Belimumab and Voclosporin for Lupus Nephritis: Effectiveness and Value

Evidence Report

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Prepared for

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Jeffrey Tice served as the lead author for the report and wrote the executive summary, background, other benefits, and contextual considerations sections of the report. Jeffrey Tice also led the systematic review and authorship of the comparative clinical effectiveness section with the support of Serina Herron-Smith and Belen Herce-Hagiwara. Foluso Agboola conducted the meta-analyses and network meta-analysis. Olena Mandrik and Praveen Thokala developed the cost-effectiveness model and authored the corresponding sections of the report with the support of James Fotheringham. Rick Chapman was responsible for the oversight of the cost-effectiveness analyses and developed the budget impact model. Steven Pearson provided methodologic guidance on the clinical and economic evaluations. We thank Professor Matt Stevenson from the University of Sheffield for his comments on the cost-effectiveness section. We would also like to thank Maggie Houle and Catherine Koola for their contributions to this report.

About ICER

The Institute for Clinical and Economic Review (ICER) is an independent non-profit research organization that evaluates medical evidence and convenes public deliberative bodies to help stakeholders interpret and apply evidence to improve patient outcomes and control costs. Through all its work, ICER seeks to help create a future in which collaborative efforts to move evidence into action provide the foundation for a more effective, efficient, and just health care system. More information about ICER is available at https://icer.org/.

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For drug topics, in addition to receiving recommendations from the public, ICER scans publicly available information and also benefits from a collaboration with IPD Analytics, an independent organization that performs analyses of the emerging drug pipeline for a diverse group of industry stakeholders, including payers, pharmaceutical manufacturers, providers, and wholesalers. IPD provides a tailored report on the drug pipeline on a courtesy basis to ICER but does not prioritize topics for specific ICER assessments.

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In the development of this report, ICER's researchers consulted with several clinical experts, patients, manufacturers, and other stakeholders. The following experts provided input that helped guide the ICER team as we shaped our scope and report. It is possible that expert reviewers may not have had the opportunity to review all portions of this draft report. None of these individuals is responsible for the final contents of this report, nor should it be assumed that they support any part of it. The report should be viewed as attributable solely to the ICER team and its affiliated researchers.

For a complete list of stakeholders from whom we requested input, please visit: https://icer.org/wp-content/uploads/2020/12/ICER_Lupus-Nephritis_Stakeholder-List_092920.pdf

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List of Acronyms and Abbreviations Used in this Report

ACR	**American College of Rheumatology**
AD	**Active disease**
AE	**Adverse event**
AHRQ	**Agency for Healthcare Research and Quality**
ASP	**Average sales price**
AZA	**Azathioprine**
BEM	**Belimumab**
CI	**Confidence Interval**
CNI	**Calcineurin Inhibitor**
CR	**Complete response**
CRR	**Complete renal response**
CYC	**Cyclophosphamide**
eGFR	**Estimated glomerular filtration rate**
EULAR	**European League Against Rheumatism**
evLYG	**Equal value life-years gained**
ESRD	**End stage renal disease**
GFR	**Glomerular filtration rate**
HCQ	**Hydroxychloroquine**
KDIGO	**Kidney Disease: Improving Global Outcomes**
KM	**Kaplan Meier**
LN	**Lupus nephritis**
LY	**Life year**
MA	**Meta-analysis**
MMF	**Mycophenolate mofetil**
NA	**Not applicable**
NMA	**Network meta-analysis**
NR	**Not reported**
NS	**Not significant**
OR	**Odds ratio**
PBO	**Placebo**
PERR	**Primary efficacy renal response**
PICOTS	**Population, Intervention, Comparator, Outcome, Timing, Setting**
PR	**Partial response**
PRISMA	**Preferred Reporting Items for Systematic Reviews and Meta Analyses**
PRR	**Partial renal response**
PSA	**Probabilistic sensitivity analysis**
QALY	**Quality adjusted life year**
RCT	**Randomized control trial**
RR	**Risk ratio**
SAE	**Serious adverse events**
SC	**Standard care**
SLE	**Systemic lupus erythematosus**
SLICC	**Systemic Lupus International Collaborating Clinics**
USPSTF	**United States Preventive Services Task Force**
VCS	**Voclosporin**
WAC	**Wholesale acquisition price**

Executive Summary

Systemic lupus erythematosus (SLE) is an autoimmune disease that affects between 300,000 and 1.5 million Americans.[1] It is more common in women (90% of diagnosed cases) and in non-Whites (four times higher prevalence in Black patients, two times higher prevalence in Hispanic patients). Approximately half of patients with SLE will be diagnosed with lupus nephritis (LN), characterized by inflammation in the kidney, proteinuria, and progressive kidney damage which can lead to kidney failure.[2,3] LN typically presents in patients who are 20 to 40 years old[4,5] and is the most common cause of death and disability in patients with SLE.

In this report, ICER reviews belimumab, a parenteral b-lymphocyte inhibitor, and voclosporin, an oral calcineurin inhibitor, for the initial treatment of patients with LN. Each drug is added to standard induction therapy for LN which is high-dose corticosteroids combined with either mycophenolate mofetil (MMF) or cyclophosphamide. The FDA approved belimumab on 12/17/2020 and voclosporin on 01/22/2021.

Belimumab increases the complete renal response (CRR) and primary efficacy renal response (PERR) at two years compared with standard therapy alone, with benefits seen after the first year appearing stable at year two. At two years, the proportion of patients receiving ≤ 5 mg of prednisone was greater in the belimumab group (36.8% versus 27.8%). There were no significant increases in adverse events or discontinuations compared with standard induction therapy for LN.

Voclosporin nearly doubled the complete response (CR) and markedly increased the partial response (PR) at one year compared with standard therapy alone. The proportion of patients on low dose steroids was not reported, but all those with PR and CR were required to be taking low dose steroids. Adverse events were comparable to standard induction therapy for LN, but the FDA added a black box warning consistent with that of cyclosporin for possible serious infections and malignancies.

Table ES1. Complete Response at One and Two Years

Outcome	One Year	Two years
Belimumab CRR§	32.5%	30.0%
Placebo CRR	25.5%	19.7%
Voclosporin CR*	42.3%	-
Placebo CR	23.3%	-

* CR: Complete response from meta-analysis. Two-year data are not available.

§ CRR: Complete renal response at one year estimated from Figure 1 in the manuscript.

See Supplement Section A1 for details on the small differences in the definition of CR and CRR.

The most important uncertainty is how these short-term assessments of renal response translate into meaningful long-term outcomes for patients in whom SLE is a lifetime illness. In addition, the length of time these therapies are used prior to tapering them to standard maintenance therapy remains to be established. Because of inadequate representation of patients from communities of color in the development trials, the limited data available are highly uncertain and cannot be used to determine the relative effectiveness of either drug among different racial and ethnic groups.

Table ES2 shows ICER's evidence ratings for the two therapies: Incremental or better – moderate certainty of a small or substantial net health benefit with high certainty of at least a small net health benefit (B+).

Table ES2. Evidence Ratings

Treatment	Comparator	Evidence Rating
Adults with LN		
Belimumab + MMF/Corticosteroids or Cyclophosphamide/Corticosteroids	MMF/Corticosteroids or Cyclophosphamide/Corticosteroids	B+
Voclosporin+ MMF/Corticosteroids	MMF/Corticosteroids	B+

ICER performed cost-effectiveness analyses of the new drugs. The annual cost of belimumab for patients remaining on treatment was estimated to be $42,720 ($39,944 when including treatment discontinuation because of adverse events). Voclosporin annual costs for patients remaining on treatment were estimated to be $92,233 ($87,068 including adverse event-related discontinuation). The annual cost figure for voclosporin differs from the drug makers' announced net price due to their incorporation of estimated real-world discontinuation and lack of full adherence that occur for reasons other than treatment-related adverse effects.

In the base case, the incremental cost-effectiveness ratio for belimumab was estimated to be approximately $90,000 per quality adjusted life year (QALY), and $78,000 per equal value of life years gained (evLYG). The corresponding results for voclosporin were approximately $149,000/QALY and $132,000/evLYG. In one-way sensitivity analyses, the incremental cost-effectiveness ratios were most sensitive to the monthly costs for patients with active kidney disease and the utilities for the active disease and complete response health states. In probabilistic sensitivity analyses, belimumab was cost effective at the $150,000/QALY threshold in 69% of the runs and voclosporin in 49% of the runs.

To explore the potential for important differences in relative effectiveness across racial and ethnic subgroups, we performed a scenario analysis for Black patients, the most prevalent ethnic subgroup. We cannot stress enough that the results are highly uncertain due to the small numbers of Black patients in the available clinical trials and the lack of data on differences among subgroups in long term outcomes. For belimumab, the estimated cost-effectiveness for Black patients was

worse than for White patients, whereas for voclosporin it was modestly improved. As noted, these results are highly uncertain. They should not guide clinical or policy decision-making but should be recognized as signaling how important it is for drug makers and clinical researchers to structure future clinical research to be able to examine the relative effectiveness of these treatments among the racial and ethnic groups that constitute the majority of patients with LN in the United States.

The Health Benefit Price Benchmarks (HBPBs) for a drug is defined as the price range that would achieve incremental cost-effectiveness ratios between $100,000 and $150,000 per QALY or per evLYG gained. We estimated that the HBPB for belimumab ranges from $45,000 to $61,000 and that the HBPB for voclosporin ranges from $72,000 to $101,000.

There are other potential benefits and contextual considerations not fully captured in the economic model. These include potentially greater benefits of these therapies for Black patients, the high lifetime burden of illness of LN, the early age of onset of the disease, and the lack of FDA approved therapies for LN prior to the availability of these drugs. On the other hand, the assumed long-term benefits of these therapies are likely to be optimistic because we assume that patients with a partial response do as well as those with complete response, so the model may overestimate the benefits of belimumab and voclosporin.

In conclusion, the evidence appears adequate to demonstrate that belimumab and voclosporin provide improved clinical outcomes for patients and may offer important benefits beyond those directly measured in clinical and cost-effectiveness analyses. Substantial uncertainty remains regarding the magnitude of the impact of short-term kidney function improvement on long-term outcomes that matter most to patients, such as progression to renal failure. Relative clinical benefits for Black patients and those from other racial and ethnic groups are not well defined from the existing clinical studies and deserves much greater focus in future research given the high unmet need in these communities.

With these uncertainties in view, our modeling suggests that belimumab's estimated net price aligns well with its' estimated long-term added benefits for patients. These findings do not include consideration of potential broader benefits of belimumab on health for patients with LN. For voclosporin, its estimated net price produces a cost-effectiveness result at the upper end of commonly accepted ranges. The results of the cost-effectiveness analyses for both drugs are sensitive to important assumptions, and policymakers should also view the results in the context of important potential other benefits and contextual considerations related to new treatments for LN.

1. Background

Systemic lupus erythematosus (SLE) is an autoimmune disease that affects between 300,000 and 1.5 million Americans.[1] It is more common in women (90% of diagnosed cases) and in non-Whites (four times higher prevalence in Black patients, two times higher prevalence in Hispanic patients). Approximately half of patients with SLE will be diagnosed with lupus nephritis (LN), a heterogenous disease characterized by inflammation in the kidney, proteinuria, and progressive kidney damage.[2,3] LN typically presents in patients who are 20 to 40 years old.[4,5] The diagnosis is suspected when there is excess protein in the urine and made with a kidney biopsy. Within 15 years of the diagnosis, between 10% to 30% of patients with LN progress to end stage renal disease (ESRD), requiring dialysis or kidney transplantation.[6-8] The prognosis of patients with LN is worse in Black patients and Hispanic patients.[9,10]

Guidelines recommend induction therapy with high dose corticosteroids combined with either mycophenolate mofetil (MMF) or cyclophosphamide, followed by maintenance therapy with MMF.[11,12] Unfortunately, fewer than half of patients with LN respond to current combination therapy, so there is a large unmet need for new therapies.

The FDA recently expanded the indication for belimumab to include LN and is expected to approve voclosporin in early 2021 (Table 1.1). Belimumab is a parenteral b-lymphocyte inhibitor that is FDA approved for SLE; the manufacturer submitted an application to expand its indication to include LN on 7/29/20. Voclosporin is an oral calcineurin inhibitor that is reported to be safer than other calcineurin inhibitors (less kidney damage); the FDA approved voclosporin on 1/22/2021 for LN.

Table 1.1. Interventions of Interest

Intervention Brand Name (Generic Name)	Mechanism of Action	Delivery Route	Prescribing Information
Benlysta (belimumab)	B-lymphocyte stimulator inhibitor	Intravenous*	10 mg/kg every 2 weeks x 3 doses, then every 4 weeks
Lupkynis™ (voclosporin)	Calcineurin inhibitor	Oral	27.5 mg twice daily

mg: milligram, kg: kilogram

*Belimumab is also available in a subcutaneous formulation, but that formulation has not been studied for the treatment of lupus nephritis

2. Patient and Caregiver Perspectives

One important source to understand the patient perspective comes from a meeting convened in September 2017 by the Lupus and Allied Diseases Association, the Lupus Foundation of America, and the Lupus Research Alliance. The purpose of this meeting was to elicit the perspectives of patients living with lupus as part of the FDA's Patient Focused Drug Development Initiative. Insights from the meeting are summarized in the report *Lupus: Patient Voices*.[13] In the report, patients with LN reported that the symptoms that most negatively affected their lives were fatigue (24%), joint and muscle pain (24%) and their kidney disease (21%). Among all patients with SLE the top three downsides of their current treatment were side effects (54%), the number of pills and other treatments taken each day (54%), and the cost of treatment (42%).[13]

From patient groups and other stakeholders, we heard how important it was to take into consideration the greater impact that LN has on communities of color. This input emphasized the importance of doing subgroup analyses in these patient populations. For example, progression to ESRD in Black LN patients is almost nine times greater than in White patients yet access to kidney transplantation is lower, and overall mortality from the condition is higher in Black patients and other non-White groups.[14,15] Disparities in outcomes between White and non-White LN patients persist even when adjusting for socioeconomic factors, signaling the possibility of both biological differences and the impact of systemic racism in the health care system and society.[16]

Patient groups also emphasized that each person is unique due to the heterogeneity and unpredictable course of the disease. Each patient has a different constellation of co-morbidities, demographics, living circumstances, and baseline medications. All of these play into the impact of LN on their lives and the potential for benefits and harms from new medications. Given the young age of onset of LN, the disease often has a huge negative impact on patients' ability to work, to have children, and to advance in their careers. It creates an emotional and financial burden to both the patient and caregiver and a huge economic burden for society to bear.

Feedback from patients also highlighted the importance to them of reducing or eliminating the need for high-dose steroids because of side effects that often include mental health issues, weight gain and changes to appearance, and manifold significant long-term harms including increased risk for diabetes, osteoporosis, hypertension, infections, coronary artery disease, glaucoma, and cataracts. We also heard that we should be mindful of the outcomes of treatment that matter most to LN patients in addition to improving their kidney disease: to mitigate fatigue and reduce or eliminate joint and muscle pain.

A final concern expressed by patients is the route of administration of therapies for LN. Given the COVID-19 pandemic, patients are understandably concerned about needing to come into infusion

centers for therapies that require intravenous infusion. Other factors that impact LN patients who receive intravenous infusions include treatment costs, child, and elder care, and in some geographic areas limited availability of infusion providers/centers and/or transportation challenges. In addition, the time and travel required to access kidney dialysis or infusion therapy is an impediment for many people. We also heard that utilization management payer policies such as step therapy restrictions present frustrations for both patients and their providers, particularly when patients are required to try and fail preferred treatments that can be ineffective or result in adverse reactions. They also highlighted issues with access to care in general and in particular for patients in communities of color and those who live in rural areas.

3. Comparative Clinical Effectiveness

3.1. Methods Overview

Please see the Supplement Section D for details of the literature search, quality assessment, and the quantitative summary methods.

Scope of Review

This review compares the outcomes of adding belimumab or voclosporin to standard therapy with the outcomes of standard therapy alone for the treatment of adults with LN. The primary outcomes are complete and partial remission over one to two years of therapy and reductions in steroid use. Unfortunately, the drug makers did not measure fatigue or quality of life, and no data are available on longer-term progression to ESRD.

Evidence Base

The clinical evidence is summarized separately below for each drug because the pivotal trials for the two drugs differed markedly in populations studied, outcome definitions, and length of follow-up. Both drugs are added to standard induction therapy for LN (either MMF or cyclophosphamide in addition to high dose corticosteroids).

Belimumab

Our search identified one randomized trial of belimumab in patients with LN, the pivotal phase 3 trial BLISS-LN with outcomes at 104 weeks[17], and two uncontrolled trial.[18,19] Detailed descriptions of the study designs can be found in Supplement Table D4.2.

Voclosporin

Our search identified two randomized trials of voclosporin in patients with LN: the pivotal phase 3 AURORA trial with primary outcomes measured at 52 weeks, and the 24-week phase 2b AURA-LV trial in which one arm received the same dose of voclosporin as in AURORA (Table 3.1). There was also one uncontrolled phase 2 trial (AURION).[20-26] The full results of the AURORA trial have not yet been published. Detailed descriptions of the study designs can be found in Supplement Table D4.2.

Table 3.1. Overview of Key Studies

Drug	Trials	N	Primary Outcome
Belimumab	BLISS-LN	446	104-week PERR
Voclosporin	AURA-LV	177	24-week CR
Voclosporin	AURORA	357	52-week CR

CR: complete response; PERR: primary efficacy renal response

Key Difference in the Clinical Trials.

The primary differences in the study populations for the two drugs were that the AURORA trial excluded patients with an eGFR < 45 ml/min and required background therapy exclusively with MMF, whereas the BLISS-LN trial only excluded patients with an eGFR < 30 ml/min and allowed background therapy with either MMF or cyclophosphamide (Supplement Table D4.2). Approximately 26% of patients in the BLISS-LN trial received cyclophosphamide. Despite these differences, the patient populations in the two pivotal trials were otherwise quite similar (88% female, mean or median age 33, Black race 13-14% in both trials). The mean eGFR for patients at entry in the AURORA trial (91 ml/min) was slightly lower than that of patients in the BLISS-LN trial (100 ml/min) despite its exclusion of patients with low eGFR. Additional baseline characteristics for patients in all of the studies are in Supplement Table D4.3.

There are several other important differences between the trials. The primary outcome for the AURORA trial was "complete response" (CR) at one year, while the primary outcome in the BLISS-LN trial was "primary efficacy renal response" (PERR) at two years. Apart from the time of assessment, the two outcomes differed in the degree of allowable proteinuria (CR UPCR ≤ 0.5; PERR UCPR ≤ 0.7) and CR required sustained, low dose or no corticosteroid use. Since the differences are small, it is reasonable to compare them at similar timepoints. There were also slight differences in the definitions used for complete response and partial response in the two trials (Supplement Section A1 describes the specifics for each definition). Lastly, the AURORA trial required a rapid taper of corticosteroids, which was not required in the BLISS-LN trial.

3.2. Results

Clinical Benefits

The primary outcomes that are used in the economic model are the complete renal response and partial renal response as defined in the clinical trials. The reduction in prednisone dose to 5 mg/day or less was measured in both trials. As noted, no measures of quality of life or patient reported outcomes such as fatigue, SF-36, EQ-5D, WHOQOL, SLEQOL, LupusQOL, or LupusPro were reported publicly or provided separately by the drug makers.

Belimumab

The key outcomes of the BLISS-LN trial are summarized in Table 3.2 below. At one year, the PERR for belimumab was approximately 10% greater than placebo, and, similarly, at two years both PERR and CRR for belimumab were about 10% greater than placebo.

Table 3.2. Key Outcomes for Belimumab in BLISS-LN

Outcome	12 months		24 months	
	Placebo	Belimumab	Placebo	Belimumab
CRR	25.5%*	32.5%*	19.7%	30.0%
PERR	35.4%	46.6%	32.0%	43.0%

CRR: Complete renal response, PERR: Primary efficacy renal response.

* The 12-month results are approximations read from Figure 1 in the NEJM publication.[17]

Figure 1 in the published results of the BLISS-LN trials shows that the proportion of patients having CRR and PERR increased over the first 40 to 48 weeks and remained relatively stable after that time. As can be seen in Table 3.3 above, the PERR decreased slightly between 12 months (52 weeks) and 24 months (104 weeks). The CRR results were not reported numerically at 12 months but were approximately 25% for the placebo group and 31% for the belimumab group mirroring the results of PERR.

A unique outcome reported in the BLISS-LN trial was the time to a renal-related event or death, which included ESRD, doubling of the serum creatinine, increased proteinuria, or impaired kidney function. In a time to event analysis, the HR for this outcome was 0.51 (95% CI 0.34-0.77) for belimumab compared with placebo.

In an abstract presented in November 2020, the investigators reported on SLEDAI-S2K scores and prednisone dosage at 104 weeks follow-up.[27] Patients randomized to belimumab had higher SLEDAI-S2K scores (62 versus 41, p=0.016) and a higher proportion of patients on 5 mg or less of prednisone (36.8% versus 27.8%, p=0.044).

Voclosporin

We performed a random effects meta-analysis of the AURA-LV and AURORA trials for complete and partial response at six and twelve months (Table 3.3 below). Detailed methods are shown in Supplement Section D1; detailed results in Supplement Section D5). The AURA-LV trial did not report PR at 12 months, so Table 3.2 includes PR from the AURORA trial at both six and twelve months. At one year, both the CR and PR for voclosporin was about 20% greater than placebo.

Table 3.3. Meta-Analysis of Key Outcomes for Voclosporin

Outcome	6 months		12 months	
	Placebo	Voclosporin	Placebo	Voclosporin
MA Complete response	19.9%	32.9%	23.3%	43.2%
MA Partial response	50.0%	70.9%	-	-
AURORA Partial response	50.0%	70.4%	51.7%	69.8%

MA: meta-analysis

Exploratory Analysis Comparing Belimumab to Voclosporin

As noted above, there were important differences in the studies of the two drugs in the study populations, co-interventions, and some of the outcomes. However, the differences in patient characteristics at baseline tended to favor belimumab (less proteinuria at baseline, better renal function at baseline [higher baseline eGFR], and longer follow-up for efficacy). We conducted a network meta-analysis comparing CRR at two years for belimumab to CR at one year for voclosporin (Supplement Section D1 for detailed methods, Section D5 for detailed results). In the NMA, there were no significant difference in CR between the two drugs when added to standard care, but the trend was for a greater proportion of patients to have a CR with one year of voclosporin compared with two years of belimumab (OR 1.62, 95% CI 0.94 to 2.77, Supplement Table D5).

Harms

Belimumab

In the BLISS-LN trial, SAEs were similar in the belimumab and placebo groups (25.9% versus 29.9%) as were adverse events thought to be related to treatment (55% versus 53%). Adverse events leading to treatment discontinuation were identical (13%). See Supplement Table D4.10 for additional details.

Voclosporin

In the AURORA trial serious adverse events (SAEs) were nearly identical in the voclosporin and placebo groups (20.8% versus 21.3%), as were adverse events thought to be related to treatment (4.5% in both groups). Adverse events leading to treatment discontinuation were less common in the voclosporin group (11.2% versus 14.6%). See Supplement Table D4.10 for additional details.

Voclosporin carries a black box warning for serious infections and malignancies that may lead to hospitalization or death based on the experience with similar immunosuppressant therapies.

Subgroup Analyses and Heterogeneity

Because of inadequate representation of patients from communities of color in the development trials, the limited data available are highly uncertain and cannot be used to determine the relative effectiveness of either drug among different racial or ethnic groups. We present the results below for transparency and to signal the importance of re-orienting future research efforts so that adequate evidence can be generated to evaluate the relative safety and effectiveness of treatments among the patient groups that suffer the greatest burden of illness from LN in the United States.

Belimumab

In the BLISS-LN trial at 104 weeks, the point estimates for the odds ratio (OR) for PERR (2.24 versus 1.53) and CRR (2.16 versus 1.75) was nominally higher for Black patients than the point estimate for non-Black patients, but neither OR was statistically significant for Black patients, likely due to insufficient power as there were only 63 Black participants in the trial (four with CRR in the placebo group, six with CRR in the belimumab group). No p-values for interaction were reported.

Heterogeneity was also seen among patients treated with belimumab based on their induction therapy. The PERR at 104 weeks was similar for patients receiving cyclophosphamide or MMF, but the OR for CRR in patients treated with cyclophosphamide was 1.07 (95% CI 0.41 – 2.78) compared with 2.01 (95% CI 1.19 – 3.38) for patients treated with MMF.

Voclosporin

In the AURORA trial, Black patients had a lower CR than White patients in the placebo group (15.8% versus 29.5%), which supports the evidence in the literature that Black patients have a worse response to standard induction therapy than White patients. In addition, Black patients had a higher CR than White patients among patients treated with voclosporin (46.2% versus 38.2%). This suggests that voclosporin may be more efficacious in Black patients, but no p-value for interaction was reported. However, the CR for voclosporin in White patients was non-significant (38.2% versus 29.5%, p =0.165), while it was significant in Black patients (46.2% versus 15.8%, p = 0.045) and Asian patients (41.5% versus 17.9%, p=0.005). There were only 45 Black participants in the trial, so these subgroup findings may be due to chance.

Uncertainty and Controversies

The most important uncertainty is how these short-term assessments of partial and complete renal response translate into meaningful long-term outcomes for patients. LN is a life-threatening, lifelong illness and the outcomes that matter most to patients are progression to ESRD or death. The available outcomes, limited to one to two-year response rates, are insufficient to demonstrate adequately the magnitude or durability of the long-term benefits of these novel therapies.

It is also unclear from the available evidence how long therapy with these novel agents should continue. For voclosporin, in particular, there is the potential for a reduction in eGFR, which has been a significant limitation for other calcineurin inhibitors. Voclosporin is thought to be safer, but long-term data are lacking. There are concerns that voclosporin is suppressing proteinuria, without changing the underlying inflammation or altering the progression of LN.

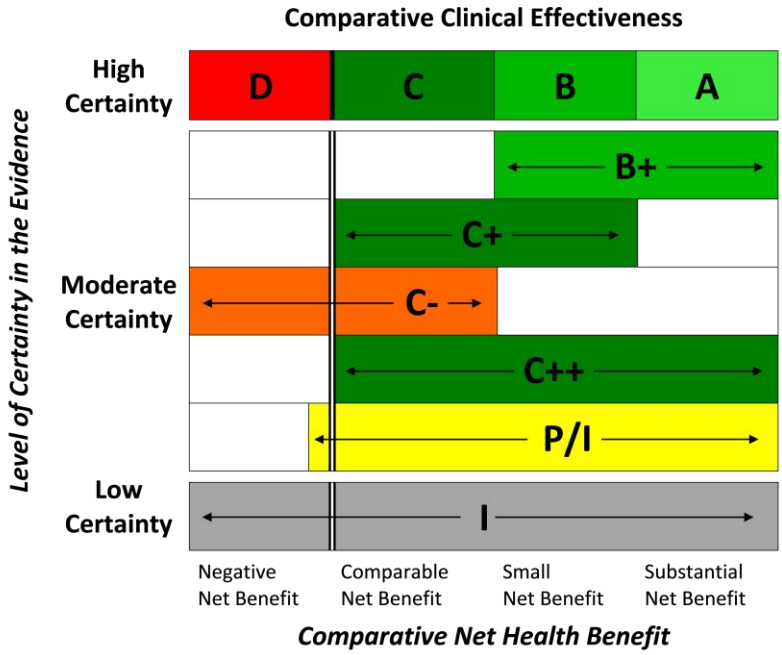
The studies have not reported on the impact of these novel therapies on fatigue, one of the most important outcomes to patients, nor are there any reports on the impact of these therapies on patients' quality of life or changes in functional status.

And, importantly, LN disproportionately impacts non-White patients. As noted above, the number of non-White patients enrolled by drug makers in pivotal trials was too small to determine relative effectiveness of either drug across racial and ethnic groups.

3.3. Summary and Comment

The ICER Evidence Rating Matrix is shown below in Figure 3.1. Full details are provided in the Supplement.

Figure 3.1. ICER Evidence Rating Matrix



A = "Superior" - *High certainty of a substantial (moderate-large) net health benefit*
B = "Incremental" - *High certainty of a small net health benefit*
C = "Comparable"- *High certainty of a comparable net health benefit*
D= "Negative"- *High certainty of an inferior net health benefit*
B+= "Incremental or Better" – *Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit*
C+ = "Comparable or Incremental" - *Moderate certainty of a comparable or small net health benefit, with high certainty of at least a comparable net health benefit*
C- = "Comparable or Inferior" *– Moderate certainty that the net health benefit is either comparable or inferior with high certainty of at best a comparable net health benefit*
C++ = "Comparable or Better" - *Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit*
P/I = "Promising but Inconclusive" *- Moderate certainty of a small or substantial net health benefit, small likelihood of a negative net health benefit*
I = "Insufficient" – *Any situation in which the level of certainty in the evidence is low*

Belimumab

Belimumab added to standard therapy significantly increases the CRR and PERR at two years compared with standard therapy alone. The benefits were seen within the first year and remained stable between years one and two. There were no significant increases in adverse events or discontinuations due to adverse events compared with standard induction therapy for LN. Although the trials were two years in duration, this remains too short a time to provide high certainty of the magnitude or duration of long-term benefit. Hence, as with voclosporin, we judge that the comparative net health benefit of belimumab added to standard therapy is "incremental or better" (B+).

Voclosporin

Voclosporin added to standard therapy nearly doubled the CR and markedly increased the PR at one year compared with standard therapy alone. Adverse events were comparable to standard induction therapy for LN. However, other calcineurin inhibitors have adverse long-term renal effects, which would not have been evident in the relatively short clinical trials performed to date. Therefore, uncertainty remains as to whether the overall health benefits of voclosporin will prove to be substantial or incremental. Hence, at this time we have assigned a rating of "incremental or better" (B+) to the comparative net health benefit of voclosporin.

