertook price reduction analyses based on the sponsor's base case and CADTH's exploratory reanalysis. Given the uncertainty of the cost-effectiveness results for belimumab plus CYC followed by AZA, and given that clinical expert feedback received by CADTH noted that CYC followed by AZA and MMF alone would likely have similar efficacy, a price reduction analysis on belimumab plus CYC followed by AZA was conducted despite it being a dominated treatment in the CADTH exploratory reanalysis. The price reduction analysis suggested that for belimumab to be considered cost-effective at a willingness-to-pay threshold of $50,000 per QALY compared to CYC followed by AZA alone, price reductions of at least 73% and 58% would be required for belimumab plus CYC followed by AZA and belimumab plus MMF, respectively (Table 7). Price reductions based on each regimen of belimumab plus ST were also conducted as scenario analyses in Appendix 4.

Table 7: CADTH Price Reduction Analyses

Analysis	ICERs for Belimumab plus MMF vs. CYC followed by AZA		ICERs for Belimumab plus CYC followed by AZA vs. CYC followed by AZA	
Price reduction	Sponsor's base case	CADTH reanalysis	Sponsor's base case	CADTH reanalysis
No price reduction	$241,084	$246,566	$448,443	$460,019
10%	$207,009	$213,137	$389,105	$404,157
20%	$173,970	$179,320	$334,263	$347,455
30%	$140,930	$145,503	$279,421	$290,752
40%	$107,891	$111,685	$224,579	$234,050
50%	$74,851	$77,868	$169,737	$177,348
60%	$41,812	$44,051	$114,895	$120,645
70%	$8,772	$10,233	$60,053	$63,943
80%	Dominant	Dominant	$5,212	$7,240
90%	Dominant	Dominant	Dominant	Dominant

AZA = azathioprine, CYC = cyclophosphamide; ICER = incremental cost-effectiveness ratio; MMF = mycophenolate mofetil; vs. = versus.
Note: Price reduction analyses were based on deterministic results.

Issues for Consideration

- **Proportion of belimumab SC use for patients with active LN is unknown.** Clinical expert feedback received by CADTH noted that although most patients (80% to 90%) would be treated with IV belimumab, SC belimumab may still be used in clinical practice. Belimumab SC is associated with a lower unit cost; however, due to a lack of efficacy data, the cost-effectiveness of SC belimumab in the population of interest remains unknown.
- **Belimumab SC has been previously reviewed by CADTH for SLE.** In the previous review for SLE, CADTH recommended that belimumab SC was not reimbursed as a result of the BLISS-SC trial results, which showcased a modest improvement in the response rate compared to placebo-treated patients and an insignificant reduction in the proportion of patients who were able to reduce their dose of prednisone. The BLISS-SC study also failed to assess the effect of belimumab SC on several other outcomes important to patients, including health-related quality of life.[25]
- **Availability of rituximab biosimilars.** Although use of rituximab for the treatment of patients with active LN is off label, several biosimilars have become available and successfully undergone pan-Canadian Pharmaceutical Alliance negotiations.[26-29] However, the cost-effectiveness of belimumab (IV and SC) compared to rituximab is unknown, as rituximab was not included as a comparator in the sponsor's economic model.

Overall Conclusions

Data from the BLISS-LN trial suggest that compared to placebo, treatment with belimumab plus ST significantly improved renal response as measured by the primary outcome — primary efficacy renal response — in adult patients with active class III, IV, and/or V LN. Time to renal-related events or death

showed statistically significant differences in favour of belimumab, with a greater proportion of patients in the belimumab group experiencing reductions in prednisone use and fewer patients in the belimumab group experiencing severe flares than in the placebo group.

As a result of the inappropriate model structure and limitations or uncertainty in the clinical data, CADTH was unable to derive a base-case analysis. Instead, CADTH undertook exploratory reanalyses to address limitations related to flare data, where an alternative extrapolation was selected to inform the time to first renal flare event (and subsequently the annual probability of a renal flare) to better align with the clinical expert feedback sought by CADTH.

Based on the CADTH exploratory reanalysis, belimumab plus MMF was associated with an ICER of $352,880 per QALY gained (incremental costs = $201,083; incremental QALYs = 0.57) versus MMF alone, whereas belimumab plus CYC followed by AZA was dominated (more costly, less effective) by belimumab plus MMF. The CADTH exploratory reanalysis results were similar to those submitted by the sponsor, in that belimumab was not cost-effective at commonly used willingness-to-pay thresholds. At a willingness-to-pay threshold of $50,000 per QALY gained, belimumab plus CYC followed by AZA would require a price reduction of 73% and belimumab plus MMF would require a price reduction of 58% to be considered cost-effective versus CYC followed by AZA alone. However, given the uncertainty around the economic model, further price reductions may be necessary to ensure the cost-effectiveness of belimumab plus ST. This is especially true for belimumab plus CYC followed by AZA, as there were significant limitations in the CYC followed by AZA subgroup data due to a small sample size and comparative results not aligning with clinical expert feedback.

There remains a significant degree of uncertainty in the cost-effectiveness of belimumab plus ST (CYC followed by AZA or MMF alone) compared to ST alone for patients with active LN. CADTH was unable to adjust for major limitations, including the inability to model the reimbursement population, uncertainties in the modelled disease progression, a model structure that failed to adequately reflect the management of active LN in clinical practice, and utility values for patients with LN. As such, the cost-effectiveness of belimumab plus ST should be interpreted with caution. Furthermore, clinical expert feedback received by CADTH noted that although most patients (80% to 90%) would be treated with IV belimumab, SC belimumab may still be used in clinical practice. Although associated with a lower unit cost, there is a lack of efficacy data, and therefore the cost-effectiveness of SC belimumab remains unknown.

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Appendix 1: Cost Comparison Table

Note this appendix has not been copy-edited.

The comparators presented in Table 8 have been deemed to be appropriate based on feedback from clinical expert(s). Comparators may be recommended (appropriate) practice or actual practice. Existing Product Listing Agreements are not reflected in the table and as such, the table may not represent the actual costs to public drug plans.

Table 8: CADTH Cost Comparison Table for Active Lupus Nephritis

Treatment	Strength / concentration	Form	Price	Recommended dosage	Annual cost[a]
Belimumab (Benlysta)	120 mg/5 mL 400 mg/20 mL	Single-use vials Lyophilized powder for IV infusion	$305.7100[a] $1,019.0100[a]	10 mg per kg every 2 weeks for the first 3 doses, then every 4 weeks	Year 1: $25,938 Year 2+: $23,263
	200 mg/mL	Solution for SC injection	$1,581.5900 for a pack of 4[a]	200 mg once weekly	$20,631
Antimalarial Drugs (Off-label Use)					
Hydroxychloroquine (Plaquenil, generic)	200 mg	Oral Tablet	0.1576	200 to 400 mg daily[b]	$58 to $115
Corticosteroids (Off-label Use)					
Prednisone (generic)	1 mg 5 mg 50 mg	Oral Tablet	0.1214 0.0220 0.1735	0.3 to 0.5 mg/kg daily[c]	$34 to $56
Immunosuppressants or Immune Modulators (Off-label Use)					
Azathioprine (generic)	50 mg	Oral Tablet	0.2405	2 mg/kg daily[c]	$246
Cyclophosphamide (Procytox)	500 mg 1,000 mg 2,000 mg	Vials Powder for Injection	97.8000[d] 177.2700[d] 326.0000[d]	500 mg every 2 weeks for 6 doses[c]	$587
Cyclosporine (generic)	10 mg 25 mg 50 mg 100 mg	Capsules	0.6770 0.7870 1.5350 3.0720	3 to 5 mg/kg daily[b]	$2,491 to $3,927
	100 mg/mL	Solution for Injection	5.4624		$4,190 to $6,983
Mycophenolic acid (Myfortic)	180 mg 360 mg	Tablets	0.9989 1.9977	2 to 3 g daily[c]	$4,054 to $6,080
Mycophenolate mofetil (Cellcept, generic)	250 mg 500 mg	Oral Tablet	0.3712 0.7423	2 to 3 g daily[c]	$1,085 to $1,627

Treatment	Strength / concentration	Form	Price	Recommended dosage	Annual cost[a]
Tacrolimus	0.5 mg 1 mg 5 mg	Capsules	1.4775 1.8900 9.4650	0.05 to 0.1 mg/kg daily[b]	$2,416 to $4,832
Monoclonal Antibodies (Off-label Use)					
Rituximab	10 mg/mL	Solution for IV Injection	29.7000	1,000 mg for 2 doses, 2 weeks apart[b]	$5,940

Note: All prices are from the Ontario Drug Benefit Formulary (accessed August 2022), unless otherwise indicated.[15] Prices do not include costs of product dispensing, dose preparation, or administration. A patient weight and body surface area of 70 kg and 1.8 m^2 was assumed. Annual period assumes 365.25 days. The calculated annual doses are based on product monograph, unless otherwise indicated. When multiple formulations were available, the least expensive type to obtain the recommended dose was used to calculate costs.

[a]Sponsor-submitted price.[3]

[b]Canadian Pharmacist Association - Therapeutic Choices.[30]

[c]European Renal Association–European Dialysis and Transplant Association (ERA-EDTA) guidelines for the management of lupus nephritis.[31]

[d]Wholesale acquisition price based on IQVIA DeltaPA database (August 2022).[14]

Appendix 2: Submission Quality

Note this appendix has not been copy-edited.

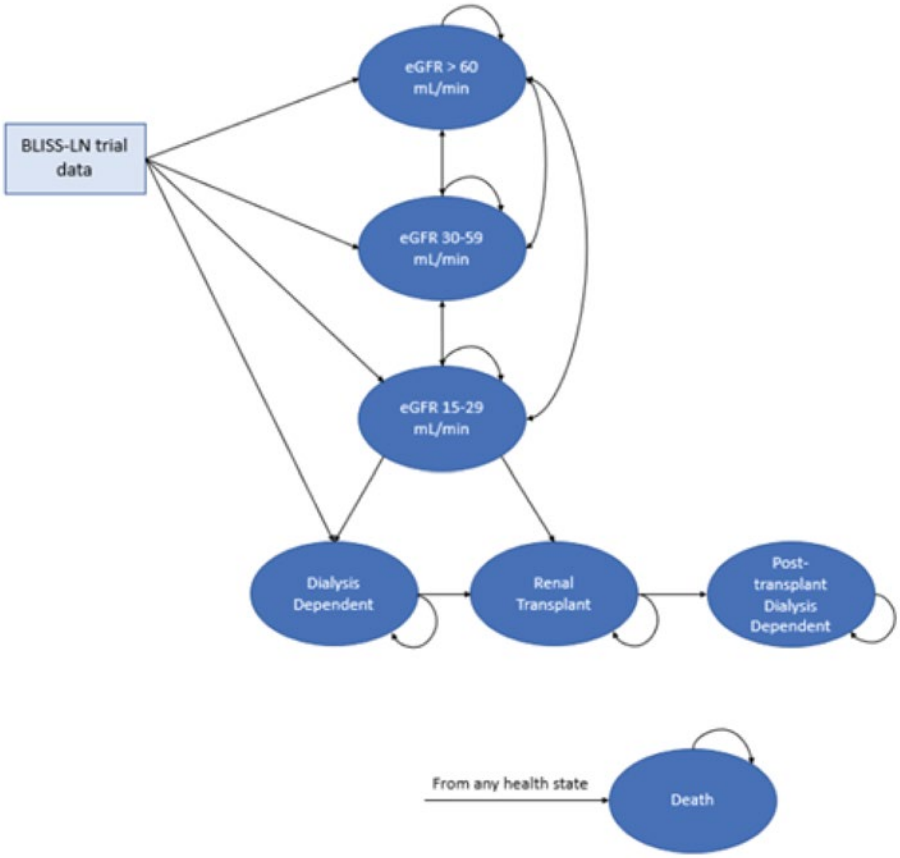
Table 9: Submission Quality

Description	Yes/No	Comments
Population is relevant, with no critical intervention missing, and no relevant outcome missing	No	Refer to CADTH appraisal. The reimbursement request population could not be modelled and analyzed.
Model has been adequately programmed and has sufficient face validity	No	Refer to CADTH appraisal. The model was overly complex.
Model structure is adequate for decision problem	No	Refer to CADTH appraisal. The model structure did not adequately reflect the management of active LN in clinical practice and failed to include relevant comparators such as calcineurin inhibitors and rituximab.
Data incorporation into the model has been done adequately (e.g., parameters for probabilistic analysis)	No	Refer to CADTH appraisal.
Parameter and structural uncertainty were adequately assessed; analyses were adequate to inform the decision problem	Yes	No comment.
The submission was well organized and complete; the information was easy to locate (clear and transparent reporting; technical documentation available in enough details)	No	Refer to CADTH appraisal. The model was overly complex, and many details (e.g., transition probability adjustments for ESRD or mortality, derivation of one-off transplant cost) were not adequately described in the report or model.

Appendix 3: Additional Information on the Submitted Economic Evaluation

Note this appendix was not copy-edited.

Figure 1: Model Structure



eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease.

Source: Sponsor-submitted report.3

Detailed Results of the Sponsor's Base Case

Table 10: Disaggregated Results of the Sponsor's Base Case (Sequential Analysis)

Parameter	CYC followed by AZA	MMF	Belimumab plus MMF	Belimumab plus CYC followed by AZA
Discounted LYs				
Total	**31.36**	**31.46**	**31.93**	**31.66**
eGFR > 60	6.17	5.70	6.65	6.18
eGFR 30-59	8.96	10.04	10.80	10.26
eGFR 15-29	7.86	8.21	9.13	8.20
Dialysis dependent	4.56	4.09	2.96	3.79
Renal transplant	1.75	1.57	1.11	1.46
Posttransplant dialysis dependent	2.06	1.85	1.28	1.77
Discounted QALYs				
Total	**24.30**	**24.46**	**25.03**	**24.71**
eGFR >60	5.26	4.86	5.67	5.27
eGFR 30-59	7.17	8.04	8.65	8.22
eGFR 15-29	5.82	6.07	6.75	6.07
Dialysis dependent	3.35	3.00	2.17	2.78
Renal transplant	1.49	1.34	0.95	1.24
Posttransplant dialysis dependent	1.51	1.35	0.93	1.29
Flare disutility	−0.44	−0.44	−0.35	−0.36
AE disutility	−0.00	−0.01	−0.01	−0.00
Steroid sparing utility increment	0.13	0.24	0.26	0.19
Discounted costs ($)				
Total	**661,474**	**672,151**	**869,053**	**875,054**
Drug acquisition cost	7,924	34,815	309,880	265,064
Administration costs	362	0	9,530	9,288
Health state costs	637,402	603,075	518,925	579,492
Flare costs	13,701	13,742	11,084	11,147
AE costs	1,480	19,915	19,039	9,462
End-of-life costs	605	603	595	600
Sequential ICER ($/QALY)	**Reference**	**65,390**	**345,269**	**Dominated**

AE = adverse event; AZA = azathioprine, CYC = cyclophosphamide, eGFR = estimated glomerular filtration rate, ICER = incremental cost-effectiveness ratio, LY= life-year, MMF = mycophenolate mofetil, QALY = quality-adjusted life-year.

