SUPPLEMENTAL MATERIAL

The Cost Effectiveness of Belimumab and Voclosporin for Patients with Lupus Nephritis in the United States

CONTENTS

Supplemental Box 1. Institute of Clinical and Economic Review Lupus Nephritis process and stakeholders engaged

Project milestones and associated public-facing documents	**Stakeholder Engagement and Consultation Throughout**
Draft and Final Scope	Patients, families, clinicians and payers American College of Rheumatology National Kidney Foundation Aurinia, GlaxoSmithKline Black Women's Health Imperative Lupus and Allied Diseases Association Lupus Foundation of America Lupus Research Alliance Kaiser Permanente
Clinical Evidence Systematic Review	
Health Economic Model Analysis Plan	
Draft and Revised Evidence Report	
Roundtable Discussion and Key Policy Implications	

https://icer.org/our-approach/methods-process/patient-engagement/

Supplemental Table 1. Assumptions of Short-Term and Long-Term Modeling

Our model includes several key assumptions stated below.

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.
Long term volcosporin therapy is not associated with deleterious effects on kidney function	Volcosporin is a calcinurin inhibitor, which have been associated with renal fibrosis in a range of settings. Long-term data on voclosporin and its impact on kidney function is not available.
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 until the end of 3 years.
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 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]
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.

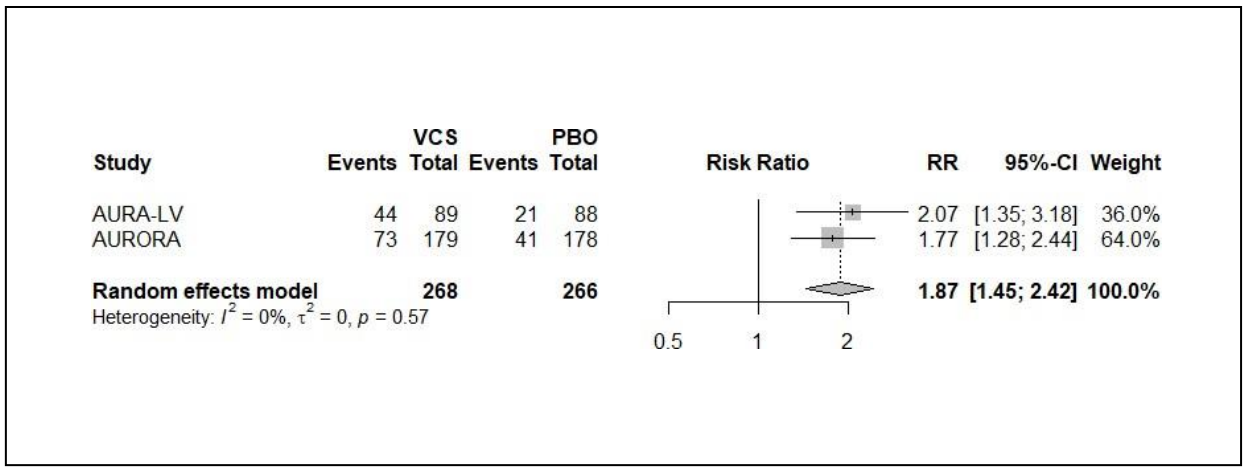
Supplemental Text. Detailed research methods