Table 3.4. Evidence Ratings

Treatment	Comparator	Evidence Rating
Adults with LN		
Belimumab + MMF/Corticosteroids or Cyclophosphamide/Corticosteroids	MMF/Corticosteroids or Cyclophosphamide/Corticosteroids	B+
Voclosporin+ MMF/Corticosteroids	MMF/Corticosteroids	B+

4. Long-Term Cost-Effectiveness

4.1. Methods Overview

The aim of the economic evaluation was to estimate the cost effectiveness of belimumab and voclosporin for patients with LN, with each drug compared to the standard of care as represented by the comparator arm in its own pivotal trial(s).

The decision analytic model assumes progression of the disease through the patients' lifetimes (i.e., lifetime horizon), using a health care sector perspective in the base case. The model, based on response-to-treatment outcomes, consists of two parts: (a) a short-term interpolation model concordant with data from the trials; (b) a long-term (lifetime) model based on extrapolation using partitioned survival modeling.

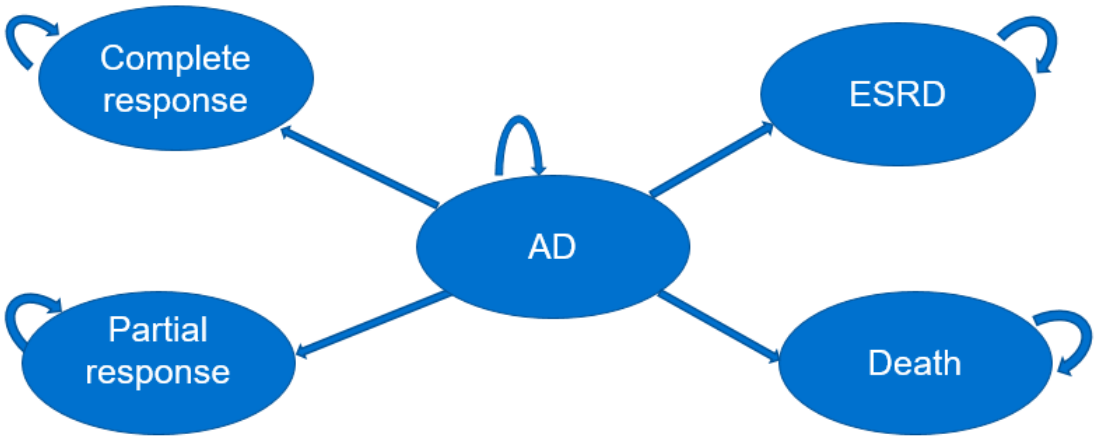
All patients start the short-term model in the active disease (AD) state. From the AD state, patients may transition to either complete response (CR), partial response (PR), end-stage renal disease (ESRD), or death (Figure 4.1). The base-case short-term model comprises three years for both belimumab and voclosporin. One-month probabilities up to the end of respective trial follow up times in the short-term model are informed by key trials: BLISS-LN for belimumab, and AURA-LV and AURORA for voclosporin. Based on clinical expert input, beyond the trial follow-up period, patients are assumed to stay in the same health states that they were in at the end of the trials (see Tables 4.2 and 4.3) until the end of the three years of the short-term model.

The long-term model involves partitioned-survival modeling based on other benchmarks of longitudinal data on the outcomes of LN patients. ESRD-free survival for the different health states based on BLISS-LN categorized outcomes was estimated from Davidson et al. (2018). The proportion of ESRD events and deaths within the ESRD-free survival endpoint was estimated based on data from Chen et al. (2008), as these data are not reported in Davidson et al.(2018).[8,18]

Utility and cost estimates for patients in the different health states were derived from multiple sources (reported in Section 4.2). The model estimated the total costs, quality adjusted life years (QALYs), and equal value of life years gained (evLYGs) by aggregating the cost/QALY/evLYG in each month depending on the proportion of patients in each health state. The details of the model are reported in Supplement Section E.

Because of no reliable data to inform long-term disease progression by racial subgroups, the base-case model reflected ethnicity considerations by selecting the US source of data with large proportion of Black population.[18] A scenario analysis was conducted with limited trial data reporting complete response in Black population.

Figure 4.1. Short-Term Model Structure



AD: active disease, ESRD: end-stage renal disease

4.2. Key Model Assumptions and Inputs

Our model includes several key assumptions reported in Table 4.1 below. The complete list of assumptions is reported in Supplement Section E2.

Table 4.1. Key Model Assumptions

Assumption	Rationale
Benefits of treatments were derived from improved kidney function only	LN is a complication of SLE. Some treatments, such as belimumab, could affect not only LN, but also SLE progression. This model reconstructs the progression of LN only i.e., the model does not reflect broader benefits of treatments, for instance their impact on progression of SLE or other comorbidities.
Belimumab and voclosporin treatments will be compared to standard therapies used in respective control arms and not to each other.	There are no head-to-head trials comparing belimumab and voclosporin. The designs of the trials, including the inclusion criteria, comparator arms, background therapy, definitions of outcomes, and study follow-up times are different, precluding comparison of the treatments to each other within the proposed framework.
In the long-term model, patients in CR and PR accrue costs and outcomes associated with time in AD before progressing to ESRD	Clinical experts suggested that patients with CR and PR are likely to spend a period of time in AD before progressing to ESRD (rather than progressing directly to ESRD from CR or PR). AD is defined by a drop in eGFR level which is necessary to transition into ESRD. In the long-term model this was implemented by incorporating costs and outcomes for the time spent in AD rather than explicitly modeling this transition. The mean time spent in AD state before progressing to ESRD for patients with relapse is extracted from Hanly et al. (2016).[28]
Patients in CR and PR states discontinue belimumab and voclosporin treatment at the end of the short-term model (unless a serious adverse event leading to drug discontinuation occurred earlier)	There are no data to inform long-term treatment effects of belimumab and voclosporin, thus no additional effectiveness or costs related to belimumab and voclosporin treatment will be accumulated beyond the short-term model. In the base-case analysis, the short-term model time horizon is three years and assumes patients stay in the same health states that they were in at the end of the trials (see Tables 4.2 and 4.3) until the end of three years. As such, the patients in CR and PR states are assumed to receive treatment for the whole duration of three years, except for those who stop treatment earlier due to adverse events.
Patients in the AD state discontinue belimumab and voclosporin treatment at 18 months	There are no data to inform mean discontinuation time of belimumab and voclosporin for patients remaining in the AD state. Data from the AURORA and BLISS-LN trials suggest an additional clinical effect between 6-12 months of treatment. The selection of 18 months for discontinuation in the AD state is based on recommendations from clinical experts to account for the likelihood of longer treatment time in clinical practice and also to mitigate potential underestimation of treatment duration in CR/PR states.
In the short-term model, treatment discontinuation due to adverse events (AEs) is included in the model	We assume that in a real-life setting, the treatment discontinuation rate will be lower than in the trial settings because of no blinding (i.e., those patients who discontinued in the trial because of the assumed lack of efficacy would continue the treatment in real life). Given we assume patients in the AD state stop treatment at 18 months in the model, only treatment discontinuation to AEs is included in the model.
Costs of interventions for patients who discontinued the trials with AEs were not	As there are no data available on time of patients' treatment discontinuation due to AEs, we assume that the treatment discontinuation is at the mid-point of the short-term model. For the patients who stop treatment due to AEs, the

accumulated after the midpoint of the short -term model	costs of interventions (belimumab and voclosporin) are not accrued beyond 18 months (the midpoint of the short-term model), though they still accumulate the costs related to their health state.
Tapered steroid use decreases costs and increases utilities in the short-term model	In BLISS-LN, more patients were reported on low-dose steroids in treatment than comparator arms. In AURORA, steroid dose was tapered down to a dose of 5 mg daily by week 8 and 2.5 mg daily by week 16. Costs of steroids and increments in utilities for patients on low-dose steroids are included in the short-term model.

Inputs

For belimumab, the proportion of patients reaching CR were extracted from the digitized curve from the BLISS-LN trial.[17] The proportions of patients reaching PR, ESRD, or death at the end of the trial follow-up of 104 weeks are reported in Table 4.2.

Table 4.2. Outcomes from BLISS-LN Trial at 104 weeks

Arm	Time	Complete Renal Response, %	Partial Renal Response, %	ESRD, %	Death, %
Belimumab	104 weeks	30.0	17.5	0.0	0.4
Placebo		19.7	17.0	0.4	0.9

ESRD: end-stage renal disease

Definitions in BLISS-LN trial: Complete Renal Response (CRR): ratio of urinary protein to creatinine of <0.5, eGFR no worse than 10% below pre-flare value or ≥90 ml/min/1.73 m2with no use of rescue therapy.

Partial Response: GFR no worse than 10% below baseline value or within normal range and at least 50% decrease in ratio of urinary protein to creatinine with one of the following: ratio of urinary protein to creatinine <1.0 if baseline ratio ≤3.0, or ratio of urinary protein to creatinine of <3.0 if baseline ratio >3.0; no treatment failure; and not complete renal response.

Outcomes of voclosporin treatment were assessed using data from our meta-analysis of the AURA-IV and AURORA trials (see Section 3 "Comparative Clinical Effectiveness") for CR at 24 and 52 weeks and for PR at 24 weeks; for death and PR at 52 weeks, data from the AURORA trial were used (Table 4.3.).

Table 4.3. Outcomes of Voclosporin from AURORA and AURA-LV Trials

Arm	Time	Complete Renal Response*, %	Partial Renal Response**, %	ESRD***, %	Death¥, %
Voclosporin	52 weeks	43.2	26.6	0.0	0.6
Placebo		23.3	28.4	0.0	2.8

ESRD: end-stage renal disease
Definitions in AURORA trial: Complete Renal Response (CRR): Decrease in UPCR to ≤0.5mg in two consecutive, first morning void urine specimens, eGFR >60ml/min per 1.73 m2 or no decrease of ≥20% of baseline eGFR on two consecutive occasions, No use of rescue therapy and presence of sustained low-dose steroids.
Partial Response:≥ 50% decrease in urinary protein: creatinine ratio from baseline in the absence of rescue medication
*Meta-analysis of AURA-IV and AURORA trials
**Difference between PR/CR rates reported in AURORA trial and CR rate calculated in meta-analysis
***Not reported in AURORA trial, assumed as zero;
¥ AURORA trial

As the clinical data are only reported at specific follow-up points, the proportions of patients in interim time cycles in the short-term model were estimated by applying linear interpolation to the data in Tables 4.2 and 4.3.

We sought input from clinical experts and judged it highly plausible that both belimumab and voclosporin will be continued for a longer period than the duration of their pivotal trials. Based on expert input we assumed that belimumab and voclosporin will be used in patients in CR and PR states for three years before discontinuation (except for those stopping treatment earlier due to adverse events). For patients remaining in the AD state, we assumed that both drugs will be used for 18 months before treatment discontinuation. Based on the maintenance of response from year one to year two in the BLISS-LN trial, our model assumes that patients stay in the same health states that they are in at the end of the trials (see Tables 4.2 and 4.3) until the end of three years. That is, the probability of being in each model state (CR, PR, AD, ESRD) until the end of the short-term three-year model was considered to be same to as the last observation in the trials' follow-up (two years for belimumab and one year for voclosporin).

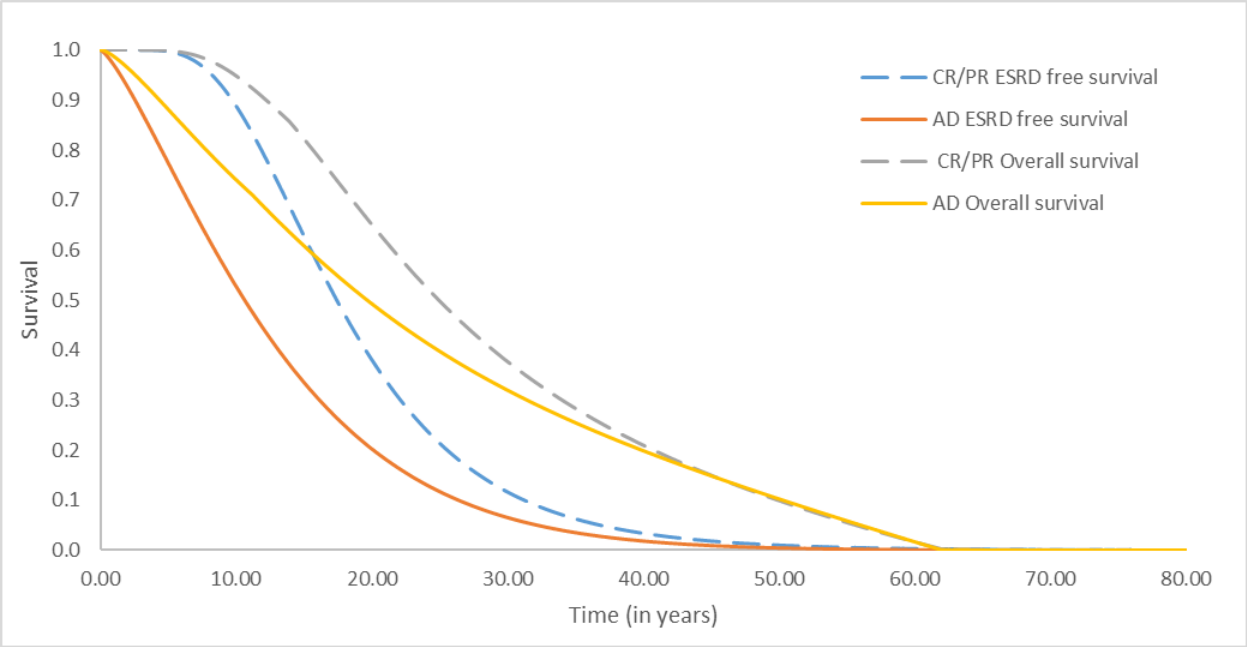
Also based on input from clinical experts, we also included treatment discontinuation due to AE in the model. We therefore assumed that 13% of patients taking belimumab and 11.2% taking voclosporin discontinue treatment due to AE in the short-term model. As there are no data from the trials to inform the time point for treatment discontinuation, this treatment discontinuation was assumed to happen at the midpoint of treatment duration (i.e., 18 months for both belimumab and voclosporin).

The long-term model used partitioned-survival modeling to estimate ESRD-free survival for the different health states (AD, CR, and PR) based on data from Davidson et al. (2018), with the proportion of ESRD events and deaths estimated based on data from Chen et al. (2008). The choice of sources in the long-term model was based on combined criteria of recent data, quality and quality of reporting, and representativeness to the US LN population (the cohort of patients in Davidson et al. included 53.4% Black patients).

The structure of the partitioned survival model does not explicitly include the transition to AD state from CR/PR, however, patients with CR/PR are likely to spend some time in AD state before progressing to ESRD. As such, we assumed that patients with CR/PR spend 1.206 years in the AD state (defined as eGFR < 30 ml/min) before progressing to ESRD, based on SLICC data.[28] An average life expectancy of 10 years (based on the difference between overall survival and ESRD free survival in the long-term model) was assumed for patients who were in ESRD at the end of the short term model.

Details on the transitions from different health states, all model assumptions, data sources, and parametric distributions selected to extrapolate survival are presented in Supplement Section E2. The survival curves used in the base-case analysis for long-term extrapolation are presented in Figure 4.2 below, with further detail also provided in Supplement Section E2. The ESRD-free survival and overall survival are assumed to be the same across the PR and CR states. The face validity of the survival curves was confirmed by the clinical experts: in the CR/PR health states, the mean ESRD-free survival is 19.38 years, and the mean OS is 28.13 years while in the AD health state, the mean ESRD-free survival is 12.98 years, and the mean OS is 23.65 years.

Figure 4.2. Survival Curves Used in the Long-Term Extrapolation Model



Both belimumab and voclosporin will be added on top of the standard therapy patients receive in the short-term model. Thus, the cost of standard therapy is not explicitly included in the model to avoid duplication as it is already reflected in the costs of health states.

The analysis assessed IV belimumab with the dose of 10 mg per kilogram of body weight (based on the distribution of the body weights of the LN population retrieved from the literature)[25] and low-dose voclosporin (oral administration) with the recommended dose of 23.7 mg twice a day. Costs of belimumab were estimated assuming all patients receive belimumab as IV administration (as it occurred in the BLISS-LN trial) and accounted for vial wastage. Cost associated with three doses of belimumab was used in the first month, and average number of monthly doses over a three-year period was used to estimate the monthly costs of belimumab beyond the first month.

Voclosporin costs were assessed considering the average daily dose of 39.1mg (mean dose weighted to the duration of patients in AURORA trial) and the price per "wallet" (containing 60 capsules 7.9mg each) of $3,950 reported by the manufacturer. The mean rebate/discount of 22.5% was then applied to calculate our estimated net price for voclosporin. This approach produces an estimated net price different from that publicly announced by the drug maker for one reason: the drug maker factored in their own estimate of real-world patient noncompliance with treatment beyond discontinuation related to adverse events captured in the clinical trials. Although there is always some degree of lack of perfect adherence in the real world, we did not adopt the drug maker's price estimate because it would not have been applicable to the clinical benefits measured in the clinical trial and the drug wastage may not directly affect the treatment costs.[29]

Table 4.4. Key Model Inputs

Parameter	Input	Source
Belimumab cost in first month	$9,811*	ASP, WAC, FSS[30-32]
Monthly cost of Belimumab	$3,560*	ASP, WAC, FSS[30-32]
Monthly cost of Voclosporin	$7,686.10	Based on the mean weighted daily dose, price per wallet (data of Aurinia) and assumed discount of 22.5%
Utility in CR health state	0.8	Bexelius et al.[33]
Utility in PR health state	0.71	Bexelius et al., Mohara et al.[34,33]
Utility in AD health state	0.624	
Utility in ESRD health state	0.549	
Annual cost in CR health state	$7,871¥	Bartels-Peculis et al.[35] Hanly et al. & Barber et al.[28,36] Li et al.[37]
Annual cost in PR health state	$8,185¥	
Annual cost in AD health state	$42,510¥	
Annual cost in ESRD health state	$120,920¥	Medicare (data provided by the Lupus Research Alliance)

CR: complete response, PR: partial response, AD: active disease, ESRD: end stage renal disease
WAC: wholesale acquisition cost, ASP: Average sales price, FSS: Federal Supply Schedule
*Based on Federal Supply Schedule as of November 7, 2020
¥ Costs are inflated to 2019 values

Costs in CR, PR, and AD states used in the model were derived from US sources with cost adjustments applied using the U.S. and Canadian data in combination with expert opinion to yield the most appropriate real-world cost estimation. The mean all-cause health care costs per LN patient per year were reported as $45,469 in 2018 by Bartels-Peculis et al.(2020) based on data on 1,039 LN patients (median age, 47 years; 83% female) recorded in a health care claims database.[35] This claims database covers members in all 50 states in the US and Washington, DC, including approximately 10 million commercial members and 2.4 million Medicare Advantage members. The costs for CR, PR, and AD health states were estimated then using ratios between the different health states.

The costs in the ESRD state were calculated as costs of people with LN, eligible for Medicare in 2016 based on ESRD alone or in combination with disability. The costs per health state are presented in the table above and further details are presented in Supplement Section E2.

Given that quality of life outcomes were neither reported nor provided by the manufacturers, health state utility values were obtained from published literature, incorporating feedback from

clinical experts and patients. The model assumed that utility values in the CR state were equal to utility values of the population with SLE who have very low disease activity, based on data from a cohort of Swedish SLE patients.[33] We estimated the utility values for patients in the PR, AD, and ESRD states by applying EQ-5D utility decrements compared to the CR state based on a cost-utility analysis from Thailand.[34] In the model, all utilities were capped at the general population utility for that age group (see Supplement Table E6 for details), to ensure they did not exceed the utilities of the general population.

For patients who have therapy with low-dose steroids (≤ 5mg/day) or no steroids (≤ 2.5mg/day), we applied a positive increment in utilities and a reduction in costs to the proportion of patients in CR, PR, and AD states reported in corresponding steroid-use categories in the AURORA and BLISS-LN trials. More details on this analysis and sources are reported in Supplement Section E2.

In the modified societal perspective analysis, indirect costs were also considered, which included costs of unemployment, absenteeism (temporary productivity loss), and caregiving. Further details on these non-medical costs are reported in Supplement Section E2.

4.3. Results

Base-Case Results

Tables 4.5 and 4.6 present the base-case results from the health care sector perspective for belimumab and voclosporin, respectively. The detailed results are presented in Supplement Tables E11 and E22.

Table 4.5. Results for the Base Case for Belimumab Compared to Standard Care

Treatment	Drug Cost	Total Cost	QALYs	Life Years	evLYGs
Belimumab	$ 93,465	$929,962	11.666	17.861	11.740
Standard Care-Belimumab	-	$886,343	11.180	17.478	11.180
Increment	-	$43,620	0.49	0.38	0.56
Incremental Cost-Effectiveness Ratios	-	-	$89,663	$113,847	$77,835

QALY: quality-adjusted life year, evLYG: equal value life years gained

Table 4.6. Results for the Base Case for Voclosporin Compared to Standard Care

Treatment	Drug Cost	Total Cost	QALYs	Life Years	evLYGs
Voclosporin	$215,296	$928,486	12.640	18.408	12.770
Standard Care-Voclosporin	-	$784,416	11.674	17.581	11.674
Increment	-	$144,070	0.97	0.83	1.10
Incremental Cost-Effectiveness Ratios	-	-	$149,260	$174,250	$131,528

QALY: quality-adjusted life year, evLYG: equal value life years gained

Sensitivity Analyses

To demonstrate effects of uncertainty on both costs and health outcomes, we varied input parameters using available measures of parameter uncertainty (i.e., standard errors) or reasonable ranges to evaluate changes in cost per additional QALY. Probabilistic sensitivity analysis (PSA) was performed by jointly varying all model parameters, using 1,000 simulation runs. Due to the lack of data, the distributions used for costs and utilities in the PSA are assumed as mean values ±10%. Tables 4.7 through 4.10 present the results of the PSAs. More details can be found in Supplement Section E4.

Table 4.7. Probabilistic Sensitivity Analyses of Cost per QALY Gained for Belimumab Compared to Standard Care

	Cost Effective at $50,000 per QALY	Cost Effective at $100,000 per QALY	Cost Effective at $150,000 per QALY	Cost Effective at $200,000 per QALY
Belimumab	25.1%	51.6%	69.0%	79%

SC-Belimumab: Standard care for Belimumab, QALY: quality-adjusted life year

Table 4.8. Probabilistic Sensitivity Analyses of Cost per QALY Gained for Voclosporin Compared to Standard Care

	Cost Effective at $50,000 per QALY	Cost Effective at $100,000 per QALY	Cost Effective at $150,000 per QALY	Cost Effective at $200,000 per QALY
Voclosporin	0.3%	11.3%	48.6%	79%

SC-Voclosporin: Standard care for Voclosporin, QALY: quality-adjusted life year

Table 4.9. Probabilistic Sensitivity Analysis Cost per evLYG for Belimumab Compared to Standard Care

	Cost Effective at $50,000 per evLYG	Cost Effective at $100,000 per evLYG	Cost Effective at $150,000 per evLYG	Cost Effective at $200,000 per evLYG
Belimumab	31.8%	62%	78.4%	86.3%

SC-Belimumab: Standard care for Belimumab, evLYG: equal value life years gained

Table 4.10. Probabilistic Sensitivity Analysis Cost per evLYG for Voclosporin Compared to Standard Care

	Cost Effective at $50,000 per evLYG	Cost Effective at $100,000 per evLYG	Cost Effective at $150,000 per evLYG	Cost Effective at $200,000 per evLYG
Voclosporin*	0.4%	21.1%	65.4%	89.3%

SC-Voclosporin: Standard care for Voclosporin, evLYG: equal value life years gained

Scenario Analyses

We performed scenario analyses to identify the effect of alternative inputs and assumptions on the cost-effectiveness results. Tables 4.11 and 4.12 presents the results from the scenario analyses.

Based on feedback from the patient groups and clinicians, we conducted a scenario analysis for the Black population (the most prevalent ethnic sub-group) using the values of CR in the Black population, as reported in the BLISS-LN and AURORA trials. However, these data on CR rates are highly uncertain due to the small sample sizes. Furthermore, due to lack of data, the rest of the model parameters were assumed to be the same for the Black LN population as overall LN population. Given the uncertainty in CR rates among Black population and the possibility that the PR rates, ESRD, death and the long-term survival is likely to differ between Black LN population and overall LN population, the results of these analyses ($156,093 per QALY gained for belimumab and $129,250 per QALY gained for voclosporin) should be treated with caution.

The second scenario analysis included a modified societal perspective, considering the impact of LN on non-medical costs and patient productivity.

We also performed additional scenario analyses using pessimistic assumptions for the long-term survival and utility values for CR/PR health states to understand the impact of these parameters on the cost-effectiveness results. These scenario analyses were thought to be useful in case the clinical experts believe that long term prognosis for those achieving response might not be as optimistic as assumed in the model. Scenario analyses were performed using lower survival (of 25.22 years overall survival and 14.49 years ESRD free survival) in CR/PR states, and another scenario analysis

using lower utilities (of 0.72 and 0.64, respectively) in CR/PR states. Further details on these scenarios are provided in Supplement Section E5.

The last group of scenario analyses used different duration of AD state for those patients in the long-term model who progressed to ESRD from CR/PR. Increasing the duration of AD state to 3 years increased incremental cost-effectiveness ratios for both treatments. The details of the scenarios are reported in Supplement Section E5.

Table 4.11. Deterministic Scenario Analysis Results for Belimumab

Treatment	Base-Case Results	Societal Perspective	Scenario Analysis Using Lower Survival in CR/PR	Scenario Analysis Using Lower Utilities in CR and PR States	Scenario Analyzing Increase in Duration of AD State
Belimumab	$89,663/QALY	$66,103/QALY	$170,113/QALY	$114,948/QALY	$108,245/QALY

CR: complete response, PR: partial response, QALY: quality-adjusted life year

Table 4.12. Deterministic Scenario Analysis Results for Voclosporin

Treatment	Base-Case Results	Societal Perspective	Scenario Analysis Using Lower Survival in CR/PR	Scenario Analysis Using Lower Utilities in CR and PR States	Scenario Analyzing Increase in Duration of AD State
Voclosporin	$149,260/QALY	$131,962/QALY	$237,389/QALY	$185,904/QALY	$173,127/QALY

QALY: quality-adjusted life year, PR: partial response, CR: complete response

Threshold Analyses

Threshold prices that would achieve commonly used cost-effectiveness thresholds are shown for each drug in Tables 4.13 and 4.14.

Table 4.13. Threshold Analysis Results per QALY

	WAC per Unit (mg)	Net Price per Unit (mg)	Unit Price to Achieve $50,000 per QALY	Unit Price to Achieve $100,000 per QALY	Unit Price to Achieve $150,000 per QALY	Unit Price to Achieve $200,000 per QALY
Belimumab	$4.52	$4.26	$3.66	$4.89	$6.13	$7.36
Voclosporin	$8.33	$6.46	$3.58	$5.03	$6.48	$7.93

QALY: quality-adjusted life year, WAC: wholesale acquisition cost

Table 4.14. Threshold Analysis Results per evLYG

	WAC per Unit	Net Price per Unit	Unit Price to Achieve $50,000 per evLYG	Unit Price to Achieve $100,000 per evLYG	Unit Price to Achieve $150,000 per evLYG	Unit Price to Achieve $200,000 per evLYG
Belimumab	$4.52	$4.26	$3.85	$5.27	$6.69	$8.11
Voclosporin	$8.33	$6.46	$3.78	$5.42	$7.07	$8.71

evLYG: equal value life years gained, WAC: wholesale acquisition cost

Model Validation

Several approaches were undertaken to validate the model, please see Supplement Section E7. First, preliminary methods and results were presented to manufacturers, patient groups, and clinical experts, with data inputs changed as needed and scenario analyses defined. Second, model input parameters were varied to evaluate the face validity of changes in results. As part of ICER's initiative for modeling transparency, we shared the model with interested manufacturers for external verification shortly after publishing the draft report for this review. The outputs from the model were validated against the trial and study data of the interventions as well as relevant observational datasets. Finally, the results were compared to other cost-effectiveness models in this therapy area.

Uncertainty and Controversies

Our analyses have important limitations. Most of these relate to the lack of availability of robust data and the assumptions required to overcome this. There is no long-term follow-up for either treatment, resulting in considerable uncertainty related to the prognosis of patients. We defined broad health states and assumed relationships between health states and ESRD-free and overall survival. Uncertainty in long-term outcomes was partially accounted for in sensitivity and scenario analyses that evaluated different assumptions. As there are no long-term data on the extrapolation of responses, the base-case analyses assume that these are sustained until death or ESRD. Treatment of LN may result to other clinical benefits for patients, not captured by the model (e.g., related to SLE management or other symptoms of chronic diseases, such as fatigue).

The base-case analysis also did not consider analysis by ethnicity. For both belimumab and voclosporin, only complete response rates in ethnic minorities (i.e., Black population) at the end of the trials follow-up were reported. While these data were used in scenario analysis to assess cost effectiveness of therapies for the Black population, the results of this scenario should be interpreted with caution and should not be used in policy or reimbursement decisions, considering that trials were not powered for sub-group analyses (i.e., small samples, statistically non-significant

results); no trial data were available on partial responses in Black population; and no data on long-term progression by ethnic subgroups were available.