Table 11: Summary of the Sponsor's Pairwise Economic Evaluation Results

Drug	Total costs ($)	Incremental costs ($)	Total QALYs	Incremental QALYs	ICER vs. ST ($/QALY)
Belimumab plus CYC followed by AZA versus CYC followed by AZA					
CYC followed by AZA	661,474	Reference	24.30	Reference	Reference
Belimumab plus CYC followed by AZA	875,054	213,581	24.71	0.41	515,277
Belimumab plus MMF versus MMF					
MMF	672,151	Reference	24.46	Reference	Reference
Belimumab plus MMF	869,053	196,902	25.03	0.57	345,269

AZA = azathioprine; CYC = cyclophosphamide; ICER = incremental cost-effectiveness ratio; MMF = mycophenolate mofetil; QALY = quality-adjusted life-year; ST = standard therapy.

Source: Sponsor's pharmacoeconomic submission.[2]

Appendix 4: Additional Details on the CADTH Reanalyses and Sensitivity Analyses of the Economic Evaluation

Note this appendix has not been copy-edited.

Table 12: Disaggregated Summary of CADTH's Economic Evaluation Results

Parameter	CYC followed by AZA	MMF	Belimumab plus MMF	Belimumab plus CYV followed by AZA
Discounted LYs				
Total	**31.35**	**31.45**	**31.93**	**31.66**
eGFR >60	6.15	5.70	6.64	6.20
eGFR 30-59	8.99	10.05	10.84	10.26
eGFR 15-29	7.86	8.21	9.13	8.21
Dialysis dependent	4.53	4.06	2.93	3.76
Renal transplant	1.77	1.58	1.12	1.46
Posttransplant dialysis dependent	2.06	1.85	1.27	1.76
Discounted QALYs				
Total	**24.26**	**24.43**	**25.00**	**24.68**
eGFR >60	5.22	4.84	5.65	5.27
eGFR 30-59	7.21	8.05	8.69	8.23
eGFR 15-29	5.80	6.06	6.74	6.06
Dialysis dependent	3.30	2.96	2.14	2.74
Renal transplant	1.50	1.35	0.95	1.24
Posttransplant dialysis dependent	1.51	1.35	0.93	1.28
Flare disutility	−0.41	−0.42	−0.34	−0.34
AE disutility	0.00	−0.01	−0.01	0.00
Steroid sparing utility increment	0.00	0.00	0.00	0.00
Discounted costs ($)				
Total	**659,831**	**670,851**	**871,934**	**878,391**
Drug acquisition cost	7,983	34,807	315,123	270,376
Administration costs	362	0	9,662	9,420
Health state costs	636,282	602,243	516,820	577,637
ST medication	0	0	0	0
Tests and diagnostic Procedures	7,886	8,093	8,317	8,133

Parameter	CYC followed by AZA	MMF	Belimumab plus MMF	Belimumab plus CYV followed by AZA
Hospitalization	143,320	139,774	131,381	137,175
Dialysis/ renal transplant	485,075	454,376	377,122	432,329
Flare costs	13,004	13,044	10,563	10,620
AE costs	1,566	20,125	19,143	9,710
End-of-life costs	633	632	623	628
Sequential ICER ($/QALY)	**Reference**	**64,701**	**352,880**	**Dominated**

AE = adverse event; AZA = azathioprine, CYC = cyclophosphamide, eGFR = estimated glomerular filtration rate, ICER = incremental cost-effectiveness ratio, LY= life-year, MMF = mycophenolate mofetil, QALY = quality-adjusted life-year.

Table 13: Summary of the CADTH Exploratory Sequential Reanalysis Results

Drug	Total costs ($)	Incremental costs ($)	Total QALYs	Incremental QALYs	ICER vs. ST ($/ QALY)
Belimumab plus CYC followed by AZA versus CYC followed by AZA					
CYC followed by AZA	659,831	Reference	24.26	Reference	Reference
Belimumab plus CYC followed by AZA	878,391	218,560	24.68	0.42	517,290
Belimumab plus MMF versus MMF					
MMF	670,851	Reference	24.43	Reference	Reference
Belimumab plus MMF	871,934	201,083	25.00	0.57	352,880

AZA = azathioprine; CYC = cyclophosphamide; ICER = incremental cost-effectiveness ratio; MMF = mycophenolate mofetil; QALY = quality-adjusted life-year; ST = standard therapy.

Note: Analysis was conducted probabilistically.

Scenario Analyses

Table 14: Summary of CADTH's Scenario Analysis (Equal Flare Probabilities) Results

Drug	Total costs ($)	Total QALYs	Sequential ICER ($/QALY)
CYC followed by AZA	659,448	24.3	Reference
MMF	670,535	24.4	67,407
Belimumab plus MMF	876,074	24.9	426,779
Belimumab plus CYC followed by AZA	882,126	24.6	Dominated

AZA = azathioprine; CYC = cyclophosphamide; ICER = incremental cost-effectiveness ratio; MMF = mycophenolate mofetil; QALY = quality-adjusted life-year.

Table 15: CADTH Price Reduction Analyses (Belimumab Plus CYC Followed by AZA Versus CYC Followed by AZA)

Analysis	ICERs for Belimumab plus CYC followed by AZA vs. CYC followed by AZA	
Price reduction	**Sponsor's base case**	**CADTH reanalysis**
No price reduction	$448,443	$460,019
10%	$389,105	$404,157
20%	$334,263	$347,455
30%	$279,421	$290,752
40%	$224,579	$234,050
50%	$169,737	$177,348
60%	$114,895	$120,645
70%	$60,053	$63,943
80%	$5,212	$7,240
90%	Dominated	Dominated

AZA = azathioprine, CYC = cyclophosphamide; CER = incremental cost-effectiveness ratio; vs. = versus.
Price reduction analyses were based on deterministic results.

Table 16: CADTH Price Reduction Analyses (Belimumab Plus MMF Versus MMF)

Analysis	ICERs for Belimumab plus MMF vs. MMF	
Price reduction	**Sponsor's base case**	**CADTH reanalysis**
No price reduction	$300,509	$308,332
10%	$255,833	$264,756
20%	$212,540	$220,260
30%	$169,247	$175,763
40%	$125,953	$131,267
50%	$82,660	$86,770
60%	$39,367	$42,274
70%	Dominated	Dominated

ICER = incremental cost-effectiveness ratio; MMF = mycophenolate mofetil; vs. = versus.
Price reduction analyses were based on deterministic results.

Appendix 5: Submitted Budget Impact Analysis and CADTH Appraisal

Note this appendix has not been copy-edited.

Table 17: Summary of Key Take-Aways

Key take-aways of the budget impact analysis

• CADTH identified the following key limitations within the sponsor's budget impact analysis
  ◦ Proportion of patients eligible for belimumab treatment is uncertain
  ◦ Uncertainty in SC vs IV user of belimumab in Canadian clinical practice
  ◦ Proportion of patients requiring belimumab induction in Year 1 was underestimated
  ◦ Uncertainty in the proportion of patients requiring induction to re-establish remission
• The CADTH reanalysis updated the proportion of patients expected to receive induction belimumab in Year 1. In the CADTH base case, when considering belimumab as add-on treatment, the budget impact of reimbursement belimumab plus ST is expected to be $2,796,447 in Year 1, $4,884,617 in Year 2, and $6,394,557 in Year 3. The 3-year total budget impact was $14,075,621.

Summary of Sponsor's Budget Impact Analysis

The sponsor submitted a budget impact analysis (BIA) to estimate the 3-year budget impact of reimbursing belimumab plus ST for the treatment of adult patients with active LN. The analysis was taken from the perspective of the Canadian public drug plan. A 3-year time horizon was used from 2023 to 2025, with 2022 as the base year. The target population size was derived with an epidemiological approach, using both prevalent and incident cases to determine the total number of patients with LN eligible for treatment each year.[32] Key inputs to the BIA are documented in Table 18.

The BIA compared 2 scenarios to determine the incremental budget impact of reimbursing belimumab plus ST. The reference case scenario assumed that 100% of eligible patients would be treated with ST alone. The new drug scenario included belimumab plus ST along with ST alone. In the sponsor's base case, costs related to drug acquisition were considered. Vial sharing was not included.[32]

State the key assumptions:

- Prevalence of the eligible LN population was assumed to be stable over the time horizon.
- 100% of patients would be eligible to receive belimumab at the time of reimbursement.
- The comparator ST alone is made of the following ST regiments: 10% CYC followed by AZA and 90% MMF.
- All patients are on high-dose corticosteroids (i.e., prednisone 10 mg per day).
- A proportion of patients (i.e., 5.8% and 13.0% of patients on belimumab plus ST and ST alone, respectively) on maintenance therapy would experience renal flares that would require induction to re-establish remission.

Table 18: Summary of Key Model Parameters

Parameter	Sponsor's estimate (reported as Year 1 / Year 2 / Year 3 if appropriate)
Target population	
Prevalence/Incidence of SLE (diagnosed)	0.1%[33] / 0.007%[33]
Patients with LN	38.3%[34]
Patients with active LN receiving treatment	60.4%[2,35]
Public payer patients	35.1%[36]
Patients eligible for belimumab	100%[a]
Number of patients eligible for drug under review	2,230 / 2,250 / 2,270
Market uptake (3 years)	
Uptake (reference scenario)	
ST alone	100% / 100% / 100%
Uptake (new drug scenario)	
Belimumab plus ST	[redacted]% / [redacted]% / [redacted]%
ST alone	[redacted]% / [redacted]% / [redacted]%
Cost of treatment[b] (per patient)	
Cost of treatment in year 1 / year 2+ Annually	
Belimumab	$25,200 / $21,842
ST Alone[c]	$1,311 / $1,019

LN = lupus nephritis, SLE = systemic lupus erythematosus, ST = standard therapy.

[a]Sponsor assumption.[32]

[b]Treatment costs include 10 mg of prednisone per day.

[c]Cost ST alone assumes the following ST regiments: 10% CYC followed by AZA and 90% MMF.

Summary of the Sponsor's BIA Results

The estimated incremental budget impact of funding belimumab plus ST for the treatment of active LN in adult patients was $2,442,280 in year 1, $4,884,617 in year 2, and $6,394,557 in year 3, for a 3-year incremental budget impact of $13,721,454.

CADTH Appraisal of the Sponsor's BIA

CADTH identified several key limitations to the sponsor's analysis that have notable implications on the results of the BIA:

- **Proportion of patients eligible for belimumab treatment is uncertain**. In the sponsor's base case, the proportion of patients with active LN eligible to receive belimumab treatment was assumed to be 100%.[32] Clinical expert feedback received by CADTH noted that this is a reasonable assumption;

however, they also noted that in clinical practice belimumab eligibility may be restricted to patients with active LN who do not attain remission after 2-3 months of therapy.

  - Due to limitations in data availability, CADTH was unable to address this limitation. However, if belimumab eligibility is to be restricted to patients who do not attain remission after 2-3 months of therapy, this is expected to decrease the 3-year incremental budget impact of belimumab.

- **Uncertainty in SC versus IV use of belimumab in Canadian clinical practice.** In the sponsor's base case, it was assumed that IV belimumab would represent 100% of the future market uptake.[32] However, clinical expert feedback received by CADTH stated that in Canadian clinical practice 80% to 90% of patients would be expected to be treated with IV belimumab, and the remaining may use SC belimumab.
  - CADTH conducted a scenario analysis assuming 85% of belimumab uptake would be IV with the remaining 15% being SC.
- **Proportion of patients requiring belimumab induction in year 1 was underestimated**. In the sponsor's base-case analysis, it was assumed that incident patients and a proportion of prevalent patients who have relapsed and are reinitiating therapy (informed by the annual renal fare rate derived from the BLISS-LN trial) would require belimumab induction, while the remaining prevalent patients would be on maintenance belimumab. Given that year 1 represents the first year of belimumab therapy availability, it is unreasonable to assume that a subset of patients would already be on maintenance therapy. Furthermore, this underestimates the budget impact of belimumab plus ST, as the year 1 costs of belimumab treatment is higher than subsequent years (due to the shorter period between the first 3 doses).
  - To address this limitation, all patients estimated to receive belimumab in year 1 were revised to receive induction therapy and the associated induction therapy costs (i.e., year 1 belimumab treatment cost).
- **Uncertainty in the proportion of patients requiring induction to re-establish remission**. In the sponsor's base case, it was assumed that a subset of patients with LN on maintenance therapy would experience renal flares (informed by annual rates from the BLISS-LN trial) over the course of the analysis, and therefore would require induction to re-establish remission. Clinical expert feedback received by CADTH agreed that patients would require induction to attempt to re-establish remission; however, patients are unlikely to be placed on their original treatment and instead would be initiated on additional/different therapies (i.e., reintroducing high-dose corticosteroids, modifying ST, and/or put patients on an alternative therapy such as rituximab in addition to ST). Therefore, it is unreasonable to assume that all relapsed patients would be captured by either belimumab plus ST or ST alone.
  - CADTH was unable to address this limitation due to limitations in data availability. The impact on the 3-year incremental budget impact of belimumab plus ST is unknown.

CADTH Reanalyses of the BIA

Based on the limitations identified, CADTH's base case estimated that all patients receiving belimumab in year 1 were expected to receive induction therapy and therefore year 1 belimumab treatment costs.

The results of the CADTH stepwise reanalysis is presented in summary format in Table 20 and a more detailed breakdown is presented in Table 21. Based on the CADTH base case, the estimated incremental budget impact of reimbursing belimumab plus ST is $2,796,447 in year 1, $4,884,617 in year 2, and $6,394,557 in year 3. The 3-year total budget impact was $14,075,621.

A scenario analysis was conducted where it was assumed that 85% of patients would receive belimumab IV and the remainder (i.e., 15%) would receive belimumab SC. The budget impact from this analysis was $13,936,784 over 3 years. Additionally, 2 price adjustment scenarios were conducted with 3-year budget impacts ranging from $3,812,297 (73% price reduction versus CYC followed by AZA) to $5,921,199 (58% price reduction versus MMF).

