AMERICAN COLLEGE of RHEUMATOLOGY
Empowering Rheumatology Professionals

Empowering rheumatology professionals to excel in their specialty

1800 M Street, NW • Suite 740S • Washington, DC 20036
Phone: (404) 633-3777 • Fax (404) 633-1870 • www.rheumatology.org

September 21, 2020

Catherine Koola
Program Manager
Institute for Clinical and Economic Review
Two Liberty Square
Ninth Floor
Boston, MA 02109

Submitted electronically

RE: Voclosporin and Belimumab for Lupus Nephritis Draft Background and Scope

Dear Ms. Koola,

The American College of Rheumatology (ACR), representing over 7,700 rheumatologists and rheumatology interprofessional team members, appreciates the opportunity to provide comments on the Institute for Clinical and Economic Review's (ICER) lupus nephritis (LN) draft background and scoping document.

ACR appreciates ICER's mission of evaluating the clinical and economic value of medical treatments as this type of research has the potential to powerfully inform physician and patient decisions about the relative merits of one treatment compared to another. While comparative effectiveness research (CER) can assist in informed medical decision making, it must not prevent or hinder a patient from accessing the most medically appropriate treatment. ACR notes that the treatments being assessed for LN have not received final approval from the Food and Drug Administration (FDA). Therefore, there is limited real-world data on the prescribing patterns and economic impact of these treatments. Recognizing the limited available data, we offer the following comments on the draft scoping document.

Background
ACR recognizes that ICER is still completing the literature review on the burden of disease of lupus nephritis. However, we urge ICER to add more up-to-date references to be more relevant in today's healthcare environment. Expressly, we submit the articles outlined in the appendix as applicable and appropriate for the review process. These references highlight the frequency and outcome of LN, an updated review of the accepted treatment approaches for patients with LN, and a review of the utilization rates of underserved populations for the treatment of end-stage renal disease with the incident of LN. It is imperative that ICER includes the most current and relevant research to be considered during the CER project. Without these studies, we fear the analysis will be incomplete.

Stakeholders
ACR commends ICER for its outreach to patient groups during the initial development of the scoping document, as outlined in the document. These groups have vital information and perspective on the burden of disease, and the quality of life measurement is critical to

determining the value of a treatment. Additionally, ACR appreciates the opportunity to be a valuable resource during the finalization of the scoping document and subsequent review and analysis. Rheumatologists and members of the rheumatology interprofessional team have significant insight into the treatment and care for patients with LN. We urge ICER to include our nephrology colleagues in these discussions as both specialties offer the most accurate clinical perspective for treating patients with LN.

Underserved populations
ACR appreciates the efforts of ICER in considering the underserved patient population in their analysis. In addition to examining the burden of disease and treatment options for rural areas, we encourage ICER to explore underserved and underrepresented populations in urban areas. While these populations have better access to care, patients in urban areas are faced with unique challenges in accessing care throughout their course of treatment. [1] Due to these access issues, we fear these populations will not be adequately factored into the overall CER analysis.

Scope of clinical evidence
While we understand ICER's rationale in conducting their analysis to coincide with the upcoming approval of voclosporin and belimumab, we remain concerned that this critical analysis will be based solely on data from the clinical trials. It is our understanding that most of the data used for analysis will be derived from the Phase III clinical trials of these treatments. While we are encouraged that ICER will use registry data from patient organizations on patient-reported outcomes, we question if using only clinical trial data provides a thorough assessment of the overall value of these treatments. In several sections, the document notes that portions of the analysis will occur "data permitting." We understand ICER is in the initial stages of this project. However, we urge complete transparency on the availability and limitations of all data used for analysis. Where appropriate, we encourage ICER to utilize historical comparisons given the extensive data available in LN studies with mycophenolate and cyclophosphamide.

Comparators
ICER aims to compare voclosporin and belimumab to each other and standard therapy. We note that this comparison will rely on two separate studies for two new therapeutics, but no head-to-head or real world data compares the new therapeutics to each other. In addition to analyzing these two studies, we urge ICER also to consider trends in the standard of care arm of the analysis, including flares, ESRD, need for steroid rescue, dropouts or treatment failures, and deaths. This information will better highlight the performance of the new therapies.

Outcomes
Categorization
We note that the first bullet in this section is focused on clinical outcomes and does not reflect the patients' concerns other than to avoid renal failure. Instead, we recommend ICER rename the first bullet to reflect the primary clinical outcome and rename the second bullet secondary

[1] Yazdany J et al. Quality of care for incident lupus nephritis among Medicaid beneficiaries in the United States. Arthritis Care Res (Hoboken). 2014 Apr;66(4):617-24. doi: 10.1002/acr.22182.

clinical outcomes. Finally, we recommend that the document include a third bullet solely dedicated to patient-important outcomes. While we recognize there may be overlap between these categories, it is essential to highlight what the patient wants as an acceptable outcome per the Patient-Centered for Outcomes Research Institute (PCORI) model. [2]

Clinical outcomes
Standardizing definitions and versions of measures are vital for an objective analysis. We note that there are varying definitions of complete and partial renal response. We urge ICER to reconcile these variations to ensure a standard definition is used during analysis. Additionally, ACR has a concern regarding disease activity measures. Specifically, we note that the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) and the British Isles Lupus Assessment Group (BILAG) has several versions. If these measures are to be used, the versions used must be consistent and transparent throughout the process. Lastly, we note the absence of steroid-sparing as a critical consideration as both patients and providers want to limit cumulative steroid exposure. We urge ICER to include steroid-sparing in its clinical outcomes analysis and final report.

Potential Other Benefits and Contextual Considerations
Recognizing the objective is to identify the overall cost and clinical outcomes for voclosporin and belimumab, we urge ICER to consider additional components of the burden of disease. This may include medication adherence, incorporating other lifestyle changes, transportation, child or elder care, the impact of caregivers, and work missed due to the disease. Without considering these components of managing LN, ICER's analysis will be incomplete.

ACR strongly supports ICER's efforts to better identify and quantify value in our healthcare system. However, this information cannot be used to hinder access to the most medically appropriate treatment. ACR welcomes the opportunity to serve as a resource throughout this process and appreciates the chance to contribute to the early stages of the project. Please contact Amanda Grimm Wiegrefe, Director of Regulatory Affairs, at awiegrefe@rheumatology.or should you have any questions or need clarification.

Sincerely,

Ellen M. Gravallese, MD
President, American College of Rheumatology

[2] Patient-Centered Outcomes Research. (2020, January 28). Retrieved September 17, 2020, from https://www.pcori.org/research-results/about-our-research/patient-centered-outcomes-research

APPENDIX

Articles for Inclusion in Background Section

Feldman CH et al. Sex Differences in Health Care Utilization, End-Stage Renal Disease, and Mortality Among Medicaid Beneficiaries With Incident Lupus Nephritis. Arthritis Rheumatol. 2018 Mar;70(3):417-426. doi: 10.1002/art.40392.

Hanly JG et al. The Frequency and Outcome of Lupus Nephritis. Results from an international inception cohort study. Rheumatol (Oxford). 2016;55(2):252-62. doi: 10.1093/rheumatology/kev311. PubMed PMID: 26342222; PMCID: PMC4939728.

Hanly JG, et al. A Longitudinal Analysis of Outcomes of Lupus Nephritis in an International Inception Cohort Using a Multistate Model Approach. Arthritis Rheumatol 2016;68(8):1932-44. doi: 10.1002/art.39674. PubMed PMID: 26991067; PMCID: PMC5858760.

Parikh SV et al. Update on Lupus Nephritis: Core Curriculum 2020. Am J Kidney Dis. 2020 Aug;76(2):265-281. doi: 10.1053/j.ajkd.2019.10.017.

Aurinia

September 21, 2020

Steven D. Pearson, MD, MSc, FRCP
President, Institute for Clinical and Economic Review
One State Street, Suite 1050
Boston, MA 02109 USA

RE: Draft Scoping for LN Assessment

Dear Dr. Pearson:

Aurinia welcomes the opportunity to comment on ICER's *Draft Background and Scoping Document for its 2020 Lupus Nephritis (LN) Assessment.* Although LN is a rare disease, it is a serious and common complication of SLE with considerable unmet medical need. Approximately 10-30% of patients with LN progress to end-stage renal disease (ESRD) within 15 years of diagnosis.[1,2] There are no FDA approved treatments for LN and the outcomes with off label options continue to be disappointing. The key LN treatment goal is rapid reduction in proteinuria which is highly predictive of long-term preservation of kidney function.[3] The current standard of care (SoC), mycophenolate mofetil (MMF) or IV cyclophosphamide (CYC) + glucocorticoids is disappointing in its ability to achieve this goal. Furthermore, a fairly high steroid dose is commonly used to treat LN (*e.g.*, prednisone 1mg/kg/po daily as starting dose). Glucocorticoids have a well characterized side effect profile adversely affecting nearly every organ system and directly related to overall glucocorticoid exposure.

LN adds to disparity of minority health care burden (above Systemic Lupus Erythematosus (SLE) alone).[4,5] ICER's assessment should strive to capture the value of LN treatment to women and minorities. 70% of all LN patients are people of color, broken down as: 47.9% African American, 15.2% Hispanic, 6.3% Asian, and 1.5% Native American.[6] Additionally, SLE affects women nine times as frequently as men and specifically for LN, prevalence is observed to be 4 times higher for women. LN disproportionally impacts young women of childbearing age at the peak of their productivity and when their maternal contribution is essential to supporting their families.[7,8]

LN treatment is predicated on rapid reduction of proteinuria to prevent kidney damage that may result in ESRD while minimizing treatment related adverse events. Voclosporin used with MMF and a rapid steroid taper has demonstrated early (statistical significance at 6 months for renal response) and meaningful declines (to Urine Protein to Creatinine Ratio (UPCR) ≤0.5 mg/mg) in proteinuria in two pivotal LN trials vs. MMF and steroids alone. We have carefully reviewed ICER's draft scope assessment of voclosporin in LN and have the following recommendations:

RECOMMENDATIONS FOR THIS ASSESSMENT

1. ICER's assessment should reflect the equity value that the therapies being evaluated bring to LN patients.

- **ICER's assessment should capture the stark differences in patient population outcomes in LN**. Black and Hispanic SLE patients tend to develop LN earlier and have poorer outcomes,

including death and development of ESRD, when compared to white patients.[9,10,11] With African Americans representing nearly half of the LN population, this is of particular concern. Notably, voclosporin's treatment effect is preserved in Hispanic and non-Hispanic populations,[12] Asian, White, Black, and Mixed race (as shown in Figure 1, in the Appendix).

- **The quality-adjusted life year (QALY), an interchangeable unit of health proposed for this assessment, discriminates against LN patients because even at full improvement, these patients numerically only represent a portion of a healthy person**. The baseline for patients with SLE without LN, disadvantages LN patients because they can never return to "full health" and so the QALY automatically deprioritizes any treatment improvement's value compared to people without LN.

- **QALYs for LN are not inclusive of non-white populations.** QALYs are neither representative, useful, nor predictive of the value of new treatments for 70% of non-white patients who suffer from LN. All LN studies that derive interchangeable measurements of health states have either measured these from majority Caucasian populations or do not specify race or ethnicity. The two most commonly used studies for LN QALYs derive the QALY from a population composed of 76% Caucasian patients, when as mentioned above, the LN population is 70% non-white (See Table 1, Appendix).[13,14,15]

- **Current LN QALY measured patient "health states" do not correlate with patient health.** LN studies that attempt to measure health states and convert these into a QALY, show an inconsistent correlation to a patient's state of health. This is a troubling finding as it means that when a patient's health is deteriorating, the QALY could be pointing to a patient feeling better. This implies that in a cost-effectiveness analysis, drugs that lead to a faster deterioration of health could be "valued" higher not as a reflection of quality of life but due to a methodological problem in how patient health has been measured (See Table 2, Appendix).