Studies on general populations and ethnic subgroups show that socio-economic status is a significant determinant of the prognosis and quality of life.[38,39] Since race/ethnicity and income are strongly correlated (with Black and Hispanic subgroups being the poorest),[40] using ethnicity-specific values would result in lower utility and life years gained for Black (comparing to White) patients which may result in worse cost-effectiveness findings in Black versus White populations, independent of the treatment effectiveness among these groups. Thus, only general (not ethnicity-specific) values were used in the base case so as not to disadvantage ethnic groups.

We could not estimate disease progression parameters (e.g., transition probabilities) without access to individual patient data from the studies. As such, the data for the different interventions during the study period were used directly in the model to estimate short-term costs and outcomes.

There were several structural assumptions in the model. As the model is based on a partitioned survival modeling approach, patients in PR/CR can only move into ESRD or death. Due to lack of data, movement into the health state AD from PR/CR is not modeled explicitly in the long-term model. However, additional costs and QALY decrements associated with time in AD for those who move from PR/CR into ESRD were included in the model.

The long-term disease progression in the model was based on assessment of the cohort of LN patients using BLISS-LN criteria, which have the closest definition of the outcomes to those used in the trials.[18] This modeling choice resulted in the same survival for CR and PR groups, likely leading to overestimation of cost effectiveness of belimumab and voclosporin treatments.

Based on consultations with clinical experts, the model assumed continuation of treatments for up to three years for patients in CR and PR states and discontinuation of treatment within on average 18 months for patients remaining in AD state or for patients with adverse events. While it is likely that discontinuation rate in clinical practice is less than in the trials (because of the blinding), it is possible that more patients in AD state will discontinue the treatment early (because of the lack of efficacy), and more patients in CR and PR states would continue treatment longer than it is currently considered in the model.

Robust utility data were lacking for these populations. As such, we used utility data derived from several sources that were believed to be coherent. The base-case analyses were complemented with sensitivity and scenario analyses to explore the uncertainty in these values.

4.4 Summary and Comment

For belimumab, our base-case results found that, at its current price, it meets traditional cost-effectiveness thresholds of $100,000/QALY. For voclosporin, at the net price, our base-case results found that it too meets traditional cost-effectiveness thresholds of $150,000/QALY. There is a higher uncertainty in cost effectiveness of voclosporin than in cost effectiveness of belimumab, though the differences in the trial's designs do not allow to have the direct comparison of both treatments.

We also conducted scenario analyses to explore questions about the cost effectiveness in a Black population, using a modified societal perspective and pessimistic assumptions about long-term prognosis. Belimumab remains cost effective in scenario analyses with lower utilities and longer duration of AD state, while incremental cost-effectiveness ratio is above the threshold for voclosporin if longer duration of AD, lower long-term survival, or lower utilities in CR and PR states are assumed.

Although there remains substantial uncertainty about whether the long-term benefits prove true, we believe that our base-case assessment of long-term benefits is the best starting point for a judgment of the value of treatments at this time.

5. Contextual Considerations and Potential Other Benefits or Disadvantages

Our reviews seek to provide information on potential other benefits that treatments may offer to the individual patient, to caregivers, the delivery system, other patients, or the public. In particular, our goal is to highlight factors that would not have been considered or were incompletely captured as part of the evidence on comparative clinical effectiveness and cost effectiveness. These elements are listed in the tables below.

Table 5.1. Contextual Considerations

Contextual Considerations	Relevant Information
Acuity of need for treatment of individual patients based on the severity of the condition being treated	The acuity of need due to the severity of the condition in the near-term is low relative to more rapidly progressive fatal conditions.
Magnitude of the lifetime impact on individual patients of the condition being treated	The burden of LN over the lifetime is high given its progression to ESRD.

Table 5.2. Potential Other Benefits or Disadvantages

Potential Other Benefits or Disadvantages	Relevant Information
Patients' ability to achieve major life goals related to education, work, or family life	LN typically affects patients in their 20s and 30s and is the major cause of premature mortality in patients with SLE. In addition, patients with ESRD on dialysis have challenges with working.
Caregivers' quality of life and/or ability to achieve major life goals related to education, work, or family life	ESRD is burdensome to caregivers as well as patients. Avoiding ESRD is likely to benefit caregivers.
Patients' ability to manage and sustain treatment given the complexity of regimen	Belimumab was given IV infusion in the pivotal clinical trial, but a SC formulation is available that is typically administered by the patient at home. The SC formulation may supplant the IV infusion in the real world, however it is more expensive that the IV formulation, it has not been studied in patients with LN, and was not modeled in this evidence report. Voclosporin is taken orally, twice a day.
Health inequities	LN disproportionately impacts non-White patients. Subgroup analyses for both belimumab and voclosporin suggest the potential for greater benefits in Black patients and have the potential to reduce historic disparities.
Other (as relevant): Preservation of kidney function with treatments that are less teratogenic may improve the chances for both women and men to bear children Additional benefits beyond renal benefits	Patient advocates and clinical experts noted the importance of this potential benefit given the preponderance of patients who are of child-bearing age and the clinical advice given to women with ESRD to avoid pregnancy. Reducing or eliminating the use of current treatments that can be teratogenic and cause infertility and miscarriages will also increase the ability of women and men with lupus to be parents. Belimumab carries an FDA indication for the treatment of SLE apart from its impact on lupus nephritis. These potential extra-renal benefits for patients with lupus nephritis have not been reported in peer reviewed publications, but may add to the cost effectiveness of belimumab.

6. Health Benefit Price Benchmarks

Health Benefit Price Benchmarks (HBPBs) information for the annual cost of treatment (net of rebates) with the intervention(s) are presented in Table 6.1 below. The HBPB for a drug is defined as the price range that would achieve incremental cost-effectiveness ratios between $100,000 and $150,000 per QALY or per evLYG gained. Using the broadest set of figures derived from these thresholds, we arrive at a HBPB for belimumab of $45,000 to $61,000; and for voclosporin the HBPB is $72,000 to $101,000.

Table 6.1. Annual Cost-Effectiveness Threshold Prices for Belimumab and Voclosporin

	Annual WAC	Annual Price at $100,000 Threshold	Annual Price at $150,000 Threshold	Discount from WAC to Reach Threshold Prices
Belimumab				
QALYs Gained	$41,614	$45,019	$56,137	No discount needed
evLYG	$41,614	$48,398	$61,205	No discount needed
Voclosporin				
QALYs Gained	$119,011	$71,864	$92,539	22% to 40%
evLYG	$119,011	$77,439	$100,901	15% to 35%

WAC: wholesale acquisition cost; evLYG: equal value life year gained; QALY: quality-adjusted life year

7. Potential Budget Impact

7.1. Overview of Key Assumptions

We used results from the cost-effectiveness model to estimate the potential total budgetary impact of belimumab and voclosporin for the population of adults with Class III, IV, or V LN. Potential budget impact is defined as the total differential cost of using each new therapy rather than the relevant existing therapy for the treated population, calculated as differential health care costs (including drug costs) minus any offsets in these costs from averted health care events. All costs were undiscounted and estimated over a five-year time horizon.

The analysis included the estimated number of individuals in the US who would be eligible for treatment. For this analysis, we assumed that the eligible population would include incident (new) cases of LN, who would be starting induction treatment and therefore eligible for the addition of either new medication, as well as those with prevalent disease who have relapsed and need additional therapy. Based on clinical expert opinion, we assumed that for every incident case, there would be approximately one relapse requiring new therapy, and used an estimate of eligible population that is twice the incident number. For LN, we used an estimated incidence of 6.9/100,000 persons from 2000-2004 US Medicaid data.[16] Applying this proportion to the projected average US adult (age ≥ 18 years) population from 2021-2025,[41] we arrive at an estimate of approximately 18,300 individuals with LN. Of those with LN, an estimated 75% of patients have Class III, IV, or V LN.[42] Applying this proportion to the estimated incident population with LN results in an eligible population of approximately 13,700 individuals. Assuming one prevalent relapse case per incident case doubles this estimate to approximately 27,400 eligible individuals. As these two treatments, if approved, would be launched within a short period of each other, we assumed that this eligible population would be split in equal proportions between the two interventions, or approximately 13,700 individuals per treatment. For the purposes of this analysis, we assume that all of these patients would be eligible to initiate treatment in the year of incidence or relapse, resulting in 13,700 eligible patients per year for each of the five years. For this analysis, we assumed that belimumab and voclosporin would be added on to standard of care (as defined above).

The aim of the potential budgetary impact analysis is to document the percentage of patients who could be treated at selected prices without crossing a potential budget impact threshold that is aligned with overall growth in the US economy. For reports begun in 2019-2020, the five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to be approximately $819 million per year for new drugs. ICER's methods for estimating potential budget impact are described in detail elsewhere.[43]

7.2. Results

Figure 7.1 illustrates the cumulative per-patient budget impact calculations for belimumab compared to standard of care, based on the net price of $42,720 per year of treatment. The average potential budgetary impact for belimumab was approximately $47,200 per patient in year one, with cumulative net cost increasing in years two and three as treatment continues, reaching approximately $87,500, before decreasing somewhat in years four and five due to net savings as patients discontinue treatment and have lower total costs than in usual care. Additional net costs per year are presented along with cumulative net costs in Supplement Table G1.

Figure 7.1. Cumulative Net Cost Per Patient Treated with Belimumab at Net Price

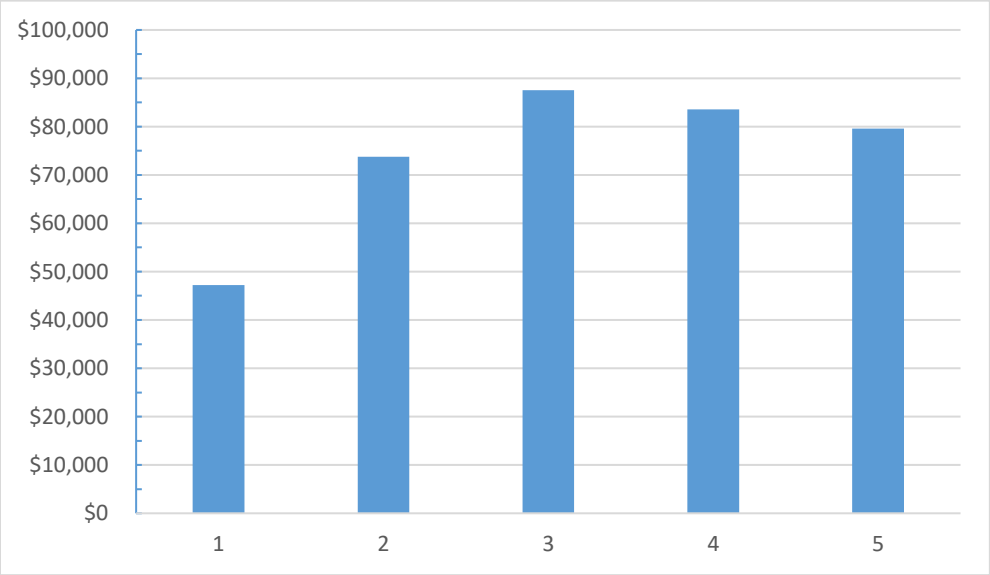


Figure 7.2 illustrates the cumulative per-patient budget impact calculations for voclosporin compared to standard of care, based on the net price of $92,233 per year of treatment. The average potential budgetary impact for voclosporin was approximately $87,200 per patient in year one, with cumulative net cost increasing in years two and three as treatment continues. As was seen with belimumab, net costs decreased somewhat in years four and five due to net savings as patients discontinue treatment and have lower total costs than in usual care. Additional net costs per year are presented along with cumulative net costs in Supplement Table G1.

Figure 7.2. Cumulative Net Cost Per Patient Treated with Voclosporin at Net Price

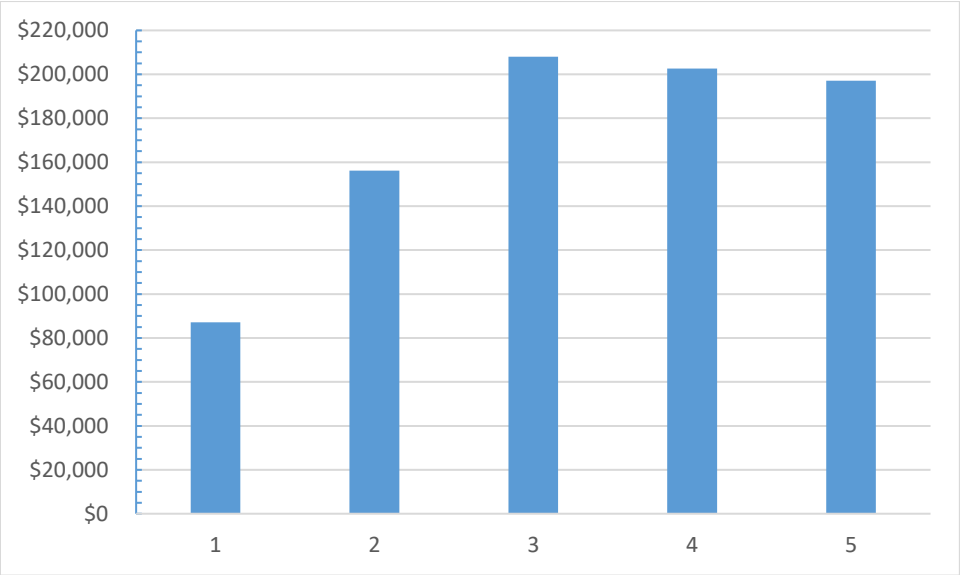
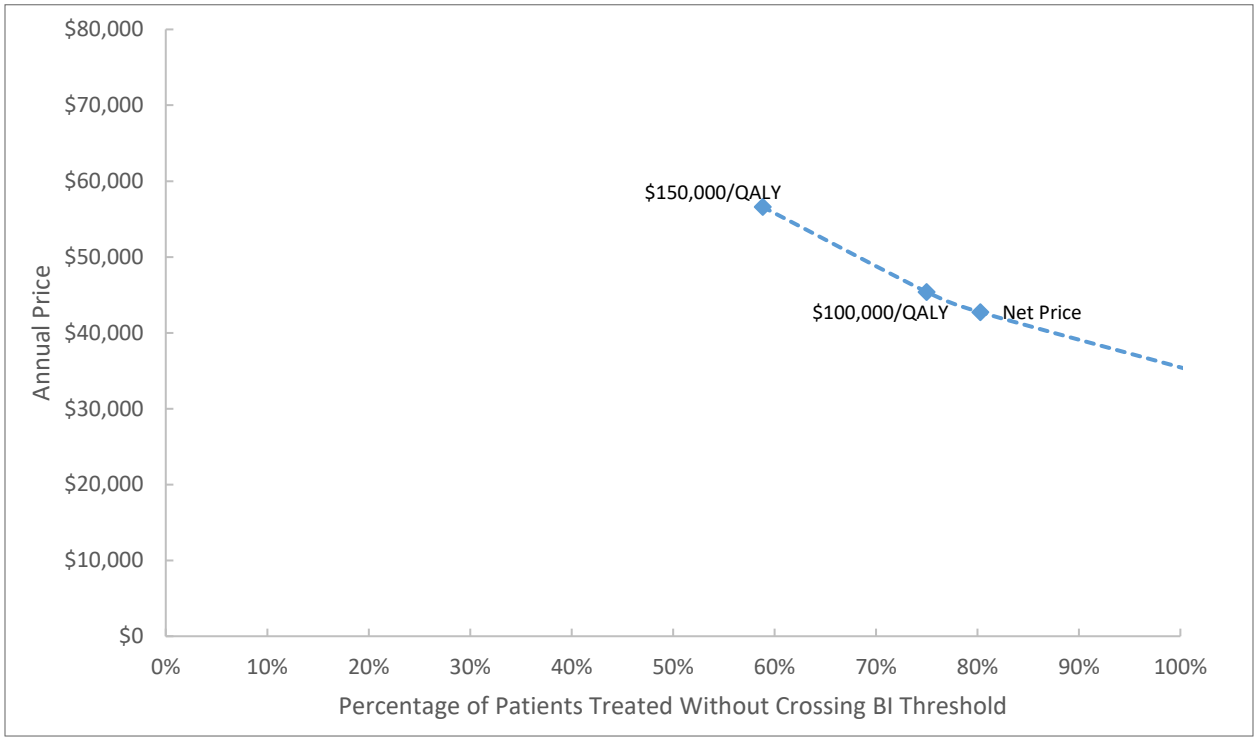


Figure 7.3 illustrates the potential budget impact of belimumab treatment of the eligible population, based on the net price ($42,720 per year of treatment), and the prices to reach $150,000, $100,000, and $50,000 per QALY (approximately $56,600, $45,400, and $34,200 per year of treatment, respectively) compared to the standard of care comparator. Approximately 80% of the approximately 13,700 eligible patients could be treated in a given year without crossing the ICER budget impact threshold of $819 million per year over five years at the net price. Approximately 59% of patients could be treated in a given year without crossing the budget impact threshold at the $150,000 per QALY threshold price, increasing to approximately 75% of the population at the $100,000 per QALY threshold price. All eligible patients could be treated at the $50,000 per QALY threshold price, reaching 97% of the potential budget impact threshold.

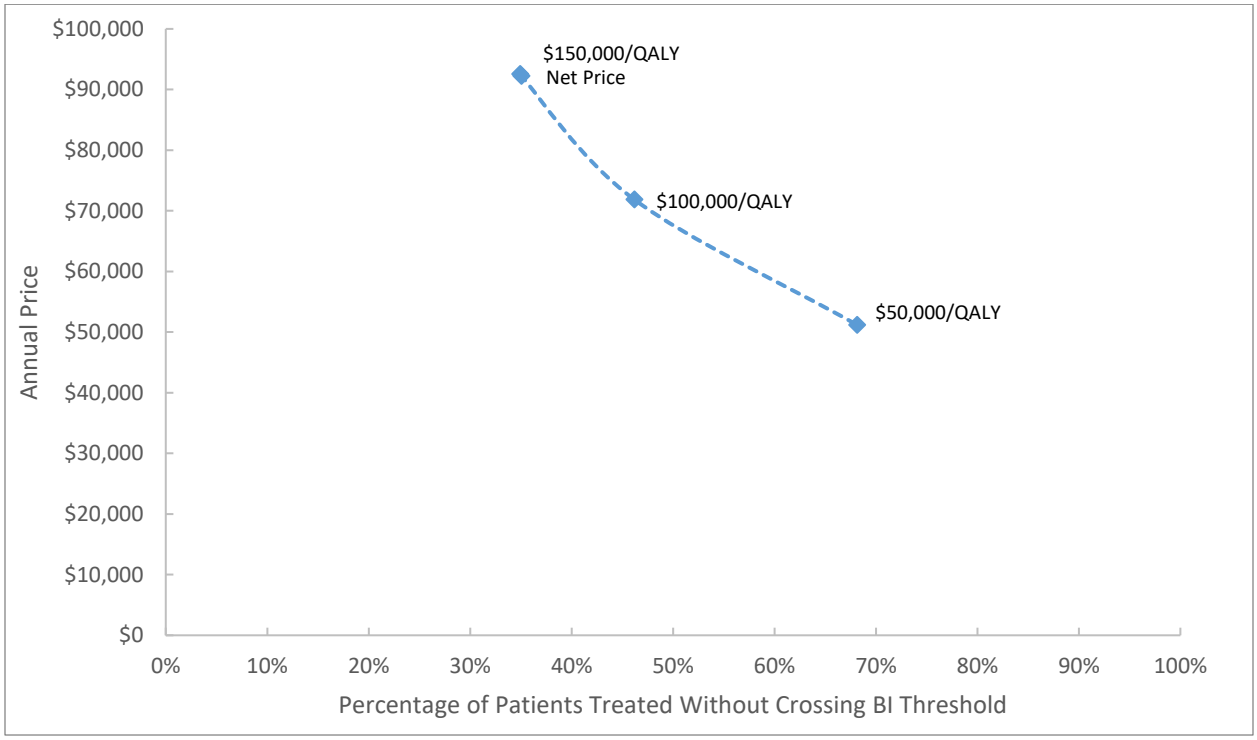
Figure 7.3. Potential Budgetary Impact of Belimumab Treatment in Adults with Class III, IV, or V LN



BI: budget impact, LN: lupus nephritis, QALY: quality adjusted life year

Figure 7.4 illustrates the potential budget impact of voclosporin treatment of the eligible population, based on the net price ($92,233 per year of treatment), and the prices to reach $150,000, $100,000, and $50,000 per QALY (approximately $92,600, $71,900, and $51,200 per year of treatment, respectively) compared to the standard of care comparator. Approximately 35% of the approximately 13,700 eligible patients could be treated in a given year without crossing the ICER budget impact threshold of $819 million per year over five years at the net price. Similarly, nearly 35% of patients could be treated in a given year without crossing the budget impact threshold at the $150,000 per QALY threshold price, increasing to approximately 68% of the population at the $50,000 per QALY threshold price.

Figure 7.4. Potential Budgetary Impact of Voclosporin Treatment in Adults with Class III, IV, or V LN



BI: budget impact, LN: lupus nephritis, QALY: quality adjusted life year

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Supplemental Materials

A. Background: Supplemental Information

A1. Definitions

Table A.1. Classification of Lupus Nephritis

Class I	Minimal Mesangial LN		
Class II	Mesangial Proliferative LN		
Class III	Focal LN (<50% glomeruli)	III (A)	Active Lesions
		III (A/C)	Active and Chronic Lesions
		III (C)	Chronic Lesions
Class IV	Diffuse LN (≥50% glomeruli)	IV (S)	Diffuse Segmental
		IV (G)	Diffuse Global
		IV (A)	Active Lesions
		IV (A/C)	Active and Chronic Lesions
		IV (C)	Chronic Lesions
Class V	Membranous LN		
Class VI	Advanced Sclerosed (≥90% glomeruli)		

Complete Response (CR) in voclosporin trials : UCPR of ≤ 0.5 mg/mg, eGFR ≥ 60 mL/min/1.73 m^2, or no confirmed decrease from baseline in eGFR of > 20% with the presence of sustained, low dose steroids and no administration of rescue medication.

Partial Response (PR) in voclosporin trials : ≥50% decrease in UPCR from baseline with the presence of sustained, low dose steroids and no administration of rescue medication.

Primary Efficacy Renal Response (PERR) in belimumab trial: UPCR≤0.7, estimated glomerular filtration rate (eGFR) was not more than 20 percent (%) below the pre-flare value or ≥60 and was not a treatment failure.

Complete Renal Response (CRR) in belimumab trial: UPCR<0.5, eGFR not more than 10% below the pre-flare value or ≥90 and was not a treatment failure.

Renal event in belimumab trial: progression to end stage renal disease, doubling of serum creatinine from baseline, renal worsening, or renal-related treatment failure.

A2. Potential Cost-Saving Measures in Lupus Nephritis

ICER includes in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create headroom in health care budgets for higher-value innovative services (for more information, see https://icer.org/our-approach/methods-process/value-assessment-framework/). These services are ones that would not be directly affected by therapies for Lupus Nephritis (e.g., reduction in ESRD, kidney transplant), as these services will be captured in the economic model. Rather, we are seeking services used in the current management of LN beyond the potential offsets that arise from a new intervention. During stakeholder engagement and public comment periods, ICER encouraged all stakeholders to suggest services (including treatments and mechanisms of care) currently used for patients with LN that could be reduced, eliminated, or made more efficient. No suggestions were received and no Choosing Wisely recommendations apply.

B. Patient Perspectives: Supplemental Information

B1. Methods

During ICER's scoping, open input, and public comment periods, we received public comment submissions from nine stakeholders (four patient advocacy groups, three manufacturers, one clinical society, and one individual) and participated in conversations with 17 key informants (five patient advocacy groups, seven clinical experts, one clinical society, two health plans, and two manufacturers). Some stakeholders played more than one role in our outreach. We also reviewed *Lupus: Patient Voices,* which summarizes a national meeting eliciting the perspectives of patients living with lupus, including those with LN. The feedback received from written input and scoping conversations helped us to discuss the impact on patients described in Chapter 2 of the draft evidence report.

C. Clinical Guidelines

American College of Rheumatology (ACR)

2012 Guidelines for Screening, Treatment, and Management of Lupus Nephritis[12]

The ACR convened a Core Executive Panel to review existing treatment guidelines for lupus nephritis (LN), which was achieved by conducting a systematic literature review and developing various clinical scenarios. The recommendations for treatment of LN were subsequently determined by a Task Force Panel's review of this work and vote on most appropriate interventions and treatment. The guidelines advise on the management of Lupus Nephritis based on histologic classification, described below.

Class I and II

The Task Force Panel recommends that generally, histologic classes I and II of LN do not require immunosuppressive treatment.

Class III and IV

The recommendation for classes III and IV are aggressive therapy with glucocorticoids and immunosuppressants. This indicates a recommended 2-3 grams of MMF daily + glucocorticoids, or administration of intravenous cyclophosphamide (CYC) + glucocorticoids.

Class V

It is recommended that when combined with classes III and IV, class V patients should be treated with the recommended therapies to treat classes III and IV alone. Patients with class V "Pure Membranous" LN should begin treatment on 0.5 mg/kg of prednisone, plus 2-3 grams MMF daily.

Class VI

In cases of class VI LN, it is recommended that patients forgo immunosuppressive agents and prepare for renal replacement therapy.

Treatment of LN in Patients who are Pregnant

There are various treatment recommendations for pregnant patients, depending on the severity and activity of disease. In patients with previous LN but no indication of active systemic or renal disease, it is not necessary to treat with nephritis medication. It is recommended that patients with mild disease activity be placed on hydroxychloroquine (HCQ), as this will likely decrease SLE activity

during pregnancy. If the patient presents with clinically active nephritis or significant extrarenal disease activity, the treating clinician should provide glucocorticoids, at a dose of their discretion. If necessary, azathioprine (AZA) can be added to treatment, but should not exceed 2 mg/kg in pregnant women.

Guidelines for Induction and Maintenance Therapy

It is recommended that all SLE patients with nephritis indications be treated with HCQ as background therapy. Induction therapy is recommended for the first six months of treatment, followed by maintenance therapy. For patients who respond to induction therapy, it is recommended that maintenance therapy includes AZA or MMF. If a patient fails to respond to the first six months of induction therapy, the guidelines suggest that the treating clinician switch the immunosuppressive agent (from MMF to CYC, or CYC to MMF) and treat the patient for three days with IV pulses of glucocorticoids.

European League Against Rheumatism (EULAR)

2019 Update of the Joint European League Against Rheumatism and European Renal Association – European Dialysis and Transplant Association (EULAR/ERA-EDTA) Recommendations for the Treatment of Lupus Nephritis[11]

The EULAR/ERA-EDTA guidelines were published in 2012 to advise on the management and treatment of individuals with LN. These recommendations were updated by EULAR in 2019 and were informed by health professionals and patients in order to incorporate the most recent evidence and available treatments.

EULAR recommends treatment options based on the 2003 classification system of LN. For classes I and II, it is recommended that patients are treated with HCQ. Stage III LN recommendations include a background therapy of HCQ, as well as immunosuppressive agents combined with glucocorticoids. These immunosuppressive agents include MMF, mycophenolate acid, low-dose intravenous cyclophosphamide, or MMF plus calcineurin inhibitors (tacrolimus or cyclosporin A). The recommended treatment for class IV and V patients is the same as class III, although rituximab should also be considered as a treatment option for immunosuppression. It is recommended that stage VI patients are only treated with HCQ.

Along with treatment recommendations based on disease classification, the EULAR guidelines propose additional overarching principles and general recommendations based on the current available evidence. For patients with indications of kidney involvement, biopsy should be considered, and the International Society of Nephrology/Renal Pathology Society classification system should be used to assess the results.

Ultimately, the goal of treatment is to preserve kidney function, and induction and maintenance will depend on the patient's class of nephritis and response to treatment. If a patient improves after the initial six-month induction period, it is recommended that the patient receives immunosuppression with MMF or azathioprine (AZA), plus prednisone for three to five years. If a patient does not respond to induction therapy, the physician may use their discretion and suggest an alternative initial treatment or consider treatment with rituximab.

For women who plan to become pregnant, treatment with MMF should be stopped at least six months prior to conception. While it is fine to continue taking certain drugs, such as HCQ, prednisone, AZA, or calcineurin inhibitors, it is recommended that pregnant patients are assessed by a multidisciplinary clinical team every four weeks.

Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guidelines for Glomerulonephritis

Chapter 12: Lupus Nephritis[44]

This Chapter of the Kidney International Supplements outlines treatment recommendations for children and adults with LN. Any SLE patient with indications for kidney involvement, proteinuria, hypertension, or active urine sediment should be considered for a kidney biopsy to confirm the presence of LN. The KDIGO treatment recommendations are based on the histological classifications of LN, described below.

This article suggests that all classes of LN patients are treated with HCQ unless there are clinical contraindications to doing so.

Class I

It is recommended that class I patients be treated based on extrarenal indications of lupus, as class I LN does not present with kidney manifestations or suggest long-term damage to kidney function.

Class II

Patients with class II LN should be treated based on proteinuria levels. For those who have proteinuria measures of < 1 gram/day, treatment should be based on extrarenal indications of lupus. It is recommended that patients with proteinuria > 3 grams/day are treated with corticosteroids or calcineurin inhibitors (CNIs).

Class III and IV

Initial therapy of corticosteroids plus cyclophosphamide or mycophenolate mofetil (MMF) is recommended for the treatment of class III and IV patients. If during the first three months of induction therapy the patient presents with exacerbated symptoms of LN, it is recommended that the treating physician consider an alternative initial therapy or an additional kidney biopsy.