Table 19: CADTH Revisions to the Submitted Budget Impact Analysis

Stepped analysis	Sponsor's value or assumption	CADTH value or assumption
Corrections to sponsor's base case		
None	—	—
Changes to derive the CADTH base case		
1. Proportion of patients requiring belimumab induction	Patients requiring induction of belimumab in year 1 include incident patients and relapsed prevalent patients	All patients receiving belimumab treatment in year 1 are assumed to receive induction therapy and the associated year 1 belimumab treatment cost
CADTH base case	Reanalysis 1	

Table 20: Summary of the CADTH Reanalyses of the BIA

Stepped analysis	Three-year total
Submitted base case	$13,721,454
CADTH reanalysis 1 and base case	$14,075,621

BIA = budget impact analysis.

Table 21: Detailed Breakdown of the CADTH Reanalyses of the BIA

Stepped analysis	Scenario	Year 0 (current situation)	Year 1	Year 2	Year 3	Three-year total
Submitted base case	ST Alone	$2,371,087	$2,392,036	$2,413,199	$2,434,578	$7,239,813
	Belimumab plus ST	$2,371,087	$4,834,317	$7,297,816	$8,829,135	$20,961,268
	Budget impact	$0	$2,442,280	$4,884,617	$6,394,557	$13,721,454
CADTH base case	ST Alone	$2,371,087	$2,392,036	$2,413,199	$2,434,578	$7,239,813
	Belimumab plus ST	$2,371,087	$5,188,483	$7,297,816	$8,829,135	$21,315,434
	Budget impact	$0	$2,796,447	$4,884,617	$6,394,557	$14,075,621
CADTH scenario analysis: 73% price reduction (vs. CYC followed by AZA)	ST Alone	$2,371,087	$2,392,036	$2,413,199	$2,434,578	$7,239,813
	Belimumab plus ST	$2,371,087	$2,166,208	$3,728,906	$4,156,997	$11,052,111
	Budget impact	$0	$774,172	$1,315,706	$1,722,419	$3,812,297
CADTH scenario analysis: 58% price reduction (vs. MMF)	ST Alone	$2,371,087	$2,392,036	$2,413,199	$2,434,578	$7,239,813
	Belimumab plus ST	$2,371,087	$3,581,744	$4,462,243	$5,117,025	$13,161,013
	Budget impact	$0	$1,189,708	$2,049,044	$2,682,448	$5,921,199
CADTH scenario analysis: Belimumab IV (85%) and SC (15%)	ST Alone	$2,371,087	$2,392,036	$2,413,199	$2,434,578	$7,239,813
	Belimumab plus ST	$2,371,087	$5,142,610	$7,257,566	$8,776,422	$21,176,598
	Budget impact	$0	$2,750,574	$4,844,367	$6,341,844	$13,936,784

AZA = azathioprine; BIA = budget impact analysis; CYC = cyclophosphamide; MMF = mycophenolate mofetil; ST = standard therapy.

Stakeholder Input

List of Tables

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Patient Input

Arthritis Consumer Experts Input

About Arthritis Consumer Experts

Canada's largest, longest running national arthritis patient organization headquartered in Vancouver, BC, Arthritis Consumer Experts (ACE) provides free, science-based information and education programs in both official languages to people with arthritis. ACE serves people living with all forms of arthritis by helping them take control of their disease and improve their quality of life through education and (em)powerment. Founded and led by people with arthritis, ACE also advocates on arthritis health policy and provides research-based education through ACE's JointHealth™ family of programs and the Arthritis Broadcast Network, directly to consumers/patients, media and government. ACE operates as a non-profit in a fully transparent manner and is guided by a strict set of guiding principles, set out by an advisory board comprised of leading scientists, medical professionals and informed arthritis consumers. Ultimately, we are guided by the needs of our members, who are people living with arthritis, and their caregivers.

Link to website: www.jointhealth.org

Information Gathering

The information was gathered from anonymous data collected from lupus patients in ACE's 2021 Survey on Virtual Care for People Living with Arthritis, ACE's 2021 Survey on Arthritis Medications Reimbursement, ACE's 2021 Survey on Arthritis Self-Advocacy, and ACE's Survey on Arthritis and Mental Health and from an in-depth interview with a female lupus patient. The questions asked in the ACE Surveys are not exactly the same as that provided in the patient input template by CADTH; however, ACE has provided answers that are relevant to each section. Where patient inputs are in French, we have provided a Google English translation below the French.

Disease Experience

How does the disease impact the patients' day-to-day life and quality of life?

Lupus is an unpredictable disease in which a person's immune system produces an excess of proteins called antibodies that attach themselves to various structures in the body. The accumulation of these antibodies in the tissues can cause inflammation, damage and pain.

From ACE's 2021 National Survey on Virtual Care for People Living with Arthritis

A total of 34 people of all the survey respondents reported they were living with lupus. Eighty-eight per cent of lupus survey respondents were women. Nearly 47% had been living with lupus for over 15 years, while 34% were living with lupus for 5 years or less.

From ACE's 2021 Survey on Arthritis Self-Advocacy

Patient 1: Woman living with lupus for 11-15 years and from Quebec: "L'arthrite est une maladie méconnu, beaucoup la sous-estime ou, car elle n'est pas toujours visible, ne croit pas à la douleur ou à la fatigue que la maladie génère."

> "Arthritis is an unknown disease, many underestimate it or, because it is not always visible, do not believe in the pain or fatigue that the disease generates." (Google English Translation)

Patient 2: Woman living with lupus for 1-5 years and from Quebec: "Mon employeur est très sensible aux problèmes personnels de ses employés. Avec la médication qui a réduit mes symptômes d'arthrite de 80%, je savais que ça ne n'empêcherait pas de faire le travail que j'avais à faire, car j'avais réussit à travailler avec des poussées de lupus pendant près d'un an."

> "My employer is very sensitive to the personal problems of its employees. With the medication that reduced my arthritis symptoms by 80%, I knew it wouldn't get in the way of doing the job I had to do, as I had managed to work with lupus flare-ups for nearly 'a year." (Google English Translation)

From ACE's 2022 Survey on Arthritis and Mental Health

Two lupus patients reported that in the last 1 to 14 days (at the time of completing the Survey), they were having trouble with their mental health, which includes stress, anxiety, depression, and emotional distress.

Another patient added: "In my experience, it has been difficult to find mental healthcare professionals who have specific experience in treating people with lupus and/or chronic conditions. This is something I would appreciate assistance with/guidance from other members of my healthcare team.

> "I was diagnosed with lupus at 50 with acute renal failure due to nephritis. I was critically ill and my mother came out to help. I could not work. Lupus 'retired' me and forced me to give away my practice with more than 2000 patients. After I got off the 'big' meds, I had a giant identity crisis and became depressed." — From a female patient living with lupus

How does the disease impact the caregivers' day-to-day life and quality of life?

From ACE's 2021 National Survey on Virtual Care for People Living with Arthritis

Patients reported challenges in managing the physical symptoms of lupus as it can be severe and debilitating, especially during disease episodes or flares. These physical symptoms also impact a patient's mental health, relationships with family and friends, and work.

> "My mother came out to help. My book group and other friends and neighbours rotated a meal to our family as they saw we needed. Extra help with childcare, driving, shopping, ironing, yard work, and handyman chores were appreciated. A friend's ear is still the best therapy in the world. Partners need to be intimately honest (relationship-wise, sexually, emotionally) and figure out together what to do and what will work)." — From a female patient living with lupus

Are there any aspects of the illness that are more important to control than others?

We have no information gathered for this question.

Experiences with Currently Available Treatments

How well are patients managing their disease/condition with currently available treatments?

From ACE's Survey on Arthritis Medications Reimbursement

Patient 3: Woman living with lupus for 11-15 years and from BC: "I only know of Fair Pharmacare in BC which requires a $ threshold, which is based on family income. I think ours is $1500, before we get any help. Also, there's this from called a special authority that you need for some meds to be included, very confusing. If there's any other programs in BC, I'd like my rheumatologist or pharmacist to tell me as they know I don't have any coverage. My daughter gets all (limited list though) her psychiatric medication paid for by our government."

Patient 4: Woman living with lupus for 1-5 years from Manitoba: "If Pharmacare would agree to cover mycophenalate on the rheumatolgoist's first request. They only started cover it after the fourth request."

Patient 5: Woman living with lupus for 15+ years and from Quebec: "Il y a des fois où ça été très long avant d'avoir une réponse des assurances."

> "There are times when it took a very long time to get an answer from insurance." (Google English Translation)

Patient 6: Woman living with lupus for 15+ years and from Quebec: "Qu'ils acceptent un renouvellement plus fréquent pour que je puisse renouveler tous mes médicaments en même temps même lorsqu'il m'en reste davantage de l'un d'entre-eux."

> "That they agree to a more frequent refill so that I can refill all my medications at the same time even when I have more of one of them left." (Google English Translation)

> "To manage my lupus, I began a treatment pathway that includes getting deliberated and regular exercise (yoga and tennis for me, but I started with walking), and having quiet time to consciously set goals. I also have my own book with questions, test results and current medications list to ensure I am prescribed the right medication and maintain good communication with my doctors." — From a female patient living with lupus

Improved Outcomes

A lack of adequate reimbursement coverage for prescribed arthritis medications has forced some lupus patients to not go on vacation, borrow money to pay for medications, seek reimbursement coverage from pharmaceutical company, or start taking a different medication – all of these may impact overall health for lupus patients.

From ACE's Survey on Arthritis Medications Reimbursement

> "I basically pick a medication that doesn't cost much right now, that's a short list. I shouldn't have to choose a medication that might work better based on the cost!!! I deserve the same care." — Patient 3

Experience with Drug Under Review

Only Patient 5 from ACE's Survey on Arthritis Medications Reimbursement have experience with belimumab: "J'ai dû appeler le programme Benlysta pour leur dire que c'était le temps de faire la demande, eux doivent communiquer avec mon rhumatologue et ensuite envoyer ça aux assurances, et 45 jours plus tard j'ai appelé les assurances pour savoir qu'ils n'avaient rien reçu. J'ai dû payer de ma poche un traitement."

> "I had to call the Benlysta program to tell them it was time to apply, they have to contact my rheumatologist and then send this to insurance, and 45 days later, I called insurance to find out that they had received nothing. I had to pay out of pocket for treatment." (Google English Translation)

Companion Diagnostic Test

Not applicable to this submission.

Anything Else?

Arthritis Consumer Experts (ACE) would like to add that lupus is associated with significant premature mortality caused by kidney disease, infections, and cardiovascular disease. The increased risk of infection is thought to be a result of the use of immunosuppressive medications and glucocorticoids. These medications inhibit the immune network and, therefore, decrease resistance to a wide variety of bacterial, viral, and fungal agents. New, safter therapies are very much needed to effectively treat lupus and improve morbidity and quality of life in people living with the disease.

Based on current medical literature and its clinical and scientific advisors, ACE believes there is unmet medication needs for people living with lupus. Increased research into the causes and potential medication treatments for lupus should bring meaningful improvements in the lives of people living with lupus. Simply put, there are unmet needs in terms of Health Canada-approved therapies to treat lupus.

In addition, in the ACE Survey on Arthritis Medications Reimbursement for People with Arthritis, 3 in 10 Survey respondents who identified as black, Indigenous or a person of colour (BIPOC) reported that the forms they needed to fill out for reimbursement were confusing. In addition, BIPOC respondents indicated there were too many forms to fill.

One patient expressed the challenges they face in getting their arthritis medication covered: "I have to pay out of pocket until I meet my deductible for my private health insurance. The private health insurance pays until I meet my pharmacy requirements deductible. My husband retired last year and now my deductible has increased. With the biologic plus other medication I take, the monetary burden for my necessity medication has gone up significantly."

Conflict of Interest Declaration — Arthritis Consumer Experts

Did you receive help from outside your patient group to complete this submission?

This submission was summarized and written solely by the staff of Arthritis Consumer Experts, free from consultation, advice, influence, or financial support from any outside individual, group or company.

Did you receive help from outside your patient group to collect or analyze data used in this submission?

No.

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

We have no direct or indirect financial support from the manufacturer of the drug under review.

Table 1: Conflict of Interest Declaration for Arthritis Consumer Experts

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
No COI	–	–	–	–

The Kidney Foundation of Canada and Lupus Canada

About The Kidney Foundation of Canada and Lupus Canada

Kidney Foundation of Canada

Over nearly six decades, the Kidney Foundation of Canada has been guided by the fundamental principles of innovation, leadership, and collaboration, and has been committed to excellent kidney health, optimal quality of life for those affected by kidney disease, and a cure.

The Kidney Foundation of Canada is the leading charity committed to eliminating the burden of kidney disease through:

- Funding and stimulating innovative research for better prevention, treatments and a cure;
- Providing education and support to prevent kidney disease in those at risk and empower those with kidney disease to optimize their health status;
- Advocating for improved access to high quality health care;
- Increasing public awareness and commitment to advancing kidney health and organ donation.

For more information, please visit kidney.ca.

Lupus Canada

Lupus Canada is the only national organization focused on lupus research, advocacy, awareness and education in Canada. No other organization provides a bigger opportunity to make an impact on lupus and those who live with it. We are fiercely committed to improving the lives of people living with lupus, their families, and their loved ones by investing in the initiatives that bring us closer to dedicated treatments and, ultimately, a cure.

Lupus Canada firmly believes in the power of awareness and having an informed public – this is where exceptional and compassionate support begins. As the national organization dedicated to lupus awareness

and support, one of our main missions is to increase public awareness and advocate on behalf of the lupus patient.

Lupus Canada is run by a talented, diverse, volunteer group of Board of Directors and three (3) employees.

For more information, please visit www.lupuscanada.org.

Information Gathering

Patient input was collected via independent surveys in July 2022 by both Lupus Canada and the Kidney Foundation of Canada. Each survey was a self-administered questionnaire directed at people living with chronic kidney disease and/or lupus nephritis, as well as their caregivers. The surveys inquired about respondents' lived experience with lupus nephritis and chronic kidney disease, including questions on medications and expectations for new drug therapies in Canada. Awareness about the surveys was generated through the Kidney Foundation's website and social media channels (Twitter and Facebook).

Lupus Canada developed an online survey to gather information directly from people living with lupus about their experiences with the disease. The survey was shared nationwide via email, social media and on the Lupus Canada website. Twenty-six (26) survey responses were received.

A total of 38 people responded to the two surveys; 29 questionnaires were fully completed and 9 were partially completed. Most respondents identified as being a person living with lupus nephritis, with Lupus Canada's survey finding that just over 15% were caregivers. The same survey found that 73% of respondents were diagnosed with lupus nephritis within a year of experiencing their first lupus symptoms.