2. **ICER's Clinical Evidence Review and Comparative Value Analysis should center on proteinuria: this is well accepted as the primary diagnostic test for LN and changes in proteinuria are widely accepted as the primary means of monitoring disease and assessing long-term outcome.**[16,17,18]

- **Persistent proteinuria in LN leads to kidney disease progression and ESRD.** Since 2015, the Kidney Disease Improving Global Outcomes (KDIGO) Practice Guidelines for Glomerulonephritis[19] for the treatment of LN state that proteinuria is the most important biomarker for LN. It is widely accepted that reduction in proteinuria correlates to favorable long-term renal outcomes.[20,21,22,23,24,25] The last two decades of research in nephrology have yielded substantial evidence that proteinuria may accelerate kidney disease progression.[26] As ICER models LN, it should consider that LN damages the kidneys and is associated with an increased risk of kidney failure.[27,28] Patients with class IV lupus nephritis have been shown in one study to have the greatest risk of ESRD, with a 15-year risk of 44%.[29] Achieving a UPCR less than 0.5 mg/mg is a key predictor of renal survival, which should be reflected in ICER's model.[30] Clinical trials have consistently shown a reno-protective effect when proteinuria is reduced.[31,32,33,34]

- **Rapidly reducing proteinuria in LN is fundamental to changing the course of disease:** Rapid reduction of proteinuria is associated with positive long-term outcomes.[35] Since a single episode of LN can dramatically shorten the lifespan of kidneys by decades, early treatment is critical.[36,37,38] In AURORA, voclosporin patients achieved 50% reductions in UPCR, approximately twice as fast as patients in the control arm.[39]

- **ICER should assess how early in the course of disease proteinuria is reduced in patients and not restrict evaluation to a single, pre-specified point in time such as one year.** With each passing week, uncontrolled LN patients continue to lose irreplaceable nephrons.

- **UPCR ≤ 0.5 mg/mg is commonly used to initially detect LN, not ≤ 0.8 mg/mg:** Furthermore, the KDIGO guideline treatment goal is a UPCR ≤ 0.5 mg/mg. Therefore, we strongly recommend ICER's comparative evaluations use the more stringent criteria of a UPCR ≤ 0.5 mg/mg.

- **Given the mechanism of action of calcineurin inhibitors (CNIs), changes in estimated glomerular filtration rate (eGFR) are an irrelevant metric over one year in assessing kidney health:** an early decline, followed by a stable eGFR, in the presence of a CNI is not indicative of nephron damage but reflects reversible vasoconstriction of the afferent arteriole.

- **ICER's analysis should focus on parameters specific to the management of LN:** changes in inflammatory markers used primarily as surrogates for SLE such as dsDNA and antinuclear antibodies (ANA) are of limited diagnostic and prognostic utility in LN.

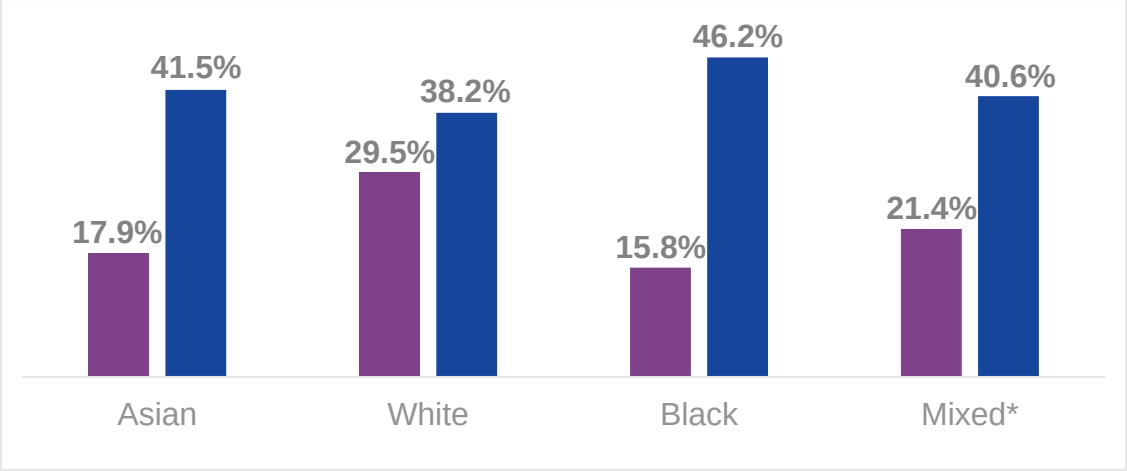
3. ICER should model LN according to the model structure that reflects active disease, complete renal response, partial renal response, ESRD, and death.

- **Modelling LN on the basis of eGFR is not predictive of outcome**. As ICER models LN, it should consider that LN damages the kidneys and is associated with a 44-fold increased risk of kidney failure.[40,41] Of the two models that ICER has suggested as possible model structures for LN, the option with a structure based on health states of active disease, complete renal response , partial renal response , ESRD, and death is reflective of real-world conditions using proteinuria as a predictor of outcome.[42,43,44,45] Model health states based on eGFR are not predictive of outcomes in LN and would not be appropriate due to the mechanism of action of voclosporin as well as the dominance of proteinuria in predicting patient outcomes. The eGFR models that ICER references also typically assume that patients need to move through all model health states up to stage 3 eGFR before developing ESRD. This assumption is not adopted for estimated proteinuria states, where possible transitions to ESRD can happen from any stage of proteinuria.[46,47]

Simrat Randhawa MD, MBA
SVP Medical & Clinical Affairs
Aurinia Pharmaceuticals

Appendix

Figure 1: AURORA Voclosporin Renal Response by Race



*Mestizo, Mulato, Other

Table 1: Derivation of LN Utilities by Race

Year	Study	Derivation of Utilities by Race
2006	Tse *et al.*[48]	Race not disclosed: small study of 12 patients (10 women, 2 men)
2007	Grootscholten *et al.*[49]	• All patients in trial: 76% Caucasian • Patients who completed 3 questionnaires: 87% Caucasian
2008	Clarke *et al.*[50]	• USA: 67.4% Caucasian • Canada: 84.8% Caucasian • UK: 77.7% Caucasian
2014	Mohara *et al.*[51]	Race not disclosed, population likely reflective of Thailand population given location of study: • *"The **generalizability of results is restricted to similar patient populations from contexts with similar characteristics to Thailand."*** • *"Issues such as the structure of healthcare delivery and **ethnicity may play an important role in limiting the use of these results in other settings** and therefore careful judgment should be used for their extrapolation."*

Table 2: Correlation of Utilities to the State of Health of LN patients

Year	Study	Correlation of Utilities to Patient State of Health
2006	Tse *et al.*[52]	*"The CTX [cyclophosphamide]-treated group's health state **did not correlate** with perceived health state/QOL[quality of life] measure."*
2007	Grootscholten *et al.*[53]	*"**HRQOL [health related quality of life] scores did not correlate with the SLEDAI [Systemic Lupus Erythematosus Disease Activity Index]and physician's VAS [visual analogue scale].** The disease activity measures correlated positively with each other."*
2008	Clarke *et al.*[54]	*"Subjective health state measured by [Systemic Lupus International Collaborating Clinics/ACR Damage Index (SLICC/ACR DI)] seemed to get better even though SLICC/ACR DI was getting worse… **Health state did not correlate with perceived health state."***
2014	Mohara *et al.*[55]	***Correlation unknown:** EQ-5D [EuroQoL 5-dimension] correlation to disease state is not reflected in publication.*

References

[1] Appel, Gerald B., *et al*. "Long-term follow-up of patients with lupus nephritis: a study based on the classification of the World Health Organization." *The American Journal of Medicine* 83.5 (1987): 877-885. Link
[2] Ortega, L. M., *et al.* "Lupus nephritis: pathologic features, epidemiology and a guide to therapeutic decisions." *Lupus* 19.5 (2010): 557-574. Link
[3] Parodis, Ioannis, Farah Tamirou, and Frédéric A. Houssiau. "Prediction of prognosis and renal outcome in lupus nephritis." *Lupus Science & Medicine* 7.1 (2020):e000389. Link
[4] Mumal I. "Women with Lupus Nephritis at Greater Risk for Problem Pregnancy." *Lupus New Today*. (2018). Link
[5] Burgos, Paula I., *et al.* "US patients of Hispanic and African ancestry develop lupus nephritis early in the disease course: data from LUMINA, a multiethnic US cohort (LUMINA LXXIV)." *Annals of the Rheumatic Diseases* 70.2 (2011): 393-394. Link
[6] Feldman, Candace H., *et al.* "Epidemiology and sociodemographics of systemic lupus erythematosus and lupus nephritis among US adults with Medicaid coverage, 2000–2004." *Arthritis & Rheumatism* 65.3 (2013): 753-763. Link
[7] *Op. Cit.* Mumal (2018). Link
[8] Wu, Jiayue, *et al.* "Management and outcomes of pregnancy with or without lupus nephritis: a systematic review and meta-analysis." *Therapeutics and Clinical Risk Management* 14 (2018): 885. Link
[9] *Op. Cit.* Burgos *et al.* 2011. Link
[10] Norris, Keith, and Allen R. Nissenson. "Race, gender, and socioeconomic disparities in CKD in the United States." *Journal of the American Society of Nephrology* 19.7 (2008): 1261-1270. Link
[11] *Op. Cit.* Burgos *et al.* 2011. Link
[12] Sin, Fang En, and David Isenberg. "An evaluation of voclosporin for the treatment of lupus nephritis." *Expert Opinion on Pharmacotherapy* 19.14 (2018): 1613-1621. Link
[13] Grootscholten, Cecile, *et al.* "Health-related quality of life and treatment burden in patients with proliferative lupus nephritis treated with cyclophosphamide or azathioprine/methylprednisolone in a randomized controlled trial." *The Journal of Rheumatology* 34.8 (2007): 1699-1707. Link.
[14] Clarke, Ann E., *et al.* "SLE patients with renal damage incur higher health care costs." *Rheumatology* 47.3 (2008): 329-333. Link.
[15] The 76% average was calculated by averaging the figures from Grootscholten *et al*. and then taking this average and adding it to the figure from Clarke *et al.* to calculate the total average.
[16] Larson, Timothy S. "Evaluation of proteinuria." *Mayo Clinic Proceedings*. Vol. 69. No. 12. Elsevier, 1994: P1154-1158. Link
[17] Reyes-Thomas, Joyce, Irene Blanco, and Chaim Putterman. "Urinary biomarkers in lupus nephritis." *Clinical reviews in allergy & immunology* 40.3 (2011): 138-150. Link
[18] *Op. Cit.* Larson (1994). Link
[19] Cattran, Daniel C., *et al.* "Kidney disease: improving global outcomes (KDIGO) glomerulonephritis work group. KDIGO clinical practice guideline for glomerulonephritis." *Kidney International Supplements* 2.2 (2012): 139-274. Link
[20] Chen, Yiann E., *et al.* "Value of a complete or partial remission in severe lupus nephritis." *Clinical Journal of the American Society of Nephrology* 3.1 (2008): 46-53. Link
[21] Tamirou, Farah, *et al.* "Long-term follow-up of the MAINTAIN Nephritis Trial, comparing azathioprine and mycophenolate mofetil as maintenance therapy of lupus nephritis." *Annals of the Rheumatic Diseases* 75.3 (2016): 526-531. Link
[22] Levey, Andrew S., *et al.* "Proteinuria as a surrogate outcome in CKD: report of a scientific workshop sponsored by the National Kidney Foundation and the US Food and Drug Administration." *American Journal of Kidney Diseases* 54.2 (2009): 205-226. Link
[23] Corapi, Kristin M., Mary Anne Dooley, and William F. Pendergraft. "Comparison and evaluation of lupus nephritis response criteria in lupus activity indices and clinical trials." *Arthritis Research & Therapy* 17.1 (2015): 1-13. Link
[24] *Op. Cit.* Chen (2008).
[25] Moroni, Gabriella, *et al*. "Lack of EULAR/ERA-EDTA response at 1 year predicts poor long-term renal outcome in patients with lupus nephritis." *Annals of the Rheumatic Diseases* 79 (2020): 1077-1083. Link
[26] Cravedi, Paolo, and Giuseppe Remuzzi. "Pathophysiology of proteinuria and its value as an outcome measure in chronic kidney disease." *British Journal of Clinical Pharmacology* 76.4 (2013): 516-523. Link
[27] Hanly, John G., *et al.* "The frequency and outcome of lupus nephritis: results from an international inception cohort study." *Rheumatology* 55.2 (2016): 252-262. Link
[28] Tektonidou, Maria G., Abhijit Dasgupta, and Michael M. Ward. "Risk of end-stage renal disease in patients with lupus nephritis, 1971–2015: a systematic review and Bayesian meta-analysis." *Arthritis & Rheumatology* 68.6 (2016): 1432-1441. Link
[29] *ibid*.
[30] *Op. Cit.* Tamirou *et al.* (2016). Link
[31] Peterson, John C., *et al.* "Blood pressure control, proteinuria, and the progression of renal disease: the Modification of Diet in Renal Disease Study." *Annals of Internal Medicine* 123.10 (1995): 754-762. Link
[32] The GISEN, Group. "Randomized placebo-controlled trial effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric, non-diabetic nephropathy." *Lancet* 349 (1997): 1857-63. Link
[33] Wapstra, F. H., *et al.* "Prognostic value of the short-term antiproteinuric response to ACE inhibition for prediction of GFR decline in patients with nondiabetic renal disease." *Experimental Nephrology* 4 (1996): 47-52. Link