Class V

For patients with class V LN, normal kidney function, and non-nephrotic levels of proteinuria, it is recommended that treatment be dictated by extrarenal manifestations of SLE. Treatment should also include antiproteinuric and antihypertensive medication. Patients with pure class V LN and nephrotic proteinuria should be treated with corticosteroids plus immunosuppression with cyclophosphamide, MMF, CNI, or azathioprine (AZA).

Indications for Induction Therapy and Maintenance

Patients with class III and IV LN should undergo six months of initial induction therapy and should be considered for transition into maintenance therapy, contingent on the clinical success of initial therapy. For patients who respond to induction, it is suggested that immunosuppressive therapy is tapered after one year of remission. Immunosuppression should only be continued in maintenance therapy for patients who achieve only partial remission.

D. Comparative Clinical Effectiveness: Supplemental Information

D1. Detailed Methods

Population, Intervention, Comparators, Outcomes, Timing, and Settings Framework (PICOTS)

Population

The population of focus for the review is adult patients with Class III, IV, or V LN ages 18 and older.

Interventions

The full list of interventions is as follows:

- Belimumab (Benlysta) plus standard therapy (defined below)
- Voclosporin plus standard therapy

Comparators

Data permitting, we intend to compare belimumab and voclosporin to standard therapy, defined as mycophenolate mofetil (MMF) plus corticosteroids or cyclophosphamide plus corticosteroids.

Outcomes

The outcomes of interest are described in the list below.

- Patient-Important Outcomes
    - Complete renal remission (normal renal function) at one year*
    - Maintenance of remission
    - Reduction in corticosteroid dose (steroid sparing)
    - Reduction in renal flares
    - Prevention of chronic kidney disease
    - Dialysis
    - Renal transplant
    - Fatigue
    - Joint and muscle pain
    - Childbearing potential

    - Adverse events (AEs) including
        - Significant adverse events
        - Adverse events leading to drug discontinuation
        - Infections
        - Acute renal failure
        - Diabetes
        - Hypertension
        - Nephrotoxicity
        - Neurotoxicity (encephalopathy, tremors, headache, seizures)
        - Progressive multifocal leukoencephalopathy (PML)
        - Hypersensitivity reactions
        - Infusion reactions
        - Depression
        - Suicide
        - Gastrointestinal (nausea, diarrhea)
        - Death
- Other Outcomes
    - Renal response
    - Partial renal response
    - Duration of complete renal response
    - 24-hour urine protein excretion (<0.25, 0.25-3.0, >3.0 g/day)
    - Change in creatinine
    - Change in estimated glomerular filtration rate (eGFR)
    - The proportion of patients with eGFR >90, 60-89, 30-59, 15-29, <15
    - Change in urine protein creatinine ratio (UPCR)
    - The proportion of patients with UPCR by categories
    - Change in serum albumin
    - Change in complement levels
    - Change in ANA level
    - Change in DS DNA level
    - Change in Quality of Life
    - SELENA-SLEDAI score

Timing

Evidence on intervention effectiveness will be derived from studies of at least 24 weeks duration and evidence on harms from studies of at least 24 weeks duration, though studies of at least one-year duration are preferred.

Settings

All relevant settings will be considered.

Table D1. PRISMA 2009 Checklist

Checklist Items		
TITLE		
Title	1	Identify the report as a systematic review, meta-analysis, or both.
ABSTRACT		
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.
INTRODUCTION		
Rationale	3	Describe the rationale for the review in the context of what is already known.
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).
METHODS		
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.

Checklist Items		
RESULTS		
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).
DISCUSSION		
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers).
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.
FUNDING		
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.

From: Moher D, Liberati A, Tetzlaff J, Altman DG. The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

Data Sources and Searches

Procedures for the systematic literature review assessing the evidence on new therapies for Lupus nephritis followed established best research methods.[45,46] We conducted the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[47] The PRISMA guidelines include a checklist of 27 items, which are described further in Appendix Table A1.

We searched MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials for relevant studies. Each search was limited to English-language studies of human subjects and excluded articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items. We included abstracts from conference proceedings identified from the systematic literature search. All search strategies were generated utilizing the Population, Intervention, Comparator, and Study Design elements described above. The proposed search strategies included a combination of indexing terms (MeSH terms in MEDLINE and EMTREE terms in EMBASE), as well as free-text terms.

To supplement the database searches, we performed manual checks of the reference lists of included trials and systematic reviews and invited key stakeholders to share references germane to the scope of this project. We also supplemented our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature when the evidence met ICER standards (for more information, see https://icer-review.org/methodology/icers-methods/icer-value-assessment-framework-2/grey-literature-policy/). Where feasible and deemed necessary, we also accepted data submitted by manufacturers "in-confidence," in accordance with ICER's published guidelines on acceptance and use of such data (https://icer-review.org/use-of-in-confidence-data/).

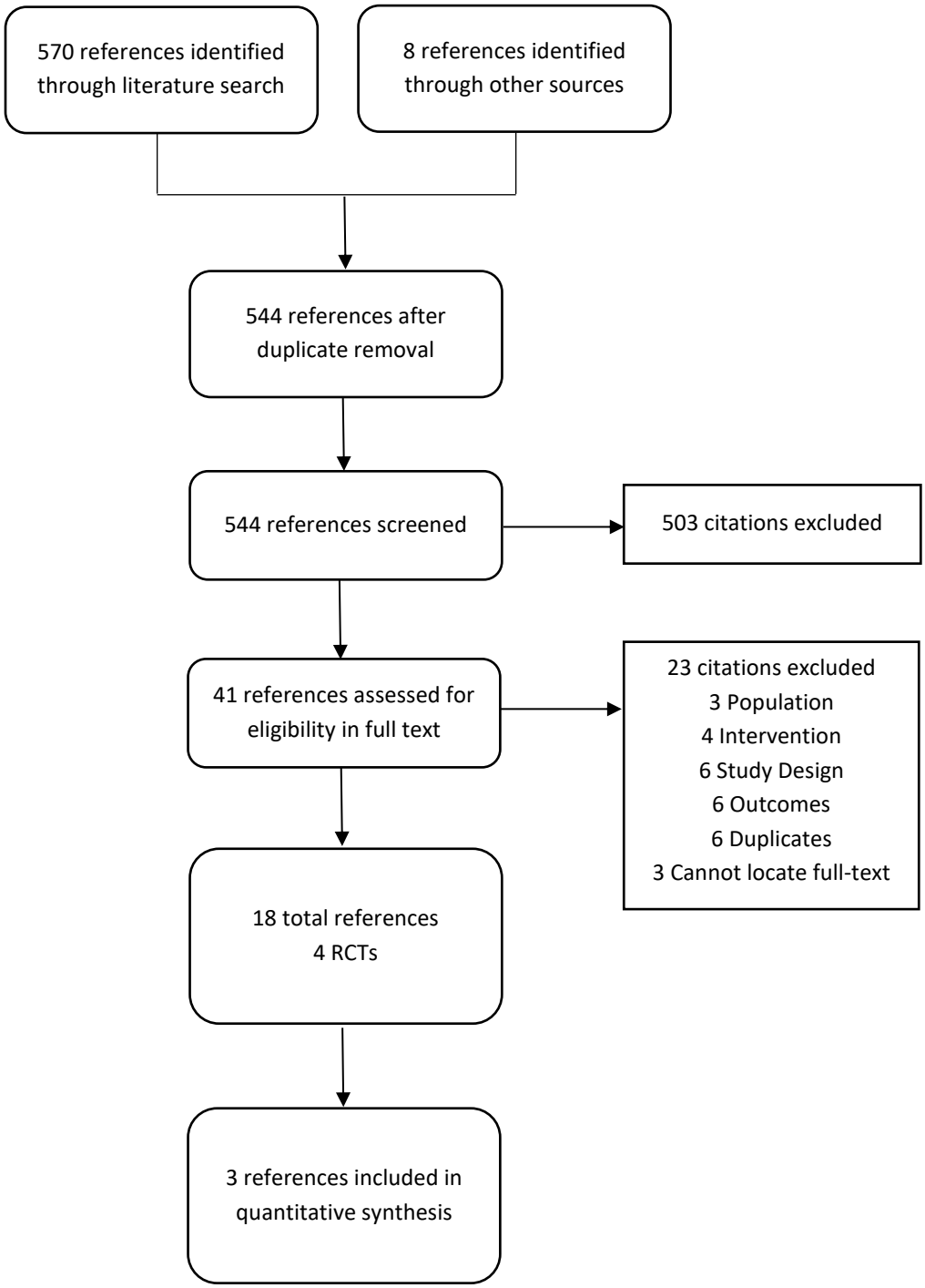
Table D2. Search Strategies for EMBASE

1	lupus nephritis'/exp
2	('lupus erythematosus nephritis' OR 'nephritis, systemic lupus erythematosus' OR 'lupoid nephritis' OR 'lupus kidney'):ti,ab
3	#1 or #2
4	voclosporin'/exp
5	('isa 247' OR 'isa247' OR 'luveniq' OR 'lx 211' OR 'lx211'):ti,ab
6	#4 OR #5
7	belimumab'/exp
8	('benlysta' OR 'lymphostat b'):ti,ab
9	#7 OR #8
10	#6 OR #9
11	#3 AND #10
12	('animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp) NOT 'human'/exp
13	#11 NOT #12
14	#13 AND [English]/lim
15	#14 AND ('chapter'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'short survey'/it)
16	#14 NOT #15

Table D3. Search Strategies for OVID

1	Exp Nephritis, Lupus/
2	("Lupus Nephritides" or "Lupus Glomerulonephritis" or "lupus nephritis").ti,ab
3	1 or 2
4	(voclosporin or ISATX247 or "ISA 247" or "ISA-247" or "ISA(TX)247").ti,ab
5	("BEL-114333" or BEL114333 or "HGS-1006" or HGS1006 or "LymphoStat-B" or "GSK-1550188" or GSK1550188 or Benlysta or belimumab).ti,ab
6	4 or 5
7	3 and 6
8	(addresses OR autobiography OR bibliography OR biography OR case reports OR clinical trial, phase I OR comment OR congresses OR consensus development conference OR dictionary OR directory OR duplicate publication OR editorial OR encyclopedia OR festschrift OR guideline OR interactive tutorial).pt
9	7 not 8
10	animals not (humans and animals).sh.
11	9 not 10
12	limit 11 to English language
13	remove duplicates from 12

Figure D1. PRISMA Flow Chart Showing Results of Literature Search for Belimumab and Voclosporin



Study Selection

We performed screening at both the abstract and full-text level. A single investigator screened all abstracts identified through electronic searches according to the inclusion and exclusion criteria described earlier. We did not exclude any study at abstract-level screening due to insufficient information. For example, an abstract that did not report an outcome of interest would be accepted for further review in full text. We retrieved the citations that were accepted during abstract-level screening for full text appraisal. One investigator reviewed full papers and provided justification for exclusion of each excluded study.

Data Extraction and Quality Assessment

We used criteria published by the US Preventive Services Task Force (USPSTF) to assess the quality of RCTs and comparative cohort studies, using the categories "good," "fair," or "poor" (see Appendix Table F2).[48] Guidance for quality ratings using these criteria is presented below, as is a description of any modifications we made to these ratings specific to the purposes of this review.

Good: *Meets all criteria: Comparable groups are assembled initially and maintained throughout the study; reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention is paid to confounders in analysis. In addition, intention to treat analysis is used for RCTs.*

Fair: *Studies were graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are addressed. Intention to treat analysis is done for RCTs.*

Poor: *Studies were graded "poor" if any of the following fatal flaws exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, intention to treat analysis is lacking.*

Note that case series are not considered under this rating system – because of the lack of comparator, these are generally considered to be of poor quality.

Assessment of Level of Certainty in Evidence

We used the ICER Evidence Rating Matrix to evaluate the level of certainty in the available evidence of a net health benefit among each of the interventions of focus (see Appendix D).[49,50]

Assessment of Bias

As part of our quality assessment, we evaluated the evidence base for the presence of potential publication bias. We performed an assessment of publication bias for belimumab and voclosporin using the clinicaltrials.gov database of trials. We scanned the site to identify studies completed more than two years ago that would have met our inclusion criteria and for which no findings have been published. The primary concern is the lack of peer-reviewed, published data for the AURORA trial.

Data Synthesis and Statistical Analyses

Data on relevant outcomes were summarized in evidence tables (see Appendix Table D4) and synthesized quantitatively and qualitatively in the body of the review. We evaluated the feasibility of conducting a quantitative synthesis by exploring the differences in study populations, study design, analytic methods, and outcome assessments for each outcome of interest. Based on data availability, we conducted random effects pairwise meta-analyses for low dose voclosporin using two randomized trials[20-23,25] on the following outcomes: CR at 24 weeks, CR at 48/52 weeks, and PR at 24 weeks. The AURA-LV trial did not report PR at 48/52 weeks. We calculated risk ratios (RRs) and their respective 95% CIs using the Mantel–Haenszel method. We assessed heterogeneity using the Cochran q test and the I2 statistic.

In an exploratory analysis, we also created a network to compare the complete response rate of voclosporin at one year to that of belimumab at two years.[51] All NMAs were conducted in a Bayesian framework with random effects on the treatment parameters using the gemtc package in R.[51] The outcomes were all binary and were analyzed using a binomial likelihood and logit link.[52] League tables were presented for the treatment effects (odds ratio [OR]) of each intervention versus each other and versus placebo along with 95% credible intervals (95% CrI).

Due to inconsistent or limited reporting of data, other outcomes are described without summary statistics across studies.

D2. Additional Clinical Evidence

All clinical evidence is described in the main report.

D3. Heterogeneity and Subgroups

The primary source of heterogeneity was anticipated to be race/ethnicity as non-White patients typically present with more severe LN that progresses more rapidly. Other subgroups of interest include sex and the background immunosuppressive therapy for LN (MMF, cyclophosphamide). When available, we present the information for those subgroups.

D4. Evidence Tables

Table D4.1. Study Quality Metrics

Study	Comparable Groups	Adequate Randomization	Allocation Concealment	Patient Blinding	Physician Blinding	Outcome Adjudication Blinding	Non-Differential Follow-up	ITT Analysis	Handling of Missing Data	Overall Quality
Voclosporin										
AURION	NA	NA	NA	NA	NA	NA	NA	NA	NR	Poor
AURA-LV	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
AURORA	Yes	Yes	NR	Yes	Yes	NR	Yes	Yes	NR	Fair
Belimumab										
BLISS-LN	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Davidson 2018	NA	NA	NA	NA	NA	NA	NA	NA	Yes	Poor

Table D4.2. Study Design of Included Trials

Trial	Interventions	Inclusion Criteria	Study Length	Key Outcomes	Dose
Voclosporin					
AURION[24,26] **Huizinga 2017, Solomons 2016** **N = 7**	Voclosporin + MMF + steroids	Renal biopsy within 24 months (Class III; IV-S, IV-G (A) or (A/C); V, III/V, IV/V, ISN/RPS); Serologic evidence of active LN UPCR ≥1.0mg/mg (III/IV) or ≥1.5mg/mg (V); eGFR >45mL/min/1.73m^2	Phase II 48-week trial duration	Complete response at 24 and 48 weeks Biomarkers (C3, C4, anti ds-DNA)	VCS 23.7 mg twice daily MMF 1-2 g/day
AURA-LV[22,25,53] **Rovin 2019, Kidney International** **N= 265** **(Dooley 2016)**	Low-Dose voclosporin + standard therapy (n=89) High-Dose voclosporin + standard therapy (n=88) Placebo (n=88)	Patients 18-75 who fulfilled at least 4 American College of Rheumatology criteria for SLE and had a kidney biopsy showing active Class III, IV or V LN within 6 months of screening Patients with class III or IV LN were required to have a UPCR > 1.5 mg/mg in 2 consecutive urine samples Patients with pure class V LN were required to have a UPCR > 2mg/mg	Phase IIb, multicenter trial 48-week trial duration	Complete renal response at 24 weeks and 48 weeks SELENA-SLEDAI score at baseline, 24 and 48 weeks	low-dose VCS (23.7 mg twice daily), high-dose VCS (39.5 mg twice daily) or low- or high-dose matched placebo
AURORA[20,21,23,53,54] **EURLAR 2020, NFK 2020, ERA-EDTA 2020** **N = 357**	Low Dose Voclosporin + standard therapy (n=179) Placebo (n=178)	Diagnosis of SLE according to ACR criteria Kidney biopsy within 6 months of study entry confirming diagnosis of LN Class III, IV, or V (alone or in combination w/ class III or IV) Proteinuria of ≥1.5mg/mg or ≥ 2 mg/mg for class V patients	Phase III 52-week duration (on-going)	Renal Response at 52 weeks eGFR ≥60 mL/min/ or no confirmed decrease from baseline in eGFR of ≥20%	low-dose VCS (23.7 mg twice daily) and low-dose matched placebo
Belimumab					

Trial	Interventions	Inclusion Criteria	Study Length	Key Outcomes	Dose
BLISS-LN[17,27,55,56] Furie 2020, JAMA Oncology N = 448 (GSK data submission 2020, Furie 2020 annals of rheumatology)	Belimumab + standard therapy (N = 224) Placebo + standard therapy (N = 224)	Patients 18+ with autoantibody-positive SLE that fulfill the 1982 ACR criteria UPCR ≥ 1 and biopsy-proven LN of International Society of Nephrology and Renal Pathology Society class II, IV, or V showing active lesions or active and chronic lesions in biopsy	Phase III, multicenter, multinational 104-week duration	PERR at 104 weeks (UPCR ≤ 0.7, eGFR ≥ 20% or at least 60mL/min/1.73m^2) Complete renal response at 104 weeks	Belimumab (10 mg/kg body weight) and matched placebo Standard therapy: Cyclophosphamide (500 mg every 2 weeks, total 6 infusions) or Mycophenolate mofetil (3g/day)
Davidson 2018[18] N = 176	N/A - retrospective study	Patients 18 and older with SLE (ACR or SLICC criteria) and biopsy record of Class III, IV, V or mixed LN.	Observational study, retrospective analysis of Hopkins Lupus Cohort study data	Long-term renal survival (survival without ESRD or mortality)	N/A
GSK Study 213039[19] N=173	N/A - retrospective study	Patients with biopsy-proven class III, IV, or V LN	Retrospective analysis of Hopkins Lupus Cohort study data	Long-term renal survival (no ESRD and/or mortality) Long-term chronic renal insufficiency-free survival	N/A
N/A: not applicable, LN: lupus nephritis, N: number, MMF: mycophenolate mofetil					

Table D4.3. Baseline Characteristics[17-19,21,24,25]

Study	AURION	AURA-LV			AURORA		BLISS-LN		Davidson 2018	GSK 213039
Arms	VCS	Low-Dose VCS	High-Dose VCS	PBO	Low-Dose VCS	PBO	Belimumab	PBO	Total	Total
N	7	89	88	88	179	178	223	223	176	173
Age, Mean (SD)	29.0 (4.8)	31.4 (11.8)	30.6 (9.6)	33.1 (10.0)	32.8 (10.9)	33.6 (11.0)	33.7 (10.7)	33.1 (10.6)	36.1 (11.81)	36.2 (11.8)
Sex, n (%)										
Male	0 (0)	13 (14.6)	7 (8.0)	15 (17.0)	18 (10.1)	26 (14.6)	26 (11.7)	27 (12.1)	15 (8.5)	15 (8.7)
Female	7 (100)	76 (85.4)	81 (92.0)	73 (83.0)	161 (89.9)	152 (85.4)	197 (88.3)	196 (87.9)	161 (91.5)	158 (91.3)
Race, n (%)										
White	NR	30 (33.7)	36 (40.9)	42 (47.7)	129 (36.1)		73 (32.7)	75 (33.6)	NR	NR
Black	NR	3 (3.4)	6 (6.8)	5 (5.7)	34 (9.5)		30 (13.5)	31 (13.9)	94 (53.4)	NR
Asian	7 (100)	52 (58.4)	44 (50)	36 (41)	109 (30.5)		114 (51.1)	109 (48.9)	NR	NR
Other	NR	4 (4.5)	2 (2.3)	5 (5.7)	0 (0)		NR	NR	82 (46.6)	NR
American Indian/Alaska Native	NR	NR	NR	NR	4 (1.1)		4 (2)	6 (3)	NR	NR
Multiple races or ethnic groups	NR	NR	NR	NR	81 (22.7)		2 (1)	2 (1)	NR	NR
Ethnicity, n (%)										
Hispanic	NR	9 (10.1)	13 (14.8)	13 (14.8)	116 (32.5)		NR	NR	NR	NR
Non-Hispanic	NR	80 (89.9)	75 (85.2)	75 (85.2)	241 (67.5)		NR	NR	NR	NR
Mean SLE disease duration (years)	NR	NR	NR	NR	NR	NR	2.28	2.35	NR	NR
Mean LN disease duration (years)	NR	NR	NR	NR	NR	NR	5.49	5.14	NR	NR

Study	AURION	AURA-LV			AURORA		BLISS-LN		Davidson 2018	GSK 213039
Time Since SLE Diagnosis, median (range)	6.1 (3.1-9.1)	3.4 (0.1-32.7)	3.5 (0.1-27.8)	3.6 (0.1-24.7)	NR	NR	3.3 (0.3-8.1)	3.3 (0.2-8.0)	NR	NR
Time Since Initial LN diagnosis, Mean (SD)	NR	4.2 (5.1)	3.2 (4.4)	3.5 (4.0)	NR	NR	0.2 (0.1-3.3)	0.2 (0.1-3.4)	NR	NR
Onset of Proteinuria (years), median (range)	NR	1.8 (0.1-31.7)	1.5 (0.1-25.8)	1.4 (0.2-17.7)	NR	NR	NR	NR	NR	NR
Biopsy Class, n (%)										
Pure Class V	3 (42)	12 (13.5)	14 (15.9)	13 (14.8)	25 (14)	25 (14)	36 (16.1)	36 (16.1)	40 (22.7)	NR
Class III	2 (29)	NR	NR	NR	NR	NR	NR	NR	44 (25.0)	NR
Class III/IV	NR	56 (62.9)	63 (71.6)	59 (67.0)	154 (86)	153 (86)	61 (27.4)	55 (24.7)	NR	NR
Class IV	2 (29)	NR	NR	NR	NR	NR	NR	NR	51 (29.0)	NR
Class III+IV and IV+V	NR	21 (23.6)	11 (12.5)	16 (18.2)	NR	NR	126 (56.5)	132 (59.2)	NR	NR
Mixed	NR	NR	NR	NR	NR	NR	NR	NR	41 (23.3)	NR
Baseline eGFR, mean (SD)	115 (34)	95.3 (28.4)	104.0 (27.3)	100.2 (27.1)	92 (31)	90 (29)	100 (37.7)	101 (42.7)	NR	NR
Baseline UPCR										
N	NR	89	88	87	178	178	91	92	176	NR
Mean (SD)	2.54 (1.56)	5.16 (4.2)	4.48 (3.0)	4.43 (3.6)	4.1 (2.7)	3.9 (2.4)	3.2 (2.7)	3.5 (3.6)	1.5 (1.80)	NR
MMF Use at Screening, n (%)										
Yes	NR	31 (34.8)	29 (33.0)	32 (36.4)	NR	NR	164 (73.5)	164 (73.5)	3 (42.9)	NR
No	NR	58 (65.2)	59 (67.0)	56 (63.6)	NR	NR	59 (27.5)	59 (27.5)	4 (57.1)	NR
MMF Dose at Screening, n (%)										
Mean (SD)	NR	1.2 (0.4)	1.3 (0.5)	1.2 (0.5)	NR	NR	NR	NR	NR	NR
Previous Treatment, n (%)										

Study	AURION	AURA-LV			AURORA		BLISS-LN		Davidson 2018	GSK 213039
Any antimalarial drug	NR	65.20%	55.70%	65.90%	NR	NR	166 (74)	154 (69)	NR	NR
ACE Inhibitor or ARB	NR	NR	NR	NR	NR	NR	147 (66)	150 (67)	NR	NR
SLEDAI-2K Score (SD)	NR	NR	NR	NR	NR	NR	12.5 (5.3)	12.2 (4.8)	NR	NR
Baseline Proteinuria										
N, mg/mg	NR	5.18	4.48	4.45	NR	NR	NR	NR	NR	NR
Non-Renal SELENA-SLEDAI Score	NR	4.9	5.1	4.9	NR	NR	NR	NR	NR	NR
Comorbidities										
Diabetes mellitus, yes	NR	4 (4.5)	7 (8.0)	5 (5.7)	NR	NR	NR	NR	29 (16.5)	NR
Hypertension, yes	NR	54 (60.7)	59 (67.0)	58 (65.9)	NR	NR	NR	NR	138 (78.4)	NR
Myocardial infarction, yes	NR	1 (1.1)	0 (0)	1 (1.1)	NR	NR	NR	NR	4 (2.3)	NR
Stroke, Yes	NR	0 (0)	2 (2.3)	1 (1.1)	NR	NR	NR	NR	NR	NR

VCS: Voclosporin, NR: not reported, SD: standard deviation, PBO: placebo, SLE: systemic lupus erythematosus, N: number

Table D4.4. Outcomes I[17-19,21,24,25]

				PERR			Complete Renal Response			Complete Renal Remission		
Study	**Arms**	**N**	**Timepoint**	**%**	**OR (95%CI)**	**P-Value**	**%**	**OR (95% CI)**	**P-Value**	**%**	**OR (95% CI)**	**P-Value**
Voclosporin												
AURION	VCS	7	24 wks	NR	NR	NR	70	NR	NR	NR	NR	NR
	VCS	7	48 wks	NR	NR	NR	NR	NR	NR	NR	NR	NR
AURA-LV	Low dose	89	24 wks	NR	NR	NR	32.6	2.03 (1.01-4.05)	P=0.046	NR	NR	NR
	High dose	88		NR	NR	NR	27.3	1.59 (0.78-3.27)	P=0.204	NR	NR	NR
	PBO	88		NR	NR	NR	19.3	Reference	Ref	NR	NR	NR
	Low dose	89	48 wks	NR	NR	NR	49.4	3.21 (1.68-6.13)	P<0.001	NR	NR	NR
	High dose	88		NR	NR	NR	39.8	2.10 (1.09-4.02)	P=0.026	NR	NR	NR
	PBO	88		NR	NR	NR	23.9	Reference	Ref	NR	NR	NR
AURORA	VCS	179	24 wks	NR	NR	NR	32.4	2.23 (1.34-3.72)	P=0.002	NR	NR	NR
	PBO	178		NR	NR	NR	19.7	Reference	Ref	NR	NR	NR
	VCS	179	52 wks	NR	NR	NR	40.8	2.65 (1.64-4.27)	P<0.001	NR	NR	NR
	PBO	178		NR	NR	NR	22.5	Reference	Ref	NR	NR	NR
AURA + AURORA pooled	VCS	268	24 wks	NR	NR	NR	31.7	2.01 (1.34-3.01)	P=0.0008	NR	NR	NR
	PBO	266		NR	NR	NR	20.3	Reference	Ref	NR	NR	NR
	VCS	268	52 wks	NR	NR	NR	43.7	2.76 (1.88, 4.05)	P=0.0001	NR	NR	NR
	PBO	266		NR	NR	NR	23.3	Reference	Ref	NR	NR	NR
Belimumab												
BLISS-LN	BEM	223	104 wks	43	1.6 (1.0-2.3)	P=0.03	30	1.74 (1.11-2.74)	P = 0.0167	NR	NR	NR
	PBO	223		32	Reference	Ref	19.7	Reference	Ref	NR	NR	NR

	BEM	223	52 wks	46.6	4.59 (1.06-2.38)	P=0.0245	NR	NR	NR	NR	NR	NR
	PBO	223		35.4	Reference	Ref	NR	NR	NR	NR	NR	NR
Davidson 2018	mALMS	176	24 mo	NR	NR	NR	NR	NR	NR	59.1	NR	NR
	mBLISS-LN			NR	NR	NR	NR	NR	NR	40.9	NR	NR
GSK 213039	Overall	173	24 mo	NR	NR	NR	65.9	NR	NR	NR	NR	NR
VCS: Voclosporin, NR: not reported, PBO: placebo, BEM: belimumab, ref: reference, OR: odds ratio, CI: confidence interval, N: number												

Table D4.5. Outcomes II[17,18,21,24,25]

				Partial Response/Remission			Time to Renal Related Event			Time to CRR	Durability	
Study	**Arms**	**N**	**Timepoint**	**%**	**OR (95%CI)**	**P-value**	**%**	**HR (95% CI)**	**P-Value**	**Median**	**Maintained**	**N**
Voclosporin												
AURION	VCS	7	24 wks	NR	NR	NR	NR	NR	NR	NR	NR	NR
	VCS	7	48 wks	NR	NR	NR	NR	NR	NR	NR	NR	NR
AURA-LV	Low dose	89	24 wks	70	2.35 (NR)	P=0.007	NR	NR	NR	19.7	NA	29
	High dose	88		66	NR	P=0.024	NR	NR	NR	23.4	NA	24
	PBO	88		49	Reference	Ref	NR	NR	NR	NR	NA	17
	Low dose	89	48 wks	NR	NR	NR	NR	NR	NR	NA	100%	46
	High dose	88		NR	NR	NR	NR	NR	NR	NA	75%	35
	PBO	88		NR	NR	NR	NR	NR	NR	NA	82%	21
AURORA	VCS	179	24 wks	70.4	2.43 (1.56-3.79)	P<0.001	NR	NR	NR	NR	NR	NR
	PBO	178		50	Reference	Ref	NR	NR	NR	NR	NR	NR
	VCS	179	52 wks	69.8	2.26 (1.45-3.51)	P<0.001	NR	NR	NR	NR	NR	NR
	PBO	178		51.7	Reference	Ref	NR	NR	NR	NR	NR	NR
Belimumab												
BLISS-LN	BEM	223	104 wks	17.5	NA	P=0.010	15.7	0.51 (0.34-0.77)	P=0.0014	NR	NR	NR
	PBO	223		17	NA	Ref	28..3	Reference	Ref	NR	NR	NR
	BEM	223	52 wks	NR	NR	NR	NR	NR	NR	NR	NR	NR
	PBO	223		NR	NR	NR	NR	NR	NR	NR	NR	NR
Davidson 2018	mALMS	176	24 mo	30.1	NR	NR	NR	NR	NR	NR	NR	NR
	mBLISS-LN			16.5	NR	NR	NR	NR	NR	NR	NR	NR