Disease Experience

One survey respondent stated that "lupus nephritis is not just a disease, it's an entire life adjustment."

In lupus nephritis, the immune system is overactive and causes immune complexes to form that lead to inflammation and scarring in the kidneys. This damages the kidneys' ability to eliminate wastes and excess fluids.

Chronic kidney disease (CKD) is the presence of kidney damage, or a decreased level of kidney function, for a period of three months or more. Kidney disease can range from mild to severe and in some cases, lead to kidney failure (sometimes referred to as end-stage kidney disease, or ESKD). There are usually no specific symptoms of kidney disease until the damage is severe. When the kidneys fail, wastes accumulate in the body and dialysis treatments or a kidney transplant are needed to survive.

Dialysis is the most common treatment for kidney failure, with kidney transplant being another option. Canadians with kidney failure and their families face significant out-of-pocket costs. This burden is further compounded by the loss of income that is often associated with starting dialysis. It is important to note that poverty is a determinant of health. This means that patients and their families that live in poverty may not be able to achieve optimal management of their medical issues.

In the early stages of chronic kidney disease, self-management strategies such as lifestyle changes; engaging in regular physical activity, maintaining a healthy body weight, stopping smoking and reducing sodium, managing other medical conditions and medications may slow or stop damage to the kidneys.

Most survey respondents reported that lupus nephritis has had a negative effect on their daily life, especially with regard to fatigue, with one respondent reporting that they were “feeling too tired and cannot focus”, and another saying, “I always have pain and fatigue, that’s why I work from home only part time.”

Other symptoms included nausea upon waking, muscle cramps, joint pain, mobility issues, swelling in feet and legs, high blood pressure, and high levels of protein in the urine. One respondent said that they experience “occasional sleep issues, memory loss, and lack of blood flow in fingers and toes".

Two respondents mentioned miscarriages, with one stating that they had “proteinuria, preeclampsia and HELPP syndrome during pregnancy loss.”

Several respondents talked about having to reduce their level of physical activity, and most reported an impact on their education or working life, with one stating “I am behind on deadlines and constantly burning out”, and another saying they were “unable to have a stable career due to unpredictable health.”

Another very common experience for survey respondents was a negative impact on mental health. Many respondents reported diminished social activities and/or family time, and some mentioned self- image issues. One said “my intimate life has been significantly impacted by it too.”

Experiences With Currently Available Treatments

Respondents all reported taking medications for lupus nephritis or CKD. Many reported taking medication to modulate their immune system. Antimalarials such as hydroxychloroquine were also common, as well as corticosteroids. Some take or have taken angiotensin-converting enzyme (ACE) inhibitors and/or angiotensin-receptor blockers (angiotensin receptor blockers), and other medications mentioned included diuretics and non-steroidal anti-inflammatory drugs.

When asked how satisfied they are with their current medication/blend of medications, most rated their effectiveness at a 3 out of 5. While some indicated that their medications improved their fatigue and swelling, many reported side-effects such as insomnia, weight gain, hair loss, nausea, and changes in appetite. Cost was reported to be an issue for some. Regarding pregnancy, one respondent said, “Cellcept has helped to return my kidney function to normal over the course of a few years but my doctor has no plans to take me off of it unless I want to become pregnant […], and it makes me nervous to have children eventually.”

Improved Outcomes

When asked about their expectations for lupus nephritis and/or CKD therapies, respondents rated these questions as most important: “Does it make me tired? Does it interfere with my sleep? Will it change my appetite? Respondents mentioned that side effects were important and one said that it was important that the medication not cause headaches and/or sleepiness.

Respondents' hopes for new therapies for lupus nephritis and CKD are that they will "make me feel better". They also hoped a dedicated lupus nephritis medication might help them have more energy, require less medication, have improved quality of life and reduced side-effects.

Experience With Drug Under Review

When asked about what treatments were received, 4 of 28 survey respondents have had experience with belimumab. Specific experience of belimumab could not be separated from the results.

Companion Diagnostic Test

Not applicable to this submission.

Anything Else?

Living with chronic kidney disease caused by lupus nephritis can involve not only health and quality of life challenges, but significant financial challenges as well. People may experience a decrease in income if they limit their working hours due to their symptoms, and out-of-pocket costs increase as they change their diet and follow up more often with their health care team.

One survey respondent indicated "that having lupus nephritis is a huge time commitment, and that it's expensive. Even though I am doing well and my kidneys are functioning, I still have to see multiple doctors and do blood work regularly (which I need to get time off work for) and take multiple expensive medications […]"

Those living with kidney disease also tend to be part of a low income and high cost population, and government coverage and financial support varies across jurisdictions, which can lead to inequities.

Should chronic kidney disease progress to kidney failure, hemodialysis is the most common treatment. The cost of hemodialysis to the health care system per person per year ranges from $56,000 to $107,000, so the savings to the system associated with slowing the progression of kidney disease is significant. Hospitalization and treatment of cardiac events in patients with chronic kidney disease also represents a significant cost to the health care system.

The combined burden of these illnesses means that many would benefit from effective, affordable treatments that they can access equitably and in a timely manner. As belimumab may slow the progression of kidney disease, it should be available as an option for people living with lupus nephritis.

Conflict of Interest Declaration — The Kidney Foundation of Canada

To maintain the objectivity and credibility of the CADTH reimbursement review process, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

Did you receive help from outside your patient group to complete this submission?

Yes, there was collaboration with Lupus Canada on the final submission.

Did you receive help from outside your patient group to collect or analyze data used in this submission?

There was assistance from Lupus Canada with data collection and analysis for this submission.

List any companies or organizations that have provided your group with financial payment over the past 2 years AND who may have direct or indirect interest in the drug under review.

Table 2: Financial Disclosures for The Kidney Foundation of Canada

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Alexion Pharma Canada Corp	–	X	–	–
Amgen Canada	–	–	–	X
Astra Zeneca Canada	–	–	–	X
GlaxoSmithKline Inc.	–	–	X	–
Horizon Pharma Inc.	–	–	–	X
Janssen Pharmaceutical Companies	–	–	–	X
Otsuka Canada Pharmaceutical Inc.	–	–	–	X
Paladin	–	–	X	–
Takeda	X	–	–	–

Conflict of Interest Declaration — Lupus Canada

To maintain the objectivity and credibility of the CADTH reimbursement review process, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

Did you receive help from outside your patient group to complete this submission?

Yes, there was collaboration with the Kidney Foundation on the final submission.

Did you receive help from outside your patient group to collect or analyze data used in this submission?

Yes, we surveyed Canadians living with lupus to collect data and analysis for this submission

List any companies or organizations that have provided your group with financial payment over the past 2 years AND who may have direct or indirect interest in the drug under review.

Table 3: Financial Disclosures for Lupus Canada

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
GSK Canada	–	–	X	–
AstraZeneca	–	–	X	–

Canadian Arthritis Patient Alliance, Arthritis Society, Canadian Skin Patient Alliance, and CreakyJoints

About the Canadian Arthritis Patient Alliance, Arthritis Society, Canadian Skin Patient Alliance, and CreakyJoints

CAPA is a grassroots, patient-driven and managed, independent, national education and advocacy organization with members and supporters across Canada. CAPA creates links between Canadians with arthritis, assists them to become more effective advocates and seeks to improve the quality of life for all people living with the disease. CAPA believes the first expert on arthritis is the individual who has the disease, as theirs is a unique perspective. We assist members to become advocates not only for themselves but for all people with arthritis. CAPA welcomes all Canadians with arthritis and those who support CAPA's goals to become members. Our website is updated regularly and can be viewed at: www.arthritispatient.ca.

The Arthritis Society has been dedicated to extinguishing the fire of arthritis since 1948. Dedicated to a vision of living in a world where people are free from the devastating effects that arthritis has on the lives of Canadians, the Arthritis Society is Canada's principal health charity providing education, programs and support to the 6 million Canadians living with arthritis. Since its founding, the Arthritis Society has been the largest non-government funder of arthritis research in Canada, investing more than $200 million in projects that have led to breakthroughs in the diagnosis, treatment and care of people with arthritis. The Arthritis Society is accredited under Imagine Canada's Standards Program. The website www.arthritis.ca provides more detailed information.

The Canadian Skin Patient Alliance (CSPA) is a national non-profit organization dedicated to supporting Canadians impacted by skin, hair and nail conditions. Our mission is to promote skin health and improve the quality of life of our community. We advocate for best care and treatment options for all skin patients; we educate on a variety of issues affecting these patients; and we support the members of our Affiliate organizations who work specifically on their disease areas such as acne, scleroderma, melanoma and psoriasis. To learn more, please visit www.canadianskin.ca.

For more than two decades, CreakyJoints has served as a digital community for millions of arthritis patients and caregivers worldwide who seek education, support, advocacy, and patient-centred research. All of our programming and services are always provided free of charge. CreakyJoints is part of the non-profit Global Health Living Foundation, whose mission is to improve the quality of life for people living with chronic illnesses. In keeping with our work at CreakyJoints USA, CreakyJoints Canada inspires, empowers, and supports arthritis patients – and patients living with other chronic conditions – and their caregivers to put themselves at the centre of their care by providing evidence-based education and tools that help people make informed decisions about the daily and long-term management of arthritis and other chronic conditions. At the heart of CreakyJoints Canada is collaboration. We will continue and strengthen our work with Canadian arthritis organizations and patient advocates that you know, love and respect. We are all stronger together. For more information, please visit www.creakyjoints.ca.

Information Gathering

A video interview and focus group were conducted to hear directly from people living with Systemic Lupus Erythematosus (SLE) and lupus nephritis about their experiences with the condition and use of belimumab (Benlysta).

One person was interviewed, and three people participated in the focus group. The interview, which can also be viewed (https://youtu.be/T7Rpj_783AE), was conducted by the Canadian Arthritis Patient Alliance (CAPA) and Lupus Ontario conducted the focus group. All focus group participants have lupus nephritis and experience using belimumab (Benlysta). Results from our previous 2019 survey for the use of belimumab (Benlysta) for SLE was also used to help inform the greater context around commonly experienced symptoms and side effects from living with SLE, and the patients' desired quality of life improvements from new medications. These patient experiences have helped to inform how belimumab may provide benefit to those living with SLE and lupus nephritis.

Disease Experience

Systemic Lupus Erythematosus (SLE) is a chronic autoimmune disease in which the body's immune system attacks and causes inflammation in its own tissues. Inflammation results in swelling, pain and other symptoms. As a result of SLE, the skin, joints, kidneys, heart, lungs, blood vessels, the nervous system and almost any other organ can be affected. Lupus nephritis happens when lupus involves the kidneys and often requires immediate medical treatment to prevent permanent damage. Lupus nephritis has very few signs or symptoms and can occur undetected for a long period of time. Regular medical checkups and urine tests can help detect lupus nephritis even if SLE symptoms have been calm for months or years.

SLE is a long-term disease with no cure that significantly impacts the lives of those with the disease. Symptoms of SLE and lupus nephritis can vary in severity from mild to very severe. Periods of very active disease are called "flares" and can be debilitating. Flares are also not predictable in terms of how severe they will be or how long they will last. How people living with SLE and lupus nephritis experience these symptoms can differ from person to person and symptoms are often unique to each person. Patients indicated a range of symptoms that are difficult to manage including, fatigue, skin rashes, nausea, loss of appetite, joint pain, bruising, cognitive dysfunction (brain fog), back pain, and mental health issues.

SLE impacts all aspects of a person's life including everyday activities such as walking, and sleeping, and makes tasks such as shopping, running errands and cooking more difficult. Patients also indicated difficulties in contributing and participating at school or work due to fatigue, pain and other symptoms.

> "It affects my energy. I have joint pain and pain from fibromyalgia. I have gastroparesis which may not be from lupus but it flares when I have a lupus flare. Gastroparesis gives me severe nausea.
>
> When I'm in a flare I get pleuritic pain. I am no longer able to work which drastically affects my quality of life. During flares I am unable to keep up with housework. My social life is greatly impacted because of my low energy."

> "The fatigue and need for 10ish hours of sleep to function makes working full time a challenge." "The second largest challenge is brain fog… the loss of words, inability to put sentences together, can't concentrate on what you're doing, you lose track of what you're doing…I often wonder if people think I'm dumb."

The impacts of the disease also extend to caregivers such as spouses/partners and children. Often, these people take on additional household chores such as cooking, cleaning, shopping, etc. to support the person living with SLE. Caregivers also take on additional activities, such as supporting their spouses/partners in getting to and from medical appointments.

> "My husband often has to come (home) after a 14-hour shift and cook dinner for us because I am too exhausted to move or stand for a long enough period of time to cook something on the stove."

> "My husband and son are amazing and have taken on more of the responsibilities at home... cooking, cleaning, gardening, etc."

> "My husband does most of the shopping and a lot of the housework. He drives to appointments as I have been sick for six months, and don't feel I can take it on again."

Experiences With Currently Available Treatments

Medications for SLE aim to control rashes, inflammation, and minimize disease activity so that no long-term joint or organ damage occurs, as there currently is no cure for the disease. Treatments used include nonsteroidal anti-inflammatory drugs (NSAIDs), antimalarial medications (hydroxychloroquine and chloroquine), corticosteroids, and immunomodulation drugs, such as methotrexate, cyclophosphamide, and canakinumab. Belimumab (Benlysta) is another treatment option specifically approved to treat lupus, though access to this medication is limited based on the type of drug coverage and can be quite cost prohibitive.

The following provides a general description of the treatments used and their side effects:

- NSAIDs are used to treat pain relating to the disease. The NSAIDS may cause many side effects, from stomach upset to changes in kidney function.
- With antimalarial medications such as hydroxychloroquine and chloroquine, the most common unwanted side effect is some stomach upset. However, if hydroxychloroquine and chloroquine are taken in a high dose and over a long period, they may accumulate in the retina and cause a loss of vision and in rare cases, blindness may occur.
- Corticosteroids are commonly used in the treatment of lupus and although effective, there are a significant amount of side effects when taken for longer durations and at higher doses. Corticosteroids can cause short-term effects such as weight gain, acne, excess facial hair, mood swings, high blood pressure, high blood sugar, increased infection, stomach ulcers, hyperactivity, and increase in appetite. Long-term effects include osteoporosis, glaucoma and cataracts, osteonecrosis, skin changes, heart disease, and stroke.