Model parameters

Short term model

In the short-term model, the proportion of patients who remain in complete response (CR), partial response (PR), active disease (AD), and end-stage renal disease (ESRD) were calculated by the linear interpolation of data from the clinical trials. Only one trial (BLISS-LN) evaluating efficacy of belimumab in LN population was identified[1]. The proportions of patients reaching complete response in the BLISS-LN trial[1] were extracted from the digitized curve which reports the proportions of patients achieving complete response over time. The proportions of patients reaching partial response, 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. Two trials assessing the efficacy of voclosporin treatment (AURA-IV and AURORA) were identified. We evaluated the feasibility of conducting a quantitative synthesis by exploring the differences in the study populations, study design, analytic methods, and outcome assessments for each outcome of interest in the trials. Based on data availability, we conducted random-effects pairwise meta-analyses on the proportion of patients achieving complete response at 52 weeks for low dose voclosporin versus placebo using the two randomized trials (see Supplemental Figure 1). The AURA-LV trial did not report partial response and death at 52 weeks; as such, we did not conduct a meta-analysis on these outcomes. Instead, we used data only from the AURORA trial to estimate these outcomes. For the meta-analysis on complete response, we calculated risk ratios and the respective 95% CIs (see Supplemental Figure 1) using the Mantel–Haenszel method. The expected proportion of patients (Supplemental Table 2 experiencing complete response at 52 weeks was calculated using the risk ratio generated from the meta-analysis by anchoring to the average placebo effect observed across the trials. We assessed heterogeneity using the Cochran Q test and the I^2 statistic. Meta-analysis was performed using R software.

Supplemental Figure 1. Results of meta-analysis for Complete Renal Response (Voclosporin compared to Placebo plus Standard Care



VCS: voclosporin; PBO: placebo (plus standard care); RR: Risk Ratio

Supplemental Table 2. Outcomes from trials on belimumab and voclosporin

Arm	Time	Complete Renal Response, %	Partial Renal Response, %	ESRD, %	Death, %	Source
Belimumab	104 weeks	30.0	17.5	0.0	0.4	BLISS-LN trial[1]
Placebo in belimumab trial		19.7	17.0	0.4	0.9	
Voclosporin	52 weeks	43.2	26.6	0.0	0.6	Meta-analysis of AURORA and AURA-IV trials
Placebo in voclosporin trials		23.0	28.7	0.0	2.8	

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 m^2 with 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.

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 m^2 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.

Treatment duration

Considering the plausibility that both 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 Supplemental Table 2) 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 adverse events 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

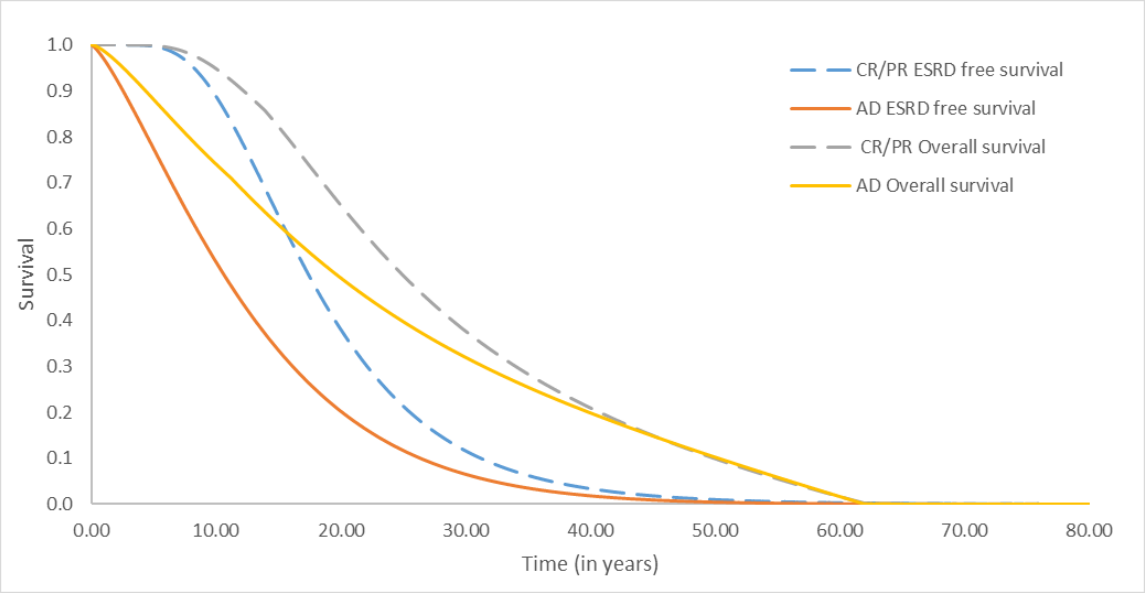
The choice of data for long-term extrapolation was based on the best available evidence, considering publication date, representativeness to the US population, and the duration of the follow-up. The long-term probability of remaining alive without ESRD, conditional on being in complete response, partial response, active disease health states at the end of the trials, was modeled by fitting survival curves to

