

Summary

KEY FINDINGS

	Belimumab (Benlysta®, GlaxoSmithKline)	Voclosporin (Lupkynis™, Aurinia Pharmaceuticals)
Evidence Rating	B+	B+
Estimated Annual Price	\$43,000	\$92,000
Annual Health-Benefit Price Benchmark	\$45,000- \$61,000	\$72,000- \$101,000
Change from Annual Price Required to Reach Threshold Price	None	None

“Lupus nephritis is a serious chronic disease, one that has a disproportionately large impact on Black, Hispanic, and other communities of color in the US. Both belimumab and voclosporin are important new treatment options. Despite remaining uncertainty about both treatments’ longer-term outcomes, their estimated net prices appear to be aligned with their anticipated clinical benefits. More research is needed to confirm these benefits, but for patients and clinicians to have responsibly priced options specifically indicated for lupus nephritis is a win for patients and the entire health system. One policy element that was discussed at the public meeting, however, is worth attention. Aurinia sought and achieved a late-stage patent on voclosporin’s dosing protocol. This unusual patent will likely deny patients access to a more affordable generic version of the treatment until 2037 – a full 10 years beyond what was previously expected. If extended patents through dosing algorithms becomes a new trend, we could see future budget headroom shrink for other innovative products, while patients and the entire health system struggle even more with affordability.”

– ICER President, **Steven D. Pearson, MD, MSc**

THEMES AND RECOMMENDATIONS

- All stakeholders have a responsibility and an important role to play in ensuring that effective new treatment options for patients with lupus nephritis are introduced in a way that will help reduce health inequities.
- Both belimumab and voclosporin are judged to be priced in reasonable alignment with estimates of their benefits for patients, and this consideration should guide payers to design coverage criteria that do not narrow coverage from the FDA label, although coverage criteria may define terms left indeterminate in the FDA label to assure appropriate use.
- Manufacturers should commit to expanding their research, both before and after regulatory approval, to include adequate representation of patients with lupus nephritis from Black and other non-white populations.
- Manufacturers should not seek to use common sense dosing algorithms as a tool to gain prolongation of their patents, thereby adding to future health care affordability concerns and reducing the headroom for future innovative therapies.
- Specialty societies should work with regulators to standardize the primary outcome used in future pivotal trials of therapies for lupus nephritis.
- Specialty societies should update their guidelines to include guidance on appropriate use of belimumab and voclosporin and commit the resources to update guidelines more frequently as evidence evolves.
- Priority should be given to developing biomarkers that can guide the choice of therapy in lupus nephritis.
- Larger observational studies describing the long-term outcome following both complete and partial response are needed.

Clinical Analyses

KEY CLINICAL BENEFITS STUDIED IN CLINICAL TRIALS

Systemic lupus erythematosus (SLE) is an autoimmune disease that affects between 300,000 and 1.5 million Americans. 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. LN typically presents in patients who are 20 to 40 years old, 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 1. 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.

Clinical Analyses

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 2 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 2. Evidence Ratings

	Belimumab + MMF/ Corticosteroids or Cyclophosphamide/ Corticosteroids	Voclosporin+ MMF/ Corticosteroids
Comparator	MMF/Corticosteroids or Cyclophosphamide/ Corticosteroids	MMF/ Corticosteroids
Evidence Rating	B+: Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit	B+: Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit

Economic Analyses

LONG-TERM COST EFFECTIVENESS

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.

Economic Analyses

Scenario Analyses

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.

POTENTIAL OTHER BENEFITS AND CONTEXTUAL CONSIDERATIONS

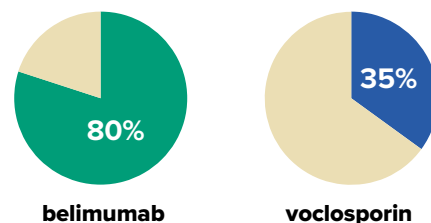
There are other potential benefits and contextual considerations not fully captured in the economic model. These include potentially greater benefits of these therapies for Black patients, the high lifetime burden of illness of LN, the early age of onset of the disease, and the lack of FDA approved therapies 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.

VOTING RESULTS

The New England CEPAC's voting results from the March 26, 2021 public meeting aligned with the results summarized above. The CEPAC Council unanimously voted that the evidence was adequate to demonstrate that both belimumab and voclosporin, each when added to standard induction therapy, offered a net health benefit when compared to standard induction therapy alone. The majority of the Council assigned a high priority to the magnitude of lifetime impact for patients with LN as an important contextual consideration for policymakers as they make judgments about long-term value for money for these therapies. Finally, the majority of the Council judged belimumab to provide a "high" long-term value for money and voclosporin to provide an "intermediate" long-term value for money, at current pricing.

POTENTIAL BUDGET IMPACT

At their net prices, approximately 80% (belimumab) and 35% (voclosporin) of eligible patients with LN could be treated in a given year before crossing the ICER potential budget impact threshold of \$819 million per year. Testimony from clinical experts at the public meeting suggested that the ideal clinical uptake of these drugs would include the chance for nearly every patient to be on one drug or the other. Given that efforts to reach this clinical target would create a short-term potential budget impact that exceeds the threshold, ICER is issuing an access and affordability alert.



Percent of eligible patients with LN that could be treated in a given year before crossing the ICER potential budget impact threshold

Conclusions

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.

About ICER

The Institute for Clinical and Economic Review ([ICER](https://www.icer.org)) is an independent nonprofit research institute that produces reports analyzing the evidence on the effectiveness and value of drugs and other medical services. ICER's reports include evidence-based calculations of prices for new drugs that accurately reflect the degree of improvement expected in long-term patient outcomes, while also highlighting price levels that might contribute to unaffordable short-term cost growth for the overall health care system.

ICER's reports incorporate extensive input from all stakeholders and are the subject of public hearings through three core programs: the California Technology Assessment Forum ([CTAF](https://www.ctaf.org)), the Midwest Comparative Effectiveness Public Advisory Council ([Midwest CEPAC](https://www.midwestcepac.org)) and the New England Comparative Effectiveness Public Advisory Council ([New England CEPAC](https://www.newenglandcepac.org)). These independent panels review ICER's reports at public meetings to deliberate on the evidence and develop recommendations for how patients, clinicians, insurers, and policymakers can improve the quality and value of health care.

For more information about ICER, please visit ICER's website (www.icer.org).