VCS: Voclosporin, NR: not reported, PBO: placebo, BEM: belimumab, ref: reference, OR: odds ratio, CI: confidence interval, N: number

Table D4.6. Outcomes III[17,18,21,24,25]

				Anti-dsDNA Levels		Change in Proteinuria		Non-Renal SELENA-SLEDAI		SELENA-SLEDAI	
Study	**Arms**	**N**	**Timepoint**	**Mean**	**P-Value**	**mg/mg**	**P-Value**	**Mean Δ**	**Score**	**Score <4**	**Score >6**
Voclosporin											
AURION	VCS	7	24 wks	NR	NR	NR	NR	NR	NR	NR	NR
	VCS	7	48 wks	NR	NR	NR	NR	NR	NR	NR	NR
AURA-LV	Low dose	89	24 wks	35.3 IU/mL	P<0.05	0.71	Significant	-3.0	1.8	NR	NR
	High dose	88		51.6 IU/mL	P<0.05	1.1	Significant	-3.4	1.8	NR	NR
	PBO	88		67.5 IU/mL	Ref	1.79	Reference	-2.6	2.1	NR	NR
	Low dose	89	48 wks	36.5 IU/mL	P<0.05	0.84	P<0.006	-3.0	2.4	NR	29.20%
	High dose	88		53.8 IU/mL	P<0.05	1.22	P<0.006	-2.6	1.7	NR	40.90%
	PBO	88		75.3 IU/mL	Ref	1.95	Reference	-2.4	2.6	NR	53.40%
AURORA	VCS	179	24 wks	NR	NR	NR	NR	NR	NR	NR	NR
	PBO	178		NR	NR	NR	NR	NR	NR	NR	NR
	VCS	179	52 wks	NR	NR	NR	NR	NR	NR	NR	NR
	PBO	178		NR	NR	NR	NR	NR	NR	NR	NR
Belimumab											
BLISS-LN	BEM	223	104 wks	97 UI/mL	NR	%Δ: -87.83%	P=0.0244	NR	NR	27.80%	NR
	PBO	223		107 UI/mL	NR	%Δ: -81.13%	Ref	NR	NR	18.40%	NR
	BEM	223	52 wks	NR	NR	NR	NR	NR	NR	NR	NR
	PBO	223		NR	NR	NR	NR	NR	NR	NR	NR
Davidson 2018	mALMS	176	24 mo	NR	NR	NR	NR	NR	NR	NR	NR
	mBLISS-LN			NR	NR	1.5	NR	NR	NR	NR	NR

VCS: Voclosporin, NR: not reported, PBO: placebo, BEM: belimumab, ref: reference, OR: odds ratio, CI: confidence interval, N: number

Table D4.7. Outcomes IV[17,18,21,24,25]

				Blood Pressure, Mean (SD)		Ordinal Renal Response without Urinary Sediment, n (%)			Complete Remission			Mean GFR (SD)
Study	Arms	N	Timepoint	Diastolic	Systolic	Complete	Partial	No	%	OR (95% CI)	P-value	mL/min/1.73m^2
Voclosporin												
AURION	VCS	7	24 wks	NR	NR	NR	NR	NR	NR	NR	NR	NR
	VCS	7	48 wks	NR	NR	NR	NR	NR	NR	NR	NR	NR
AURA-LV	Low dose	89	24 wks	78.01	117.61	NR	NR	NR	28.1	2.12 (1.01-4.46)	0.047	NR
	High dose	88		79.83	121.66	NR	NR	NR	25	1.74 (0.82-3.70)	0.151	NR
	PBO	88		74.37	115.9	NR	NR	NR	15.9	Reference	Ref	NR
	Low dose	89	48 wks	76.54	118.14	NR	NR	NR	NR	NR	NR	NR
	High dose	88		79.45	120.95	NR	NR	NR	NR	NR	NR	NR
	PBO	88		75.99	116.56	NR	NR	NR	NR	NR	NR	NR
AURORA	VCS	179	24 wks	NR	NR	NR	NR	NR	NR	NR	NR	NR
	PBO	178		NR	NR	NR	NR	NR	NR	NR	NR	NR
	VCS	179	52 wks	NR	NR	NR	NR	NR	NR	NR	NR	NR
	PBO	178		NR	NR	NR	NR	NR	NR	NR	NR	NR
Belimumab												
BLISS-LN	BEM	223	104 wks	NR	NR	67(30)	39(18)	117(52)	NR	NR	NR	111.3 (35.75)
	PBO	223		NR	NR	44(20)	38(17)	141(63)	NR	NR	NR	100.8 (29.18)
	BEM	223	52 wks	NR	NR	NR	NR	NR	NR	NR	NR	NR
	PBO	223		NR	NR	NR	NR	NR	NR	NR	NR	NR
Davidson 2018	mALMS	176	24 mo	NR	NR	NR	NR	NR	NR	NR	NR	NR
	mBLISS-LN			NR	NR	NR	NR	NR	NR	NR	NR	NR

VCS: Voclosporin, NR: not reported, PBO: placebo, BEM: belimumab, ref: reference, OR: odds ratio, CI: confidence interval

Table D4.8. Outcomes V[17,18,21,24,25]

				Time to UPCR <0.5 mg/mg			Prednisone daily dose ≤ 5mg			Prednisone daily dose ≤ 7.5mg		
Study	**Arms**	**N**	**Timepoint**	**Days**	**HR (95% CI)**	**P-Value**	**%**	**OR (95% CI)**	**P-value**	**%**	**OR (95% CI)**	**P-value**
Voclosporin												
AURION	VCS	7	24 wks	NR	NR	NR	NR	NR	NR	NR	NR	NR
	VCS	7	48 wks	NR	NR	NR	NR	NR	NR	NR	NR	NR
AURA-LV	Low dose	89	24 wks	NR	NR	NR	NR	NR	NR	NR	NR	NR
	High dose	88		NR	NR	NR	NR	NR	NR	NR	NR	NR
	PBO	88		NR	NR	NR	NR	NR	NR	NR	NR	NR
	Low dose	89	48 wks	NR	NR	NR	NR	NR	NR	NR	NR	NR
	High dose	88		NR	NR	NR	NR	NR	NR	NR	NR	NR
	PBO	88		NR	NR	NR	NR	NR	NR	NR	NR	NR
AURORA	VCS	179	24 wks	NR	NR	NA	NR	NR	NR	NR	NR	NR
	PBO	178		NA	NR	NA	NR	NR	NR	NR	NR	NR
	VCS	179	52 wks	169	2.02 (1.51-2.70)	P<0.001	NR	NR	NR	NR	NR	NR
	PBO	178		372	2.05 (1.62-2.60)	P<0.001	NR	NR	NR	NR	NR	NR
Belimumab												
BLISS-LN	BEM	223	104 wks	NR	NR	NR	36.8	1.51 (1.01-2.27)	P=0.0444	40.8	1.65 (1.11-2.45)	P=0.0139
	PBO	223		NR	NR	NR	27.8	Reference	Ref	29.6	Reference	Ref
	BEM	223	52 wks	NR	NR	NR	NR	NR	NR	NR	NR	NR
	PBO	223		NR	NR	NR	NR	NR	NR	NR	NR	NR
Davidson 2018	mALMS	176	24 mo	NR	NR	NR	NR	NR	NR	NR	NR	NR
	mBLISS-LN			NR	NR	NR	NR	NR	NR	NR	NR	NR

VCS: Voclosporin, NR: not reported, PBO: placebo, BEM: belimumab, ref: reference, OR: odds ratio, CI: confidence interval

Table D4.9. Outcomes VI[17,18,21,24,25]

				Risk of Renal Event or Death			Time to first severe SFI flare			Median Time [50%] UPCR < 0.5	
Study	**Arms**	**N**	**Timepoint**	**%**	**HR (95% CI)**	**P-Value**	**%**	**HR (95% CI)**	**P-Value**	**Days**	**P-Value**
Voclosporin											
AURION	VCS	7	24 wks	NR	NR	NR	NR	NR	NR	NR	NR
	VCS	7	48 wks	NR	NR	NR	NR	NR	NR	NR	NR
AURA-LV	Low dose	89	24 wks	NR	NR	NR	NR	NR	NR	NR	NR
	High dose	88		NR	NR	NR	NR	NR	NR	NR	NR
	PBO	88		NR	NR	NR	NR	NR	NR	NR	NR
	Low dose	89	48 wks	NR	NR	NR	NR	NR	NR	NR	NR
	High dose	88		NR	NR	NR	NR	NR	NR	NR	NR
	PBO	88		NR	NR	NR	NR	NR	NR	NR	NR
AURORA	VCS	179	24 wks	NR	NR	NR	NR	NR	NR	NR	NR
	PBO	178		NR	NR	NR	NR	NR	NR	NR	NR
	VCS	179	52 wks	NR	NR	NR	NR	NR	NR	169	P<0.001
	PBO	178		NR	NR	NR	NR	NR	NR	372	Ref
Belimumab											
BLISS-LN	BEM	223	104 wks	15.7	0.5 (0.34-0.77)	P<0.01	18.8	0.6 (0.4, 0.8)	P=0.004	NR	NR
	PBO	223		28.3	Ref	Ref	31.4	Reference	Ref	NR	NR
	BEM	223	52 wks	NR	NR	NR	NR	NR	NR	NR	NR
	PBO	223		NR	NR	NR	NR	NR	NR	NR	NR
Davidson 2018	mALMS	176	24 mo	NR	NR	NR	NR	NR	NR	NR	NR
	mBLISS-LN			NR	NR	NR	NR	NR	NR	NR	NR

VCS: Voclosporin, NR: not reported, PBO: placebo, BEM: belimumab, ref: reference, OR: odds ratio, CI: confidence interval

Table D4.10. Subgroup Data[17,21,24,25]

					Complete Renal Response			Partial Renal Response		
Study	**Population**	**Arms**	**Group**	**Timepoint**	**%**	**OR (95% CI)**	**P-Value**	**%**	**OR (95% CI)**	**P-Value**
AURION	Overall	VCS	NA	24 wks	70	NR	NR	NR		
AURA-LV	Overall	Low dose	NA	24 wks	32.6	2.03 (1.01-4.05)	P=0.046	NR		
		High Dose			27.3	1.59 (0.78-3.27)	P=0.204			
		PBO			19.3	reference	NS			
		Low dose		48 wks	49.4	3.21 (1.68-6.13)	P<0.001			
		High Dose			39.8	2.10 (1.09-4.02)	P=0.026			
		PBO			23.9	reference	NS			
	Hispanic/ Non-Hispanic	Low dose	NR							
		High Dose								
		PBO								
	Race	Low-Dose	White	24 wks	40.7	3.88 (1.38-10.95)	P=0.01	NR		
			Other		9.6	NS	NS			
		High Dose	White		44.3	3.28 (1.22-8.81)	P=0.019			
			Other		10.2	NS	NS			
		PBO	NR		NR	NR	NR			
		Low-Dose	White	48 wks	40.7	3.64 (1.34-9.90)	P=0.011			
			Other		9.6	NS	NS			
		High Dose	White		44.3	2.83 (1.09-7.31)	P=0.032			
			Other		10.2	NS	NS			
		PBO	NR		NR	NR	NR			
	MMF Use	Low-Dose	Yes	24 wks	33.9	1.09 (0.33-3.61)	P=0.889			
			No		66.1	2.72 (1.15-6.44)	P=0.023			
		High Dose	Yes		34.1	0.25 (0.05-1.34)	P=0.106			
			No		65.9	2.80 (1.18-6.64)	P=0.020			
		PBO	NR		NR	NR	NR			
		Low-Dose	Yes	48 wks	33.9	2.28 (0.79-6.62)	P=0.128			
			No		66.1	3.75 (1.66-8.46)	P=0.001			
		High Dose	Yes		34.1	1.29 (0.43-3.84)	P=0.649			
			No		65.9	2.75 (1.21-6.26)	P=0.016			
		PBO	NR		NR	NR	NR			

					Complete Renal Response			Partial Renal Response		
AURORA	Overall	VCS	NA	52 wks	40.8	2.65 (NR)	P<0.001	69.8	2.26 (1.45-3.51)	P<0.001
		PBO			22.5	Reference	Ref	51.7	Reference	Ref
	Hispanic/ Non-Hispanic	VCS	Hispanic	Unclear	38.6	NR	P=0.006	68.4	NR	P=0.060
			Non		41.8	NR	P=0.005	70.5	NR	P=0.002
		PBO	Hispanic		18.6	NR	Ref	52.5	NR	Ref
			Non		24.6	NR	Ref	50.8	NR	Ref
	Race	VCS	Asian		41.5	NR	P=0.005	NR		
			Black		46.2	NR	P=0.045			
			White		38.2	NR	P=0.165			
			Mixed		40.6	NR	P=0.054			
		PBO	Asian		17.9	NR	Ref			
			Black		15.8	NR	Ref			
			White		29.5	NR	Ref			
			Mixed		21.4	NR	Ref			
AURA-LV + AURORA	Hispanic/ Non-Hispanic	VCS	Hispanic	52 wks	37.9	NR	NR	NR		
			Non		NR	NR	NR	NR		
		PBO	Hispanic		19.4	NR	NR	NR		
			Non		NR	NR	NR	NR		
BLISS-LN	Overall	BEM	NA	104 wks	30	1.74 (1.11, 2.74)	P=0.02	NR		
		PBO			19.7	Reference	Ref			
	Induction	BEM	CyC/AZA	104 wks	18.6	1.07 (0.41, 2.78)	NR			
		PBO			18.6	Reference	NR			
		BEM	MMF		34.1	2.01 (1.19, 3.38)	P=0.0085	15.2	NA	0.0253
		PBO			20.1	Reference	Ref	19.5	NA	Ref
		BEM	MMF	52 wks	NR	NR	NR	NR		
		PBO			NR	NR	NR			
	Race	BEM	Black	104 wks	19.4	2.16 (0.49, 9.43)	NR			
		PBO			12.5	Reference	NR			
		BEM	Non-Black		31.8	1.75 (1.08, 2.83)	NR			
		PBO			20.9	Reference	NR			

VCS: Voclosporin, NR: not reported, PBO: placebo, BEM: belimumab, ref: reference, OR: odds ratio, CI: confidence interval, NS: not significant, NA: not applicable, CYC: cyclophosphamide, AZA: azathioprine, MMF: mycophenolate mofetil

* Primary Efficacy Renal Response (PERR) subgroup data not available for any trials except for BLISS-LN, excluded from table.

Table D4.11. Harms[17,18,21,24,25,53,54]

Study	AURA-LV			AURORA		AURA-LV + AURORA			BLISS-LN		Davidson 2018
Arms	Low dose	High Dose	PBO	VCS	PBO	Low dose	High Dose	PBO	BEM	PBO	Total
N	89	88	88	178	178	267	88	266	224	224	NR
Any AE	82 (92.1)	85 (96.6)	75 (85.2)	162 (91)	158 (88.8)	NR	NR	NR	214 (95.5)	211 (94.2)	NR
Any Serious AE	25 (28.1)	22 (25.0)	14 (15.9)	37 (20.8)	38 (21.3)	61/268 (22.8)	NR	50 (18.8)	58 (25.9)	67 (29.9)	NR
Any Treatment-related AE	45 (50.6)	55 (62.5)	15 (17.0)	8 (4.5)	8 (4.5)	NR	NR	NR	123 (55)	119 (53)	NR
Any Serious Treatment-related AE	4 (4.5)	7 (8.0)	1 (1.1)	NR	NR	NR	NR	NR	23 (10)	25 (11)	NR
Any AE leading to study discontinuation	16 (18.0)	14 (15.9)	9 (10.2)	20 (11.2)	26 (14.6)	NR	NR	NR	29 (12.9)	29 (12.9)	NR
Any AE leading to death	10 (11.2)	2 (2.3)	1 (1.1)	1 (0.6)	5 (2.8)	NR	NR	NR	6 (3)	5 (2)	NR
Treatment-related AE leading to death	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	NR	NR	NR	4 (1.8)	3 (1.3)	NR
Infections and Infestations	11 (12.4)	12 (13.6)	7 (8.0)	18 (10.1)	20 (11.2)	146 (54.7)	58 (65.9)	166 (62.4)	15 (7)	18 (8)	NR
Serious infections	NR	NR	NR	NR	NR	27 (10.1)	10 (11.3)	27 (10.2)	31 (13.8)	38 (17.0)	NR
Pneumonia	5 (5.6)	3 (3.4)	2 (2.3)	NR	NR	NR	NR	NR	3 (1)	4 (2)	NR
Urinary tract infection	2 (2.2)	1 (1.1)	0 (0.0)	NR	NR	27 (10)	NR	16 (6)	15 (7)	13 (6)	NR
Gastroenteritis	1 (1.1)	2 (2.3)	1 (1.1)	NR	NR	NR	NR	NR	NR	NR	NR
Sepsis	1 (1.1)	2 (2.3)	1 (1.1)	NR	NR	NR	NR	NR	NR	NR	NR
Nervous system disorders	4 (4.5)	3 (3.4)	1 (1.1)	NR	NR	74 (27.7)	24 (27.2)	44 (16.5)	0	3 (1)	NR
Blood and lymphatic system disorders	1 (1.1)	0 (0.0)	2 (2.3)	NR	NR	NR	NR	NR	3 (1)	2 (1)	NR
Herpes zoster	NR	NR	NR	NR	NR	NR	NR	NR	13 (6)	10 (4)	NR
Nasopharyngitis	NR	NR	NR	NR	NR	NR	NR	NR	8 (4)	8 (4)	NR

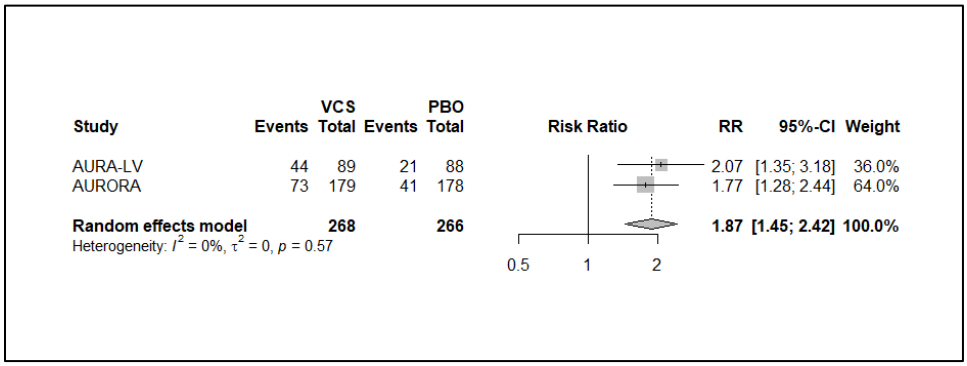
Study	AURA-LV			AURORA		AURA-LV + AURORA			BLISS-LN		Davidson 2018
Upper respiratory tract infection	NR	NR	NR	NR	NR	NR	NR	NR	26 (12)	24 (11)	NR
Headache	NR	NR	NR	NR	NR	40 (15)	NR	NR (8)	9 (4)	5 (2)	NR
Cancer (excluding skin cancer)	NR	NR	NR	NR	NR	NR	NR	NR	2 (0.9)	0	NR
Cancer (including skin cancer)	NR	NR	NR	NR	NR	4 (1.5)	NR	NR	3 (1.3)	0	NR
Additional Harms											
Depression, Suicide, or self-injury	NR	NR	NR	NR	NR	NR	NR	NR	11 (5)	16 (7)	NR
Death	1 (1.1)	10 (11.2)	2 (2.3)	1 (0.6)	5 (2.8)	NR	NR	NR	6 (3)	5 (2)	NR
Poor renal outcome: ESRD or dialysis or renal transplant, n	0	2	4	NR	NR	NR	NR	NR	NR	NR	NR
Renal Worsening, n	NR	NR	NR	NR	NR	NR	NR	NR	17	39	NR
Progression to ESRD, n	NR	NR	NR	NR	NR	NR	NR	NR	0	1	NR
ESRD or death, n (%)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	18 (10.2)
Chronic renal insufficiency, n (%)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	45 (25.6)
Glomerular filtration rate decrease	NR	NR	NR	NR	NR	70 (26.2)	27 (30.7)	25 (9.4)	NR	NR	NR
Hypertension	NR	NR	NR	NR	NR	51 (19.1)	16 (18.2)	23 (8.6)	NR	NR	NR
Diarrhea	NR	NR	NR	NR	NR	51 (19)	NR	35 (13)	NR	NR	NR
Anemia	NR	NR	NR	NR	NR	32 (12)	NR	16 (6)	NR	NR	NR
Cough	NR	NR	NR	NR	NR	29 (11)	NR	5 (2)	NR	NR	NR
Abdominal pain upper	NR	NR	NR	NR	NR	19 (7)	NR	5 (2)	NR	NR	NR
Dyspepsia	NR	NR	NR	NR	NR	16 (6)	NR	8 (3)	NR	NR	NR
Alopecia	NR	NR	NR	NR	NR	16 (6)	NR	8 (3)	NR	NR	NR
Renal Impairment	NR	NR	NR	NR	NR	16 (6)	NR	8 (3)	NR	NR	NR

Study	AURA-LV			AURORA		AURA-LV + AURORA			BLISS-LN		Davidson 2018
Abdominal pain	NR	NR	NR	NR	NR	13 (5)	NR	5 (2)	NR	NR	NR
Mouth ulceration	NR	NR	NR	NR	NR	11 (4)	NR	3 (1)	NR	NR	NR
Fatigue	NR	NR	NR	NR	NR	11 (4)	NR	3 (1)	NR	NR	NR
Tremor	NR	NR	NR	NR	NR	8 (3)	NR	3 (1)	NR	NR	NR
Acute kidney injury	NR	NR	NR	NR	NR	8 (3)	NR	3 (1)	NR	NR	NR
Decreased appetite	NR	NR	NR	NR	NR	8 (3)	NR	3 (1)	NR	NR	NR

VCS: Voclosporin, NR: not reported, PBO: placebo, BEM: belimumab, ref: reference, OR: odds ratio, CI: confidence interval
* No data on harms reported for the AURION study

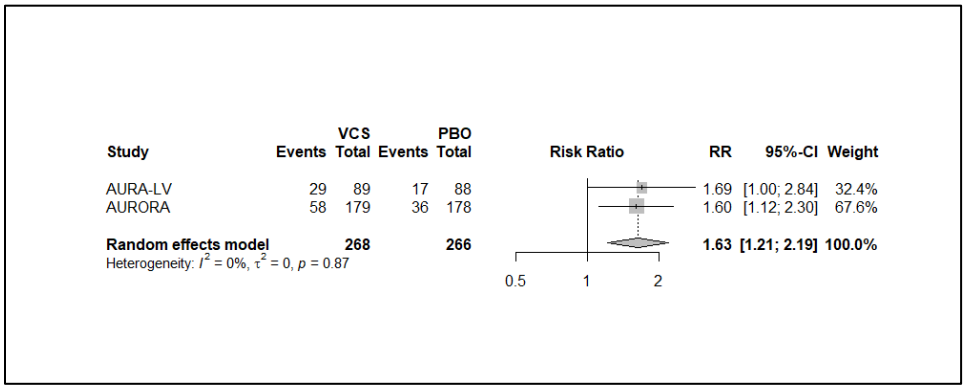
D5. Supplemental MA and NMA Information

Figure D2. MA of Complete Response at 48/52 Weeks. Voclosporin (VCS) versus Placebo (PBO)



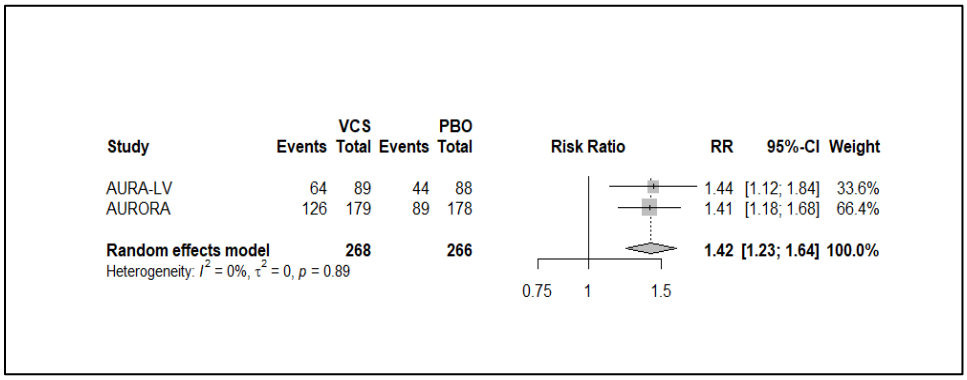
95% CI: 95% confidence interval, I2: I-squared, RR: risk ratio, τ2: between-study-variance estimator

Figure D3. MA of Complete Response at 24 Weeks. Voclosporin (VCS) versus Placebo (PBO)



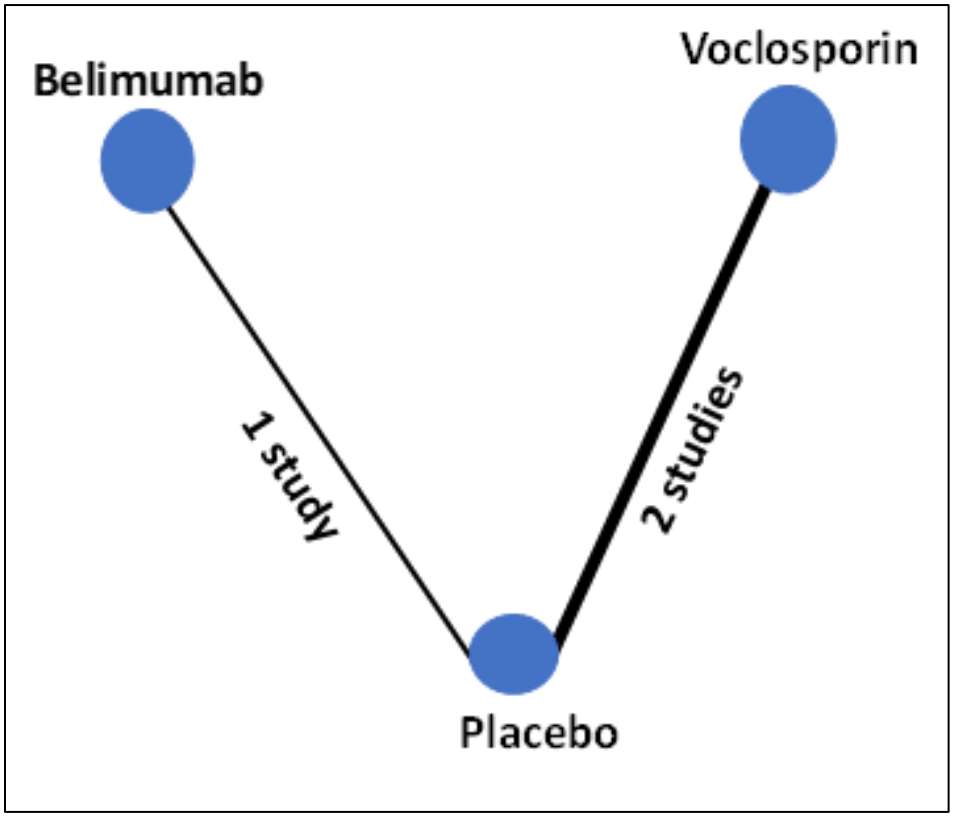
95% CI: 95% confidence interval, I2: I-squared, RR: risk ratio, τ2: between-study-variance estimator

Figure D4. MA of Partial Response at 24 Weeks. Voclosporin (VCS) versus Placebo (PBO)



95% CI: 95% confidence interval, I2: I-squared, RR: risk ratio, τ2: between-study-variance estimator

Figure D5. NMA figure



Belimumab vs. placebo study: BLISS-LN
Voclosporin vs. Placebo studies: AURA-LV & AURORA

Table D5. NMA Results of Complete Renal Response (Fixed Effect model): Odds Ratio (95% Credible Interval)

Voclosporin		
1.62 (0.94, 2.77)	Belimumab	
2.57 (1.77, 3.75)	1.59 (1.08, 2.34)	Placebo

Table D6. NMA Results of Complete Renal Response (Random Effect model): Odds Ratio (95% Credible Interval)

Voclosporin		
1.65 (0.36, 8.02)	Belimumab	
2.62 (1.07, 6.76)	1.59 (0.45, 5.55)	Placebo

D6. Ongoing Studies

Table D7. Ongoing Studies

Title / Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Dates
Voclosporin					
AURORA 2: Aurinia Renal Response in Lupus with Voclosporin **Aurinia Pharmaceuticals Inc.** **NCT03597464**	Interventional (Clinical trial), randomized, parallel assignment. Estimated enrollment: 227 Actual enrollment: 216	Placebo oral capsule	Inclusion - Subjects who completed 52 weeks treatment with study drug in AURORA 1 study - Patient willing to continue taking MMF during duration of study - Age 18-75 Exclusion - Patients taking medications/food items prohibited by study - Renal dialysis - Planned kidney transplant - Any medical condition associated with increased risk to patient - Pregnant, breast feeding, not using adequate contraceptives - Vaccines using live organisms/virus/bacteria	- Adverse events (AE) profile - Routine biochemical and hematological assessments	August 2021
Belimumab					