- Traditional immunomodulation drugs such as methotrexate are also commonly used and have a range of side effects that are difficult to manage. Side effects include nausea, vomiting, hair loss, diarrhea, decrease in white blood count, bone marrow toxicity, liver toxicity, and bladder-related problems. Less commonly used forms of immunomodulation medications used to supress symptoms include cyclosporine, leflunomide.
- Belimumab (Benlysta) is a medication developed to treat lupus, though it carries side effects such as nausea, diarrhea, fever, stuffy or runny nose and sore throat, persistent cough, trouble sleeping, leg or arm pain, depression, headache, and pain, redness, itching, or swelling at the site of injection (when given subcutaneously), in addition to also causing potential allergic reaction. Antihistamine with belimumab (Benlysta) is a regular recommended course of medication administration. It is also not covered generally by public drug plans and largely only accessible to those with private drug coverage.

Patients noted many challenges in finding the right combination of drugs to help manage their SLE and lupus nephritis, and responses to medications can vary significantly. Some medications are effective for some, while not effective for others. Some treatments may also only manage the disease for a short period of time before the patient's immune system adapts to a drug's presence (therefore becoming non-responsive to it) and they will have to switch to another medication.

People living with SLE and lupus nephritis reported that current treatments are difficult to tolerate because of side effects such as nausea, stomach upset, allergic reaction, anxiety and depression. The cumulative impact of how certain treatments may compound existing issues or cause the development of other issues is of concern to patients. Many patients also expressed a desire to reduce their use of steroids due to concerns of increased bone density loss.

Financial barriers in accessing certain medications like belimumab (Benlysta) were also a concern, as costs to patients without drug coverage are upwards of $2500/month. Patients also expressed difficulty in receiving reimbursement for medications, and had this to say:

> "It has been a huge obstacle to get cellcept covered because it is only recognized for transplant patients and not to prevent needing a transplant by controlling lupus. It usually takes months of argument with insurance and [the] province to get it covered and I need to renew annually. Benlysta has been good but working full time is impossible because no job lets you take a half day every month for the infusion and the self-injector needs to be refrigerated which doesn't work well for travel. I think a lot more could be done for this issue."

Improved Outcomes

The expectations of the drug are to offer another treatment option for patients with lupus nephritis. New treatment options have the potential to ease the burden on patients, their families, caregivers and the healthcare system. Overall, there are several outcomes of importance to people living with lupus nephritis including:

- a reduction in fatigue, joint and muscle pain, rash and skin irritations

- increased mobility and participation in physical activities
- ability to participate in school activities and work
- ability to carry out activities of daily living and social roles
- route of drug administration (pills vs. infusion vs. self-injections)
- reduced infection rates
- affordability of the medication
- increased quality of life

Experience With Drug Under Review

All three participants in the focus group and six previous survey responders have experience with belimumab (Benlysta) for treating their SLE symptoms. Patients shared both positive and negative side effects of taking belimumab (Benlysta). One patient suffered from negative side effects, such as extreme nausea, sleep deprivation, depression, and psychosis. Another patient did not have any change in symptoms or side effects while taking belimumab (Benlysta). All other patients reported an overall decrease in their disease symptoms and increased ability to participate in activities of daily living:

> "Benlysta has been a lifesaver... the side effects are minimal...headache and tiredness. With benlysta I am rarely tired at the end of a work week. My joint pain is almost nonexistent. ALL my hair has grown back no more ulcers in my mouth. I expect that continued use of benlysta will only improve my health further."

> "I'm still in the very early stages of my treatment with Benlysta but so far no side effects"

> "No side effects and symptoms seem well managed except for lesions on my fingers of unknown cause."

> "… Prednisone use has been greatly reduced. Blood counts totally into the normal range. Still mild joint pain, likely due to osteoarthritis. Continuing with small doses of prednisone. No side effects that I can tell. I attend the infusion clinic for treatments with no significant disruption to my regular routine. Benlysta is the best thing that has happened for me with my SLE. Best overall health I've had in years!"

Companion Diagnostic Test

Not applicable.

Anything Else?

Some patients commented on the inability to work due to the severity of their symptoms. If patients cannot access treatments that are effective, many will be unable to work and become dependent on the public system instead of being able to access employee health insurance. This not only affects the health care and public drug programs, but more importantly, does not help patients manage their disease effectively.

Belimumab (Benlysta) has been used as a treatment option for certain SLE patients in several EU countries for a number of years. The real-world evidence of these countries should be considered as part of the review. Belimumab (Benlysta) for lupus nephritis has been authorized for use by the European Union, noting the high unmet medical need for this condition. In November 2021, England's National Institute for Health and Care Excellence (NICE) approved belimumab (Benlysta) as a treatment for active auto-antibody positive SLE (guidance document published Dec 15,2021). As a result of this decision, NHS England, NHS Wales and Northern Ireland now provide coverage of belimumab as an option to be added to standard therapy for SLE patients. This decision, together with the other EU countries noted above, provides a precedent for reimbursement and should be taken under consideration.

Conflict of Interest Declaration — Canadian Arthritis Patient Alliance, Arthritis Society, Canadian Skin Patient Alliance, and CreakyJoints

Did you receive help from outside your patient group to complete this submission?

Not applicable.

Did you receive help from outside your patient group to collect or analyze data used in this submission?

The focus group was conducted by Lupus Ontario and the Arthritis Society was able to participate.

List any companies or organizations that have provided your group with financial payment over the past 2 years AND who may have direct or indirect interest in the drug under review.

Table 4: Conflict of Interest Declaration for the Canadian Arthritis Patient Alliance

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Abbvie Corporation	—	—	X	—
ACE Planning and Consulting	—	—	—	—
Canadian Rheumatology Association	X	—	—	—
CAPDM	X	—	—	—
Jannssen	X	—	—	—
CORECOM	X	—	—	—
Government of Canada	X	—	—	—
GSK	X	—	—	—
Brooks Group	X	—	—	—
UCB Canada	—	X	—	—
CADTH	X	—	—	—
SmithSolve LLC	X	—	—	—
The University of British Columbia	X	—	—	—

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Arthritis Society	X	–	–	–
University of Alberta	X	–	–	–
Children's Hospital of Eastern Ontario	X	–	–	–
Sick Kids Hospital	X	–	–	–
Dalhousie University	X	–	–	–

Table 5: Conflict of Interest Declaration for the Arthritis Society

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Abbvie	–	–	X	–
Alcon	–	–	–	–
Amgen	–	–	X	–
Boehringer Ingelheim	–	–	X	–
BMS	–	–	X	–
Celgene	–	–	–	–
Eli Lilly	X	–	–	–
Eupraxia Pharmaceuticals	–	–	–	–
Gilead	–	–	–	–
Innovative Medicines Canada	–	–	–	–
J+J Shared Services	–	–	–	–
Janssen	–	X	–	–
Merck	–	–	X	–
Novartis	X	–	–	–
Pfizer	–	–	–	X
Sanofi	–	–	–	–
UCB	–	–	–	–

Table 6: Conflict of Interest Declaration for the Canadian Skin Patient Alliance

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
AbbVie Canada	–	–	–	X
Janssen Canada	–	–	X	–
Merck Canada	–	–	X	–
Novartis Canada	X	–	–	–
Pfizer Canada	–	–	–	X

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Sanofi Canada	–	–	–	X
UCB Canada	–	–	X	–

Table 7: Conflict of Interest Declaration for CreakyJoints Canada

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
AbbVie Corporation	–	–	X	–

Lupus Ontario

About Lupus Ontario

Lupus Ontario is the largest provincial voluntary organization dedicated to improving the lives of people living with lupus. Our members currently number almost 6,400 and include lupus patients, friends, family and allies.

Our mission: Lupus Ontario's mission is to provide vital support, education, awareness, advocacy and research through the fundraising efforts of our staff and volunteer community to help those with lupus live longer, healthier and better lives.

Our goal: Life without Lupus

Website: www.lupusontario.org

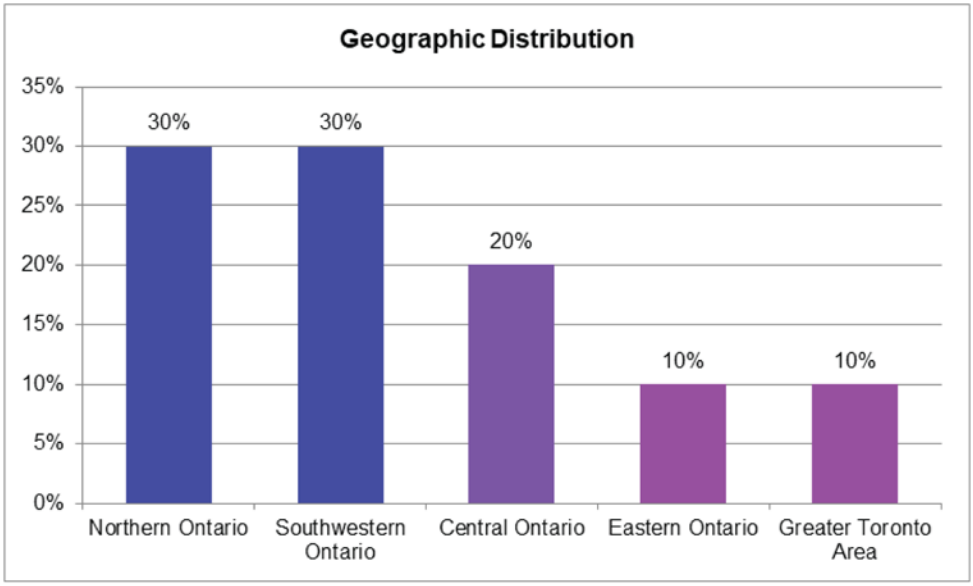
Information Gathering

Information was gathered from lupus patients through surveys and focus group discussions. The participants resided across the province of Ontario. Focus group surveys and meetings were held during January to February 2022. The focus group consisted of ten lupus patients half of whom had kidney involvement.

Table 8: Demographics of Participants

Demographic	Result		
Gender	Female = 90%	Male = 10%	–
Age	25-54 = 40%	55-64 = 50%	65+ = 10%
Employment status	Full time = 40%	Part time = 10%	Retired = 50%
SLE Severity	Mild = 30%	Moderate = 40%	Severe = 30%

Figure 1: Geographic Distribution of Participants



Disease Experience

Focus group patients with Systemic Lupus Erythematosus (SLE) experienced a major impact on their day-to-day life and quality of life due to a variety of symptoms, comorbidities and damage to major organs. Half the participants in the Focus Group had kidney involvement. In addition, the length of time to determine diagnosis of the disease in 60% of the group was measured in years resulting in added mental and physical stress. All focus group participants required care from family, friends and third-party caregivers during flares. Participants noted that both work and personal activity levels were impacted severely and in some cases resulted in having to stop work. All focus group participants noted an impact on work and a reduction in personal physical activity levels.

Table 9: Major Impact on Day-To-Day Life and Quality of Life for Group Patients with SLE

Impact	Length of time (%)		
Time Taken to Diagnose Lupus	5 Years+ = 40% 1-3 Years = 20%	7-12 months = 30%	Less than 6 months = 10%
Symptoms	Fatigue = 90% Rashes = 90% Sun sensitivity = 90%	Joint Pain = 80%	Anemia = 40% Mouth ulcers = 40%
Major Organ Involvement	Kidneys = 50%	Skin = 40%	Brain = 30% Heart = 30% Lungs = 30%
Comorbidities	Arthritis = 60%	Fibromyalgia = 50%	Raynauds = 40%
Flare Frequency	5-8 years = 10% 1-5 years = 40%	7-12 months = 10% 0-6 months = 10%	No pattern = 30%

Impact	Length of time (%)		
Self-Care During Flare	All of the time = 20%	Most of the time = 50%	Some of the time = 30%
Caregiver Required	Family/friends = 90%	Third-party = 10%	
Work Imycophenolic Acidct	Stopped working = 40%	Changed careers = 20% Modified hours = 20%	Virtual = 10%

Based on the data gathered above and the group discussions following, the most important aspects of the disease to be managed are fatigue, joint pain and flares.

Experiences With Currently Available Treatments

CADTH examines the clinical benefit and cost-effectiveness of new drugs compared with currently available treatments. We can use this information to evaluate how well the drug under review might address gaps if current therapies fall short for patients and caregivers.

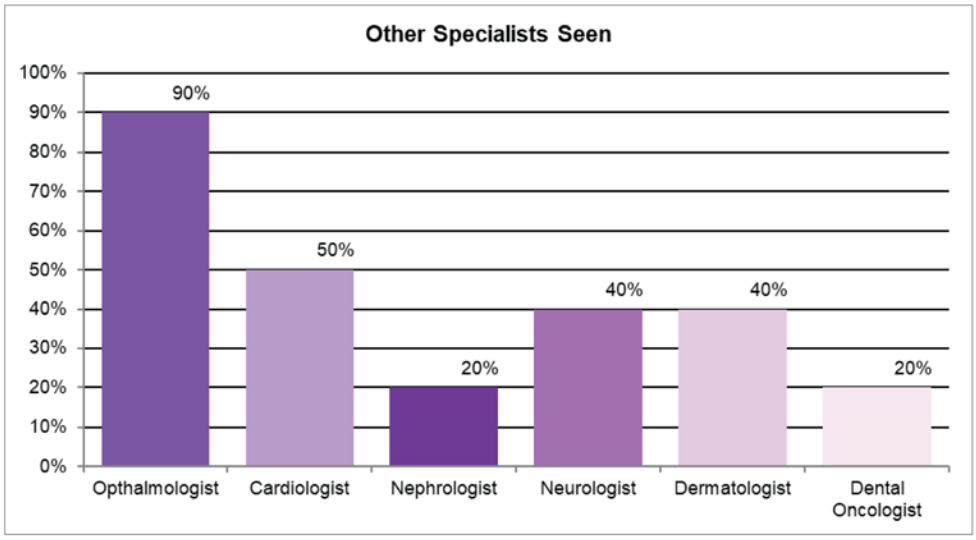
Describe how well patients and caregivers are managing their illnesses with currently available treatments (please specify treatments). Consider benefits seen, and side effects experienced and their management. Also consider any difficulties accessing treatment (cost, travel to clinic, time off work) and receiving treatment (swallowing pills, infusion lines).

Current Treatments

The majority of the focus group participants (60%) indicated that current medications/treatments were effectively managing their disease however they experience multiple side effects such as headaches, brain fog, additional fatigue, frequent infections, osteoporosis, gastric issues, eye issues, insomnia, hair loss, weight gain/loss and mood swings. Note that 30% of the participants stated that the current medications were not effective at managing their disease.

Major medical impacts experienced from the current treatments/medications were: 70% eye issues, 50% cognitive issues, 30% high blood pressure, 30% mental health, 30% severe weight gain. Additionally, half the participants had at least four or more specialists involved in their medical treatment as a result of the disease or side effects from medications prescribed.