[34] Lewis, Edmund J., *et al.* "The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy." *New England Journal of Medicine* 329.20 (1993): 1456-1462. Link
[35] *Op. Cit.* Tamirou *et al.* (2016). Link
[36] Sprangers, Ben, Marianne Monahan, and Gerald B. Appel. "Diagnosis and treatment of lupus nephritis flares—an update." *Nature Reviews Nephrology* 8.12 (2012): 709. Link
[37] Anders, Hans-Joachim, *et al.* "Lupus nephritis." *Nature Reviews Disease Primers* 6.1 (2020): 1-25. Link
[38] Fanouriakis, A, *et al.* "2019 update of the EULAR recommendations for the management of systemic lupus erythematosus." *Annals of the Rheumatic Diseases.* 1.78 (2019):736-45. Link
[39] Arriens, C., *et al.* "OP0277 AURORA PHASE 3 STUDY DEMONSTRATES VOCLOSPORIN STATISTICAL SUPERIORITY OVER STANDARD OF CARE IN LUPUS NEPHRITIS (LN)." *Annals of the Rheumatic Diseases.* (2020): 172-173. Link
[40] *Op. Cit.* Hanly *et al.* (2016). Link
[41] *Op. Cit.* Tektonidou *et al.* (2016). Link
[42]Kim, Soyoung, *et al.* "Cost–effectiveness of tacrolimus for the treatment of moderate-to-severe lupus nephritis in China." *Journal of Comparative Effectiveness Research* 8.13 (2019): 1125-1141. Link
[43] Mohara, Adun, *et al.* "A cost–utility analysis of alternative drug regimens for newly diagnosed severe lupus nephritis patients in Thailand." *Rheumatology* 53.1 (2014): 138-144. Link
[44] Nee, Robert, *et al.* "Cost-utility analysis of mycophenolate mofetil versus azathioprine based regimens for maintenance therapy of proliferative lupus nephritis." *International Journal of Nephrology* 2015 (2015): 917567. Link
[45] Wilson, E. C. F., *et al.* "The cost-effectiveness of mycophenolate mofetil as firstline therapy in active lupus nephritis." *Rheumatology (Oxford).* (2007): 1096-1101. Link
[46] Hanly, John G., *et al.* "A longitudinal analysis of outcomes of lupus nephritis in an international inception cohort using a multistate model approach." *Arthritis & Rheumatology* 68.8 (2016): 1932-1944. Link
[47] Barber, Megan RW, *et al.* "Economic evaluation of lupus nephritis in the Systemic Lupus International Collaborating Clinics inception cohort using a multistate model approach." *Arthritis Care & Research* 70.9 (2018): 1294-1302. Link
[48] Tse, K. C., *et al.* "Quality of life comparison between corticosteroid and-mycofenolate mofetil and corticosteroidand-oral cyclophosphamide in the treatment of severe lupus nephritis." *Lupus* 15.6 (2006): 371-379. Link
[49] *Op. Cit.* Grootscholten *et al.* (2007). Link
[50] *Op. Cit.* Clarke *et al.* (2008). Link.
[51] *Op. Cit.* Mohara *et al.* (2014). Link
[52] *Op. Cit.* Tse *et al.*(2006). Link
[53] *Op. Cit.* Grootscholten *et al.* (2007). Link
[54] *Op. Cit.* Clarke *et al.* (2008). Link
[55] *Op. Cit.* Mohara *et al.* (2014). Link

BLACK WOMEN'S HEALTH IMPERATIVE

The Black Women's Health Imperative (BWHI) writes in response to ICER's Draft Scoping Document for its 2020 Lupus Nephritis (LN) Assessment. LN is a serious, life-threatening complication of SLE that disproportionately burdens women of color at the peak of their childbearing and career potential. There are no FDA-approved treatments for LN. The off-label treatment regimens comprising the existing standard of care (SoC) have an unsatisfactory side effect and adverse event profile, particularly given the disproportionate failure of these treatments in Black and Latinx patients.

BWHI applauds ICER's June 2020 statement recognizing that institutionalized and systemic racism has enabled and perpetuated a health system in which race is a determining factor in life expectance. This LN assessment offers a unique opportunity for ICER to act on its pledge to be part of the long-overdue change our communities, and this nation, need. Our comments are offered as a first step in what we hope will be a robust and continuing discussion in partnership toward that pledge.

BWHI urges ICER to ensure that its assessment accurately captures and appropriately quantifies the value of a new FDA-approved treatment for non-white LN patients, as well as the societal value of eliminating race as the primary determinant in LN outcomes.

BWHI'S RECOMMENDATIONS FOR ICER'S LN ASSESSMENT (References attached)

ICER should expand its stakeholder engagement beyond general, disease-specific advocacy organizations to include entities with knowledge and expertise relevant to the real-world experience in black and brown communities generally and in women of color living with LN specifically. ICER's list of entities for stakeholder engagement was comprised of organizations that lack a specific focus on the health care experience and needs of non-white LN patients. This limited stakeholder engagement is likely to skew ICER's perception of patient disease burden and treatment value toward an aggregate that is not meaningful to either white or non-white patients. ICER should bolster its available evidence base with real-world information specific to non-white LN patient populations. This might include patient and provider interviews, stakeholder surveys, and other sources of qualitative data to ensure a robust model and accurate assumptions with respect to each assessed intervention and its safety/efficacy profile across relevant subpopulations.

ICER's assessment must give significant weight and consideration to the race-specific variability in LN prevalence, disease severity and treatment response, and assess each treatment from the lens of real-world experiences in patient subpopulations. This includes accounting for the fact that side effects, adverse events, reliable access to a standard of care, and inadequate treatment response can further widen the gap in health outcomes based on race and/or ethnicity. Failing to account for these differences (e.g., through sensitivity analyses in modeling to explore heterogeneity of disease severity and treatment effects), or aggregating subpopulation outcomes toward a single conclusion, would ignore the systemic health care disparities ICER acknowledged and committed to address.

- Progression to ESRD in Black patients is almost 9 times greater than in white patients. Disparities in outcomes between white and non-white LN patients persist even when adjusting socioeconomic factors, signaling a clear unmet need in these subpopulations;
- Non-white LN patients have a pronounced reduction in 10-year survival rate (white 81%, black 59%, other 73%);

- LN is more aggressive in non-white individuals who are more likely to be prescribed both immunosuppressive treatment and high doses of corticosteroids; and
- Remission rates with the ICER-identified standard of care demonstrate significant racial disparities (white 52%, black 29%, other 27%);
- Although kidney transplant is the SoC for ESRD patients, Black LN patients progressing to ESRD are far less likely to have kidney transplant as an available option given that the wait for a deceased donor organ is 1.43 longer than in white patients. The disparity for living donor kidneys is even more pronounced with just 12.8% of living donor kidneys coming from black individuals.

ICER's assessment must respond to racial disparities in access to care by adjusting control group outcomes to approximate real-world care experience in Black and Latinx LN patients. The level of care provided to a placebo/standard of care cohort within the controlled setting of a clinical trial exceeds the real-world care experience of the LN patients most likely to benefit from a new self-administered treatment option.

- Data indicate that in underserved areas, LN patients have less than a 50% chance of receiving treatment approximating the standard of care;
- Individuals of color are more likely to encounter fragmented care, inadequate follow-up, and treatment plans that fail to consider rapid progression to ESRD associated with aggressive LN;
- The highly variable care patterns LN patients experience can further widen the gap in health outcomes in non-white LN patients.

BWHI believes that introduction of an FDA-approved treatment option for LN that can demonstrate effectiveness through rapid proteinuria reduction in Black and Latinx patient subpopulations renders the safety and efficacy profile for off-label treatment options unacceptable for these patients. Even when Black and Latinx LN patients have access to treatment according to the SoC, they are more likely to receive treatments with high toxicity to address their aggressive LN and are less likely to respond than their white counterparts. For the relative few patients successfully achieving remission (29% in Black patients; 27% in Latinx and Asian patients), side-effects and adverse events can have a profound and lasting impact on long-term health and quality of life, particularly for non-white women of child-bearing age.

- Corticosteroid use contributes to development or worsening of health conditions that already disproportionately impact Black and Latinx patients, including hypertension, obesity, diabetes, and osteoporosis;
- Costs of managing adverse events associated with longer-term use of corticosteroids (60 days or more) can actually be higher than disease-related medical costs;
- Immunosuppressive medications are associated with minor side effects such as nausea, as well as very serious and relatively common adverse events such as ovarian failure in 38-52% of women, severe opportunistic infections, and higher risk of cancer with 2-3 years of use.
- Although Belimumab (an infused treatment) offered hope for LN patients, it failed to demonstrate statistically significant improvement on outcomes for Black LN patients.

QALY use, without separate subpopulation analyses and significant adjustments to the underlying model and its inputs, will distort the resultant value determination and perpetuate race-specific

health inequities for LN patients. The quality adjusted life-year (QALY) framework ICER uses in assessing treatment options was crafted before racial inequities in care access and delivery were recognized as drivers of health outcomes and do not capture differences in burden of disease, outcome preferences, or viability of comparative treatments.

- QALYs generally fail to account for non-health benefits and indirect costs that can have a greater impact on future health outcomes in communities of color given the existing health inequities patients encounter, potentially high prevalence of food and housing insecurity, and reduced access to care due to loss of employer-sponsored health coverage. This is especially relevant during and in the wake of the COVID-19 pandemic. These non-health benefits and indirect costs include ability to continue or return to work, better school performance, costs of caregiving, mental health challenges, daily functioning, time accessing medical care, income loss, loss of productivity, and travel costs to access care;
- QALYs utility scores also tend to disadvantage patients with progressive chronic conditions. For LN patients, the baseline QALY (and LN patient inability to reach a state approximating full health) fails to capture both the full impact of the condition and the true value of each assessed treatment. ICER could accommodate this deficiency with "weighting" to reflect preferences within relevant LN subpopulations. Methods such as multiple criteria decision analysis (MCDA) could enhance relevance of QALY to LN patients likely to benefit from treatment or suffer from having it withheld.

ICER should ensure that its model considers childbearing potential as a priority outcome that must be factored into value. Because women are urged to avoid pregnancy when LN is active, being able to reach and sustain remission is, for many patients, an overwhelmingly high priority. This is especially true for women of color who face disproportionate risk of pregnancy-related death and for whom postponing pregnancy beyond age 30 is associated with a 4-5 times higher mortality risk in comparison to white women. The maternal mortality risk disparity continues to widen with age.

The LN assessment must recognize that adequate management of chronic conditions like LN is essential during the COVID-19 pandemic, and does not become less urgent once the immediate crisis has resolved. LN patients face difficult treatment decisions within the COVID-19 pandemic, and must balance the risk of serious COVID-19 disease associated with LN against the potential that ICER-identified LN SoC options impact the immune system and further exacerbate the already-high risk of severe COVID-19 disease in communities of color. Non-white patients also suffer severe disease, and even die, at disproportionate rates from seasonal influenza and pneumonia. Without an effective treatment alternative, patients are left without a good option for managing disease within the pandemic and as new infectious disease risks emerge.

ICER should model LN to reflect real-world disease progression and health outcomes (active disease, complete renal remission, partial renal remission, ESRD and death). Evidence suggests that early and effective treatment can aid in long-term preservation of kidney function, and that monitoring treatment efficacy with biomarkers such as proteinuria is helpful in determining treatment response. Use of reduction in proteinuria to assess treatment response is not only appropriate within the context of ICER's review, but an important part of an emerging SoC that could close the racial disparities on patient outcomes by offering a standard, objective means of assessing treatment adequacy, follow-up plans, and the need for treatment plan modifications.

REFERENCES (BWHI Comments to ICER Draft Scoping Document for LN)

Albuquerque BC, Salles VB, Paulo Tajra RD, Raodirgues CE. Outcome and Prognosis of patients with lupus nephritis submitted to renal transplantation. Nature: Scientific Reports. Aug 2019; 9: 11611.

Appel GB, Cohen DJ, Pirani CL, Meltzer JI, Estes D. Long-term follow-up of patients with lupus nephritis: a study based on the classification of the World Health Organization. The American journal of medicine. 1987 Nov 1;83(5):877-85.

Bailey ZD, Krieger N, Agénor M, Graves J, Linos N, Bassett MT. Structural racism and health inequities in the USA: evidence and interventions. Lancet 2017;389:1453–63.