Title / Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Dates
Synergetic B-cell Immunomodulation in SLE - 2nd Study **Leiden University Medical Center** **NCT03747159**	Interventional, randomized, parallel assignment (single-center), phase 2 proof-of-concept study Estimated Enrollment: 30	Experimental 1. Belimumab injection 2. Rituximab infusion 3. Standard of care Nonexperimental 1. Standard of care	Inclusion - SLE diagnosis - Severe, active SLE - New, persisting, progressive disease activity despite use of conventional maintenance treatment - Positive for SLE-specific antibodies Exclusion - Active pregnancy - Hypogammaglobulinemia (IgG < 4.0 g/L) or IgA deficiency (1gA < 0.1 g/L) - Immunization with live vaccine 1 month before screening - Active infection - HIV positive - History primary immunodeficiency - Neutrophil count < 1.5x10E9/L - Significant infection history - Drug/alcohol abuse - Active malignant neoplasm - Suicidal risk/behavior	- Reduction of disease relevant autoantibodies present at baseline (anti-dsDNA in particular)	Primary: October 2020 Study: October 2023
Cyclosporin (cyclophosphamide)					

Title / Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Dates
BAFF Levels and Lupus Nephritis (LN) **Universidad de Antioquia** **NCT04369495**	Observational, prospective, case-only Estimated enrollment: 30	Arm 1: Cyclophosphamide Arm 2: Mycophenolate	Inclusion - Patients aged 18 or older - Diagnosed with SLE - Diagnosis with Lupus Nephritis - Patients with new onset LN or a relapse after successful remission - Class III or IV with or without class V Exclusion - Women who are pregnant - Class I, II or V without class III or IV - Active malignancy - Kidney disease, active infection, leukopenia - eGFR <30mg/ min	- Levels of BAFF - Lupus clinical manifestations - Serological findings - Inflammatory Cytokine Levels	March 2022
Mycophenolate mofetil (MMF)					
Fixed-dose vs. Concentration-controlled Mycophenolate Mofetil for the Treatment of Active Lupus Nephritis **Chulalongkorn University** **NCT03920059**	Interventional (Clinical Trial, Phase 4), Randomized, Parallel Assignment Estimated Enrollment: 90	Arm 1: Placebo (Fixed-Dose) Arm 2: Active (Concentration Controlled)	Inclusion - Age 18-65 - SLE diagnosis - Active LN Exclusion - eGFR < 20mL/min/1.73 m2 - Crescentic glomeruli > 30% - Severe extra-renal involvement of SLE	- Response rate at 48 weeks of therapy	Primary: April 30, 2025 Study: April 30, 2027

Title / Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Dates
			- Condition requiring treatment with systemic corticosteroid (excluding topical or inhaled steroids) within 52 weeks prior to screening - Treatment with ≥ 1 g cyclophosphamide within the past 24 weeks - Received ≥ 3 g of IV pulse methylprednisolone within the past 12 weeks - Received prednisolone more than 30 mg/day for longer than 30 days within the past 12 weeks - MMF treatment at ≥ 1.5 g/day for over 4 weeks within the past 12 weeks - On treatment with Tacrolimus or Cyclosporine on the day of screening - Treatment with any biologic B-cell depleting therapy (e.g., anti CD-20, anti CD 22) within 52 weeks - Receiving concomitant medication interfering PK of MPA: Cholestyramine, Rifampin		

Title / Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Dates
Comparison Between Mycophenolate and Cyclophosphamide in the Treatment of Lupus Nephritis **Al-Azhar University** **NCT04424602**	Interventional (Clinical Trial), Randomized, Parallel Assignment Estimated Enrollment: 40	Cyclophosphamide	Inclusion - Age 20-50 - Female - History or new diagnosis of SLE with LN - All stages of LN except stage I, V, VI Exclusion - Acute inflammatory process (e.g., arthritis) - Patients taking other immunosuppressive therapy - Malignancies - Patients with HCV, HBV, HIV - Patients with NL stage I, V, VI	- Serine creatinine (sCR) - Blood urea nitrogen - Erythrocyte sedimentation rate (ESR) - Anti dsDNA - Complement 3 (C3) - Complete Blood count (CBD) - 24h urine test for creatinine clearance & protein excretion	Primary: January 5, 2021 Study: February 9, 2021
The Effect of Mycophenolate Mofetil and Cyclophosphamide on the Lymphocyte Subsets in Patients with Proliferative Lupus Nephritis **University of Hong Kong** **NCT02954939**	Interventional (Clinical Trial), Randomized, Parallel Assignment Estimated Enrollment: 50	Active Comparator: MMF-MMF (Prednisolone + MMF as induction-maintenance therapy) Placebo Comparator: CTX-AZA (Cyclophosphamide followed by Azathioprine)	Inclusion - Age 18-80 - Patients with biopsy proven class III/IV +/- V LN and active nephritis Exclusion - Patients who have received calcineurin inhibitors/proliferation signal inhibitors as maintenance immunosuppression in last 3 months	- Lymphocyte subset profile, Naïve & memory B cells, plasma cells	Primary: March 2021 Study: June 2021

Title / Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Dates
			- Patients receiving biologics therapy (rituximab, abatacept) in last 12 months - Pregnant or lactating patients		

Source: www.ClinicalTrials.gov (NOTE: studies listed on site include both clinical trials and observational studies)

D7. Previous Systematic Reviews and Technology Assessments

We identified two previous systematic reviews – one reviewing immunosuppressive treatments for lupus nephritis and one reviewing the renal effects of belimumab. These reviews are summarized below.

Tunnicliffe DJ, Palmer SC, et al. Immunosuppressive Treatment for Proliferative Lupus Nephritis. Cochrane Review.[57]

Cochrane researchers conducted a systematic review of immunosuppressive treatments for use in adults and children with biopsy-proven class III, IV, V+III and V+VI lupus nephritis. In total, 74 studies were included in the review with 67 studies on induction therapy and nine studies on maintenance therapy. The included studies evaluated treatments such as cyclophosphamide, mycophenolate mofetil (MMF), azathioprine, and tacrolimus used alone or with MMF.

The 67 included studies that focused on induction therapy ranged from 2.5 to 48 months (median 12 months) in duration and enrolled 4791 participants in total. The main results reported by CADTH concluded that MMF plus corticosteroids may lead to increased complete disease remission (RR: 1.17, 95% CI: 0.97 to 1.42; I^2 = 0%) compared to cyclophosphamide at six months as well as the stabilization of kidney function (RR: 1.05, 95%CI: 0.94 to 1.17; I^2 = 0%) although the certainty in the evidence is low. Researchers also reported that tacrolimus plus MMF may improve the induction of complete renal remission at six months (RR: 2.38, 95% CI: 1.07 to 5.30; I^2 = 57) as well as the induction of stable kidney function (RR 1.78, 95%CI: 1.40 to 2.26; I^2 = 0%) though the generalizability is low because the majority of patients included in the study are Asian.

The nine studies reporting on maintenance therapy ranged from 6 to 36 months in duration and enrolled 767 participants. Researchers concluded that Azathioprine probably increased renal relapse (RR 1.75, 95% CI: 1.20 to 2.55; I^2 = 0%) versus MMF but there was no difference in other outcomes like injection or alopecia, according to the review.

Sciascia S, Radin M et al. Efficacy of belimumab on renal outcomes in patients with systemic lupus erythematosus: A systematic review. 2017.[58]

The identified systematic review summarizes the potential effect of belimumab on renal parameters in patients with systematic lupus erythematosus (SLE) focusing on those with lupus nephritis (LN). 11 total articles were included: 1 post-hoc analysis of a randomized control trial, four observational studies, and six case reports all reporting the effect of belimumab on renal parameters in patients with LN. From a total of 2004 identified patients with SLE, 326 (16.3%) had LN at baseline and of those, 234 (71.8%) were being treated with belimumab (10 mg/kg).

Of the 234 LN patients being treated with belimumab, 129 (55.1%) showed improvements in renal parameters including renal flare, renal remission, and/or renal organ disease improvement assessed by SELENA-SLEDAI, SLEDAI-2K, BILAG, and/or SLAM indexes. Comparing LN patients receiving belimumab versus placebo, those receiving belimumab achieved a higher percentage of renal remission (68.1% versus 58.7%, chi-square value = 4.9814, p = 0.025) and a shorter median time to renal remission (139.5 versus 167 days). From the included randomized trails, adding belimumab to standard of care increased rate of renal remission by 10% compared to placebo. As for rate of renal flare, LN patients receiving belimumab had a lower rate (1.95% versus 3%, chi-square value = 1.8742, p = 0.17) although this difference was not statistically significant. Given the evidence from the 11 included studies, investigators determined that it is not possible to make definitive recommendations for the off-label use of belimumab for LN. However, the published evidence supports the continued investigation of belimumab in treating LN.

E. Long-Term Cost-Effectiveness: Supplemental Information

E1. Detailed Methods

Table E1. Impact Inventory

Sector	Type of Impact (Add additional domains, as relevant)	Included in This Analysis from […] Perspective?		Notes on Sources (if quantified), Likely Magnitude & Impact (if not)
		Health Care Sector	Societal	
Formal Health Care Sector				
Health Outcomes	Longevity effects	X	X	
	Health-related quality of life effects	X	X	
	Adverse events	X	X	
Medical Costs	Paid by third-party payers	X	X	
	Paid by patients out-of-pocket	☐	☐	
	Future related medical costs	☐	☐	
	Future unrelated medical costs	☐	☐	
Informal Health Care Sector				
Health-Related Costs	Patient time costs	NA	☐	
	Unpaid caregiver-time costs	NA	☐	
	Transportation costs	NA	☐	
Non-Health Care Sector				
Productivity	Labor market earnings lost	NA	X	
	Cost of unpaid lost productivity due to illness	NA	X	
	Cost of uncompensated household production	NA	☐	
Consumption	Future consumption unrelated to health	NA	☐	
Social services	Cost of social services as part of intervention	NA	☐	
Legal/Criminal Justice	Number of crimes related to intervention	NA	☐	
	Cost of crimes related to intervention	NA	☐	
Education	Impact of intervention on educational achievement of population	NA	☐	

Sector	Type of Impact (Add additional domains, as relevant)	Included in This Analysis from […] Perspective?		Notes on Sources (if quantified), Likely Magnitude & Impact (if not)
		Health Care Sector	Societal	
Housing	Cost of home improvements, remediation	NA	☐	
Environment	Production of toxic waste pollution by intervention	NA	☐	
Other	Other impacts (if relevant)	NA	☐	

NA: not applicable
Adapted from Sanders et al.[59]

Target Population

The population of focus for this economic evaluation includes adult SLE patients with Class III, IV, or V LN. The model uses a mean start age of 35 years assuming patients' characteristics (gender and age) are similar to the population described in Davidson et al. (2018) study.[18]

Treatment Strategies

The list of interventions for LN was developed with input from patient organizations, clinicians, manufacturers, and payers on which treatments to include for LN. The full list of interventions is as follows:

- Belimumab (Benlysta®, GlaxoSmithKline), IV, 10 mg/kg of body weight, plus standard therapy
- Voclosporin (Aurinia), oral, mean daily dose of 39.1 mg a day, plus standard therapy

For belimumab, the comparator was standard therapy, defined as IV CYC or oral MMF, IV dose of steroids (500-1000 mg), and then oral prednisone (0.5 to 1.0 mg/kg per day). For voclosporin, the comparator was standard therapy, defined as oral MMF, IV dose of steroids (500-1000 mg), then oral steroids 20-25 mg daily tapered down to 5 mg daily by week 8 and 2.5 mg daily by week 16.

E2. Model Inputs and Assumptions

Our model includes several key assumptions stated below.

Table E2. Assumptions of Short-Term and Long-Term Modeling

Assumption	Rationale
Benefits of treatments were derived from improved kidney function only	LN is a complication of SLE. Some treatments, such as belimumab, could affect not only LN, but also SLE progression. Since this model reconstructs the progression of LN only, it is not able to reflect broader benefits of treatments, for instance their impact on progression of SLE or other comorbidities.
Belimumab and voclosporin treatments are compared to standard therapies used in respective control arms and not to each other.	There are no head-to-head trials comparing belimumab and voclosporin. The designs of the trials, including the inclusion criteria, comparator arms, background therapy, definitions of the outcomes, and the study follow-up times are too different, precluding comparing the treatments to each other.
LN Progression and Mortality	
The patients remaining in AD, CR, and PR at the end of the short-term model transition independent of the previous treatment received.	There are no long-term data on survival for patients on belimumab and voclosporin. Also, there is no clinical reason why response achieved by one treatment will have different survival to response achieved on a different treatment. Thus, long-term modeling was based on survival analyses of LN patients, conditional on achieving AD, CR, and PR at the end of each trial.[18]
The proportion of ESRD events and deaths are estimated based on data from Chen et al. (2008).	The data from Davidson et al. (2018) only report on ESRD-free survival, but not ESRD and death separately. As such, the proportion of ESRD events and deaths in the model was estimated based on data from Chen et al. (2008), which reported KM curves for ESRD-free survival and overall survival separately.
Patients in CR and PR accrue costs and outcomes associated with time in AD before progressing to ESRD.	Clinical experts suggested that patients with CR and PR are likely to spend a period of time in AD before progressing to ESRD (rather than progressing directly to ESRD from CR or PR). AD is defined by a drop in eGFR level which is necessary to transition into ESRD. This was implemented in the long-term model by incorporating the costs and outcomes for the time spent in AD rather than explicitly modeling this transition. The time spent in AD state was extracted from Hanly et al. (2016).
Treatment	
Patients in CR and PR discontinue belimumab and voclosporin treatment at the end of the short-term model (unless serious adverse event leading to drug discontinuation occurred).	There are no data to inform long-term treatment effects of belimumab and voclosporin, thus no additional effectiveness or costs related to belimumab and voclosporin treatment were accumulated beyond the short-term model. In the base-case analysis, the short-term model time horizon is three years assuming patients stay in the same health states that they were in at the end of the trials (see Tables 4.2 and 4.3) until the end of 3 years.

Assumption	Rationale
Patients in the AD state discontinue belimumab and voclosporin treatment at 18 months	There are no data to inform mean discontinuation time of belimumab and voclosporin used for LN treatment for patients remaining in AD state. Data from AURORA and BLISS-LN trials suggest an additional clinical effect between 6-12 months of treatment. The time of 18 months for AD state is selected to account for underestimation of treatment duration in CR/PR states, as it was informed by clinicians.
Adverse events are not explicitly modeled but considered captured in costs and utilities associated with each health state, as well as the survival.	The adverse events reported in both trials were comparable in the intervention and comparator arms (i.e., neither belimumab nor voclosporin treatment resulted in more adverse events than standard therapy).
Belimumab treatment is provided in IV vial form to all LN patients.	There was no agreement among physician experts regarding the belimumab drug forms that are going to be prescribed to LN patients. Since only IV drug form was used in the BLISS-LN trial, costs of belimumab in vials were used in the base-case analysis.
Costs	
Drug wastage for belimumab treatment was considered in the base-case analysis.	Based on the prescribing information for belimumab and the feedback from clinical experts, the modeling considered drug wastage in calculating the annual cost of belimumab treatment.
MMF costs or CYC costs were not be included in the model.	Both voclosporin and belimumab are assumed to be added on to standard care (i.e., MMF for voclosporin, and MMF or CYC for belimumab). Therefore, the costs of these therapies are assumed to be the same between the standard care and intervention arms for their respective comparisons. Given the costs of standard care are already included in the health state costs, these are not incorporated separately, to avoid double counting.
Costs of interventions for patients who discontinued the trials with AEs were not accumulated after the midpoint of the short-term model.	As there are no data is available on time of patients' treatment discontinuation due to AEs, we assume that the treatment discontinuation is at the mid-point of the short-term model (i.e., 18 months for both belimumab and voclosporin). For the patients who stop treatment due to AEs, the costs of interventions (belimumab and voclosporin) were not accrued beyond the midpoints of short-term model, although they still accumulated the costs related to their health state.
Impact of Low-Dose Steroid Use	
Tapered steroid use decreases costs and increases utilities in the short-term model.	In BLISS-LN, more patients were reported on low-dose steroids in treatment than comparator arms. In AURORA, steroid dose was tapered down to a dose of 5 mg daily by week 8 and 2.5 mg daily by week 16. Costs of steroids and increment in utilities for patients on low-dose steroids were included in the short-term model.[33]

Assumption	Rationale
Low-dose steroid use in the trials does not affect costs in the long-term model.	There is no evidence on how the steroid dosages change after treatment with belimumab or voclosporin is discontinued. Thus, the impact of low-dose steroids was limited to the duration of treatment with belimumab and voclosporin.

Model Inputs

Clinical Inputs

In the short-term model, the proportion of patients who remain in CR, PR, AD, and ESRD were calculated by the linear interpolation of data from the clinical trials. The proportions of patients reaching CR in the BLISS-LN trial[17] were extracted from the digitized curve which reports the proportions of patients achieving CR over time. The proportions of patients reaching PR, ESRD, or death at the end of the trial follow-up (104 weeks), were used in the short-term model to estimate the proportions in interim time cycles.

Table E3. Outcomes on Belimumab from BLISS-LN Trial

Arm	Time	Complete Renal Response, %	Partial Renal Response, %	ESRD, %	Death, %
Belimumab	104 weeks	30.0	17.5	0.0	0.4
Placebo		19.7	17.0	0.4	0.9

ESRD: end-stage renal disease

Definitions in BLISS-LN trial: Complete Renal Response (CRR): ratio of urinary protein to creatinine of <0.5, eGFR no worse than 10% below pre-flare value or ≥90 ml/min/1.73 m2with no use of rescue therapy.

Partial Response: GFR no worse than 10% below baseline value or within normal range and at least 50% decrease in the ratio of urinary protein to creatinine with one of the following: ratio of urinary protein to creatinine <1.0 if baseline ratio ≤3.0, or ratio of urinary protein to creatinine of <3.0 if baseline ratio >3.0; no treatment failure; and not complete renal response.

Outcomes of voclosporin treatment were assessed using the data from a meta-analysis of the AURA-IV and AURORA trials (see Section 3 "Comparative Clinical Effectiveness") for CR at 24 and 52 weeks and for PR at 24 weeks; for death and PR at 52 weeks, data from the AURORA trial were used.

Table E4. Outcomes on Voclosporin from AURORA and AURA-LV Trials

Arm	Time	Complete Renal Response*, %	Partial Renal Response**, %	ESRD***, %	Death¥, %
Voclosporin	52 weeks	43.2	26.6	0.0	0.6
Placebo		23.3	28.4	0.0	2.8

ESRD: end-stage renal disease

Definitions in AURORA trial: Complete Renal Response (CRR): Decrease in UPCR to ≤0.5mg in 2 consecutive, first morning void urine specimens, eGFR >60ml/min per 1.73 m2 or no decrease of ≥20% of baseline eGFR on 2 consecutive occasions, No use of rescue therapy and presence of sustained low-dose steroids

Partial Response:≥ 50% decrease in urinary protein: creatinine ratio from baseline in the absence of rescue medication

* Meta-analysis of AURA-IV and AURORA trials; **Difference between PR/CR rates reported in AURORA trial and CR rate calculated in meta-analysis; ***Not reported in AURORA trial, assumed as zero; ¥ AURORA trial.

Treatment Duration

Considering the plausibility that both of the drugs will be used longer than the duration of the trials, it was assumed that belimumab and voclosporin will be used in patients in CR and PR states for three years before discontinuation, based on consultations with clinical experts. For patients remaining in AD state, we assumed that both drugs will be used for 18 months before treatment discontinuation. In the model, the patients are assumed to stay in the same health states that they were in at the end of the trials (see Tables E3 and E4) until the end of three years. That is, the probability of being in each model state (CR, PR, AD, ESRD) after the end of the trials' follow-up (two years for belimumab and one year for voclosporin) in the short-term three-year model was considered to be same as the last observation in the trials.

Discontinuation due to adverse events

In the model, based on consultations with clinical experts, treatment discontinuation due to AE was considered, to reflect the clinical practice of patients staying longer on the therapies than in trial settings. Based on the data from the phase III (BLISS-LN and AURORA) trials, 13% in the belimumab arm of BLISS-LN and 11.2% in the voclosporin arm of AURORA discontinued due to AEs.

As such, these proportions (13% in belimumab arm and 11.2% in voclosporin arm) were assumed to discontinue treatment in the short-term model. As there are no data from the trials to inform the time point for treatment discontinuation, this treatment discontinuation was assumed to happen in the model at the midpoint of treatment duration (i.e., 18 months for both belimumab and voclosporin).

Long-term Extrapolation

The inputs for long-term extrapolation were common for both treatments, and as such are presented together.

The long-term model used partitioned-survival modeling to estimate ESRD-free survival for the different health states (AD, CR, and PR) based on data from Davidson et al. (2018), with the proportion of ESRD events and deaths estimated based on data from Chen et al. (2008).[8,18] The structure of the partitioned survival model does not include the AD state, calculating the costs and benefits for the proportion of people without ESRD, with ESRD, and those who died. Since patients do spend some time in AD state (and ignoring this would lead to lower costs, higher benefits, and so more favorable cost-effectiveness ratio for the drugs), we added the costs and utilities relevant for AD state for those patients who progress to ESRD. It was assumed that patients spend 1.206 years in the AD state (defined as eGFR < 30 ml/min) before progressing to ESRD, based on SLICC data.[28]

As there are no data on long-term LN progression in patients receiving belimumab or voclosporin treatments, the base-case analysis assumed that long-term disease progression depends only on whether patients achieve CR, PR, or AD at the end of the short-term model (and not the treatment received).

The long-term probability of remaining alive without ESRD, conditional on being in AD, CR, and PR health states at the end of the trials, was modeled by fitting survival curves to the digitized published Kaplan-Meier (KM) data.[18] The probability to remain without ESRD or death was obtained from the KM curves for CR, PR, and AD states defined by mBLISS-LN criteria; these criteria were selected as having definitions more close to those used in both of the trials (Table E5).[17,20,21,23]

Table E5. Definitions of the Outcomes in Different Studies

Study and Reference	Complete Renal Remission /Response	Partial Remission /Response
Davidson et al. (2018)	Occurrence of estimated creatinine clearance within the normal range Urinary protein:creatinine ratio < 0.5.	Creatinine clearance of no more than 10% below the baseline value or within normal range; ≥ 50% decrease in urinary protein:creatinine ratio to < 1.0 (if the baseline ratio were ≤ 3.0) or < 3.0 (if the baseline ratio was > 0.3).
BLISS-LN	Urinary protein:creatinine ratio < 0.5. eGFR that was no worse than 10% below the pre-flare value or ≥90 ml per minute per 1.73 m2 No use of rescue therapy.	eGFR no worse than 10% below baseline value or within normal range; Decrease in urinary protein:creatinine ratio with one of the following: ratio <1.0 if baseline ratio was ≤ 3.0 or <3.0 if the baseline ratio was >3.0; No receipt of prohibited (rescue) therapy resulting in treatment failure
AURORA	Decrease in UPCR to ≤0.5 mg in 2 consecutive, first morning void urine specimens eGFR >60ml/min per 1.73 m2 or no decrease of ≥20% of baseline eGFR on 2 consecutive occasions No use of rescue therapy and presence of sustained low-dose steroids	≥ 50% decrease in urinary protein:creatinine ratio from baseline in the absence of rescue medication

Because of the substantial overlap in the survival curves for patients remaining in PR and CR reported by Davidson et al. (2018), patients in these states were assumed to have the same ESRD-free survival. The KM data were digitized, and individual data were reconstructed using the methods described in Guyot et al. (2012).[60]

The characteristics of the cohort used in the Davidson et al. (2018) study defined the approach for data extrapolation. The analysis was based on the Hopkins Lupus Cohort which had the average follow-up time per patient of 6.4 years and drop-out rate of approximately 10% per year.[61] Considering the large loss to follow-up, small number of events, and clinical plausibility of observed data informed by the clinical experts (i.e., the implausibility of not having a single ESRD/death event

in multiple years of follow-up among patients with AD), the digitized KM curves were truncated to the last event: 3.8 years for AD and nine years for PR/CR curves.

Different parametric distributions were fitted to these survival data, with the best-fitting curves identified based on a combination of visual inspection, fit statistics such as Akaike information criteria (AIC)/Bayesian information criteria (BIC), and clinical plausibility. Given very similar AIC (53-55 for all except an exponential distributions of PR/CR curves and 100-102 for all distributions of AD curves) and BIC (53-55 for all except exponential distributions of PR/CR curves and 102-106 for all except gengamma distributions of AD curves) values between the different curves, clinical plausibility was the key factor in determining the selection of the parametric distributions for extrapolation.

For each health state, a single parametric distribution was selected to calculate the proportion of the cohort remaining alive without ESRD each year. Weibull distribution for AD (Figure E1) and lognormal for CR/PR (Figure E2) were selected, based on the feedback from clinical experts considering similarity in AIC/BIC for most of the distributions applied.

Figure E1. ESRD-Free Survival Probabilities with Different Extrapolation Approaches for Patients in AD State

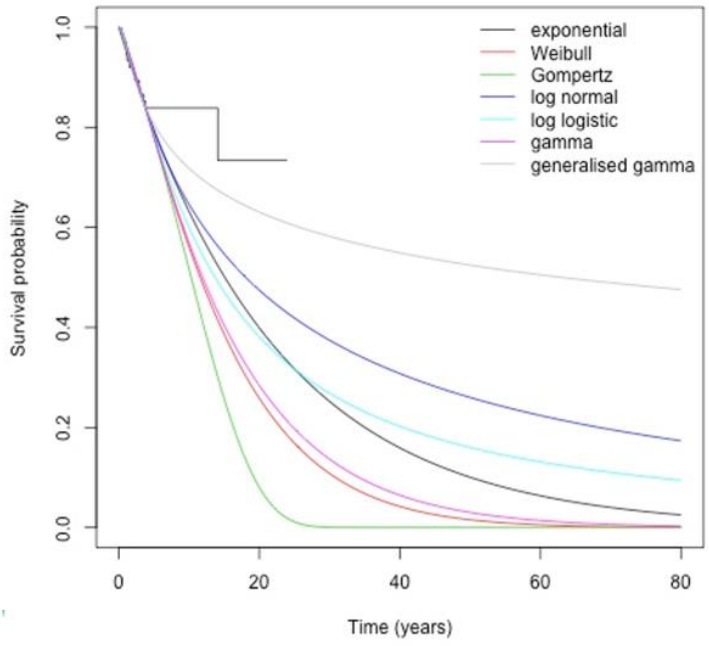
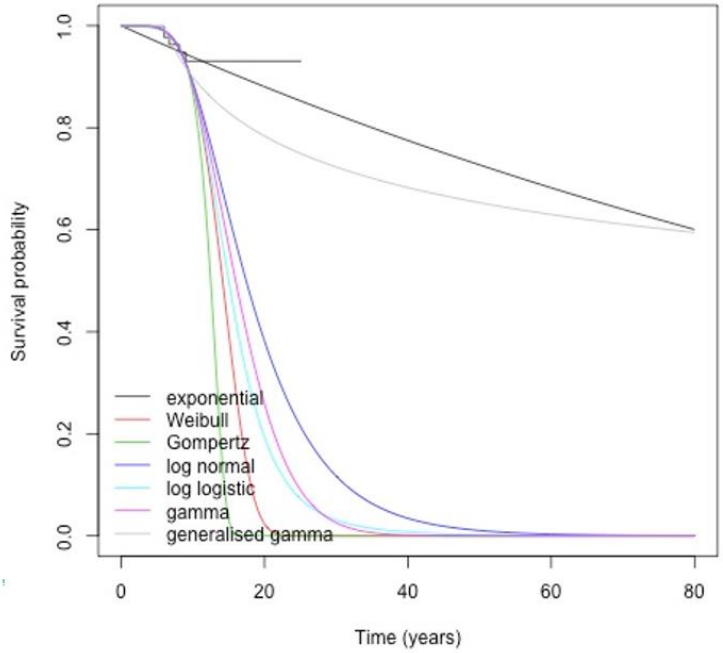


Figure E2. ESRD-Free Survival Probabilities with Different Extrapolation Approaches for Patients in CR/PR State



Mortality

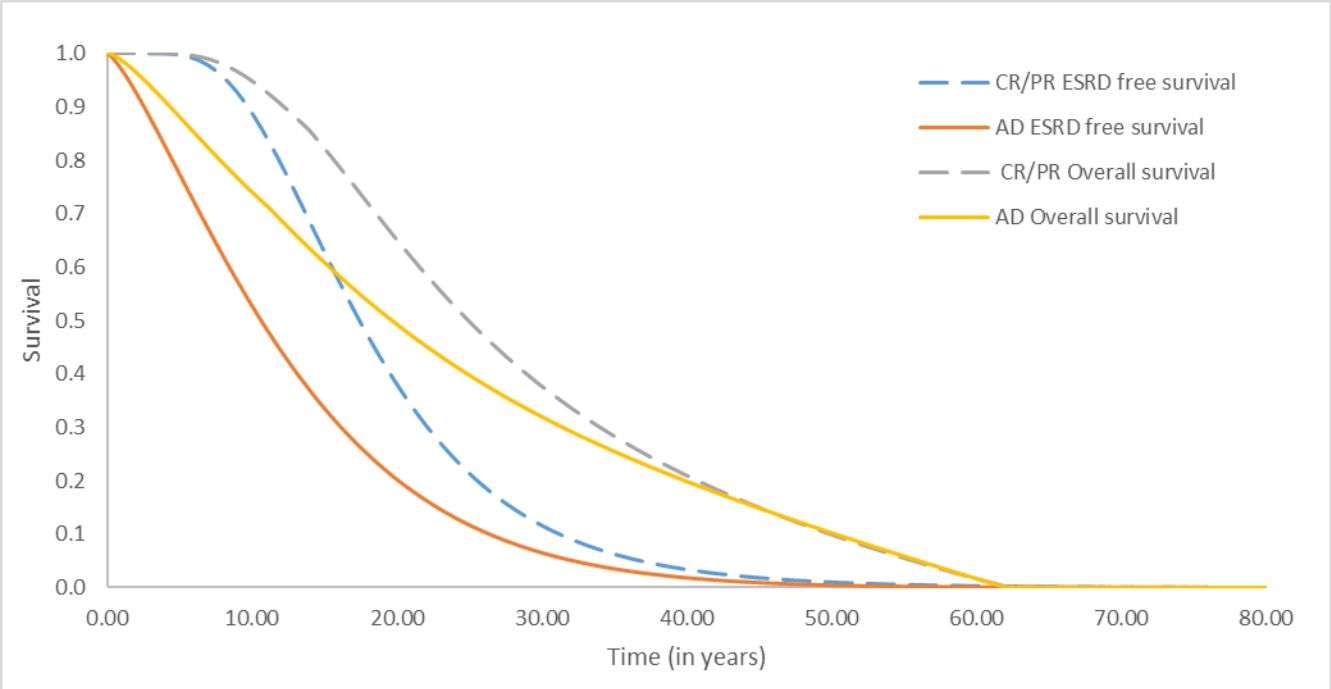
The monthly probability of death in the short-term model was estimated from interpolation of the trial data assuming a constant hazard between time points. In the long term model, the probability of deaths over time in the CR, PR and AD health states was estimated based on the digitized published KM data from Chen et al.(2008) which reports both ESRD-free survival and overall survival.[8] An average life expectancy of 10 years was assumed for patients who were in ESRD at the end of the short term model, based on the difference between overall survival and ESRD-free survival in the long-term extrapolation.