Figure 2: Other Specialists Seen for Medical Treatment



The current treatments being used for SLE are Benlysta, Imuran, NSAIDs, Plaquenil, Cellcept, Cytoxin, Methotrexate, Rituximab and OTC pain medications. Note that 30% of participants have used Benlysta as a medication.

Table 10: Access to Medical Specialists and Facilities

Access	Length of time (%)		
Time to travel one-way to rheumatologist or clinic	8+ hours = 10%	4-8 hours = 30%	1-2 hours = 20% < 1 hour = 40%
Time to travel one-way to hospital	1-2 hours = 10%	< 1 hour = 90%	—
Out of pocket costs	$1500+ = 10% $1001-$1500 = 30%	$100-$500 = 50%	< $100 = 10%

Improved Outcomes

CADTH is interested in patients' views on what outcomes we should consider when evaluating new therapies. What improvements would patients and caregivers like to see in a new treatment that is not achieved in currently available treatments? How might daily life and quality of life for patients, caregivers, and families be different if the new treatment provided those desired improvements? What trade-offs do patients, families, and caregivers consider when choosing therapy?

Experience With Drug Under Review

Three of the Focus Group participants had access to the drug since it has been approved for SLE. Two additional patients who were not part of the Lupus Ontario Focus Group but were on Benlysta were added in order to provide more information for this section of the submission. All 5 patients had SLE and were also diagnosed with LN. The drug was covered through different approaches: out of pocket, private insurance and the Federal government drug plan.

Table 11: Improvements Desired in New Therapies

Improvement	Length of time (%)		
Outcomes	Fatigue reduction = 90% Pain reduction = 90%	Flare reduction = 70% Fewer side effects = 70%	Steroid reduction = 50%
Impact from new treatments on quality of life	Eliminate other medications = 90% Improved quality of life = 80%	Increased life span = 70%	Improve engagement in social activities = 70%
Trade-offs when choosing therapy	Side effects = 90% Cost of medications = 70%	Cost of access = 60% Clinical trials using their demographic = 60%	Oral or IV infusion = 30%

Patients experienced several benefits by being on the drug. Points noted below were not experienced by all 5 patients but by at least one of the patients:

- Several patients had their Prednisonne either eliminated or reduced to a minimal daily dosage which eliminated the various side effects and long-term damage generated by prolonged Prednisone usage.
- One patient noted that none of the other treatments/medications were able to help with her lupus and without Benlysta she would have died of liver disease. She was put on Benlysta for 2 years and her blood counts returned to normal, inflammation and joint point were gone. All her other medications were removed. She is now off Benlysta and her joint pain and fatigue are back but at a manageable level.
- One patient with Class V LN stopped the cycle of flares and subsequent hospitalizations. Doctors do not think he will flare again.
- Patients were able to increase their physical activity levels.
- Joint pain and fatigue were reduced.

Patients also experienced several disadvantages/side effects of being on the drug. Points noted below were not experienced by all 5 patients but by at least one of the patients:

- One patient had a severe allergic reaction on first dosage and the drug had to be stopped
- Frequent urinary tract infections
- Depression (patient felt this might have been a build-up from long-term (4 years) usage)
- Needles were quite painful
- Lack of sleep
- Vomiting with the IV infusion
- Had to be on a strict diet

Overall patients felt the advantages/benefits outweighed the disadvantages since there were able to materially reduce the time spent being hospitalized with flares and reduce the long-term impact of Prednisone (Osteoporosis, high blood pressure, brain fog, more infections, dental issues, etc.) on their physical health. The side effects were managed by the patients at home or at the doctor's office rather than being admitted to a hospital. Most of the side effects could be managed by the GP or the Rheumatologist

rather than requiring appointments with multiple other specialists. The improvement in physical activity and reduction in pain created an improvement in quality of life for the patients, families and caregivers.

The drug was easy to use and is available by IV infusion or self injection at home. Previous drugs range between pill form to IV infusion so similar in usage depending on which previous drugs the patients were given. None of the patients had an issue with the method of usage. One disadvantage noted was the storage of the drug if the patient was travelling since it requires freezing.

Drugs used prior to using Benlysta varied among patients but included prednisone, methotrexate, azathioprine, hydroxychloroquine, Cellcept, colsechin, cyclophosemide and rituxin. The major difference between the drugs used before and after the use of Benlysta is prednisone or the material reduction in prednisone and sometimes other lupus medications subsequent to using Benlysta. The second major difference is that patients of child bearing age do not want to be treated with cyclophosemide since this sterilizes the reproduction system. The use of Benlysta allows the control of LN and still allows for the procreation of children.

Key values important to patients suffering with SLE/LN is to be able to live as normal a life as possible while living with lupus. This means having a family, a career, friends and living a longer productive life.

Companion Diagnostic Test

Not applicable.

Anything Else?

Is there anything else specifically related to this drug review that CADTH reviewers or the expert committee should know?

No.

Conflict of Interest Declaration — Lupus Ontario

To maintain the objectivity and credibility of the CADTH reimbursement review process, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

Did you receive help from outside your patient group to complete this submission?

No.

Did you receive help from outside your patient group to collect or analyze data used in this submission?

No.

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Table 12: Conflict of Interest Declaration for Lupus Ontario

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
GSK	–	–	–	X
AstraZeneca	–	–	X	–

Clinician Input

Canadian Network for Improved Outcomes in Systemic Lupus Erythematosus and Associated Physicians

About the Canadian Network for Improved Outcomes in Systemic Lupus Erythematosus and Associated Physicians (Rheumatologists, Nephrologists)

The Canadian Network for Improved Outcomes for Systemic Lupus Erythematosus (CaNIOS) is a group of Canadian clinicians and researchers spanning the country. CaNIOS is registered as a not-for-profit Canadian Corporation. Our overarching mission statement is to facilitate the care of Canadian lupus patients and to improve the outcome of lupus patients across the country through collaborative research. Additional goals are to facilitate research in lupus and related autoimmune diseases; to describe the lupus patient population in Canada through a National Registry; to provide a large patient base to address clinically important issues through research; to look at subgroups of the Canadian lupus population, and to contribute to the global and international effort on lupus research through the uniqueness of the Canadian lupus population. CaNIOS was originally created in 1995 with the specific goal of running multicentre studies, recognizing that the relatively low prevalence along with the heterogeneity of lupus required Canada-wide collaborations to detect clinically important differences and conduct meaningful research.

Collectively, CaNIOS members provide care for more than 4000 SLE patients.

The current document is also endorsed by clinicians and researchers that are not CaNIOS members and are signed below.

Dr. Konstantinos Tselios, Dr. Robert Ting, Dr. Janet Pope, Dr. Alexandra Legge, Dr. William Fung, Dr. Andrew House, Dr. Dafna D. Gladman, Dr. Navdeep Tangri, Dr. Justin Shamis, Dr. Murray B. Urowitz, Dr. Sahil Koppikar, Dr. Amanda Steiman, Dr. Thomas Appleton, Dr. Sylvie Ouellette, Dre Josiane Bourré-Tessier, Dr. Catherine Ivory, Dr. Maqbool Sheriff, Dr. Christine Peschken, Dr. Sean Barbour, Dr.Stephanie Keeling, Dr. Hugues Allard-Chamard, Dr. Michele Tupchong, Dr. Shelly Dunne, Dr. Ceri Anne Richards, Dr. Juris Lazovskis, Dr. Megan R.W. Barber, Dr. Laura Ellen Berall, Dr. Derek Haaland, Dr. Louise Moist, Dr. Hctor Arbigalla, Nathalie Rozebojm, RN

Information Gathering

The information provided herein was gathered from the relevant scientific/medical literature.

Current Treatments

Systemic Lupus Erythematosus (SLE) is a chronic, systemic autoimmune disease with multiple clinical manifestations, including musculoskeletal, mucocutaneous, renal, central and peripheral nervous system, blood, heart and lungs involvement. The majority of lupus patients are women (around 90% in large cohorts) diagnosed at a young age (20-40 years old). The etiology of the disease remains unknown. Its course is characterized by unpredictable relapses and remissions. The current treatment strategies aim at the suppression/modulation of the autoimmune response and include several agents that carry a significant risk for adverse events.

The major drugs that have been used in SLE therapeutics can be divided into 4 broad categories.

Antimalarials. These include mainly chloroquine (CQ) and hydroxychloroquine (HCQ) with the latter being available in Canada. Antimalarials are considered the cornerstone of lupus management and recommended for all lupus patients without specific contra-indications. They are associated with multiple beneficial effects (symptom control, reduction of risk for future flares, improved metabolic profile, decreased rate of thrombotic complications and overall damage and improving survival).

Glucocorticoids. These are widely available in Canada, both in oral and intravenous forms. They are mainly used for aggressive disease manifestations and often maintained at low-to-moderate doses (5-20mg/day) for disease activity control. While they are very effective in suppressing the autoimmune response, they are associated with multiple side effects including weight gain, osteoporosis and fractures, osteonecrosis, diabetes, hypertension, accelerated atherosclerosis, cataracts etc. It has been estimated that half of the chronic irreversible damage that occurs to lupus patients is attributable to glucocorticoids.

Immunosuppressives. This category includes a series of agents such as methotrexate, azathioprine, mycophenolate mofetil, cyclophosphamide, cyclosporine, tacrolimus, sirolimus, leflunomide, thalidomide etc. that are used in combination with antimalarials and glucocorticoids to control refractory disease or in the setting of certain disease manifestations. They carry a significant risk for side effects that differ for each medication. A universal side effect is the increased risk of infections.

Biologics. Belimumab was approved for non-renal, non-neuropsychiatric SLE in 2011 and more recently for lupus nephritis. Anifrolumab was also recently approved for the same indication (December 2021). Rituximab is used occasionally although it has not been approved for use in lupus (off-label). Other biologics are used less often on an individual, off-label basis.

Apart from the systemic (oral and intravenous) treatments, topical treatments (glucocorticoid or immunosuppressive creams) are often prescribed for cutaneous manifestations.

Non-pharmaceutical treatments include photoprotection (sunscreen) and maintaining a healthy lifestyle with a balanced diet and regular exercise. Vitamin D and calcium supplements are also recommended to prevent osteoporosis, particularly in chronic glucocorticoid users.

Lupus nephritis (LN), in particular, is the most impactful manifestation of SLE and affects approximately 40% of patients. Diagnosis of LN largely relies on kidney biopsy and six (6) distinct pathologic forms

have been characterized by the International Society of Nephrology/Renal Pathology Society. The most prevalent forms are the proliferative LN (class III and IV) and the membranous nephropathy (class V), which itself can present as an overlap with class III or IV. The main disease manifestations include proteinuria, hematuria, active urinary sediment (casts) and increased blood pressure. Treatment includes a remission induction phase with high doses of glucocorticoids and immunosuppressives (as well as adjunct therapy with antimalarials, anti-hypertensives etc.) and a maintenance phase with lower doses of glucocorticoids and immunosuppressives depending on the response and side effects of the used medications. The overall therapeutic approach is usually based on the guidelines of the American College of Rheumatology (ACR 2012) and/or the European Alliance of Associations for Rheumatology (EULAR 2019). Both guidelines recommend the use of glucocorticoids (0.3-1mg/kg) with or without intravenous pulses at disease onset along with immunosuppressives (mycophenolate mofetil or cyclophosphamide) in high doses for 6 months, followed by maintenance immunosuppressives for 3-5 years.

Despite major advancements in LN therapeutics, its long-term prognosis remains poor with 17% of the patients developing end-stage kidney disease (ESKD) within 10 years after diagnosis. This number is substantially larger (around 34%) for patients with the most aggressive forms of LN (diffuse proliferative or class IV) and underlines the unmet needs in LN. This is particularly worrisome given the young age of these patients (mean age at LN diagnosis 30-35 years old), many of whom will end up in renal replacement therapy (dialysis and/or transplantation) at a relatively young age (40-45 years old).

In general, only the antimalarials, belimumab and, most recently, anifrolumab have been approved for use by Health Canada and exclusively for use in non-renal, non-neuropsychiatric lupus. The use of all other medications is based on extensive data from clinical and observational trials and is recommended by international associations such as the ACR and EULAR. For LN, in particular, the use of glucocorticoids and immunosuppressives is based on several randomized, controlled trials (RCTs) and recommended by both the ACR and EULAR. Most of these agents are currently available in Canada.

There are no treatments available through special access programs.

The current treatments modify the underlying pathogenetic mechanisms. However, the exact pathogenetic pathway that is impacted is not known for the majority of the non-specific immunosuppressives (including mycophenolate mofetil and cyclophosphamide) and antimalarials. Belimumab targets the maturation and functional differentiation of B cells, a subset of lymphocytes that produce the autoantibodies that are related to lupus pathogenesis. Anifrolumab targets the interferon pathway, considered to be a central mechanism in disease pathogenesis.

Treatment Goals

The ideal treatment for LN should be able to suppress the renal inflammatory process and preserve renal function without increasing the risk of adverse events while minimizing the use of more harmful drugs that are used concomitantly (such as glucocorticoids). It should also diminish the risk for subsequent flares as well as mitigate the long-term complications of the disease, improve the quality of life of lupus patients and increase survival.

The treatment goal for LN (as defined by the 2019 EULAR guidelines) includes a 25% reduction from baseline proteinuria at 3 months post diagnosis, 50% reduction in proteinuria at 6 months and complete remission (proteinuria less than 0.5 grams/24 hours) at 12 months. At all time points, kidney function should be preserved with serum creatinine less than 120% of its baseline value. It is also recommended that glucocorticoids should be kept at a low dose (prednisone less than or equal to 7.5mg/day) at 12 months post diagnosis.

Treatment Gaps (Unmet Needs)

Considering the treatment goals, please describe goals (needs) that are not being met by currently available treatments.

Several longitudinal studies have demonstrated that complete remission within 12 months from LN diagnosis offers the best possible outcomes regarding the long-term renal survival. However, based on extensive data from randomized clinical trials and observational studies, more than 50% of LN patients will not achieve this target. These results were described with both mycophenolate mofetil and cyclophosphamide, the main immunosuppressive agents currently used for remission induction. These patients are at increased risk of kidney function impairment and eventually develop ESKD at higher rates, even if they achieve complete remission at a later disease stage (after 2 or 3 years after onset).