the digitized published Kaplan-Meier data from Davidson *et al.* (2018).[2] We used the probability to remain without ESRD or death defined by mBLISS-LN criteria since this definition is closer than others to those used in BLISS-LN and AURORA trials.[1 3-5] Because of the substantial overlap in the survival curves for patients remaining in complete and partial responses reported by Davidson *et al.* (2018), [2] patients in these states were assumed to have the same ESRD-free survival.

The characteristics of the cohort used in the Davidson *et al.* (2018) [2] 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.[6] 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 Kaplan-Meier curves were truncated to the last meaningful event: 3.8 years for active disease and 9 years for response curves.

The individual data were reconstructed using the methods described in Guyot et al. (2012).[7] 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 and Bayesian information criteria, and clinical plausibility. For each health state, a single parametric distribution was selected to calculate the proportion of the cohort remaining alive without ESRD each year. Given that multiple parametric distributions fitted the observed data similarly, clinical plausibility was the key factor in determining the selection of the parametric distributions for extrapolation: Weibull distribution for active disease and lognormal for response states (Supplemental Figure 2).

Supplemental Figure 2. Survival Curves Used in the Long-Term Extrapolation Model



While progression from response to the active disease state were not modeled explicitly, it was assumed that patients spend a certain amount of time in the active disease state (defined as eGFR < 30 ml/min and equal to 1.206 years) before progressing to ESRD, based on the Systemic Lupus International Collaborating Clinics data.[8] 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 response or active disease states at the end of the

short-term model and not the treatment received.

Mortality

The monthly probability of death in the short-term model was estimated from interpolation of the trial data. In the long term model, the probability of deaths over time in the response and active disease health states was estimated based on the digitized published Kaplan-Meier data from Chen et al.(2008) which reports both ESRD-free survival and overall survival (in contrast to Davidson et al reporting ESRD-free survival only).[9] Beyond the last observation in the Kaplan-Meier 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) to ensure clinical plausibility of the analysis. 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).[2]

The predictions on mortality in the LN population in treatment response and active disease states were validated by clinical experts. Since ESRD progression was assumed to be similar in partial and complete response groups,[2] the ESRD free survival and overall survival also assumed to be the same for these states. In the response health state, the mean ESRD-free survival is 19.38 years and the mean overall survival is 28.13 years, while in the active disease health state, mean ESRD-free survival is 12.98 years and the mean overall survival is 23.65 years.

Utilities

Health state utilities used in the model were derived from published literature. No US-specific preference-based utility values for LN states (treatment response and active disease), reflecting the total health utility and measured on zero to one (or zero to 100) scales, were found in the literature. Given the potential for other complications from underlying SLE, it was assumed implausible for utility values of complete response state to be as high as those in general population of similar ages. 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 complete response were assumed to be the same as for individuals who scored 0-9 points on Systemic Lupus Activity Questionnaire (0.8±0.16) in a cohort of 182 Swedish patients.[10] Additionally, all utilities were capped at the general population utility for that age group, to ensure they did not exceed the utilities of the general population.

We estimated the utility values for patients in the partial response, active disease, and ESRD states by applying utility decrements compared to the complete response state. A cost-utility analysis of alternative drug regimens for newly diagnosed severe LN patients in Thailand[11] reported utility values of 0.94 for complete response, 0.85 for partial response, 0.764 for active disease, 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 complete response state. The calculated utility values are reported in Supplemental Table 3.