To retrieve clinically plausible predictions for the CR, PR and AD health states, a multi-stage approach was utilized. First, the published KM curves reporting ESRD-free survival (either ESRD or death) and overall survival were digitized and reconstructed. Then, the proportions of deaths and ESRD events over time were estimated from the predictions of survival at each month up to the time of the last follow-up for the patients with AD, CR, and PR. Beyond the last observation in the KM curves reported by Chen et al. (2008), the proportions were estimated by assuming 100% mortality of population at age 100 to interpolate the ESRD-free survival and the overall survival

reported by Chen et al. (2020). These proportions of deaths versus ESRD events over time were applied to the ESRD-free survival curves estimated based on data from Davidson et al. (2018).[18]

The predictions on mortality in the LN population in CR/PR and AD states were validated by clinical experts. The survival curves used in the base-case analysis for long-term extrapolation are presented in Figure E3. The ESRD free survival and overall survival is assumed to be the same between PR and CR states. In the CR/PR health states, the mean ESRD-free survival is 19.38 years, and the mean overall survival is 28.13 years, while in the AD health state, mean ESRD-free survival is 12.98 years, and the mean overall survival is 23.65 years.

Figure E3. Survival Curves Used in the Long-Term Extrapolation Model



Adverse Events

Costs or disutilities for AEs were not explicitly included in the model, as the impact of AEs related to standard therapy on costs and utilities were reflected in the values assigned to each health state (CR, PR, AD, and ESRD). Also, similar rates of AEs in treatment and comparator arms were reported in the AURORA and BLISS-LN trials, so no AEs related to interventions were included additionally in modeling.

Utilities

Health state utilities used in the model were derived from published literature. No US-specific preference-based utility values for LN states (CR, PR, and AD), reflecting the total health utility and measured on zero to one or zero to 100 scales, were found in the literature, and no data on utilities have been provided by the manufacturers.

Previous cost-effectiveness models in LN have assumed that the quality of life of patients in CR is similar to that of the general population. The cost-effectiveness model of Wilson et al. (2007) assumed utilities of one for CR[62], and a CEA in Thailand reported EQ-5D values for CR of 0.94, comparable to utilities for a healthy population in the US.[34,63] However, given the potential for other complications from underlying SLE, clinical experts and patient groups suggested that it is implausible that the utility values for LN patients would be as high as general population utilities. Thus, the model assumed that utility values in the CR state are equal to utility values of the population with SLE who have very low disease activity. As such, the utility values for patients in CR were assumed to be the same as for individuals who scored 0-9 points on Systemic Lupus Activity Questionnaire in a cohort of 182 Swedish patients (0.8±0.16).[33]

We estimated the utility values for patients in the PR, AD, and ESRD states by applying utility decrements compared to the CR state. A cost-utility analysis of alternative drug regimens for newly diagnosed severe LN patients in Thailand[34] reported utility values of 0.94 for CR, 0.85 for PR, 0.764 for AD, and 0.689 for ESRD. These values were used to estimate utility decrements in our model by subtracting the corresponding decrements from the utility value for the CR state: 0.09 for PR, 0.176 for AD, and 0.251 for ESRD. The utility values in this study were calculated based on 216 observations conducted on 18 patients (mean age 40), enrolled in four tertiary care hospitals in Thailand. The utility values for the ESRD state that are reported by Mohara et al. (2014) are comparable to the mean EQ-5D score for ESRD dialysis patients younger than 65 years in a cohort of North American dialysis patients[64] and to the EQ-5D scores among patients with CKD on dialysis reported in a systematic review by Cooper et al. (2020) [0.44-0.78 in US, Canadian, UK, and international studies].[65]

In the model, all utilities were capped at the general population utility for that age group (see Table E6), to ensure they did not exceed the utilities of the general population.[66]

Table E6. General Population Utility Values

Age group	Mean utility
18-29	0.922
30-39	0.901
40-49	0.871
50-59	0.842
60-69	0.823
70-79	0.790
>=80	0.736

Utilities Related to Steroid Use

Patient representatives and clinical experts advised that the benefits to patients of reduced steroid use should be recognized as an important potential benefit of treatment. The short-term model therefore included an incremental gain in utilities related to low-dose steroid and no steroid use. Since no measured utilities were provided by the manufacturers, these utility adjustments were based on published literature and expert clinical opinion. The preferred option to include the increment in utilities associated with lower steroid use was to use the mean difference in steroid use in treatment and comparator arms for both drugs; however, no data on mean steroid use in the voclosporin AURORA trial was provided.

Thus, in the short-term model for belimumab, we used the minimum relative increment in utilities for the proportion of patients on low-dose steroids (<5 mg) in the BLISS-LN trial.[17] In the short-term model for voclosporin, for both treatment and comparator arms, no increment in utilities was applied during the first eight weeks of the trial, an increment related to low-dose steroid use was applied from week 8 to 16, and an increment related to no steroid use from week 16 onwards.

We reflected the possible impact of low-dose corticosteroid use by using a utility increment, which was estimated as equal to the average of the increment measured using the five-item EQ-5D instrument (which showed no increment in utilities related to low-dose steroid use) and a visual analog scale (VAS) EQ-5D in a cohort of patients in Sweden.[33] In addition, an increment in EQ-5D utility for no steroid use, from the same study, was applied (Table E7).

Table E7. Utility Values for Health States

	Baseline	Increment in Utilities for Low-Dose Steroids	Increment in Utilities for Treatments with No Steroids	Source
CR	0.80	0.025	0.09	[33,34]
PR	0.71	0.025	0.09	
AD	0.62	0.025	0.09	
ESRD	0.55	0.025	0.09	

AD: active disease, CR: complete response, ESRD: end-stage renal disease, PR: partial response

Economic Inputs

Drug Acquisition Costs

Average sales price (Table E8) was used to calculate the costs of belimumab. Since no body weight was reported in the published BLISS-LN trial, the annual cost calculation included the distribution of body weights of the LN population from the literature (with mean weight of 65.92 kg) to estimate the dosage of belimumab (assuming 10mg/kg as in BLISS-LN).[17,67] It was assumed that all patients receive belimumab as intravenous administration, as in the BLISS-LN trial.

Assuming a standard deviation of 10 kg around the mean weight, including drug wastage resulted in mean dose of 690 mg in the base-case analysis. This mean dose was multiplied by the unit cost ($46.84 per 10 mg) to get the cost per dose of $3,198. An additional administration cost of $72.18 was added for each administration of belimumab (assuming all patients receive belimumab as intravenous administration as in the BLISS-LN trial). In the first month for belimumab, the costs included three doses to reflect the treatment schedule for belimumab in the BLISS-LN trial, resulting in belimumab treatment costs of $9,811 for the first month. Beyond the first month, the cost per dose was multiplied by the average number of monthly doses over a three-year period, based on dosage from the BLISS-LN trial (one dose each 28 days), to estimate the monthly cost of belimumab as $3,560.

Voclosporin costs were assessed considering the average daily dose of 39.1mg (mean dose weighted to the duration of patients in AURORA trial) and the price per wallet (containing 60 capsules 7.9mg each) of $3,950 reported by the manufacturer. The mean discount of 22.5% was used to calculate the net price for voclosporin.

Table E8. Drug Cost Inputs

Interventions	Administration		ASP* per 10mg	WAC per mg‡	Mean Monthly Drug Cost
Belimumab, Vials	$72.18	$46.84	$4.26	$4.52	$3,560‡
Voclosporin	-	-	-	-	$7,686.10§

*Average sales price (ASP) + 6% markup

‡ WAC provided by the GSK

‡For belimumab, mean monthly costs are based on weight distribution in population (mean weight 65.92 kg).

§For voclosporin, mean monthly costs are based on average monthly dose of 39.1mg, price per wallet of $3,950 reported by the manufacturer, and 22.5% discount rate. .

Costs of Health States

A review of the literature identified multiple sources on costs of LN; however, there were no sources reporting costs split out for being in the AD, CR, and PR model states. The modeling approach considered here used data from the literature sources in combination with expert opinion to yield the most appropriate real-world costs estimation.

The base-case analysis estimated the costs for each health state using total mean all-cause health care costs (medical and pharmacy costs) per LN patient per year as a starting point, then applying cost ratios between the different health states.

The mean all-cause health care costs per LN patient per year were reported as $45,469 in 2018 by Bartels-Peculis et al.(2020) based on data on 1,039 LN patients (median age, 47 years; 83% female) recorded in a health care claims database.[35] This claims database covers members in all 50 states in the US and Washington, DC, including approximately 10 million commercial members and 2.4 million Medicare Advantage members.

The costs of being in AD, CR, and PR were calculated as the following. First, the cost of the ESRD state was calculated using relationships between costs for patients with ESRD and without ESRD, compared to overall LN costs. These ratios were estimated as 1.95 and 0.69 respectively from Li et al. (2009).[37] Then the costs of being in AD, CR, and PR were calculated from the proportional costs of ESRD and different eGFR states reported by Barber et al. (2019). Although their eGFR categories do not correspond exactly with the definitions of response states in the model, clinical experts suggested that the cost ratios for ESRD and eGFR states retrieved from the Systemic Lupus International Collaborating Clinics (SLICC) inception cohort are a reasonable approximation.[28,36] As such, it was assumed that costs in eGFR >60 ml/min are equal to those in CR (=0.075*ESRD costs), eGFR 30-60 ml/min to PR (=0.078*ESRD costs), and eGFR < 30 ml/min to AD (=0.406*ESRD costs). The calculated costs of each state in the model, inflated to 2019, are reported in Table E9.

Considering that patients in ESRD state qualify for Medicare coverage, cost in ESRD state then was calculated as costs of people with LN, eligible for Medicare in 2016 based on ESRD alone or in combination with disability.

Table E9. Costs of Each Model State*

State	Annual Costs, US$
Complete response	$7,871
Partial response	$8,185
Active disease	$42,510
ESRD	$120,920

*Costs are inflated to 2019values

Costs of Steroids

A reduction in costs related to lower steroid drug cost use was assigned to each model state in the short-term model, using price data from the Redbook.[30] It was calculated that the mean annual cost of oral prednisone with dose of 10 mg/day is $169; the cost of 5 mg/day and 2.5 mg/day were assumed to be one-half and one-quarter of the 10 mg/day cost, respectively.

Indirect Costs

Indirect costs included costs of unemployment, absenteeism (temporary productivity loss), and caregiving. The costs of absenteeism were estimated from data specific to LN patients, while the other costs were estimated from similar populations, as described below.

In the absence of data on US indirect costs for each LN state (CR, PR, AD, and ESRD), data on patient unemployment and productivity loss associated with caregiving were retrieved from a study of the societal economic burden of autosomal dominant polycystic kidney disease (ADPKD) in the US in 2018 (Table E8).[68] Considering that eGFR level is an indicator of kidney function, based on clinical advice we assumed that CKD 1-3 (eGFR ≥30 ml/min) corresponds to the CR/PR states in the model and CKD 4-5 (eGFR < 30 ml/min) to the AD state in the model.

We assessed the unemployment rate related to LN by subtracting from the unemployment to population ratio in each health state (CR, PR, AD, ESRD) the unemployment to population ratio in the US, based on data from Cloutier et al. (2020).

The cost of absenteeism because of LN symptoms was assigned to the proportion of the employed population, applying data from a six-month longitudinal survey of SLE patients in the US.[69] Garris et al. (2013) reported the work hours missed weekly due to SLE by severity of symptoms (assessed as self-perceived disease activity). We estimated these costs assuming that patients in the CR/PR state

have mild symptoms, patients in AD state have moderate symptoms, and patients in ESRD state have severe symptoms.

The costs of caregiving were calculated using the data reported by Cloutier et al. (2020), estimating on average 3.1, 27.0, and 46.7 hours of caregiving annually for patients with CKD stages 1-3 (assumed equal to CR/PR), CKD stages 4-5 (assumed equal to AD), and ESRD, respectively.[68] In addition, the incremental direct health care costs associated with caregiving were also included in the costs of caregiving.

The indirect costs were calculated by multiplying the time on unemployment, absenteeism among those who are employed, and time spent caregiving, with the mean earnings (estimated as weighted average of the proportions of men and women in Davidson et al., and their respective wages extracted from data from the Bureau of Labor Statistics 2020[70]) and adding the additional health care costs associated with caregiving. The estimated indirect costs are presented in Table E10. The model considered productivity losses for population up to the retirement age and costs of caregiving for the population lifetime.

Table E10. Indirect Costs (Societal Perspective) Estimated Using Median Earnings

Annual Mean Costs*	Values		
	CR/PR	AD	ESRD
Unemployment Cost	$3,199	$11,220	$19,623
Absenteeism Costs	$1,766	$2,764	$3,038
Productivity Loss and Additional Direct Health Care Costs Associated with Caregiving	$175	$793	$1,496
Total Indirect Costs	$5,140	$14,777	$24,157

CR: complete response, PR: partial response, AD: active disease, ESRD: end state renal disease
*2020 data.

Description of evLYG Calculations

The cost per evLYG considers any extension of life at the same "weight" no matter what treatment is being evaluated. Below are the stepwise calculations used to derive the evLYG.

1. First, we attribute a utility of 0.851, the age- and gender-adjusted utility of the general population in the US that are considered healthy.[71]

2. For each cycle (Cycle I) in the model where using the intervention results in additional years of life gained, we multiply this general population utility with the additional life years gained (ΔLYG).

3. We sum the product of the life years and average utility (cumulative LYs/cumulative QALYs) for Cycle I in the comparator arm with the value derived in Step 2 to derive the equal value of life years (evLY) for that cycle.

4. If no life years were gained using the intervention versus the comparator, we use the conventional utility estimate for that Cycle I.

5. The total evLY is then calculated as the cumulative sum of QALYs gained using the above calculations for each arm.

6. We use the same calculations in the comparator arm to derive its evLY.

Finally, the evLYG is the incremental difference in evLY between the intervention and the comparator arms.

E3. Results

Tables E11 and E12 present the base-case results from the health care sector perspective. Table E11 presents the results for belimumab, while Table E12 presents the results for voclosporin.

The total costs in the belimumab arm were approximately $930,000 , which is higher than the total costs in the standard care arm of around $886,000. However, the belimumab arm has higher QALYs, LYs and evLYGs (11.67 QALYs, 17.86 LYs, and 11.74 evLYGs respectively) compared to the standard care arm (11.18 QALYs, 17.48 LYs, and 11.18 evLYGs respectively). This resulted in an incremental cost per QALY gained of approximately $90,000, an incremental cost per LY gained of $114,000 for belimumab compared to standard care, and incremental cost per evLYG of approximately $78,000.

Table E11. Discounted Base-Case Results for Belimumab versus Standard Care: Health Care Sector Perspective

	Intervention Costs, $	Total Costs, $	QALYs	LYs	evLYG
Belimumab	$93,465	$929,962	11.666	17.861	11.740
Standard Care	-	$886,343	11.180	17.478	11.180
Belimumab vs. Standard Care	Incremental Costs, $		Incremental QALYs	Incremental LYs	Incremental evLYG
	$43,620		0.49	0.38	0.56
Belimumab vs. Standard Care			Cost per QALY Gained, $	Cost per Life Year Gained, $	Cost per evLYG, $
			$89,663	$113,847	$77,835

The total costs in the voclosporin arm were approximately $929,000, which is higher than the total costs in the standard care arm of around $784,000. However, the voclosporin arm has higher QALYs, LYs and evLYGs (12.64 QALYs, 18.41 LYs, and 12.77 evLYGs respectively) compared to the standard care arm (11.67 QALYs, 17.58 LYs, and 11.67 evLYGs respectively). This resulted in an incremental cost per QALY gained of approximately $149,000 an incremental cost per LY gained of $174,000 for voclosporin compared to standard care, and incremental cost per evLYG of approximately $132,000.

Table E12. Discounted Base-Case Results for Voclosporin versus Standard Care: Health Care Sector Perspective

	Treatment Costs, $	Total Costs, $	QALYs	LYs	evLYG
Voclosporin	$215,296	$928,486	12.640	18.408	12.770
Standard Care	-	$784,416	11.674	17.581	11.674
Voclosporin vs. Standard Care	Incremental Costs, $		Incremental QALYs	Incremental LYs	Incremental evLYG
	$144,070		0.97	0.83	1.10
Voclosporin vs. Standard Care			Cost per QALY Gained, $	Cost per Life Year Gained, $	Cost per evLYG, $
			$149,260	$174,250	$131,528

Results from Undiscounted Analysis

Tables E13 and E14 present the undiscounted base-case results from the health care sector perspective for belimumab and voclosporin, respectively.

Table E13. Base-Case Undiscounted Results for Belimumab versus Standard Care: Health Care Sector Perspective

	Treatment Costs, $	Non-Treatment Health Care Costs, $	Total Costs, $	QALYs	LYs	evLYG	Incremental Results		
							Cost/QALY Gained, $	Cost/LY Gained, $	Cost/evLYG, $
Belimumab	$96,443	$1,627,622	$ 1,724,065	18.307	28.677	18.443	$43,079	$48,858	$36,545
Standard Care	-	$1,691,480	$1,691,480	17.551	28.010	17.551	-	-	-

Table E14. Base-Case Undiscounted Results for Voclosporin versus Standard Care: Health Care Sector Perspective

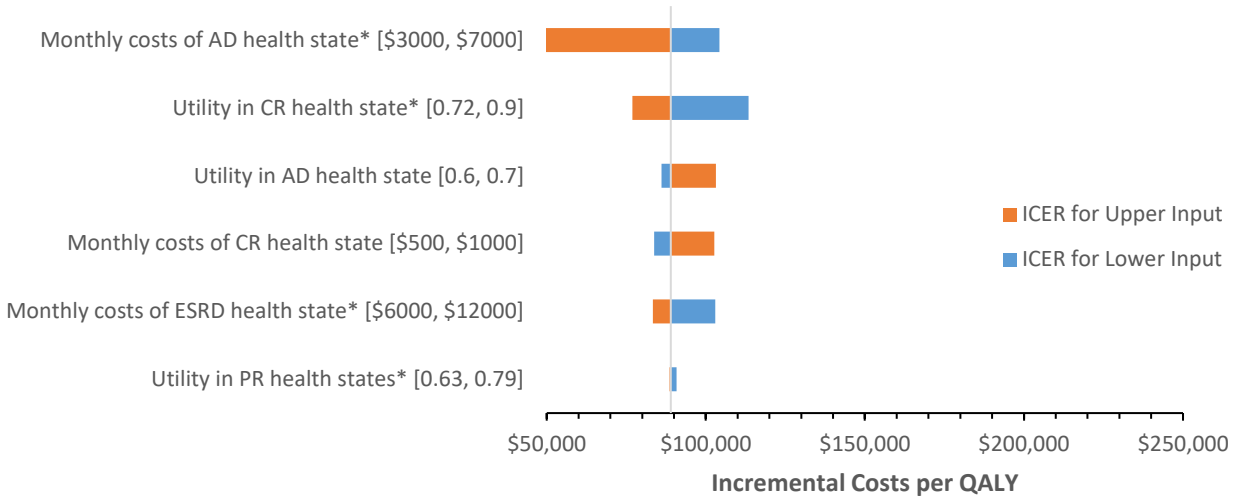
	Treatment Costs, $	Non-Treatment Health Care Costs, $	Total Costs, $	QALYs	LYs	evLYG	Incremental Results		
							Cost/QALY Gained, $	Cost/LY Gained, $	Cost/evLYG, $
Voclosporin	$223,549	$1,459,278	$1,682,827	19.694	29.623	19.933	$92,255	$98,563	$79,420
Standard Care	-	$1,546,212	$1,546,212	18.213	28.237	18.213	-	-	-

E4. Sensitivity Analyses

Sensitivity Analyses Results for Belimumab

To demonstrate effects of uncertainty on both costs and health outcomes, we varied input parameters using available measures of parameter uncertainty (i.e., standard errors) or reasonable ranges to evaluate changes in cost per additional QALY. For the belimumab versus standard care comparison, the results of sensitivity analyses demonstrate high certainty in cost effectiveness of this treatment (Figure E4 and Table E15).

Figure E4. Tornado Diagram for One-Way Sensitivity Analyses of Belimumab versus Standard Care



*Lower input corresponds to higher incremental cost-effectiveness ratio and vice versa.

Table E15. Tornado Diagram Inputs and Results for One-Way Sensitivity Analyses of Belimumab versus Standard Care

Input Name	Lower ICER	Upper ICER	Lower Input	Upper Input
Utility in PR health states* [0.63, 0.79]	$90,766	$88,589	0.63	0.79
Monthly costs of ESRD health state* [$6000, $12000]	$103,025	$83,359	$6,000	$12,000
Monthly costs of CR health state [$500, $1000]	$83,759	$102,691	$500	$1,000
Utility in AD health state [0.6, 0.7]	$86,106	$103,155	0.6	0.7
Utility in CR health state* [0.72, 0.9]	$113,403	$76,975	0.72	0.9
Monthly costs of AD health state* [$3000, $7000]	$104,283	$-3,515	$3,000	$7,000

*Lower input corresponds to higher incremental cost-effectiveness ratio and vice versa.

Table E16 presents the results of the probabilistic sensitivity analysis (PSA). Due to the lack of data for many inputs, the distributions used for costs and utilities in the PSA are mean values ±10%.

Table E16. Results of Probabilistic Sensitivity Analysis for Belimumab versus Standard Care

	Belimumab		Standard Care		Incremental	
	Mean	Credible Range	Mean	Credible Range	Mean	Credible Range
Total						
Total Costs	$934,663	($896,233, $973,093)	$ 886,305	($845,508, $927,103)	$48,357	($23,007, $73,708)
Total QALYs	11.700	(11.310, 12.089)	11.192	(10.795,11.589)	0.51	(0.30,0.71)
ICER	-	-	-	-	$95,269	($90,106, $100,371)

Figure E5 presents cost-effectiveness clouds (i.e., the scatterplot of costs vs. QALYs) from the probabilistic sensitivity analysis (PSA) for belimumab and standard care.

Figure E5. Cost-Effectiveness Clouds for Belimumab and Standard Care

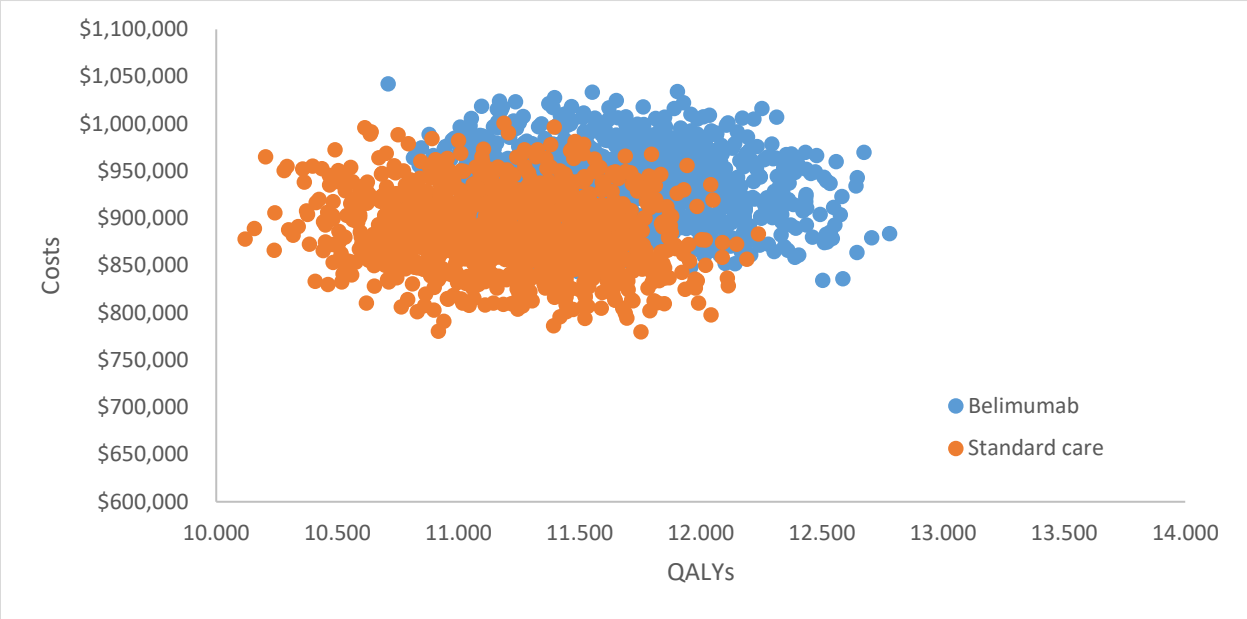
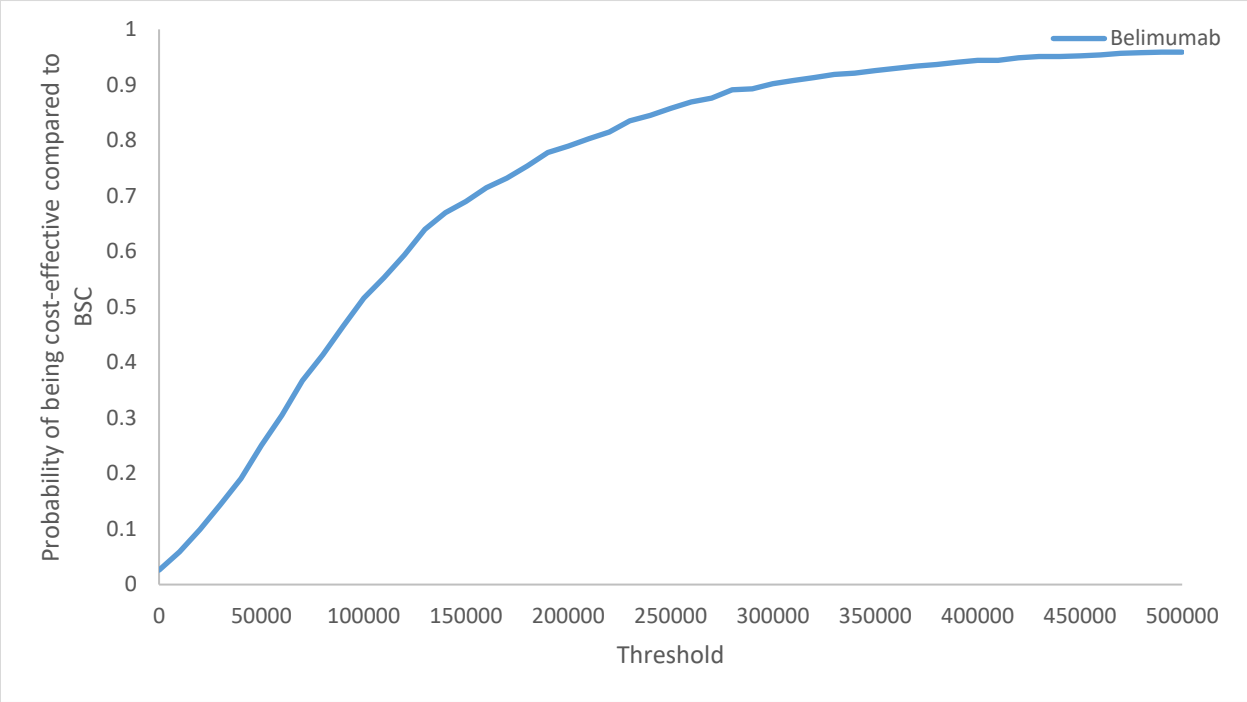


Figure E6 below presents the cost-effectiveness acceptability curve for belimumab versus standard care. At a threshold of $50,000/QALY, belimumab had 25% chance of being cost-effective, a 52% chance of being cost-effective at a threshold of $100,000/QALY and a 69% chance of being cost-effective at a threshold of $150,000/QALY.