Burgos Pi, McGwin G, Pons-Estel GJ, Reveille JD, Alarcon GS, Vila LM. US patients of Hispanic and African ancestry develop lupus nephritis early in the disease course: data from LUMINA, a multiethnic US cohort (Lumina LXXIV). Ann Rheum Dis. 2011; 70: 393-394

CDC, Racial and Ethnic Disparities Continue in Pregnancy-Related Deaths - Black, American Indian/Alaska Native women most affected. https://www.cdc.gov/media/releases/2019/p0905-racial-ethnic-disparities-pregnancy-deaths.html

CDC. Disparities in Incidence of COVID-19 Among Underrepresented Racial/Ethnic Groups in Counties Identified as Hotspots During June 5–18, 2020 — 22 States, February–June 2020. (early release, August 14, 2020). https://www.cdc.gov/mmwr/volumes/69/wr/mm6933e1.htm

CDC. Health equity considerations and racial and ethnic minority groups. Atlanta, GA: US Department of Health and Human Services, CDC; 2020. https://www.cdc.gov/coronavirus/2019-ncov/community/health-equity/race-ethnicity.html

Dooley M, et al., Cyclophosphamide therapy for lupus nephritis: Poor renal survival in black Americans, Kidney International, Vol. 51 (1997), pp. 1188—1195. https://www.kidney-international.org/article/S0085-2538(15)60002-3/pdf

Feldman CH, Hiraki LT, Liu J, Fischer MA, Solomon DH, Alarcon GS. Epidemiology and Sociodemographics of Systemic Lupus Erythematosus and Lupus Nephritis among U.S. Adults with Medicaid Coverage, 2000-2004. Arthritis Rheum. Mar 2013; 65(3): 753-763

Hutchins SS, Fiscella K, Levine RS, Ompad DC, McDonald M. Protection of racial/ethnic minority populations during an influenza pandemic. Am J Public Health. 2009;99 Suppl 2(Suppl 2):S261-S270. doi:10.2105/AJPH.2009.161505.

ICER Statement on Racism in America (June 3, 2020). https://icer-review.org/blog/race_in_america/

Izmirly PM, et al., The Incidence and Prevalence of Systemic Lupus Erythematosus in New York County (Manhattan), New York: The Manhattan Lupus Surveillance Program, Arthritis & Rheumatology, Vol. 69, No. 10, October 2017, pp 2006–2017 DOI 10.1002/art.40192.

Kabani, N., Ginzler, E.M. Is ethnicity linked to the severity of SLE manifestations?. Nat Rev Rheumatol 15, 515–516 (2019). https://doi.org/10.1038/s41584-019-0271-1

Korbet SM, Schwartz MM, Evans J, Lewis JE, Severe Lupus Nephritis: Racial Differences in Presentation and Outcome, JASN Jan 2007, 18 (1) 244-254; DOI: 10.1681/ASN.2006090992

Lupus Among Asians and Hispanics, https://www.cdc.gov/features/lupus-asians-latinos/index.html.

Mavragani CP, Moutsopoulos HM, Lupus nephritis: current issues, Annals of the Rheumatic Diseases 2003;62:795-798.

Mumal I., Women with Lupus Nephritis at Greater Risk for Problem Pregnancy. May 30, 2018.

National Minority Quality Form White Paper: Traditional Value Assessment Methods Fail Communities of Color and Exacerbate Health Inequities. https://www.nmqf.org/nmqf-media/traditional-value-assessment-methods

Palmer W, Lupus is More Severe in Racial/Ethnic Minorities (June 4, 2019), Rheumatology Network, https://www.rheumatologynetwork.com/view/lupus-more-severe-racialethnic-minorities

Parodis I, Tamirou F, Houssiau FA. Prediction of prognosis and renal outcome in lupus nephritis. BMJ Lupus Science & Medicine. 2020 Feb 1;7(1).

Selden TM, Berdahl TA. COVID-19 and racial/ethnic disparities in health risk, employment, and household composition. Health Aff (Millwood) 2020. Epub July 14, 2020.

Tesar V, Hruskova Z: Lupus Nephritis: A Different Disease in European Patients? Kidney Dis 2015;1:110-118. doi: 10.

Vart P, Powe NR, McCulloch CE, Saran R, Gillespie BW, Saydah S, Crews DC. National Trends in the Prevalence of Chronic Kidney Disease Among Racial/Ethnic and Socioeconomic Status Groups, 1988-2016. JAMA network open. 2020 Jul 1;3(7):e207932.

Ward MM. Access to care and the incidence of endstage renal disease due to systemic lupus erythematosus. J Rheumatol. 2010;37(6):1158–63.

Wortham JM, Lee JT, Althomsons S, et al. Characteristics of persons who died with COVID-19—United States, February 12–May 18, 2020. MMWR Morb Mortal Wkly Rep 2020;69:923–9

Wu J, Ma J, Zhang WH, Di W. Management and outcomes of pregnancy with or without lupus nephritis: a systematic review and meta-analysis. Therapeutics and Clinical Risk Management. 2018;14:885.

Yancy CW. COVID-19 and African Americans. JAMA. Published online April 15, 2020.

Yazdany J, Feldman CH, Liu J, Ward MM, Fischer MA, Costenbader KH. Quality of care for incident lupus nephritis among Medicaid beneficiaries in the United States. Arthritis Care Res (Hoboken) 2014;66(4):617–24.

Genentech
A Member of the Roche Group

September 21, 2020

Institute for Clinical and Economic Review (ICER)
One State Street, Suite 1050
Boston, MA 02109

Dear ICER Review Panel:

Genentech, a member of the Roche Group, appreciates the opportunity to provide comments on the Draft Scoping Document for the assessment of treatments for lupus nephritis (LN). We are deeply committed to addressing the unmet medical needs of patients with LN and support the development of new treatment options that may benefit the lupus community. We provide the following recommendations to enhance the utility of the report and more comprehensively assess the value of therapies for LN:

1. Discuss how heterogeneity in the definition of complete renal remission (CRR) in the clinical studies influences report outcomes;
2. Conduct subgroup analyses based on race/ethnicity to quantify the benefit in key patient subgroups.

1. Discuss how heterogeneity in the definition of CRR in the clinical studies influences report outcomes.

ICER should describe how the clinical studies defined CRR differently and discuss how the differences will influence the outcomes of the report. There is no universally accepted definition for remission in LN, and the lack of a standard definition makes it challenging to compare and pool results across studies.[1-3] Differences in the time of assessment (e.g. Week 24 vs Week 52) and requirements (e.g. urinary sediment, serum creatinine, urine protein to creatinine ratio) can affect the proportion of patients who would be considered to have achieved a CRR.[2,4] Similar to previous reports, ICER should summarize these differences in a table and discuss the potential impacts on the network meta-analysis and cost-effectiveness model in the results or "Heterogeneity and Subgroups" subsections.[5-8] By clearly addressing the heterogeneity in how this key outcome is defined, ICER can improve the credibility of the report and better inform decision-making.

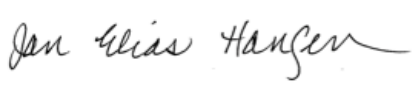
2. Conduct subgroup analyses based on race/ethnicity to quantify the benefit in key patient subgroups.

ICER should explore treatment effects in racial and ethnic subgroups given the disproportionate impact of SLE and LN on people from racial and ethnic minorities.[9,10] Patients of Asian, African Caribbean, African American, and Hispanic ethnicities are more likely to present with more

severe LN than other ethnic groups. Moreover, non-white race has been associated with poor prognosis and outcomes in patients with LN. While the effects in these populations could be discussed qualitatively in the "Other Potential Benefits and Contextual Considerations" section, quantifying the impact through subgroup analyses can better inform policy and treatment decisions.

We believe that the incorporation of these recommendations will enhance the utility and credibility of the report and allow for a more comprehensive assessment of value. We welcome the opportunity to discuss these recommendations further.

Sincerely,



Jan Elias Hansen, Ph.D.
Vice President, Evidence for Access Medical Unit
U.S. Medical Affairs,
Genentech, Inc.

References:

1. Tunnicliffe DJ, Palmer SC. Immunosuppressive Treatment for Proliferative Lupus Nephritis: Summary of a Cochrane Review. American journal of kidney diseases : the official journal of the National Kidney Foundation. Nov 2018;72(5):756-757.
2. van Vollenhoven R, Voskuyl A, Bertsias G, et al. A framework for remission in SLE: consensus findings from a large international task force on definitions of remission in SLE (DORIS). Annals of the rheumatic diseases. Mar 2017;76(3):554-561.
3. The American College of Rheumatology response criteria for proliferative and membranous renal disease in systemic lupus erythematosus clinical trials. Arthritis and rheumatism. Feb 2006;54(2):421-432.
4. Amoura Z, Remy P, Porras L, et al. Alternative Renal Response Definitions in a Randomized, Controlled Trial of Obinutuzumab for Proliferative Lupus Nephritis. Presented at: European Congress of Rheumatology; June 3-6, 2020, 2020; Frankfurt, Germany.
5. Institute for Clinical and Economic Review. 2020-2023 Value Assessment Framework. 2020; https://icer-review.org/meeting/2020-value-assessment-framework/. Accessed September 10,, 2020.
6. Institute for Clinical and Economic Review. Targeted Immune Modulators for Ulcerative Colitis: Effectiveness and Value Evidence Report. 2020; https://icer-review.org/topic/ulcerative-colitis/. Accessed September 11, 2020.
7. Institute for Clinical and Economic Review. Janus Kinase Inhibitors and Biosimilars for Rheumatoid Arthritis: Effectiveness and Value Final Evidence Report and Meeting Summary. 2019; https://icer-review.org/meeting/rheumatoid-arthritis-condition-update/. Accessed September 10, 2020.
8. Institute for Clinical and Economic Review. Biologic Therapies for Treatment of Asthma Associated with Type 2 Inflammation: Effectiveness, Value, and Value-Based Price Benchmarks Final Evidence Report. 2018; https://icer-review.org/material/asthma-final-evidence-report/. Accessed September 10,, 2020.
9. Drenkard C, Lim SS. Update on lupus epidemiology: advancing health disparities research through the study of minority populations. Current opinion in rheumatology. Nov 2019;31(6):689-696.
10. Saxena R, Mahajan T, Mohan C. Lupus nephritis: current update. Arthritis research & therapy. 2011;13(5):240.

September 21, 2020

Matthew D. Rousculp, Ph.D, M.P.H.
Head, US Value, Evidence and Outcomes
GlaxoSmithKline
Five Moore Drive
PO Box 13398
Research Triangle Park
North Carolina 27709-3398
www.gsk.com

Steven D. Pearson, MD, MSc
Institute for Clinical and Economic Review
Two Liberty Square, 9th Floor, Boston, MA 02109

Re: ICER's Assessment of Treatments for Lupus Nephritis: Draft Scope

Dear Dr. Pearson,

GlaxoSmithKline (GSK) appreciates the opportunity to provide comments in response to the Institute for Clinical and Economic Review's (ICER) Draft Scoping Document on the assessment of the comparative clinical effectiveness and value of voclosporin and belimumab for the treatment of lupus nephritis (LN). LN is one of the most common and life-threatening complications of systemic lupus erythematosus (SLE). There are limited treatment options for LN; which, in part, speaks to the clinical development challenges and the large unmet need of SLE patients with kidney involvement. It is notable that the two products awaiting FDA evaluation as LN treatments, have been granted FDA Priority Review; perhaps confirming the gap in efficacious and safe therapies for such a severe manifestation of SLE.

Please find below our concerns and suggested modifications to the Draft Scoping Document pertaining to:

- Comparative Value Analyses
- Outcomes of Interest
- Economic model to Assess Lifetime Cost-effectiveness

Comparative Value Analyses - Indirect Treatment Comparison between Voclosporin and Belimumab
ICER states on Page 4 of the Draft Scoping Document that, data permitting, ICER intends to compare voclosporin to belimumab however, there are inherent differences in trial design for the respective interventions that make an indirect treatment comparison challenging; potentially limiting its interpretation and increasing the likelihood of misinterpretation. Some key differences between the voclosporin (AURORA) and belimumab (BLISS-LN) clinical trials are summarized below:

- Induction and maintenance therapy:
  - AURORA: voclosporin + MMF (2 grams) + steroids
  - BLISS-LN: belimumab + MMF (induction 3 grams, maintenance 1-3g per day) OR CYC (+AZA for maintenance) + steroids;
- Composite primary endpoint / time point:
  - AURORA: Renal Response at week 52
  - BLISS-LN: Primary Efficacy Renal Response (PERR) at week 104;
- Specification of composite primary endpoint; e.g., the uPCR (urine protein:creatinine ratio) threshold was specified as ≤ 0.5 mg/mg in AURORA as compared to ≤ 0.7 mg/mg in BLISS-LN;
- Steroid tapering within primary endpoint: BLISS-LN required that patients achieve 10mg/d or less of steroids by week 24 and that this was maintained from week 24-104, AURORA required the low dose steroid between weeks 44-52 only. BLISS-LN patients had to achieve PERR at weeks 104 and 100;

- Differences in patient exclusion criteria, BLISS-LN allowed for a lower eGFR threshold of 30 ml/ min whereas the value was 45 ml/ min in AURORA

These examples demonstrate the heterogeneity in clinical trial design that will make an indirect treatment comparison challenging. GSK recommends ICER adopt a transparent and scientifically sound approach in consideration of an indirect comparison, especially when the outputs may be used as parameter inputs in an economic model.