Considering that multiple (including international) sources were used to assess utility values, we assessed their plausibility by comparing to other literature. 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[12] 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].[13]

An incremental gain in utilities related to low-dose steroid and no steroid use was included in the short-term model upon the consultations with patients and clinical experts. Considering that belimumab and voclosporin trials reported steroid use heterogeneously, different strategies to add utility increments were applied. 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.[1] 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. The value of utility increment related to low-dose steroid use 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.[10] In addition, an increment in EQ-5D utility for no steroid use, from the same study, was applied (Supplemental Table 3).

Treatment Costs

Average sales price 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).[1 14] 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 (1 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. With the mean discount of 22.5%, the net price for voclosporin resulted in $7,686.

Health state costs

No literature sources reporting costs split out for being in the complete response, partial response, and active disease model states were identified. Thus, 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.[15] 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 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).[16]

The costs of being in complete response, partial response, and active disease were calculated from the proportional costs of ESRD and different eGFR states reported by Barber et al. (2019)[17]. 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.[8 18] As such, it was assumed that costs in eGFR >60 ml/min are equal to those in CR, eGFR 30-60 ml/min to PR, and eGFR < 30 ml/min to AD. 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. The calculated costs of each state in the model, inflated to 2019, are reported in Supplemental Table 3.

Supplemental Table 3. Key Model Inputs

Parameter	Input	Source
Utilities in model states		
Utility in CR health state	0.8	Bexelius et al.[10]
Utility in PR health state	0.71	Bexelius et al., Mohara et al.[11,10]
Utility in AD health state	0.624	
Utility in ESRD health state	0.549	
Steroid-related utility increase		
Increment in utilities for low-dose steroids	Utility value + 0.025	Cooper *et al* [13]
Increment in utilities for treatments with no steroids	Utility value + 0.09	Cooper *et al* [13]
Drug costs		
Belimumab cost in first month	$9,811*	ASP, WAC, FSS[19-21]
Monthly cost of Belimumab	$3,560*	ASP, WAC, FSS[19-21]
Monthly cost of Voclosporin	$3,204	Assumption
Costs in model states		
Annual cost in CR health state	$7,871	Bartels-Peculis et al.[15]
Annual cost in PR health state	$8,185	Barber et al.[8 18]
Annual cost in AD health state	$42,510	Li et al.[16]
Annual cost in ESRD health state	$104,685	
Steroid-related cost reduction		
Annual cost reduction with low-dose steroids	$84.5	Redbook.[19]
Annual cost reduction with no steroids	$126.8	Redbook.[19]

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

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.[19] 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 (Supplemental Table 4). 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 (complete response, partial response, active disease, 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.[22] Considering that eGFR level is an indicator of kidney function, 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 active disease state in the model.

We assessed the unemployment rate related to LN by subtracting from the unemployment to population ratio in each health state (complete response, partial response, active disease, and ESRD) the unemployment to population ratio in the US, based on data from Cloutier et al. (2020)[22]. 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.[23] Garris et al. (2013) reported the work hours missed weekly due to SLE by severity of symptoms (assessed as self-perceived disease activity)[23]. We estimated these costs assuming that patients in the response state have mild symptoms, patients in active disease 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 patients in treatment response state), CKD stages 4-5 (assumed equal to be equal to patients in active disease state), and ESRD, respectively.[22] 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[24]) and adding the additional health care costs associated with caregiving. The estimated indirect costs are presented in Supplemental Table 4. The model considered productivity losses for population up to the retirement age and costs of caregiving for the population lifetime.

Supplemental Table 4. Indirect Costs (Societal Perspective) Estimated Using Median Earnings

Annual Mean Costs*	**Values**		
	CR/PR	**AD**	**ESRD**
Unemployment	$3,199	$11,220	$19,623
Absenteeism	$1,766	$2,764	$3,038
Productivity	$175	$793	$1,496
Total	$5,140	$14,777	$24,157

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

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