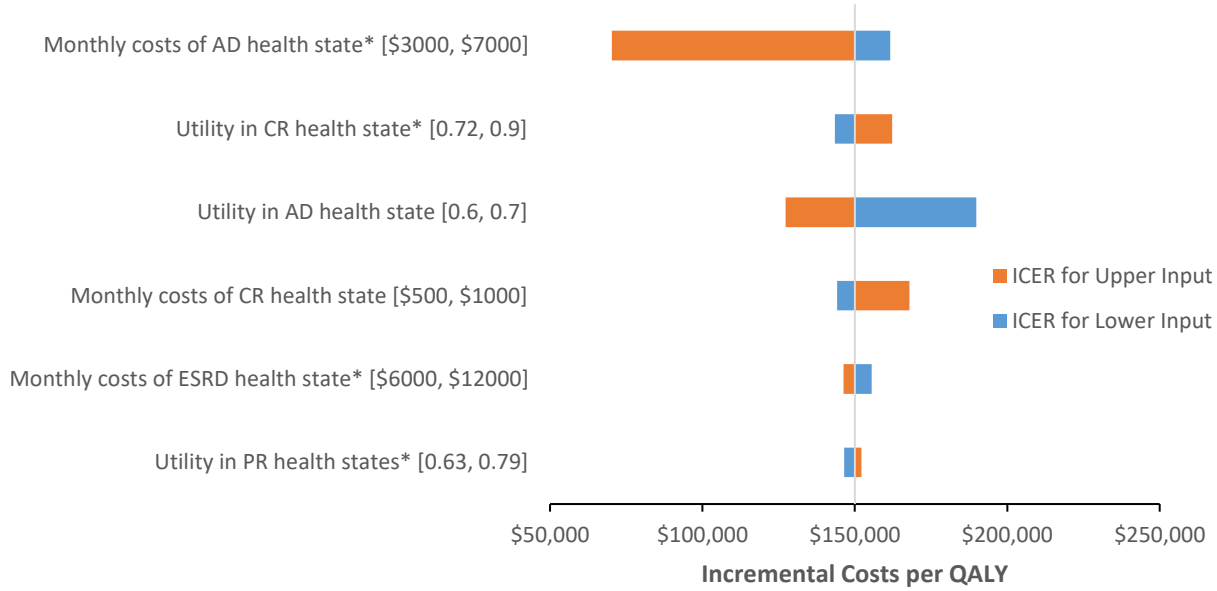
Figure E6. Cost-Effectiveness Acceptability Curve for Belimumab versus Standard Care



Sensitivity Analyses Results for Voclosporin

To demonstrate effects of uncertainty on both costs and health outcomes, we varied input parameters using available measures of parameter uncertainty (i.e., standard errors) or reasonable ranges to evaluate changes in cost per additional QALY. For the voclosporin versus standard care comparison, key drivers of uncertainty included monthly costs and utility values in the CR and AD health states (Figure E7 and Table E17).

Figure E7. Tornado Diagram for One-Way Sensitivity Analyses of Voclosporin versus Standard Care



*Lower input corresponds to higher incremental cost-effectiveness ratio and vice versa.

Table E17. Tornado Diagram Inputs and Results for One-Way Sensitivity Analyses of Voclosporin versus Standard Care

Input Name	Lower ICER	Upper ICER	Lower Input	Upper Input
Utility in PR health states* [0.63, 0.79]	$146,446	$152,177	0.63	0.79
Monthly costs of ESRD health state* [$6000, $12000]	$155,550	$146,293	$6,000	$12,000
Monthly costs of CR health state [$500, $1000]	$144,203	$167,907	0.72	0.9
Utility in AD health state [0.6, 0.7]	$189,881	$127,235	0.6	0.7
Utility in CR health state* [0.72, 0.9]	$143,404	$162,185	$500	$1,000
Monthly costs of AD health state* [$3000, $7000]	$161,649	$70,306	$3,000	$5,000

*Lower input corresponds to higher incremental cost-effectiveness ratio and vice versa.

Table E18 presents the results of the probabilistic sensitivity analysis (PSA). Due to the lack of data, the distributions used for costs and utilities in the PSA are mean values ±10%.

Table E18. Results of Probabilistic Sensitivity Analysis for Voclosporin versus Standard Care

	Voclosporin		Standard Care		Incremental	
	Mean	Credible Range	Mean	Credible Range	Mean	Credible Range
Total Costs	$ 928,107	($895,716, $960,498)	$783,688	($746,628, $820,748)	$ 144,419	($121,013, $167,826)
Total QALYs	12.641	(12.252, 13.029)	11.680	(11.309, 12.051)	0.96	(0.76, 1.16)
ICER	-	-	-	-	$ 150,334	($145,690, $154,958)

Figure E8 presents cost-effectiveness clouds (i.e., the scatterplot of costs versus QALYs) from the probabilistic sensitivity analysis (PSA) for voclosporin and standard care. Due to the lack of data, the distributions used for costs and utilities in the PSA are mean values ±10%.

Figure E8. Cost-Effectiveness Clouds for Voclosporin and Standard Care

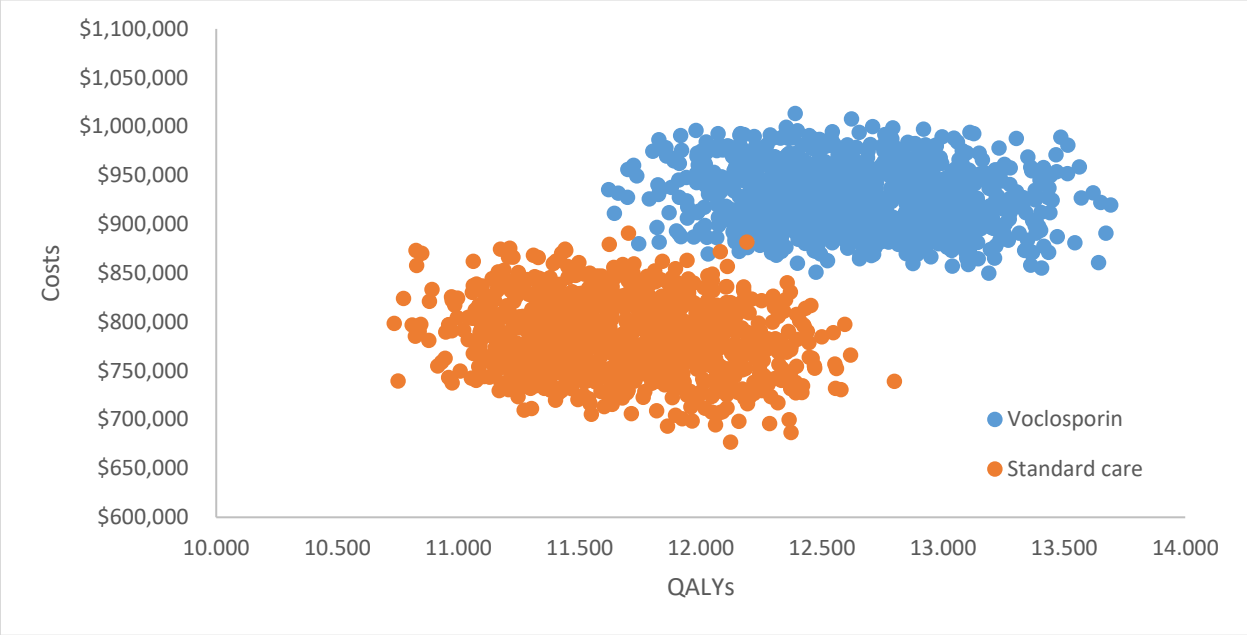
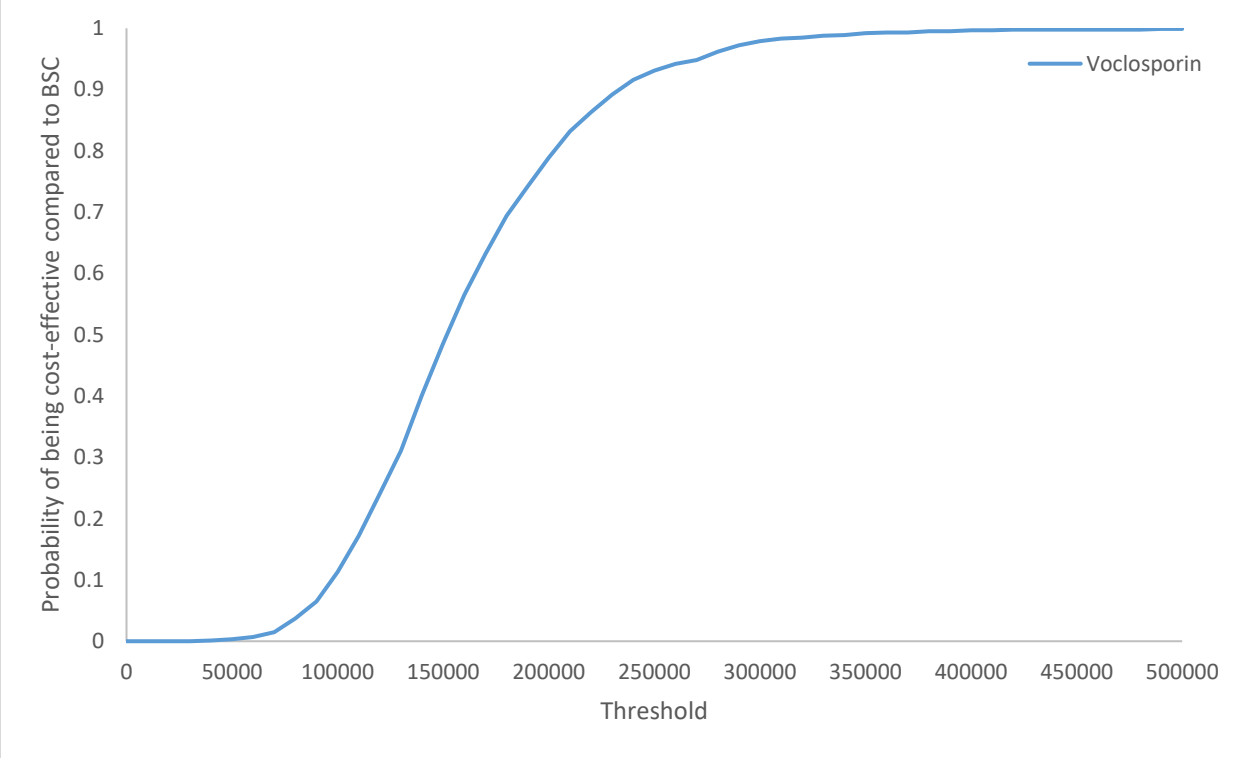


Figure E9 below presents the cost-effectiveness acceptability curve for voclosporin versus standard care. At a threshold of $50,000/QALY, voclosporin had 0.3% chance of being cost-effective, a 11.3% chance of being cost-effective at threshold of $100,000/QALY and a 48.6% chance of being cost-effective at threshold of $150,000/QALY.

Figure E9. Cost-Effectiveness Acceptability Curve for Voclosporin versus Standard Care



E5. Scenario Analyses

We performed scenario analyses to identify the effect of alternative inputs and assumptions on the cost-effectiveness results.

Tables E19 and E20 present the results from a scenario analysis taking a modified societal perspective, which includes costs of unemployment, absenteeism (temporary productivity loss), and caregiving, along with patient QALYs, LYs, and health care costs. Table E19 presents the results for belimumab, while Table E20 presents the results for voclosporin.

Table E19. Base-Case Results for Belimumab versus Standard Care: Modified Societal Perspective

	Total Costs, $	QALYs	LYs	evLYG	Incremental Results		
					Cost/QALY Gained, $	Cost/LY Gained, $	Cost/evLYG, $
Belimumab	$1,126,351	11.666	17.861	11.740	$66,103	$83,933	$57,383
Standard Care	$1,094,193	11.180	17.478	11.180	-	-	-

Table E20. Base-Case Results for Voclosporin versus Standard Care: Modified Societal Perspective

	Total Costs, $	QALYs	LYs	evLYG	Incremental Results		
					Cost/QALY Gained, $	Cost/LY Gained, $	Cost/evLYG, $
Voclosporin	$1,095,833	12.640	18.408	12.770	$131,962	$154,055	$116,285
Standard Care	$968,460	11.674	17.581	11.674	-	-	-

Table E21 and E22 present the results from a scenario analysis utilising CR rates in Black population in BLISS-LN and AURORA trials. Table E21 presents the results for belimumab, while Table E22 presents the results for voclosporin.

Table E21. Scenario Analysis Results Assuming CR Rate Specific to Black population in BLISS-LN Trial

	Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	evLYG	Incremental Results		
							Cost/QALY Gained	Cost/LY Gained	Cost/evLYG
Belimumab	$87,884	$891,396	979,280	11.243	17.585	11.305	$156,093	$187,230	$132,893
Standard Care	-	$924,124	$924,124	10.890	17.290	10.890		-	-

Table E22. Scenario Analysis Results Assuming CR Rate Specific to Black Population in AURORA Trial

	Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	evLYG	Incremental Results		
							Cost/QALY Gained	Cost/LY Gained	Cost/evLYG
Voclosporin	$215,296	$713,045	$928,341	12.681	18.408	12.809	$129,250	$173,633	$115,869
Standard Care	-	$784,781	$784,781	11.570	17.581	11.570		-	-

Tables E23 and E24 present the results from a scenario analysis assuming lower survival (of 25.22 years overall survival and 14.49 years ESRD-free survival) in the CR and PR states. These scenario analyses were thought to be useful in case the clinical experts believe that long-term survival for those achieving response might not be as optimistic as assumed in the model. Table E23 presents the results for belimumab, while Table E24 presents the results for voclosporin.

Table E23. Scenario Analysis Results Assuming Lower Survival in CR/PR Health States for Belimumab versus Standard Care: Health Care Perspective

	Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	evLYG	Incremental Results		
							Cost/QALY Gained	Cost/LY Gained	Cost/evLYG
Belimumab	$93,465	$888,150	$981,615	10.991	17.221	11.036	$170,113	$233,207	$149,514
Standard Care	-	$926,225	$926,225	10.665	16.983	10.665	-	-	-

Table E24. Scenario Analysis Results Assuming Lower Survival in CR/PR Health States for Voclosporin versus Standard Care: Health Care Perspective

	Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	evLYG	Incremental Results		
							Cost/QALY Gained	Cost/LY Gained	Cost/evLYG
Voclosporin	$215,296	$789,086	$1,004,382	11.649	17.466	11.739	$237,389	$281,114	$210,105
Standard Care	-	$840,567	$840,567	10.959	16.884	10.959	-	-	-

Tables E25 and E26 present the results from a scenario analysis assuming lower utilities (of 0.72 and 0.64, respectively) in the CR and PR states. These scenario analyses were thought to be useful in case the clinical experts believe that long term QoL for those achieving response might not be as high as assumed in the model.[34,33] Scenario analyses were performed using Table E25 presents the results for belimumab, while Table E26 presents the results for voclosporin.

Table E25. Scenario Analysis Results Assuming Lower Utilities in CR and PR Health States for Belimumab versus Standard Care: Health Care Perspective

	Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	evLYG	Incremental Results		
							Cost/QALY Gained	Cost/LY Gained	Cost/evLYG
Belimumab	$93,465	$836,497	929,962	11.212	17.861	11.298	$114,948	113,847	$93,770
Standard Care	-	$886,343	886,343	10.833	17.478	10.833	-	-	-

Table E26. Scenario Analysis Results Assuming Lower Utilities in CR and PR Health States for Voclosporin versus Standard Care: Health Care Perspective

	Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	evLYG	Incremental Results		
							Cost/QALY Gained	Cost/LY Gained	Cost/evLYG
Voclosporin	$215,296	$713,190	$928,486	11.959	18.408	12.126	$185,904	$174,250	$152,969
Standard Care	-	$784,416	$784,416	11.184	17.581	11.184	-	-	-

Tables E27 and E28 present the results from scenario analyses assuming longer duration of AD state among those patients who progressed to ESRD and had a relapse in the long-term model. The scenario analyses were performed to address the concern of clinical experts that the time patients with relapse remain in AD state before progressing to ESRD may be longer than in the base-case analysis. Table E27 presents the results for belimumab, while Table E28 presents the results for voclosporin.

Table E27. Scenario Analysis Results Assuming Longer Duration of AD State for Patients with Relapse who Progressed to ESRD: Belimumab

	Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	evLYG	Incremental Results		
							Cost/QALY Gained	Cost/LY Gained	Cost/evLYG
AD duration: 2 years									
Belimumab	$93,465	$838,812	$932,278	11.525	17.861	11.599	$97,156	$115,221	$83,560
Standard Care	-	$888,132	$888,132	11.071	17.478	11.070	-	-	-
AD duration: 3 years									
Belimumab	$93,465	$841,729	$935,194	11.347	17.861	11.421	$108,245	$116,951	$91,843
Standard Care	-	$890,385	$890,385	10.933	17.478	10.933	-	-	-
AD duration: 5 years									
Belimumab	$93,465	$847,561	$941,026	10.992	17.861	11.065	$138,501	$120,412	$113,345
Standard Care	-	$894,891	$894,891	10.658	17.478	10.658	-	-	-

Table E28. Scenario Analysis Results Assuming Longer Duration of AD State for Patients with Relapse who Progressed to ESRD: Voclosporin

	Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	evLYG	Incremental Results		
							Cost/QALY Gained	Cost/LY Gained	Cost/evLYG
AD duration: 2 years									
Voclosporin	$215,296	$716,593	$931,889	12.432	18.408	12.562	$159,038	$175,317	$139,168
Standard Care	-	$786,936	$786,936	11.521	17.581	11.521	-	-	-
AD duration: 3 years									
Voclosporin	$215,296	$720,878	$936,174	12.171	18.408	12.301	$173,127	$176,661	$149,992
Standard Care	-	$790,111	$790,111	11.327	17.581	11.327	-	-	-
AD duration: 5 years									
Voclosporin	$215,296	$729,448	$944,744	11.648	18.408	11.778	$209,393	$179,349	$176,888
Standard Care	-	$796,459	$796,459	10.940	17.581	10.940	-	-	-

E6. Heterogeneity and Subgroups

It is likely that LN progression will differ by ethnicity,[72] and modeling using SLICC data which considered ethnicity was our preferred approach. However, the manufacturers did not provide the requested data that would have allowed us to implement this modeling approach. As such, the model did not consider differing probabilities of disease progression by ethnicity. The scenario analysis considered complete response rate in Black population according to BLISS-LN and AURORA trials data; however, because of the substantial limitations of these data, these results should be considered with extreme caution.

The cost values in the long-term model were independent of ethnicity. The distribution of patients in Medicaid by ethnicity shows a higher percentage of Black than White population.[37,73] This would result in differences in health state costs by ethnic sub-group because Medicaid costs differ from costs on private insurance.[73] To avoid the potential ethical implications of valuing health states differently for certain groups, the analysis assumed average costs independent of ethnicity.

The model also did not consider utility values of health states by ethnicity. Studies on general populations and ethnic subgroups show that socio-economic status is a significant determinant of the quality of life.[38,39] Since race/ethnicity and income are strongly correlated,[40] using ethnicity-specific utilities could result in lower utility values for Black (compared to White) patients in the CR state, while similar utilities for Black and White population in the ESRD state.[63] This could result in worse cost-effectiveness findings in Black versus White populations, independent of the treatment effectiveness among these groups. Thus, only general (not ethnicity-specific) utility values were used in the study, so as to avoid potentially disadvantaging ethnic groups with lower utility values.

E7. Model Validation

Several approaches were undertaken to verify and validate the model. Model verification followed standard practices in the field. We tested all mathematical functions in the model to ensure they were consistent with the report (and supplemental materials). Model input parameters were varied to evaluate the face validity of changes in results. We also conducted sensitivity analyses with null input values to ensure the model was producing findings consistent with expectations. Further, independent modelers tested the mathematical functions in the model as well as the specific inputs and corresponding outputs.

For model validation, preliminary methods and results were presented to manufacturers, patient groups, and clinical experts, with data inputs changed as needed and scenario analyses defined. As part of ICER's initiative for modeling transparency, we shared the model with interested manufacturers for external verification shortly after publishing the draft report for this review. The

outputs from the model were validated against the trial and study data of the interventions as well as any relevant observational datasets.

Model validation was also conducted in terms of comparisons to other model findings. We searched the literature to identify models that were similar to our analysis, with comparable populations, settings, perspective, and treatments. Our model results were compared to other cost-effectiveness models in this therapy area.

Prior Economic Models

Three models compared cost effectiveness of alternative drug regimens for LN patients in the past ten years (Table E27).[9,34,74] All three identified models (one for US and two for Asian countries) used the response/remission structure to reflect the disease progression. None of the models evaluated the cost effectiveness of either belimumab or voclosporin, with Kim et al. (2019) assessing cost effectiveness of tacrolimus, while Mohara et al. (2014) and Nee et al. (2015) assessed the cost effectiveness of multiple standard regiments of LN treatment. Only Kim et al. (2019) provided the definitions of the outcomes used, which were defined according to the 2012 Clinical Practice Guideline on Glomerular Diseases.[74]

None of the previous models considered ethnical diversity of the LN population, with the other US model by Nee et al. (2015) modeling the population reflecting demographic and ethnicity in trials (i.e. underrepresented Black population).[9] The study of Davidson et al. (2018) applied in this modeling, gives an advantage of more accurate representation of ethnicity in LN population in the US.

While Nee et al. (2015) used life-time horizon to calculate the costs, only therapy costs incurred during the first 3-years were considered in the analysis.[9] The other model with the lifetime horizon, by Kim et al. (2019), included the cost of maintenance treatment until the patient relapsed.[74] These assumptions differ from the current model assuming that (a) even if progressed, patients would not stop the standard treatment (rather would change the treatment scheme), and (b) chronic LN condition would require patients to have standard therapy over their lifetime.

Two Asian models used comparable utility values to this model.[34,74] Nee et al. (2015) combined utility values from sources of different origin and applying different measurement scales, as a result the utility value of patients on dialysis (ESRD) in Nee's et al. model was higher than the utility value of the relapse state (0.67 versus 0.60). To accurately reflect an impact of LN development on quality of life (i.e., a more advanced state has lower utility values), this model used adjustment to utility values instead of combining the utility values from multiple sources.

The previous cost-effectiveness models predicted accumulating 9.4-9.7,[34] 11.3-11.5,[74] and 14.2-15.10 QALYs for patients treated with standard therapies in comparison to 11.2 – 11.7 QALYs on standard treatment predicted by this model. The difference between this and the other US model can be explained by the approach to utility values described above.

The prior cost-effectiveness models predicted total costs for patients on standard treatment (converted to USD inflated to 2019 values) in the ranges $48-121k,[74] $174-180k,[34] and $669-677k.[9] The total lifetime costs on the standard care in this model were equal to $784-886k. Considering that the US model of Nee et al. (2015) applied maintenance costs only for three years, the predictions of the two models may be considered comparable.

Table E27. Comparison of the Modeling Studies in Lupus Nephritis

First Author (Year)	Country	Model Type	States	Definitions	Compared Therapies	Population	Horizon Cycle Length Discount	Utility Sources and Values
Kim et al.[74] (2019)	China	Induction phase: decision tree Maintenance phase: Markov model	AD (start), CR, PR, ESRD, kidney transplant, post-kidney transplant	CR: return of serum creatinine to baseline, plus a decline in UPCR to <500 mg/g PR: stabilization (±25%) or improvement of serum creatinine, but not to the baseline, plus a ≥50% decrease in UPCR	9 scenarios for induction and maintenance therapies	(1) patients with focal or diffuse proliferative LN (Class III-V) (2) mean age at baseline – 18y	(1) 20 y (2) 3 m (3) 3%	EQ-5D from Mohara et al.: CR – 0.940, PR – 0.850, AD – 0.764, ESRD – 0.689
Mohara et al.[34] (2013)	Thailand	Markov model	AD (start), CR, PR, ESRD, death	No definitions	Baseline (i.v. CYC → i.v. CYC) + 3 comparators for induction and maintenance therapies (CYC → AZA, i.v. CYC → MMF and MMF → low-dose MMF)	(1) Newly diagnosed active severe LN patients (2) mean age at baseline – 40y	(1) Lifetime (2) 6m for the Y1 and 12m afterward (3) 3%	Measured EQ-5D (216 patients) : CR – 0.940, PR – 0.850, AD – 0.764, ESRD – 0.689
Nee et al.[9] (2015)	US	Markov model	Remission (start), relapse requiring MMF, relapse requiring CYC, ESRD, death	No definitions	3-year maintenance regimens (MMF vs. AZA) [assumed patients do not need immunosuppressive agents after this time]	(1) patients with proliferative LN (2) range 20-40 y (reflecting demographic/ ethnicity in trials)	(1) Lifetime (2) 12m (3) 3%	VAS from a Dutch reference: remission – 0.70, relapse – 0.6; TTO ESRD – 0.67

First Author (Year)	Country	Model Type	States	Definitions	Compared Therapies	Population	Horizon Cycle Length Discount	Utility Sources and Values
ICER model	US	Trial-based and partitioned-survival model	AD (start), CR, PR, ESRD, death	CR: UPCR <0.5, eGFR no worse than 10% below pre-flare value or ≥90 ml/min/1.73 m2with no use of rescue therapy. PR: GFR no worse than 10% below baseline or within normal range and at least 50% decrease in UPCR with UPCR <1.0 if baseline ratio ≤3.0, or UPCR <3.0 if baseline ratio >3.0; no treatment failure; and not CR.	Belimumab vs. standard therapy; Voclosporin vs. standard therapy	(1) Newly diagnosed LN patients (2) mean age at baseline – 35y.	(1) Lifetime (2) 1m (3) 3%	EQ-5D score in Swedish population; an impact of disease severity on EQ-5D is adjusted using Mohara et al. data: CR – 0.8, PR – 0.71, AD – 0.624, ESRD – 0.549

States: AD: Active disease; CR: Complete remission; PR: partial remission; ESRD: End-stage renal disease; **Treatments**: AZA: Azathioprine; CYC: cyclophosphamide; MMF: mycophenolate mofetil; **Other abbreviations:** eGFR: glomerular filtration rate (assessment of renal function); ICER: incremental cost-effectiveness ratio; LE: lupus erythematosus; LN: lupus nephritis; TTO – time trade-off, QALY: quality-adjusted life-years.

F. Potential Other Benefits and Contextual Considerations

QALY Shortfalls

One important contextual consideration to consider is the argument that society should give preference to treatments for patients with more severe conditions,[75] and that giving priority to treatments according to "lifetime burden of illness" or "need" best represents the ethical instincts of a society or other decision-makers.[76,77] To inform this contextual consideration, ICER provides empirical results for the absolute QALY shortfall and proportional QALY shortfall. The absolute QALY shortfall is defined as the total absolute amount of future health patients with a condition are expected to lose without the treatment that is being assessed.[78] The ethical consequences of using absolute QALY shortfall to prioritize treatments is that conditions that cause early death or that have very serious lifelong effects on quality of life receive the greatest prioritization. Thus, certain kinds of treatments, such as treatments for rapidly fatal conditions of children, or for lifelong disabling conditions, score highest on the scale of absolute QALY shortfall.

The proportional QALY shortfall is measured by calculating the proportion of the total QALYs of remaining life expectancy that would be lost due to untreated illness.[79,80] The proportional QALY shortfall reflects the ethical instinct to prioritize treatments for patients whose illness would rob them of a large percentage of their expected remaining lifetime. As with absolute QALY shortfall, rapidly fatal conditions of childhood have high proportional QALY shortfalls, but the highest numbers can also often arise from severe conditions among the elderly who may have only a few years left of average life expectancy but would lose much of that to the illness without treatment.

For this population of adults with SLE and Class III, IV, or V LN, the absolute shortfall was estimated to be 21.2 QALYs, with a proportional shortfall of 0.55, representing a loss of 55% of total quality-adjusted life expectancy (QALE) relative to individuals without the condition. To provide some anchoring of these results, we also present a league table of absolute and proportional QALY shortfalls for a variety of conditions from prior ICER reports (Table F1), using a burden of disease calculator developed by Dutch investigators (https://imta.shinyapps.io/iDBC/) that allows for calculation of absolute and proportional QALY shortfalls under different assumptions.[77]

Table F1. League Table of Absolute and Proportional QALY Shortfalls for Selected Conditions

	From ICER Reports			From iDBC tool[81]	
Condition	Age	% Male	Total Undiscounted QALYs with Standard of Care	Absolute Shortfall	Proportional Shortfall
SLE with Class III, IV, or V LN	35	9	17.5	21.2	0.55
Cystic Fibrosis	2	52	25.8	42.3	0.62
Secondary Progressive Multiple Sclerosis	48	39	3.0	24.5	0.89
Hemophilia A	18	100	38.6	13.3	0.26
Treatment-Resistant Major Depression	46	33	20.5	8.7	0.30
Moderate-to-Severe Ulcerative Colitis	40	59	27.4	6.2	0.19
BCG-Unresponsive High-Risk NMIBC	72	80	4.9	5.7	0.54

QALY: quality-adjusted life year

G. Potential Budget Impact: Supplemental Information

Table G1. Cumulative Net Cost Per Patient Treated with Belimumab or Voclosporin at Net Prices Over a Five-Year Time Horizon

	Belimumab		Voclosporin	
Year	Additional Costs per Year (Non-Cumulative)	Cumulative Cost	Additional Costs per Year (Non-Cumulative)	Cumulative Cost
Year 1	$47,223	$47,223	$87,153	$87,153
Year 2	$26,511	$73,734	$69,084	$156,237
Year 3	$13,779	$87,513	$51,828	$208,065
Year 4	-$3,918	$83,595	-$5,408	$202,657
Year 5	-$3,990	$79,605	-$5,522	$197,135