Outcomes of Interest

GSK applauds ICER for the comprehensive list of outcomes, many of which reflect patient-centric outcomes. However, despite referencing the FDA's Patient Focused Drug Development Initiative (Lupus and Allied Diseases Association LFoA, 2018) and elicitation of perspectives of patients living with lupus, the very symptoms identified in the initiative and referenced by ICER as those that most negatively affected patients' lives (e.g., fatigue, joint and muscle pain, and cutaneous manifestations) were not explicitly listed in the Outcomes of Interest.

Perhaps of greater methodological importance is the selection of 'Complete Renal Remission (normal renal function) at One Year' as the first sub-bullet under Patient-Important Outcomes. As noted in the previous section, inherent differences in trial design may prevent a congruent definition of response, whether defined as 'Complete Renal Remission' or complete/partial response/remission or maintenance of remission. Furthermore, the Draft Scoping Document would appear to undervalue belimumab's 104-week trial (BLISS-LN) while placing greater importance on complete renal remission at 52 weeks; thereby discounting the very data that we believe decision makers (patients, physicians and payers) have long called for and valued, especially in a chronic illness such as LN. GSK looks to ICER to consider in their clinical and economic review the difference in LN trial durations, as well as the over 10 years of efficacy and safety data supporting belimumab for the treatment of SLE.

Additional comments relating to Outcomes of Interest for consideration include the following:

- Absence of renal flares; despite evidence of the significant morbidity of flares and the detrimental effect each additional flare has on the life of the kidney (Anders 2020);
- Absence of extra-renal SLE domains; LN patients are SLE patients; as such and in concordance with published guidelines, goals of treatment include not only renally-related outcomes, but also non-renal SLE-outcomes; e.g., low disease activity / remission, prevention of disease flares, prevention of organ damage and management of comorbidities;
- Absence of chronic renal insufficiency (CRI); although end stage kidney disease (ESKD) and dialysis are the important consequent events we are looking to avoid, individuals progress through chronic renal insufficiency which itself is associated with significant morbidity and costs to the system;
- Incomplete list of adverse events, considering the treatments being assessed. As such, we recommend ICER consider adding the following: metabolic disorders (eg, diabetes), nephrotoxicity, hypertension, and neurotoxicity (eg, posterior reversible encephalopathy syndrome, tremors, headache, seizures).

Economic Model to Assess Lifetime Cost Effectiveness

ICER notes a modified societal perspective will be considered. This is an important point; given LN patients are relatively young, between late 20's and late 40's (Carls, 2009; Feldman, 2018); and there is a notable productivity cost associated with the disease. One study which examined costs in LN patients with a median

age of 36.5 years (Aghdassi, 2011) demonstrated that almost half of those with LN were employed and missed on average 8.5 days per month while caregivers missed on average 8.5 hours per month. Therefore, it is important that an economic evaluation of the treatments for LN includes lost productivity cost for both patients and their caregivers occurring during active disease and through premature loss of life.

As highlighted above and in our Open Input Period response, LN is one of the most common and serious complications of SLE; SLE is a complex, chronic, autoimmune disease that can affect many systems of the body and is characterized by a heterogeneous presentation of symptoms. When an SLE patient experiences a renal flare and is subsequently diagnosed with LN, they frequently experience concurrent extra-renal symptoms. While we appreciate the need for economic models and the underlying assumption that models are a simplification of the complex world, GSK cautions ICER with respect to the appropriateness of an economic modeling exercise in LN. The simplification of a complex disease like LN via an economic model may not sufficiently capture the patient journey; thereby underestimating the value of interventions aimed at improving LN patient outcomes. These models need to appropriately account for all the benefits that medicines have in this disease area e.g. CRI, ESKD, extra-renal outcomes in LN patients.

Belimumab

Belimumab is a B-lympocyte stimulator (BLyS)-specific inhibitor that has been subject to a comprehensive clinical development program that has consistently shown the benefits of belimumab for the treatment of SLE. Based on four positive, randomized clinical trials, belimumab is indicated in the United States for the treatment of patients aged 5 years and older with active, autoantibody positive, SLE who are receiving standard therapy. In the pivotal Phase 3 SLE clinical trials, subjects with severe active LN were excluded. GSK has since conducted BLISS-LN (Furie, 2020) (a FDA post-approval commitment), a Phase 3, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of intravenous (IV) belimumab plus standard therapy compared to placebo plus standard therapy in adult subjects with active LN. BLISS-LN included patients with active Class III $\pm$ V, IV $\pm$ V, V LN, and is the largest LN clinical trial to date, with 448 subjects randomized. BLISS-LN met the primary (PERR at week 104) and all four key secondary efficacy endpoints. The proportion of patients with adverse events and serious adverse events were similar in the belimumab and placebo arms.

In summary, LN is a manifestation of a complex autoimmune disease and the complexity in the diagnosis, management and progression of disease will make an assessment of clinical effectiveness and value challenging. Inherent differences in clinical trial design will make indirect treatment comparisons challenging. Furthermore, the choice of structural assumptions, characterization of care pathways and estimation of input parameters will directly impact cost-effectiveness estimates. As such, the approaches adopted to address these complexities and manage uncertainty will ultimately serve as the gauge to the robustness, validity and ultimately the credibility of the proposed review.

Please feel free to contact us should you wish to discuss these recommendations in further detail.
Sincerely,

Matthew D. Rousculp, Ph.D., M.P.H.

Head, U.S. Value, Evidence and Outcomes

References

Aghdassi E, Zhang W, St-Pierre Y et al. Healthcare Cost and Loss of Productivity in a Canadian Population of Patients with and without Lupus Nephritis. The Journal of Rheumatology. 2011; 38:4. doi:10.3899/jrheum.10048

Anders HJ, Saxena R, Zhao MH, Parodis I, Salmon JE, Mohan C. Lupus nephritis. *Nat Rev Dis Primers.* 2020;6(1):7. doi: 10.1038/s41572-019-0141-9.

Carls G, Li T, Panopalis P, Wang S, Mell AG, Gibson TB, et al. Direct and indirect costs to employers of patients with systemic lupus erythematosus with and without nephritis. J Occup Environ Med. 2009;51(1):66–79.

Feldman CH, Broder A, Guan H, Yazdany J, Costenbader KH. Sex Differences in Health Care Utilization, End-Stage Renal Disease, and Mortality Among Medicaid Beneficiaries With Incident Lupus Nephritis. Arthritis and Rheumatology. 2018;70(3):417–26.

Furie R, Rovin B, Houssiau F, Malvar , Onno Teng K, et al. Two-Year Randomized, Controlled Trial of Belimumab in Lupus Nephritis. New England Journal of Medicine. 2020; 383(12).

Lupus and Allied Diseases Association LFoA, and the Lupus Research, Alliance. Lupus: Patient Voices. 2018; http://lupuspfdd.org/LupusPatientVoicesFINAL.pdf.

P.O. Box 170
Verona, N.Y. 13478
315-829-4272

info@ladainc.org
www.ladainc.org

Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109
Submitted via e-mail: publiccomments@icer-review.org

September 21, 2020

RE: Voclosporin and Belimumab for Lupus Nephritis: Draft Background and Scope Response

Dear ICER LN Review Team Members:

On behalf of Lupus and Allied Diseases Association, Inc. (LADA), we thank you for the opportunity to comment on the Institute for Clinical and Economic Review (ICER) draft scoping document for Voclosporin and Belimumab for Lupus Nephritis. LADA is dedicated to improving access to care and quality of life by wielding the patient voice as a catalyst to ensure that the patient viewpoint is included as an equal stakeholder in the research, healthcare, regulatory and public policy arenas. As a national organization led by people with lupus and allied diseases who represent at least 322,000 to 1.5 million people with lupus,[1] loved ones, care partners, and healthcare professionals that deal with serious health conditions on a daily basis, we certainly understand the importance of addressing medical costs while still advancing innovation to discover better diagnostics, superior treatments, causes and cures.

We are excited to participate in this initiative because we are frustrated with the present state of lupus and lupus nephritis therapies. The current standards of care and treatment are totally unacceptable to us; hence new therapies are eagerly awaited by the community and long overdue.[2] Our mantra is "we need better drugs for lupus." Lupus cut us down in the prime of our lives and drastically impacted our future, stealing our hopes, dreams, and aspirations, and precious time from us; as well as the opportunities to have a successful career, financial security, or that of being a parent.[3] Most of us living with lupus desperately cling to the belief that there will be more effective treatments and a cure during our lifetime.[4]

In reviewing the draft scoping document, we have identified several areas of concern that may lead to inequitable assessment and submit the following input. As previously noted in our open comment submission to ICER, lupus is a highly heterogeneous disease with various underlying diagnoses and manifestations often described as being under a "lupus umbrella."[5] Due to the complex, heterogeneous nature of the disease, no two cases are alike and treatment is highly individualized; thus there is no cookie cutter approach, so effectively treating people with lupus is like balancing on a pinhead.[6]

We can tell you from firsthand experience that Lupus is: extremely complex, difficult to diagnose, potentially fatal, presently incurable, totally capricious, painfully limiting, life altering, dream stealing, career ending, and financially, emotionally, and physically devastating.[7] In addition, lupus is a debilitating, progressive disease in which inflammation impacts other systems including the kidneys, lungs, brain, heart, blood, joints and skin.[8] The wide ranging array of lupus manifestations means that two lupus patients with "active disease" can end up having non-overlapping manifestations that may not be properly accounted for in an underlying activity score.[9] To make matters worse, as many as one in three individuals with lupus also have multiple co-morbid autoimmune conditions that require distinctive strategies to manage their care.[10] ICER must consider that while this scoping document is unique to lupus nephritis, this specific subpopulation is not only dealing with kidney involvement, but also with lupus in general; therefore, the ability to distill the differences in terms of "value" will be important.

Another area in the scoping document requiring in depth examination includes use of current treatments, namely high dose corticosteroids. While steroids may provide benefits to people with lupus and lupus nephritis, significant side effect profiles exist[11] and can be connected with increases in infections, significant bone loss, osteoporosis, hypertension, diabetes, atherosclerosis, obesity, psychosis, glaucoma,

cataracts, stroke[12] and an increased risk of morbidity.[13] As noted in the literature, patients receiving long-term prednisone therapy are at significant risk of morbidity due to permanent organ damage and prednisone daily dosages above 6 mg have been shown to increase the risk of future organ damage by 50%.[14] The risk of irreversible organ damage increases dramatically with the cumulative steroid dose being used.[15]

In 2019, the ALPHA Project, a global committee of lupus experts that includes thought leaders, people with lupus, advocates and industry partners, developed recommendations to identify and prioritize the top barriers in lupus impacting diagnosis, care, treatment and research. In addition, the group explored views on lupus as a spectrum of related diseases and seek to provide a framework to generate actionable approaches to the identified high-priority barriers. The body's top recommendation focused on simplifying and standardizing outcomes; concentrating on steroid sparing measures as part of clinical development.[16]

While this recommendation came forth after the completion of both product trials, the manufacturers had already accounted for the potential value by designing the trials with lower steroids in mind. LADA encourages ICER to closely examine the impact of high dose steroids on people with LN and account for the value that may be created by achieving better efficacy on clinically meaningful endpoints in the presence of lower doses of steroids.