The majority of the patients who do not achieve remission are continuously treated with moderate or high doses of glucocorticoids (prednisone greater-than over equal to 7.5mg/day or equivalent) that greatly increases the risk for multiple complications. For example, 10-12% of these patients will develop osteonecrosis and about half of them will require a total joint replacement in the next 12 months. Of note, osteonecrosis is extremely rare in non-glucocorticoid users. Osteoporosis is detected in 30-35% of lupus patients with glucocorticoids acting as a leading risk factor. This results in osteoporotic fractures in approximately 15-20% of them. Accelerated atherosclerosis is well documented in SLE patients and is associated with both traditional and disease-related factors. Glucocorticoids increase the risk for (or may aggravate pre-existing) diabetes, hypertension and dyslipidemia; hence their contribution to this process is significant. Despite advances in the management of such co-morbidities, 4-5% of SLE patients will suffer a major cardiovascular event (myocardial infarction and/or stroke) at a relatively young age. Overall, half the irreversible damage that occurs in SLE patients derive from glucocorticoids and the reduction of their cumulative dose over time is a major goal in LN therapeutics.

Flares are a cardinal characteristic of LN. Even patients who achieve timely remission are at increased risk of flare, particularly if maintenance therapy is terminated early. Approximately 10-20% of the patients will experience a disease flare in the first 5 years from disease onset and require escalation of their systemic treatment. Flares have been associated with worse outcomes; for example, a 4-fold risk for subsequent end-stage renal disease and renal replacement therapy. Thus, prevention of flares is another major goal in LN management.

Adherence is an additional obstacle in the long-term management of LN. Approximately 40-75% of lupus patients have suboptimal adherence to their treatment in the first few years after diagnosis. Multiple factors

account for this phenomenon including polypharmacy. For example, a newly diagnosed patient with lupus nephritis may need 20-30 tablets of different drugs daily for a prolonged period of time. Moreover, treatment is prolonged (in many cases lifelong), and many patients have difficulties in maintaining adherence.

Based on the above, the unmet needs in LN therapeutics include the modest efficacy of the currently existing options, the increased risk for adverse events, the inability to minimize flares and the suboptimal adherence.

Which patients have the greatest unmet need for an intervention such as the drug under review?

Based on the previous section, the patients with the greatest unmet needs for an intervention with belimumab are:

Patients who will not achieve at least partial remission (less than 50% of the baseline proteinuria) in a reasonable time period (3-6 months) after commencing treatment with the currently available medications.

Patients who experience early flares and cannot reduce their daily prednisone dose below 7.5 mg/day (or equivalent) by 12 months ("steroid-dependent disease").

Patients who experience frequent flares from any organ/system.

Patients in whom adherence (adherence) is a major factor for treatment failure.

Based on observational studies, these patients (with the exception of item 4) comprise 50% of the LN population. Some characteristics that identify these patients with more refractory disease include the particular form of LN (diffuse proliferative or class IV with or without membranous characteristics), the magnitude of kidney function impairment at baseline as well as sustained serologic activity (increased anti-dsDNA antibodies and/or decreased complements C3 and C4). Adherence has been associated with several other factors.

Belimumab is expected to address these unmet needs. In the relevant randomized, placebo-controlled, clinical trial (BLISS-LN), it demonstrated superior results in achieving timely complete remission, reducing the need for concomitant glucocorticoids as well as minimizing early flares.

Belimumab also comes with a substantial body of evidence in non-renal, non-neuropsychiatric SLE. A recent post-hoc analysis of 5 RCTs, incorporating results from 3086 patients, demonstrated excellent results in patients with severely active disease (as defined by an SLE Disease Activity index >10) as well as patients with active serology (increased anti-dsDNA antibodies and/or decreased complements C3 and C4). Most patients with LN fall in this category (SLEDAI>10 with active serology); therefore, it is anticipated that they will display improved response rates. Moreover, belimumab has been shown to substantially decrease damage accrual in SLE patients in a recent analysis with an average of 8 years of follow-up. Given that LN therapy is prolonged (3-5 years according to the current guidelines), it is expected that belimumab will exert a similar benefit for LN patients. Furthermore, belimumab is expected to improve adherence since it is administered intravenously every 4 weeks or subcutaneously every week.

Place in Therapy

How would the drug under review fit into the current treatment paradigm?

Belimumab exerts its effects by modulating the maturation and functional differentiation of the B cells. These cells produce autoantibodies that are central in SLE pathogenesis and tissue damage. The presence of multiple autoantibodies is universal in SLE patients and particularly LN. B cells also have several other functions in the propagation of the autoimmune response by interacting with other immune cells. These mechanisms lead to tissue damage from various organ/systems. Most patients with LN also have globally active disease with clinical manifestations from several systems. Therefore, it is reasonable to expect a meaningful impact of belimumab on disease activity across a range of affected organ/systems and not only restricted to LN, as has been already shown from several RCTs.

Belimumab is the first approved drug to address this disease mechanism.

Belimumab was tested as an add-on treatment to the current standard-of-care (glucocorticoids and immunosuppressives). Based on the current knowledge, it should be used in combination with these agents in refractory cases (where treatment goals are not achieved after a reasonable time).

Belimumab is expected to cause a shift in the current treatment paradigm for LN. Its unique mechanism of action renders it the most suitable to address the unmet needs. Moreover, it is expected that belimumab will have a major impact for the subpopulation of patients who will not achieve timely remission, those with frequent flares as well as patients with “steroid dependence”.

Please indicate whether or not it would be appropriate to recommend that patients try other treatments before initiating treatment with the drug under review. Please provide a rationale from your perspective.

Belimumab has demonstrated a clinically meaningful benefit for patients with active LN. The current treatment paradigm for LN requires high doses of glucocorticoids and immunosuppressives (based on the ACR and EULAR recommendations) for a prolonged period of time. However, more than 50% of such patients will not achieve remission within the first year from diagnosis; thus, their risk for developing ESKD is increased substantially.

With regards to concomitant therapy, glucocorticoids and immunosuppressives in high doses are the current standard-of-care in LN.

Glucocorticoids should be administered in all cases to mitigate the autoimmune response as soon as possible. However, every effort should be made to minimize the daily dose to the lowest possible dose that will maintain remission. This dose should be 7.5mg/day or less by 12 months post diagnosis in order to prevent long-term complications. According to some studies, this dose should be 5mg/day or less.

Mycophenolate mofetil or cyclophosphamide should be administered concomitantly to maximize the chance of remission and maintain a favorable response. In refractory cases, calcineurin inhibitors (mainly tacrolimus) and rituximab have also been used.

In cases where the combination (glucocorticoids and mycophenolate mofetil or cyclophosphamide) is not effective or other factors (e.g., intolerance) are prohibitive, belimumab should be a choice. Based on the mechanism of action, it is suggested that belimumab should become available for use at an early disease stage (3-6 months post diagnosis). In LN, any delay in treatment is reflected in loss of kidney function;

therefore, introduction of belimumab at a later disease stage where irreversible damage has occurred seems meaningless.

Patients who experience renal flares are also at higher risk of developing ESKD. In such patients, we recommend belimumab as an add-on to the existing therapies upon the confirmation of flare. Moreover, patients who experience frequent flares (>1/year for more than 2-3 years) from any organ/system are more likely to respond to belimumab and minimize the need for additional glucocorticoids.

Finally, we recommend belimumab for "steroid-dependent" patients (i.e., those who are not able to reduce the daily prednisone dose below 7.5mg/day without flaring). It is very likely that these patients will develop irreversible damage over time with deleterious effects to their overall health and well-being secondary to chronic glucocorticoid use. Moreover, these patients will incur significant costs to the health system related to the treatment needed for the side effects that arise from prolonged glucocorticoid use (i.e. weight gain, hypertension, diabetes, osteoporosis and fractures, osteonecrosis and total joint replacement). The goal of treatment with belimumab should be the reduction of the daily prednisone dose below 7.5mg/day at 12 months post diagnosis.

How would this drug affect the sequencing of therapies for the target condition?

The sequence of therapies for LN includes glucocorticoids and immunosuppressives. For patients without private insurance coverage, there are currently no available options after treatment failure.

Belimumab should become available through public access to such patients. This is not a significant departure from the current practice but rather addresses the management of refractory patients where current therapies are associated with inefficacy and/or significant toxicity.

There should be an opportunity to treat patients in a subsequent line of therapy (patients with frequent flares and "steroid-dependent" patients).

Which patients would be best suited for treatment with the drug under review?

The patients most likely to respond to belimumab are:

Patients who do not achieve at least partial remission (less than 50% of the baseline proteinuria) in a reasonable time period (3-6 months) after commencing treatment with the currently available medications or experience severe side effects from the current therapy.

Patients who experience early flares and cannot reduce their daily prednisone dose below 7.5 mg/day (or equivalent) by 12 months ("steroid-dependent disease").

Patients who experience frequent flares in any organ/system.

Patients in whom adherence is a major factor for treatment failure.

These patients are in most need of an intervention.

How would patients best suited for treatment with the drug under review be identified?

We believe that the patients that are best suited for belimumab should be identified from the aforementioned categories and assessed by a physician with expertise in the management of LN before commencing the drug.

LN diagnosis is at times challenging, particularly if there is no availability for a kidney biopsy. However, most cases are diagnosed timely and can be followed by specialists (rheumatologists and/or nephrologists). Underdiagnosis is believed to be rare. Nevertheless, delayed diagnosis where patients present with advanced chronic kidney disease is not uncommon, particularly in cases without any other organ/system involvement.

In most cases, LN does not cause severe symptoms. Decisions on treatment are based on the severity of kidney disease that is reflected by parameters such as proteinuria, hematuria, kidney function etc. These are objective measures of disease activity and eliminate bias. There is no evidence to suggest any benefit from belimumab in inactive LN (without proteinuria or progressive kidney dysfunction).

Which patients would be least suitable for treatment with the drug under review?

Patients who achieve sustained remission under immunosuppressives alone or combined with low dose prednisone (<7.5mg/day).

Is it possible to identify those patients who are most likely to exhibit a response to treatment with the drug under review?

These patients can be identified on clinical and serological/laboratory grounds based on the aforementioned criteria.

All the required tests are widely available in Canada.

What outcomes are used to determine whether a patient is responding to treatment in clinical practice?

The outcomes of interest in LN include the preservation of kidney function (as expressed by serum creatinine and estimated glomerular filtration rate), the level of proteinuria and the presence (or absence) of active urinary sediment.

Other outcomes include the decrease in the daily prednisone dose, the delay in damage accumulation as well as the normalization of serologic activity.

What would be considered a clinically meaningful response to treatment?

A clinically meaningful response to treatment should include any of the following:

- Complete remission (proteinuria less than 0.5grams/24 hours) at 12 months
- Reduction of daily prednisone dose to levels lower than 7.5mg/day.
- Reduction of the frequency and intensity of flares

These outcomes will lead to a significant improvement of the patients' prognosis.

How often should treatment response be assessed?

Response to treatment should be assessed on a quarterly basis. Sufficient time (at least 12 months) should be allowed for the outcomes to be observed.

What factors should be considered when deciding to discontinue treatment?

Treatment should be discontinued:

- Immediately in cases of allergy/intolerance
- After 12 months, in cases where no response can be demonstrated
- After 12 months, if the daily prednisone dose exceeds 7.5mg (or more than 50% from baseline) in "steroid-dependent" patients
- After 12 months, if severe flares requiring treatment escalation (particularly with glucocorticoids and/or immunosuppressives) continue to occur

What settings are appropriate for treatment with the drug under review?

Hospital and specialty infusion clinics with experience in the intravenous administration of biologic drugs are the most appropriate for belimumab infusion. Subcutaneous injections are also available (administered on a weekly basis) and may reduce the administrative cost that is relevant to intravenous administration.

For non-oncology drugs, is a specialist required to diagnose, treat, and monitor patients who might receive the drug under review?

Physicians with expertise in the management and treatment of patients with LN (rheumatologists and/or nephrologists) should be the physicians who diagnose prescribe and monitor patients treated with belimumab.

Additional Information

The prevalence of SLE in North America is estimated at 1-2 per 1000 people, accounting for 37000-74000 patients in Canada. The annual incidence is approximately 7-8 patients per 100,000 population, meaning that approximately 2600-3000 patients are newly diagnosed every year in Canada. The prevalence and incidence are relatively higher in certain ethnic minorities including African Canadians and First Nations. For LN, in particular, it is estimated that 500-600 patients are newly diagnosed in Canada every year. Although considered a rare disease, SLE has a disproportionate impact on society based on the following facts:

The mean age at onset is 20-40 years of age (in approximately 70% of the patients) and the vast majority (almost 90%) are women. This means that major complications such as end-stage renal disease and cardiovascular events occur early in life (5^{th} or 6^{th} decade).

The 10-year survival is estimated at 95% in developed countries. The mean age at death is approximately 60 years in Ontario in the last decade whereas life expectancy of the general population is estimated at 82 years.

Approximately 17-33% of LN patients will develop end-stage kidney disease requiring dialysis (and/or transplantation) after 10 years.

About 10-12% of lupus patients on prolonged glucocorticoids will develop osteonecrosis in one or more large joints (including hips and knees). About half of them will need a total joint replacement in the next 12 months from symptom initiation.

About one-third of lupus patients will develop glucocorticoid-induced osteoporosis. Approximately 11% will suffer fragility fractures.

Approximately 5-10% of lupus patients will suffer a major cardiovascular event (myocardial infarction, stroke) during their disease course.

Cognitive impairment is detected in 30-45% of lupus patients during the disease course.

The complications/co-morbidities described above clearly demonstrate the tremendous impact of SLE on patients. The cardinal factors that contribute to these are disease activity and concomitant glucocorticoids. Most of these complications occur early and severely affect the patients' quality of life (QoL). In general, about 20-30% of lupus patients are unable to work after the first five years from diagnosis. After 10 years, about half of lupus patients are not able to work while this number grows to 75% after 25 years. Practically, very few lupus patients will be working until normal retirement age.

QoL is significantly impaired in SLE patients by both the burden of the disease and the administered treatments. Several studies have demonstrated an impact on physical, mental and social health aspects. The most important associated factors are chronic pain, fatigue and accumulated damage. Remission is associated with improved quality of life measures for both the physical and mental components of QoL indices.

Given that most related damage is attributed to active disease and concomitant medications (mainly glucocorticoids), the aforementioned complications are particularly prevalent in patients with LN, who represent the most severe cases as well as the ones who will receive the highest glucocorticoid doses cumulatively. Therefore, LN patients are at the highest risk for complications amongst SLE patients.