With respect to the progression of LN to ESRD, which may require 3-5 years of dialysis while awaiting a kidney transplant, there is also the resulting impact on mortality.[17] The presence of renal damage is the most important predictor of early mortality in SLE patients[18]; in fact, it has been shown that renal damage reduces the survival of lupus patients by approximately 24 years, compared to the general population[19] and LN patients who develop ESRD have a 26-fold increased risk of mortality.[20]

Within the background section of the LN scoping document, there is a non-detailed examination and mention of the progression of LN to ESRD and corresponding impact on diverse populations. The global burden of Lupus and LN clearly falls much more on non-Caucasian populations, particularly in the United States. Disease prevalence ranges from approximately 40/100,000 in Caucasians to 200/100,000 amongst Afro-caribbeans.[21] In addition, greater than 40% reductions in 10-year renal survival has been reported for African-Americans compared with Caucasian patients.[22] Racial disparities have also been described after renal transplantation, with African-Americans demonstrating decreased graft survival compared with other races in studies not limited to patients with ESRD from LN.[23] Most recently African-American kidney transplant recipients with LN were at increased risk for graft loss and death compared with non-AF.[24] It is clear from recent evidence that any therapeutic gains in either delaying progression or reducing the risk of progression to ESRD in LN patients would have a significant impact on reducing current health disparities that exist in the US healthcare system for LN patients.

The ultimate impact of LN-derived ESRD on survival and/or overall mortality is well established with an outsized impact across diverse populations. "African Americans are at significantly increased risk of death compared with non-African Americans with LN-caused ESRD at age 18 to 40 years, a racial disparity risk that is 10 years longer than that in the general ESRD population."[25] The ability of products to potentially impact the ESRD progression continuum is vitally important. Allowing that these benefits may be relevant to an underserved community, these products may play a role in reducing known health disparities and in so far as the ICER review can adjust or account for this will be crucial.

LADA commends ICER for considering low-value services in the treatment of LN. Specifically, we recommend that the impact for care partners, overall productivity, and including patient perspectives in treatment decision-making such as preferred drug administration method as low-value services to consider. Including these services has the potential to reduce the negative impact to informal care for family members and care partners, and improve overall productivity with respect to a patient or care partner's ability to return to work or school.[26] "Our loved ones travel every step of the way with us in our lupus journey, even carrying us when we cannot continue on our own."[27] Providing that these products may play

a role in preventing ESRD, and subsequent dialysis, transplant and multiple infusion and medical visits; consequently reducing the burden of informal care–impact on care partners and family members, thus to the degree that the ICER review can adjust or account for this contextual consideration will be important.

Since the onset of lupus typically coincides with critical years for education and career advancement, the disease profoundly disrupts working lives. Thirty-three percent of people with lupus in the US are on work disability.[28] The annual per patient cost to employers, including medical care, work absence and short-term disability, is higher than for other chronic diseases such as diabetes, chronic obstructive pulmonary disease, and heart disease.[29] "Lupus is one of the leading causes of work disability in the United States, accounting for about 20% of the more than estimated 1.5 million Americans with a work disability. The symptoms of lupus as well as drug effects can have a profound impact on the person's employment. Studies have shown that loss in work hours cost the nation nearly $13 billion annually. The loss also impacts the individual's work, quality of life, self-management, and self-efficacy."[30]

Lupus inflicts a substantial toll on people with lupus and their loved ones and is a burden on society.[31] Major factors that negatively impact work outcomes are fatigue, disease activity, and organ damage. In one lupus cohort, of the 511 patients employed at diagnosis, 249 (49%) experienced work loss within an average disease duration of 13 years. The proportion of patients who lost their jobs since diagnosis was almost doubled for African Americans than for whites.[32] Assuming that both treatments have the potential to reduce inflammation, address symptomology and disease activity with less toxicity, and have a significant impact on improving return to work and/or overall productivity vs. the comparator; therefore, to the extent that ICER can adjust or account for this contextual consideration will be substantial.

Finally, there are several mechanisms for delivery for LN medications including oral formulations, subcutaneous injections, and infused therapies. Promoting shared decision-making that includes patients and care partners in the process of choosing the best treatment delivery method can improve adherence, outcomes and the value of the treatment. As stated at the Lupus PFDD Meeting and captured in *Lupus: Patient Voices,* "Some treatments impacted their ability to go to work or school, both because of the time required for treatments such as infusions and because medication side effects made them feel too ill. The time and travel required to access kidney dialysis or infusion therapy was also selected as an impediment for many people."[33] Effective treatment can reduce the severity and frequency of lupus disease activity and decelerate its progression, circumvent debilitating symptoms, and avoid complications and long-term disability, thus enabling individuals to remain productive.

In conclusion, we commend ICER for your goal to review potential lupus nephritis therapies but are concerned that there are significant gaps within the current scoping document that require examination. As we have noted, there are other contextual considerations for people with lupus and lupus nephritis such as educational progression, professional development and motherhood that are not commonly captured in quality of life scores yet their importance to the person with the disease and/or their care partners cannot be understated.[34] We submit the testimony of lupus warriors from the Lupus PFDD meeting while working to address the quantification of this value through future research. As ICER embarks on its research, we strongly recommend that your analyses reflect the true diversity of the LN population and the racial disparities, the overall impacts of ESRD, as well as the heterogeneity of LN, the steroid sparing effect, the impacts to productivity, the burden of informal care, and patient choice in treatment administration method with the goal to improve productivity and overall quality of life.

Thank you for the opportunity to provide our unique patient-driven perspective on this important issue and we look forward to continuing to engage with ICER as this review moves forward.

Respectfully submitted,

Kathleen A. Arntsen, LADA President & CEO

[1] National Institute of Arthritis and Musculoskeletal and Skin Diseases *National Institutes of Health Action Plan for Lupus Research*, 2015.
[2] Lupus and Allied Diseases Association, Lupus Foundation of America, Lupus Research Alliance, *Lupus: Patient Voices, Report Summary*, 2018;2.
[3] Lupus and Allied Diseases Association, Lupus Foundation of America, Lupus Research Alliance, *Lupus Patient-Focused Drug Development Meeting: Community Representative, Opening Remarks*, 2018; At 15:20 – 35:00. https://youtu.be/nG6sDBgeKUM
[4] Lupus and Allied Diseases Association, Lupus Foundation of America, Lupus Research Alliance, *Lupus: Patient Voices, Treatment preferences and perspectives on an ideal treatment*, 2018;28.
[5] Manzi S, Raymond S, Tse K, et al. Global consensus building and prioritisation of fundamental lupus challenges: The ALPHA project. *Lupus Sci Med*. 2019 Jul 19;6(1):e000342.
[6] Lupus and Allied Diseases Association, Lupus Foundation of America, Lupus Research Alliance, *Lupus Patient-Focused Drug Development Meeting: Community Representative, Opening Remarks*, 2018; At 15:20 – 35:00. https://youtu.be/nG6sDBgeKUM
[7] Lupus and Allied Diseases Association, Lupus Foundation of America, Lupus Research Alliance, *Lupus Patient-Focused Drug Development Meeting: Community Representative, Opening Remarks*, 2018; At 15:20 – 35:00. https://youtu.be/nG6sDBgeKUM
[8] Wallace, D.J., & Hahn, B.H. (2018). Dubois' lupus erythematosus and related syndromes. (9th ed.) Philadelphia, PA: Elsevier.
[9] Manzi S, Raymond S, Tse K, et al. Global consensus building and prioritisation of fundamental lupus challenges: The ALPHA project. *Lupus Sci Med*. 2019 Jul 19;6(1):e000342.
[10] Bichile T, Petri M. Prevention and management of co-morbidities in SLE. *Presse Med*. 2014;43(6 Pt 2):e187-e195. doi:10.1016/j.lpm.2014.03.009.
[11] Lupus and Allied Diseases Association, Lupus Foundation of America, Lupus Research Alliance, *Lupus: Patient Voices, Negative impacts of treatment*, 2018;26.
[12] Kasturi S, Sammaritano LR. Corticosteroids in Lupus. *Rheum Dis Clin North Am*. 2016;42(1):47-viii. doi:10.1016/j.rdc.2015.08.007.
[13] Zonana-Nacach A, Barr SG, Magder LS, Petri M. Damage in systemic lupus erythematosus and its association with corticosteroids. *Arthritis Rheum*. 2000;43(8):1801-1808. doi:10.1002/1529-0131(200008)43:8<1801::AID-ANR16>3.0.CO;2-O.
[14] Stojan G, Petri M. The risk benefit ratio of glucocorticoids in SLE: have things changed over the past 40 years?. *Curr Treatm Opt Rheumatol*. 2017;3(3):164-172. doi:10.1007/s40674-017-0069-8.
[15] Thamer M, Hernán MA, Zhang Y, Cotter D, Petri M. Prednisone, lupus activity, and permanent organ damage. *J Rheumatol*. 2009;36(3):560-564. doi:10.3899/jrheum.080828.
[16] Manzi S, Raymond S, Tse K, et al. Global consensus building and prioritisation of fundamental lupus challenges: The ALPHA project. *Lupus Sci Med*. 2019 Jul 19;6(1):e000342.
[17] Almaani S, Meara A, Rovin BH. Update on Lupus Nephritis. *Clin J Am Soc Nephrol*. 2017;12(5):825-835. doi:10.2215/CJN.05780616.
[18] Danila MI, Pons-Estel GJ, Zhang J, Vila LM, Reveille JD, Alarcon GS. Renal damage is the most important predictor of mortality within the damage index: data from LUMINA LXIV, a multiethnic US cohort. Rheumatology. 2008;48:542–545.
[19] Mok CC, Kwok RC, Yip PS. Effect of renal disease on the standardized mortality ratio and life expectancy of patients with systemic lupus erythematosus. *Arthritis Rheum*. 2013;65(8):2154-2160. doi:10.1002/art.38006.
[20] Yap DYH, Tang CSO, Ma MKM, Lam MF, Chan TM. Survival analysis and causes of mortality in patients with lupus nephritis. Nephrol Dial Transplant. 2012;27:3248–3254.
[21] Tektonidou MG, Lewandowski LB, Hu J, et al.: Survival in adults and children with systemic lupus erythematosus: A systematic review and bayesian meta-analysis of studies from 1950 to 2016. *Annals of the rheumatic diseases* (2017) annrheumdis-2017-211663\
[22] Korbet SM, Schwartz MM, Evans J, Lewis EJ. Severe lupus nephritis: racial differences in presentation and outcome. Journal of the American Society of Nephrology. 2007 Jan 1;18(1):244-54.
[23] Butkus DE, Meydrech EF, Raju SS. Racial differences in the survival of cadaveric renal allografts: overriding effects of HLA matching and socioeconomic factors. New England Journal of Medicine. 1992 Sep 17;327(12):840-5.
[24] Nee R, Jindal RM, Little D, Ramsey-Goldman R, Agodoa L, Hurst FP, Abbott KC. Racial differences and income disparities are associated with poor outcomes in kidney transplant recipients with lupus nephritis. Transplantation. 2013 Jun 27;95(12):1471-8.
[25] Nee R, Jindal RM, Little D, Ramsey-Goldman R, Agodoa L, Hurst FP, Abbott KC. Racial differences and income disparities are associated with poor outcomes in kidney transplant recipients with lupus nephritis. Transplantation. 2013 Jun 27;95(12):1471-8.
[26] Lupus and Allied Diseases Association, Lupus Foundation of America, Lupus Research Alliance, *Lupus: Patient Voices, Treatment preferences and perspectives on an ideal treatment*, 2018;28.

[27] Lupus and Allied Diseases Association, Lupus Foundation of America, Lupus Research Alliance, *Lupus Patient-Focused Drug Development Meeting: Community Representative, Opening Remarks*, 2018; At 15:20 – 35:00. https://youtu.be/nG6sDBgeKUM

[28] Baker K, Pope J. Employment and work disability in systemic lupus erythematosus: a systematic review. *Rheumatology* 2009, 48:281.

[29] Demas KL, Costenbader KH. Curr Opin Rheumatol. 2009, 21: 102.

[30] Agarwal N, Kumar V. Burden of lupus on work: Issues in the employment of individuals with lupus. *Work.* 2016;55(2):429-439. doi:10.3233/WOR-162398

[31] Lupus and Allied Diseases Association, Lupus Foundation of America, Lupus Research Alliance, *Lupus: Patient Voices, Conclusion*, 2018;34.

[32] Drenkard C, Bao G, Dennis G, et al. Burden of systemic lupus erythematosus on employment and work productivity: data from a large cohort in the southeastern United States. *Arthritis Care Res (Hoboken)*. 2014;66(6):878-887. doi:10.1002/acr.22245

[33] Lupus and Allied Diseases Association, Lupus Foundation of America, Lupus Research Alliance, *Lupus: Patient Voices, Negative impacts of treatment*, 2018;26.

[34] Lupus and Allied Diseases Association, Lupus Foundation of America, Lupus Research Alliance, *Lupus: Patient Voices, Kidney Problems*, 2018;15.