The medical costs of SLE are substantial, with a mean total medical care cost of 52000 USD over four years. SLE flares are experienced by more than 90% of patients during disease course, with an average of 2.6 flares per patient per year. Patients with at least one severe flare during the follow-up period had an annual cost of 50000 USD. Patients with at least one severe flare had more than twice the costs of patients with moderate or mild flares. SLE patients have significantly higher health care utilization and higher overall expenditures than patients without SLE (11000 USD more total cost per year). The overall cost of lupus in the US is estimated at $13 billion. That means that in Canada, this cost may exceed $1.3 billion (USD). Regarding LN, the annual cost is estimated to be 15-20 times more for patients with advanced chronic kidney disease and 40-50 times more for patients with ESKD on dialysis.

Based on the above, it is clear that better treatment strategies are needed for the management of patients with LN. According to the currently available data, we believe that belimumab will offer a solution to refractory patients and this will translate into improved outcomes in the near future. Therefore, we trust that

you will consider this application positively and approve the public reimbursement of belimumab for certain patient groups.

Conflict of Interest Declarations — Canadian Network for Improved Outcomes in Systemic Lupus Erythematosus and Associated Physicians

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict-of-interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please refer to the Procedures for CADTH Drug Reimbursement Reviews (section 6.3) for further details.

Did you receive help from outside your clinician group to complete this submission?

No.

Did you receive help from outside your clinician group to collect or analyze any information used in this submission?

No.

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. Please note that this is required for *each clinician* who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.

Declaration for Clinician 1
Name: Dr. Konstantinos Tselios, MD, PhD

Position: Assistant Professor, Department of Medicine, McMaster University

Date: 24-07-2022

Table 13: COI Declaration for CANIOS and Associated Physicians — Clinician 1

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Astra Zeneca	–	X	–	–
GlaxoSmithKline	–	X	–	–

Declaration for Clinician 2
Name: Dr. Robert Ting, MD, FRCPC

Position: Nephrologist

Date: 24-07-2022

Table 14: COI Declaration for CANIOS and Associated Physicians — Clinician 2

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Astra Zeneca	—	—	X	—
GlaxoSmithKline	X	—	—	—
Otsuka	X	—	—	—
Janssen	X	—	—	—
Novo-Nordisk	X	—	—	—
Bayer	X	—	—	—

Declaration for Clinician 3
Name: Dr. Janet Pope, MD

Position: Professor, Department of Medicine, Western University

Date: 24-07-2022

Table 15: COI Declaration for CANIOS and Associated Physicians — Clinician 3

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Astra Zeneca	—	X	—	—
GlaxoSmithKline	—	X	—	—
Lily	—	X	—	—
AbbVie	—	—	X	—
BMS	—	X	—	—

Declaration for Clinician 4
Name: Dr. Alexandra Legge, MD, MSc

Position: Assistant Professor, Department of Medicine, Dalhousie University

Date: 24-07-2022

Table 16: COI Declaration for CANIOS and Associated Physicians — Clinician 4

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
No COI	—	—	—	—

Declaration for Clinician 5
Name: Dr. William Fung, MD

Position: Clinical Associate, Department of Medicine, University of Toronto

Date: 24-07-2022

Table 17: COI Declaration for CANIOS and Associated Physicians — Clinician 5

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Astra Zeneca	X	—	—	—
Abbvie	X	—	—	—
Viatris	X	—	—	—
Jannsen	X	—	—	—

Declaration for Clinician 6
Name: Dr. Andrew A. House

Position: Professor and Chair of Nephrology, Western University and London Health Sciences Centre

Date: 24-07-2022

Table 18: COI Declaration for CANIOS and Associated Physicians — Clinician 6

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
AstraZeneca	X	—	—	—
Horizon Pharmaceuticals	X	—	—	—
Baxter	X	—	—	—

Declaration for Clinician 7
Name: Dr. Dafna D. Gladman, MD, FRCPC

Position: Professor of Medicine, University of Toronto

Date: 24-07-2022

Table 19: COI Declaration for CANIOS and Associated Physicians — Clinician 7

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
AstraZeneca	X	—	—	—
GSK	X	—	—	—
BMS	X	—	—	—

Declaration for Clinician 8
Name: Dr. Navdeep Tangri, MD, PhD

Position: Professor, Department of Medicine, University of Manitoba

Date: 07-24-2022

Table 20: COI Declaration for CANIOS and Associated Physicians — Clinician 8

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Astra Zeneca	–	–	X	–
GlaxoSmithKline	–	X	–	–
Boehringer Ingelheim	–	X	–	–
Janssen	X	–	–	–
Otsuka	–	X	–	–
Tricida	–	–	–	X
Bayer	–	–	X	–
Pulsedata	–	X	–	–
Renibus	–	X	–	–

Declaration for Clinician 9
Name: Dr. Justin Shamis, MD

Position: Rheumatologist, Department of Medicine, North York General Hospital

Date: 24-07-2022

Table 21: COI Declaration for CANIOS and Associated Physicians — Clinician 9

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Janssen	–	X	–	–
AbbVie	X	–	–	–

Declaration for Clinician 10
Name: Dr. Murray B. Urowitz, MD, FRCPC

Position: Professor of Medicine, Department of Medicine, University of Toronto

Date: 24-07-2022

Table 22: COI Declaration for CANIOS and Associated Physicians — Clinician 10

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Astra Zeneca	X	–	–	–
GSK	–	–	X	–
Merck	X	–	–	–
Syneos	X	–	–	–

Declaration for Clinician 11
Name: Dr. Sahil Koppikar

Position: Assistant Professor, Department of Medicine, University of Toronto

Date: 25-07-2022

Table 23: COI Declaration for CANIOS and Associated Physicians — Clinician 11

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
AbbVie	–	X	–	–
Fresenius Kabi	X	–	–	–
Janssen	–	X	–	–
Novartis	X	–	–	–

Note: Janssen- honorarium (<$10,000); Pfizer - unrestricted grant (research/QI support)

Declaration for Clinician 12

Name: Dr. Amanda Steiman, MD, MSc, FRCPC

Position: Assistant Professor, Department of Medicine, University of Toronto

Date: 25-07-2022

Table 24: COI Declaration for CANIOS and Associated Physicians — Clinician 12

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Pfizer	–	–	–	X
Janssen	–	X	–	–

Declaration for Clinician 13

Name: Dr. Thomas Appleton, MD, PhD

Position: Assistant Professor, Department of Medicine, Western University, Canada

Date: 25-07-2022

Table 25: COI Declaration for CANIOS and Associated Physicians — Clinician 13

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
AbbVie	–	X	–	–
Astra Zeneca	X	–	–	–
Amgen	X	–	–	–
Bristol Myers Squibb	X	–	–	–
Celgene	X	–	–	–
Fresenius Kabi	–	X	–	–
Janssen	–	X	–	–
Novartis	–	X	–	–

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Organon	–	X	–	–
Pfizer	–	X	–	–
Hoffman LaRoche	X	–	–	–
Sandoz	X	–	–	–
Sanofi-Genzyme	X	–	–	–
UCB	–	X	–	–

Declaration for Clinician 14
Name: Dr. Sylvie Ouellette

Position: Rheumatologist, The Moncton Hospital, New Brunswick

Date: 25-07-2022

Table 26: COI Declaration for CANIOS and Associated Physicians — Clinician 14

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Amgen	X	–	–	–
Novartis	X	–	–	–
AbbVie	X	–	–	–
Merck	X	–	–	–
Eli Lilly	X	–	–	–
Janssen	X	–	–	–
UCB	X	–	–	–

Declaration for Clinician 15
Name: Dr. Josiane Bourré-Tessier, MD, MSc

Position: Assistant Professor, Department of Medicine, Université de Montréal

Date: 25-07-2022

Table 27: COI Declaration for CANIOS and Associated Physicians — Clinician 15

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Astra Zeneca	X	–	–	–
GlaxoSmithKline	–	–	X	–
AbbVie	X	–	–	–
Novartis	X	–	–	–
Teva	X	–	–	–

Declaration for Clinician 16
Name: Dr. Catherine Ivory, MD, PhD

Position: Assistant Professor, Department of Medicine, University of Ottawa

Date: 19-07-2022

Table 28: COI Declaration for CANIOS and Associated Physicians — Clinician 16

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Astra Zeneca	X	–	–	–
GlaxoSmithKline	X	–	–	–
Novartis	X	–	–	–
Abbvie	X	–	–	–
Boehringer Ingelheim	X	–	–	–

Declaration for Clinician 17
Name: Dr. Maqbool Sheriff

Position: Rheumatologist, Nanaimo, BC

Date: 25-07-2022

Table 29: COI Declaration for CANIOS and Associated Physicians — Clinician 17

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Astra Zeneca	X	–	–	–
GlaxoSmithKline	X	–	–	–

Declaration for Clinician 18
Name: Dr. Christine A. Peschken, MD, MSc

Position: Professor, Department of Medicine, University of Manitoba

Date: 25-07-2022

Table 30: COI Declaration for CANIOS and Associated Physicians — Clinician 18

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Astra Zeneca	X	–	–	–
GlaxoSmithKline	X	–	–	–

Declaration for Clinician 19
Name: Dr. Sean Barbour, MD, MSc

Position: Associate Professor, Division of Nephrology, University of BC

Date: July 25, 2022

Table 31: COI Declaration for CANIOS and Associated Physicians — Clinician 19

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Visterra	X	–	–	–
Chinook	X	–	–	–
Alexion	–	–	–	X
Roche	–	–	X	–
Novartis	–	–	–	X
MorphoSys	X	–	–	–
Vera	X	–	–	–
Pfizer	X	–	–	–
Eledon	X	–	–	–
BioCryst	X	–	–	–

Declaration for Clinician 20

Name: Dr. Stephanie Keeling, MD MSc FRCPC

Position: Professor, Department of Medicine, University of Alberta

Date: 07-26-2022

Table 32: COI Declaration for CANIOS and Associated Physicians — Clinician 20

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Astra Zeneca	–	X	–	–
GlaxoSmithKline	–	–	X	–
Pfizer	–	X	–	–
Abbvie	–	–	X	–
Sandoz	X	–	–	–
Janssen	–	X	–	–

Declaration for Clinician 21

Name: Dr. Hugues Allard-Chamard, MD, PhD

Position: Assistant Professor, Department of Medicine, Université de Sherbrooke

Date: 26 July 2022

Table 33: COI Declaration for CANIOS and Associated Physicians — Clinician 21

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Astra Zeneca	—	X	—	—
Pfizer	—	X	—	—
Abbvie	—	X	—	—
Sanofi	—	X	—	—
Novartis	—	—	X	—
Amgen	—	X	—	—
Roche	—	X	—	—
Eli Lilly	—	—	X	—
BMS	—	X	—	—
Janssen	—	—	X	—
Sobi	—	X	—	—
Sandoz	—	X	—	—

Declaration for Clinician 22
Name: Dr. Michele Tupchong MD, FRCPC

Position: Rheumatologist, Markham, Ontario

Date: July 27, 2022

Table 34: COI Declaration for CANIOS and Associated Physicians — Clinician 22

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Janssen	X	—	—	—
Pfizer	X	—	—	—

Declaration for Clinician 23
Name: Dr. Shelly Dunne, MD, FRCPC

Position: Rheumatologist, North York, ON

Date: 27-07-2022

Table 35: COI Declaration for CANIOS and Associated Physicians — Clinician 23

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
No COI	—	—	—	—

Declaration for Clinician 24
Name: Dr. Ceri Anne Richards, MD, FRCPC

Position: Rheumatology

Date: 07-27-2022

Table 36: COI Declaration for CANIOS and Associated Physicians — Clinician 24

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Novartis	X	—	—	—
Lilly	X	—	—	—
Pfizer	X	—	—	—
Abbvie	X	—	—	—

Declaration for Clinician 25

Name: Dr. Juris Lazovskis, MD, FRCPC

Position: Assistant Professor, Department of Medicine, Dalhousie University

Date: 27-07-2022

Table 37: COI Declaration for CANIOS and Associated Physicians — Clinician 25

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
No COI	—	—	—	—

Declaration for Clinician 26

Name: Megan R.W. Barber, MD, PhD, FRCPC

Position: Clinical Assistant Professor, University of Calgary

Date: 27-07-2022

Table 38: COI Declaration for CANIOS and Associated Physicians — Clinician 26

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Janssen	X	—	—	—
AstraZeneca	X	—	—	—
AbbVie	X	—	—	—
GSK	X	—	—	—
Sanofi Genzyme	X	—	—	—

Declaration for Clinician 27

Name: Dr. Laura Ellen Berall, MD, MSc, FRCPC

Position: Nephrologist, Glomerulonephritis Lead, Humber River Hospital

Date: July 28, 2022

Table 39: COI Declaration for CANIOS and Associated Physicians — Clinician 27

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Astra Zeneca	X	—	—	—
GlaxoSmithKline	X	—	—	—

Declaration for Clinician 28

Name: Dr. Derek Haaland, M.D., M.Sc., F.R.C.P.C.

Position: Rheumatologist, Clinical Immunologist & Allergist; Medical Director, The Waterside Clinic, Barrie, ON; Associate Clinical Professor, McMaster University, Hamilton, ON; Assistant Professor, Northern Ontario School of Medicine, Laurentian University Campus, Sudbury, ON

Date: July 28, 2022

Table 40: COI Declaration for CANIOS and Associated Physicians — Clinician 28

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
AbbVie	—	—	X	—
Amgen	—	—	X	—
AstraZeneca	—	—	X	—
Bristol-Myers Squibb	—	—	X	—
Eli-Lily	—	—	X	—
GlaxoSmithKline	—	—	X	—
Janssen	—	—	X	—
Merck	—	—	X	—
Novartis	—	—	X	—
Pfizer	—	—	X	—
Roche	—	—	X	—
Sanofi Genzyme	—	—	X	—
Takeda	—	—	X	—
UCB	—	—	X	—

Declaration for Clinician 29

Name: Dr. Louise Moist, MD, MSc

Position: Professor, Department of Medicine, Western University

Date: 28-07-2022

Table 41: COI Declaration for CANIOS and Associated Physicians — Clinician 29

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Astra Zeneca	—	—	X	—
GlaxoSmithKline	X	—	—	—
Otsuka	—	—	X	—
Bayer	—	—	X	—
Boehringer Ingelheim	X	—	—	—
Janssen	—	X	—	—

Declaration for Clinician 30
Name: Dr. Hector Arbillaga, MD, FRCPC

Position: Clinical Associate Professor, Cumming School of Medicine, University of Calgary

Date: 28-07-2022

Table 42: COI Declaration for CANIOS and Associated Physicians — Clinician 30

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
No COI	—	—	—	—

Declaration for Clinician 31
Name: Nathalie Rozenbojm, RN

Position: Toronto Lupus Clinic, University of Toronto

Date: 28-07-2022

Table 43: COI Declaration for CANIOS and Associated Physicians — Clinician 31

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
No COI	—	—	—	—