Help Us Solve
The Cruel Mystery
LUPUS
FOUNDATION OF AMERICA

RE: **Response to Draft Background & Scope for Assessment of Comparative Clinical Effectiveness and Value of voclosporin (Aurinia Pharmaceuticals, Inc.) and belimumab (BENLYSTA®, GlaxoSmithKline).**

The Lupus Foundation of America (LFA) is pleased to provide comments and recommendations on the draft scoping document for ICER's planned assessment of voclosporin (Aurinia Pharmaceuticals, Inc.) and belimumab (BENLYSTA®, GlaxoSmithKline) to treat lupus nephritis. We appreciate the opportunity to comment and to actively participate in this review.

COMMENTS ON DRAFT SCOPING DOCUMENT

Given the limited treatment options available to people with lupus, including lupus nephritis (LN), the ICER review must be conducted with careful consideration of the unmet medical need and the well-documented complexity of this disease. In particular, the ICER review must be appropriately sensitive to the disproportionate burden of LN on Black and Hispanic/Latino, Native American and Asian Americans, as well as the fact that specific medications may have greater value for specific subpopulations. In the following material, LFA offers input on specific sections of the draft scoping document. We urge ICER to continue to engage LFA and other key stakeholders for input throughout the assessment process. In addition to sharing resources developed by LFA, we are prepared to connect ICER with clinicians experienced in treating lupus nephritis and patients living with this disease to provide critical insights for the assessment. We also are prepared to aggregate patient or provider experience for ICER as needed.

Populations

ICER has stated its intent to focus the assessment on adult patients with Class III, IV, or V LN lupus nephritis. As described above, people of color, especially Black and Hispanic/Latino Americans, are disproportionately impacted by LN. People in these populations are more likely to have worse health outcomes and lower quality of care than white patients. As such, we strongly urge ICER to include a focus on these populations in the assessment. We also encourage ICER to include other underserved groups in the analysis, such as those with lower socioeconomic status, and living in rural and urban areas. Although we understand ICER will not include pediatric populations in this analysis, we encourage sensitivity to the impact of LN on children and teens. Up to 20 percent of people with systemic lupus erythematosus are diagnosed during childhood and many (40-70 percent) will develop LN.[i] Individuals diagnosed as children may see more rapid disease progression and the mortality rate for pediatric individuals is 19 times higher than for adults.[ii] It may be helpful for ICER to use this as context for its assessment of the value of the therapies, such as how effective the treatments are in adults diagnosed as children compared to those whose disease symptoms emerged later in life.

Comparators

ICER has stated its intent to compare voclosporin and belimumab to one another, but LFA is not aware of any reliable head-to-head data comparing these two treatments. As such, we recommend ICER focus on a comparison of each of the therapies with standard treatment. We are concerned that in the absence of solid evidence to support a comparative analysis there will be unintended harm to subpopulations which may respond more strongly to one therapy or another or who may have specific preferences for one therapy or the other. As noted earlier, most people with lupus, even those on immunosuppressants, take more than one treatment to manage their symptoms. The draft scoping document does not describe how ICER intends to account for effects of background medications in its assessment of the two new treatments compared to standard therapy. We urge ICER to consider how potential effects (both benefits and side effects)

of background medications can be factored into the assessment.

Settings

Although the focus of the assessment is on outpatient settings in the United States, we encourage ICER to consider international trial data as well. Most trials of prospective lupus therapies include a substantial number of international participants from countries outside the United States. Given the underrepresentation of certain racial and ethnic populations in many trials, the inclusion of trial participants from outside the United State is important to provide a more complete understanding of the value of these therapies.

Outcomes

Although the measures currently identified by ICER touch on some outcomes that are important to people with lupus, such as achieving disease remission and avoiding renal failure, they do not account for reduction in other symptoms that have a significant impact on patients' daily lives. The 2017 survey, which included 427 people with lupus nephritis, asked respondents to select the symptoms that have the most negative impact on their daily lives. Twenty one percent of these individuals selected renal failure, but a greater percentage of respondents cited fatigue (24 percent) and joint and muscle pain or swelling (24 percent) as the symptoms having the most negative impact.[iii] We strongly urge ICER to consider adding patient-centric outcomes that focus on these symptoms when assessing the effectiveness of voclosporin and belimumab. A significant challenge of currently available lupus treatment options are the severity and frequency of side effects. In the 2017 survey of more than 2,000 lupus patients, over half of respondents said that side effects were the biggest downside of their current treatments, more so than any other factor.[iv] Common side effects include fatigue, skin problems or rashes, site locations, eye problems and bone thinning. As such, we urge ICER to closely consider potential side effects of voclosporin and belimumab when assessing their value as compared to standard care. ICER also should include steroid-sparing as a key outcome. Steroids are often a first line of defense against lupus symptoms, but long-term use of these drugs can be highly detrimental. A review of recent lupus clinical trials found that even in cases where the primary trial endpoint was not met, secondary or composite endpoints that included steroid-sparing outcome measures were met.[v] Given that the standard treatment in this assessment include steroids, ICER should consider how steroid-sparing effects may factor into the value of voclosporin and belimumab.

Timing

In the Outcomes section of the scoping document, ICER noted its intent to use proteinuria to gauge complete renal remission after one year. The Timing section of the document, however, says that studies of at least 24-weeks duration will be considered. We ask ICER to provide additional clarity on the duration of studies to be included and the points at which outcomes will be assessed. We ask ICER to ensure that studies that may be shorter in duration are considered as many studies do not go on for a year.

Potential Benefits and Other Contextual Considerations

We commend ICER for including productivity changes and other indirect costs in its analysis of the cost of LN. Improving productivity is a very important outcome for LN patients. The chronic nature of lupus, with worsening symptoms during periodic flares, makes it difficult for many people with this disease to regularly attend school or work. Even when they are able to attend, symptoms such as fatigue and joint pain can make it difficult for them to perform well. Productivity also can be negatively impacted by the administration of treatments, which may require patients to take time away from work or school. Those in underserved areas may have to

travel long distances to access their treatments and the time and money spent traveling represent other indirect costs that may be relevant to ICER's assessment. A survey of over 2,000 lupus patients conducted by LFA and partner organizations in 2017 found that over 80% of respondents' symptoms have a moderate impact on their daily lives on their best days, and nearly 68% of respondents said their symptoms have a very high impact on their lives on their worst days. The survey[vi], which included 427 people with lupus nephritis, asked respondents to select what factors they take into account when making a decision about a treatment plan. Nearly 40 percent of the 427 people with LN selected how it will impact their ability to get through the work or school day. Respondents also took multiple medications to manage their disease but over 50 percent said their disease is only under moderate control (defined as having some flares and possibly requiring dose changes in current medications).[vii] Moreover, a 2014 study showed on average people with lupus take nearly eight medications to manage all their medical conditions, including lupus.[viii] In the same study, the majority of people with lupus surveyed (89%) answered lupus impacts their work life. More than half (55%) of people with lupus surveyed whose work was affected were working part-time, intermittently or were unemployed because of lupus. Many people with lupus are also concerned about the burden that their disease places on family members and caregivers.[ix] These burdens can include missing work to care for the person with lupus, healthcare and prescription drug costs, and the emotional burden of caring for a loved one with a chronic, progressive disease. We urge ICER to consider whether the selected treatments may result in a reduced burden not only for people with LN, but their family and caregivers, as well.

We note that ICER intends to use quality-adjusted life years (QALYs) gained as a measure of clinical benefit of belimumab and voclosporin. This measure is problematic because, as is true for individuals living with other chronic diseases, even if people with LN experience significant benefits and symptom improvement from a treatment, their QALY measurement will still be lower compared to a fully healthy person. Given the significant unmet medical needs of the lupus population, symptom improvement would be a meaningful benefit of a treatment. By relying on QALYs gained as a key measurement of treatment value, ICER risks having study results that support more limited coverage for lupus treatments that offer valuable benefits but fall short of restoring patients to entirely good health. In addition, QALYs gained is a problematic measure of value because it is not representative of non-white populations. Two frequently used studies on lupus QALYs focus on a population that is 76 percent white,[x,xi] thereby making them unreliable references for assessing treatment outcomes for a disease that disproportionately impacts people of color. The diversity of the lupus population makes it essential for ICER's outcome measures to be applicable to people of all races and ethnicities, so we urge ICER to reconsider the use of QALYs gained in its assessment.

The Lupus Foundation stands ready to be a resource for a well-informed and comprehensive process. If you have any questions, please contact me at wildman@lupus.org.

Sincerely,

Pat Wildman
Vice President, Advocacy & Government Relations

[i] Wenderfer, S., Ruth, N. & Brunner, H. Advances in the care of children with lupus nephritis. Pediatr Res 81, 406–414 (2017). https://doi.org/10.1038/pr.2016.247

[ii] Pinheiro SVB, Dias RF, Fabiano RCG, Araujo SA, Silva ACSE. Pediatric lupus nephritis. J Bras Nefrol. 2019;41(2):252-265. https://doi.org/10.1590/2175-8239-JBN-2018-0097

[iii] Lupus and Allied Diseases Association, Lupus Foundation of America, Lupus Research Alliance. Lupus: Patient Voices. 2017. http://lupuspfdd.org/LupusPatientVoicesFINAL.pdf

[iv] Lupus and Allied Diseases Association, Lupus Foundation of America, Lupus Research Alliance. Lupus: Patient Voices. 2017. http://lupuspfdd.org/LupusPatientVoicesFINAL.pdf

[v] e Oon S, Huq M, Nikpour M. Systematic review, and meta-analysis of steroid-sparing effect, of biologic agents in randomized, placebo-controlled phase 3 trials for systemic lupus erythematosus. Seminars in Arthritis and Rheumatism. Vol 48, Issue 2 (2018). http://www.sciencedirect.com/science/article/pii/S0049017217305796

[vi] Lupus and Allied Diseases Association, Lupus Foundation of America, Lupus Research Alliance. Lupus: Patient Voices. 2017. http://lupuspfdd.org/LupusPatientVoicesFINAL.pdf

[vii] Lupus and Allied Diseases Association, Lupus Foundation of America, Lupus Research Alliance. Lupus: Patient Voices. 2017. http://lupuspfdd.org/LupusPatientVoicesFINAL.pdf

[viii] Al Sawah, S et al. "The caregiver burden in lupus: findings from UNVEIL, a national online lupus survey in the United States." *Lupus* vol. 26,1 (2017): 54-61. doi:10.1177/0961203316651743

[ix] Al Sawah, S et al. "The caregiver burden in lupus: findings from UNVEIL, a national online lupus survey in the United States." *Lupus* vol. 26,1 (2017): 54-61. doi:10.1177/0961203316651743

[x] Grootscholten C., Snoek F. J., Bijl M., et al. Health-related quality of life and treatment burden in patients with proliferative lupus nephritis treated with cyclophosphamide or azathioprine/ methylprednisolone in a randomized controlled trial. Journal of Rheumatology.2007;34(8):1699–1707. Link.

[xi] Clarke A. E., Panopalis P., Petri M., et al. SLE patients with renal damage incur higher health care costs. Rheumatology. 2008;47(3):329–333.

Additional References for consideration

There is a robust body of literature on the lupus disease burden, economic burden, disparities in care, and patient perspectives on these topics. As ICER refines the draft scoping document, we encourage reviewers to consider existing research on these topics, including articles referenced earlier in LFA's open comment period letter. In addition, we recommend ICER review the following articles during the assessment process.

- Evidence for Management of Lupus Nephritis at Different Stages of Disease Progression: Management of lupus nephritis: a systematic literature review informing the 2019 update of the joint EULAR and European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations (2020).
- Economic Burden: Economic evaluation of lupus nephritis in the Systemic Lupus International Collaborating Clinics inception cohort using a multistate model approach (2018).
- Impact of Lupus Nephritis on Minorities: Quality of Care for Incident Lupus Nephritis Among Medicaid Beneficiaries in the United States (2013).
- Impact of Lupus on Pediatrics Patients
    - Pediatric lupus nephritis (2018).
    - Predictors of disability in a childhood-onset systemic lupus erythematosus cohort: results from the CARRA Legacy Registry (2017).
- Quality of Life: Quality of life comparison between corticosteroid- and-mycofenolate mofetil and corticosteroid- and-oral cyclophosphamide in the treatment of severe lupus nephritis. *Lupus* vol. 15,6 (2006)

Steven D. Pearson, MD, MSc, President
Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109
Via email: publiccomments@icer-review.org

September 21, 2020

Re: Comments on Draft Scoping Document for Lupus Nephritis

Dear Dr. Pearson,

Thank you for the opportunity to provide input on ICER's Draft Background and Scope document for lupus nephritis. On behalf of the Lupus Research Alliance, I am submitting these comments for your consideration.

The Lupus Research Alliance (LRA) is the largest non-governmental, non-profit funder of lupus research worldwide. The LRA aims to transform treatment while advancing toward a cure by funding the most innovative lupus research, fostering diverse scientific talent, stimulating collaborations and driving discovery toward better diagnostics, improved treatments and ultimately a cure for lupus. Lupus Therapeutics (LT), an affiliate of the LRA, aims to accelerate drug discovery and diagnostic innovation for all patients living with lupus. LT engages with biotechnology and pharmaceutical industry, as well as other investigators, to bring clinical trials to real people living with lupus. Together we aim to place the patient voice at the center with the most creative clinicians and scientists in the world.

In the draft document, ICER encourages stakeholder comments on the elements in Table 1.2, Potential Other Benefits or Disadvantages and Contextual Considerations. As indicated in our comments submitted on August 26 in response to the open input period, we currently have several projects underway to better understand the management of lupus nephritis from healthcare providers as well as the experience of people with lupus nephritis. We will take this opportunity to share some preliminary findings for contextual considerations.

First, we would like to address the Patient-Important Outcomes listed on page 4 of the draft scope document. These are not necessarily the concerns most important to patients. In the survey conducted for the externally-led Patient-Focused Drug Development initiative and reported in *Lupus: Patient Voices*, people with lupus nephritis indicated that fatigue, joint and muscle pain and/or swelling, along with renal disease or renal failure as the top three symptoms that most negatively impact their life. These

are important quality-of-life issues that may not be captured in clinical trial data. ICER's 2020-2023 Value Assessment Framework acknowledges that clinical trial data may not capture what is most important to patients but that there are important contextual considerations to be included in this process.

We feel it is important to reiterate that lupus disproportionately impacts people of color. Recruitment of these traditionally underserved populations to participate in clinical trials has proven particularly challenging; therefore, clinical trial data may not fully capture the experience of these populations. African American and Hispanic lupus patients in the United States are disproportionately affected by lupus nephritis. The disease incidence in this population is significantly higher than in white patients.[i] Furthermore, Black and Hispanic lupus patients develop lupus nephritis earlier and have poorer outcomes compared to their white counterparts.[iiiii] Disturbingly, nearly half of the patients with end-stage renal disease (ESRD) due to lupus nephritis are African American.[iv] Thus, it is critically important that medications for lupus nephritis be made accessible to the patient populations affected most severely by this disease and that real-world evidence is captured to fully understand the clinical effectiveness.

There are concerns that value assessments such as QALYs do not do a good job of accounting for patient heterogeneity. Given that lupus is a heterogeneous disease as is the population impacted, we would like to understand how ICER will address this in its evaluation of lupus nephritis treatments.

The Lupus Research Alliance and National Kidney Foundation (NKF) are collaborating to better understand the management of lupus nephritis from the perspective of healthcare providers and patients. Two surveys were conducted, one among those who treat lupus nephritis and one among those who live with it. Combined, these surveys provide vital information on how lupus nephritis is being managed and the need for new targeted treatments. We are sharing some preliminary results from the patient survey to help inform contextual considerations.

Five-hundred fifty-one adults with chronic kidney disease (CKD), lupus, and lupus nephritis, singly or in any combination completed the second survey exploring the awareness and experience related to these conditions. When asked about how often respondents faced certain barriers in managing their health, anywhere from 70% to 84% reported they experienced the following at least some of the time: side effects or reactions to treatment medications, cost of medication, insufficient disease control with treatment, limitation of available treatments, difficulty following all recommended care and treatment, and access to medication. Of note, when looking at the responses by race, non-white respondents reported experiencing all these barriers at a higher percentage then their white counterparts.

We aim to eliminate barriers to care for all patients with lupus and lupus nephritis so they can live lives that are not focused on the daily burden of their disease. In order to do so, we need to understand and address the disparities experienced by people of different races and socio-economic status. We would

like to ensure that the heterogeneity of lupus nephritis is addressed in your review and recommendations. This is a complex disease in which the provider and patient should determine the best course of care for each individual.

Conducting an assessment on medications that have yet to be approved by the U.S. Food and Drug Administration for which there is only clinical trial data and no real-world, long-term evidence could contribute to rather than alleviate some of the barriers noted above. We encourage you to take this under consideration, and we appreciate the opportunity to provide input.

Sincerely,

Kenneth M. Farber
President and Chief Executive Officer

---

[i] Bastian HM, Roseman JM, McGwin Jr G et al. Systemic lupus erythematosus in three ethnic groups. XII. Risk factors for lupus nephritis after diagnosis. *Lupus*. 2002. 11:152–160.

[ii] Burgos PI, McGwin G, Pons-Estel GJ, et. al.: US patients of Hispanic and African ancestry develop lupus nephritis early in the disease course: Data from LUMINA, a multiethnic US cohort (LUMINA LXXIV). *Ann Rheum Dis*. 2011. 70:393–394.

[iii] Contreras G, Lenz O, Pardo V, et. al.: Outcomes in African Americans and Hispanics with lupus nephritis. *Kidney Int*. 2006. 69:1846–1851.

[iv] Nee R, Martinez-Osorio J, Yuan CM, et. al.: Survival Disparity of African American Versus Non-African American Patients With ESRD Due to SLE. *Am J Kidney Dis*. 2015. 66:630–637.

UNIVERSITY OF MINNESOTA

Twin Cities Campus
College of Pharmacy

Graduate Program in Social & Administrative Pharmacy

7-155 Weaver-Densford Hall
308 Harvard Street S.E.
Minneapolis, MN 55455

Dr S D Pearson
President
Institute for Clinical and Economic Review
Two Liberty Square, 9th Floor
BOSTON MA 02109

20 September 2020

Submitted via Email

Email: publiccomments@icer-review.org

My dear Dr Pearson

VOCLOSPORIN AND BELIMUMAB FOR LUPUS NEPHRITIS

COMMENT ON DRAFT BACKGROUND AND SCOPE

Thank you for this valuable opportunity to comment on this background and scope.

I want to restrict my comments to the standards of normal science: the presumption that any claims made, comparative or otherwise, should be credible, empirically evaluable and replicable across target treating populations. Otherwise we have a value assessment plan that is pseudoscience; it lacks empirically evaluable claims and joins with the standards set in intelligent design (as opposed to evolutionary biology or natural selection).

You are, I know, aware of the criticisms that that have been directed to your reference case approach to value assessment: the construction of a lifetime simulation model, driven by assumptions, to create imaginary information (it is certainly not evidence that would meet the scientific definition) [1]. This is, as I have noted on many previous occasions, nonsensical [2]. Of course it can be defended by the argument that it is the attempt to create and model quality adjusted life years (QALYS). This is ridiculous: a QALY is an impossible mathematical construct [3] [4]. This failure, applying the axioms of fundamental measurement, is well established as the EQ-5D-3L or other multiattribute utility you propose to use to create QALYs is an ordinal measure. You cannot multiply time spent by an ordinal

measure. You have recognized this when unable to provide a proof that the EQ-5D, as an example, only has ordinal scaling properties. Your defense has been that 'you have the understanding' the EQ-5D has ratio properties. This is insufficient [5].

A review of the various outcomes measures either developed for lupus (typically systemic lupus erythematosus) or a generic instrument applied to a lupus target group demonstrates, with one notable exception (the L-QoI) a failure to understand the limitations imposed by the axioms of fundamental measurement. The Holloway et al review takes a classical test theory perspective without understanding the need for at least interval scale properties [6]. None of the instruments reviewed for application and reporting in lupus populations met the required measurement standards. They are all ordinal measures. The Yazdany review of the LupusQoL, SLEQoL and L-QoL review, although arguing for disease specific measures (correctly) in lupus response to therapy, overlooks also the limitations imposed by the axioms of fundamental measurement [7]. Indeed, little if any though seems to have been given by authors or reviewers to the need for unidimensionality and the assessment of therapy response. If you think there is an instrument with ratio utility scale properties to support QALYS then you will have a fruitless search (even if you try to argue for a generic instrument such as the Eq-5D-3L). It is worth noting the last few sentences of the L-QoL paper:

> ***It is concluded that the psychometric and scaling properties of the L-QoL indicate that researchers and clinicians can have confidence in the scores obtained by respondents on the measure. The fit to the Rasch model provides an interval scale translation for use in parametric analysis, including the calculation of change scores. It will serve as a valuable tool for assessing the impact of SLE and is treatment on QoL in clinical settings, trials and research studies. Such an instrument will allow accurate measurement of the effectiveness of interventions from the patient's perspective [8].***

Needless to say, the L-QoL is not a ratio scale (and was never intended to be). It cannot support multiplication and division and hence QALYs.

Alas, it would appear from your document that you intend, despite criticisms, to follow precisely this route. You propose to ignore the axioms of fundamental measurement (an unnecessary distraction?) and develop an economic model to provide imaginary information in support of non-evaluable lifetime cost-per-QALY claims. Indeed, you propose two alternative imaginary frameworks. Imaginary non-evaluable health outcomes for each product you are proposing include imaginary averted clinical cases, patients avoiding dialysis, kidney transplants avoided, life years gained, quality adjusted life years gained and equal value of life years gained. Presumably there is any number of lupus lifetime imaginary models that could produce any number of non-evaluable competing claims.

My concern is that any recommendations you may make for pricing, access and budget impact may lead to denial of access to products by formulary committees who take your modeling at face value. In short, patients are at risk. Imaginary modeled information is not the answer. While you refer to this

imaginary confection as providing 'evidence', it certainly is not evidence that would meet the standards of normal science.

I recognize that you will brush these criticisms aside. However, I feel it important that other stakeholders including patients, advocates and manufacturers are aware at this early stage of these fatal limitations on your proposed value assessment, recognizing that the value assessment framework is, frankly, a waste of time. Even if defended by proposed scenarios and uncertainty parameters, it is still a waste of time. Nothing you conclude is empirically evaluable in treatment settings: we don't know if you are right, if you are wrong and we will never know (perhaps we were never intended to know). You might suggest an alternative framework that has scientific credibility.

If you or any stakeholder wishes additional information on inappropriate value assessment claims please feel free to contact me.

Yours sincerely

Paul C. Langley, Ph.D.
Adjunct Professor
College of Pharmacy
University of Minnesota
MINNEAPOLIS MN
Director
Maimon Research LLC
TUCSON AZ
Email: langley@maimonresearch.com
Website: www.maimonresearch.net

REFERENCES

[1] Langley P. Nonsense on Stilts – Part 1: The ICER 2020-2023 value assessment framework for constructing imaginary worlds. *Inov Pharm*. 2020;11(1):No. 12
https://pubs.lib.umn.edu/index.php/innovations/article/view/2444/2348

[2] Langley PC. More Unnecessary Imaginary Worlds – Part 4: The ICER Evidence Report for Crizanlizumab, Voxelotor and L-Glutamine for Sickle Cell Disease. *Inov Pharm*. 2020; 11(2): No.7
https://pubs.lib.umn.edu/index.php/innovations/article/view/3123/2375

[3] Langley P. The Great I-QALY Disaster. *Inov Pharm*. 2020;11(3): No 7
https://pubs.lib.umn.edu/index.php/innovations/article/view/3359/2517

[4] Langley PC and McKenna SP. Measurement, modeling and QALYs [version 1; peer review: awaiting peer review] F1000Research 2020, 9:1048 https://doi.org/10.12688/f1000research.25039.1

[5] Langley P. The Impossible QALY and the Denial of Fundamental Measurement: Rejecting the University of Washington Value Assessment of Targeted Immune Modulators (TIMS) in Ulcerative Colitis for the Institute for Clinical and Economic Review (ICER). *InovPharm*.2020;11(2): No 17
https://pubs.lib.umn.edu/index.php/innovations/article/view/3330/2533
https://doi.org/10.24926/iip.v11i3.3330

[6] Holloway L, Humphrey L, Heron L et al. Patient-reported outcome measures for systematic lupus erythematosus clinical trials,: a review of content validity, face validity and psychometric performance. *Health Quality Life Outcomes.* 2014;12:116

[7] Yazdany J. Health-related quality of life measurement in systematic lupus erythematosus: The LupusQoL, SLEQoL and L-QoL. *Arthritis Care Res (Hoboken)*. 2011;63(11): S413-S419

[8] Doward LC, McKenna SP, Whalley D et al. The development of the L-QoL: a quality of life instrument specific to systemic lupus erythematosus. *Ann Rheum Dis*. 2009;68:196-200