COLLEGE OF PHARMACY
UNIVERSITY OF UTAH

L. S. SKAGGS PHARMACY INSTITUTE

UTAH MEDICAID DUR REPORT
JANUARY 2022

NEWLY APPROVED MEDICATIONS FOR LUPUS NEPHRITIS: BELIMUMAB (BENLYSTA) VOCLOSPORIN (LUPKYNIS)

Report Finalized in December 2021

Report Presented in January 2022

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Abbreviations

ACR, American College of Rheumatology

BLyS, B-lymphocyte stimulator-specific inhibitor

CDC, Centers for Disease Control and Prevention

CNI, calcineurin inhibitor immunosuppressant

EULAR/ERA-EDTA, European League Against Rheumatism and European Renal Association–European Dialysis and Transplant Association

ICER, Institute for Clinical and Economic Review

ISN/RPS, International Society of Nephrology/ Renal Pathology Society

KDIGO, Kidney Disease, Improving Global Outcomes

LN, lupus nephritis

MMF, mycophenolate mofetil

MPA, mycophenolic analog

NSAIDs, non-steroidal anti-inflammatory drugs

RBC/hpf, red blood cells by high power field

SLE, systemic lupus erythematosus

SLICC, Systemic Lupus International Collaborating Clinics

WBC/hpf, while blood cells by high power field

Introduction

Lupus nephritis (**LN**) is a kidney disease caused by the chronic autoimmune disorder, systemic lupus erythematosus (**SLE**), also referred to as lupus. SLE causes inflammation and damage that can be widespread among various tissues and organs (eg, skin, joints, heart, lung, kidneys, blood cells, and brain), in addition to the kidneys.[1] LN manifests as chronic kidney inflammation, proteinuria, hematuria, and compromised kidney function that can ultimately progress to kidney failure. SLE is estimated to affect about 204,000 individuals in the US,[2] and approximately 38% of these individuals also have lupus nephritis.[3-5] Treatment goals are generally to control and prevent disease flares, reduce organ damage accrual, and slow or prevent kidney function decline in order to ultimately extend patient survival and improve disease-related quality of life.[6]

Belimumab and voclosporin are the first immunosuppressants approved for the treatment of lupus nephritis, following pivotal-trial demonstration of positive kidney-related outcomes with these therapies as add-on to standard immunosuppressants (eg, corticosteroids, mycophenolate, etc) in adults. Of these, belimumab (Benlysta) has additional approval for the treatment of SLE in general, in both pediatric and adults (prior approvals).[7] Belimumab is a B-lymphocyte stimulator-specific (BLyS) inhibitor that is administered parenterally (subcutaneously [SC] or intravenously [IV] for adults, or by IV route for pediatric patients).[8] Voclosporin (Lupkynis) is an oral calcineurin-inhibitor taken twice daily.[9]

The focus of this report is concerning the management of **lupus nephritis** and the two agents approved specifically for this manifestation of SLE.[8,9] Additional drugs are approved for the treatment of SLE[*] *but not LN*, and others may be used off-label for LN (some considered standard therapy); these agents are not reviewed in full, yet some background information may be included. **Table 1** provides the approved indications and recommended dosage for belimumab and voclosporin.

Table 1. FDA-Approved Uses and Dosage for Belimumab and Voclosporin[8,9]

Belimumab (Benlysta): supplied as a vial of 120 mg or 400 mg powder for reconstitution, for IV use (adult and pediatric use); 200 mg/mL prefilled autoinjector or single dose prefilled syringe for SC use (intended for adult use only); must be refrigerated

Indications

- **For adults with active lupus nephritis**, in combination with standard therapy
- **Systemic lupus erythematosus** in patients ≥5 years of age who have autoantibody-positive SLE and who are taking standard therapy
- *Limitations*: has not been evaluated in severe active central nervous system lupus or in combination with other biologics; thus, its use is not recommended in these situation.

IV dosage (for patients 5 years or older)

- Dose for SLE and LN: 10 mg/kg every 2-weeks for initial 3 doses, then every 4-weeks thereafter
- Must be reconstituted, diluted, and administered over a period of 1 hour by a healthcare provider equipped to respond to a possible anaphylaxis event. Consider premedication to prevent hypersensitivity. Monitor patients during infusion and after intravenous administration to address potential hypersensitivity and/or infusion related reaction

[*] For example, anifrolumab-fnia, was approved in 2021 for moderate to severe SLE along with standard therapy. However, it has not been evaluated in severe active lupus nephritis so is not recommended for use in this scenario per labeling.

Table 1. FDA-Approved Uses and Dosage for Belimumab and Voclosporin[8,9]

SC dosage (for patients 18 years or older)

- Dose for LN: 400-mg dose (two 200-mg injections or 2 prefilled syringes) once weekly for 4 doses, then 200 mg once weekly thereafter. Administered into abdomen or thigh
- Dose for SLE: 200 mg once weekly (into abdomen or thigh)
- The first SC dose should be under the supervision of a healthcare professional having provided proper training on technique and education about signs and symptoms of hypersensitivity reactions
- Refer to package insert for if transitioning between IV or SC route

Voclosporin (Lupkynis): supplied as 7.9 mg oral capsules

- **Indicated for adults with active lupus nephritis,** in combination with background immunosuppressive therapy
- *Limitations*:
  - Treatment beyond 1 year was not evaluated; consider risks vs. benefits of longer duration in light of the patient's response to therapy and risk of worsening nephrotoxicity[a]
  - Safety/ efficacy have not been established in combination with cyclophosphamide and is not recommended in this scenario
- Staring dose: **23.7 mg orally, twice a day**
  - Dose adjust with renal or hepatic impairment (see page 29). Not recommended in patients with baseline eGFR ≤ 45 mL/min unless benefits > risk; if used with severe renal impairment at baseline, initiate at a lower dosage (15.8 mg twice daily)
  - Swallow whole on an empty stomach; take as close to a 12-hour schedule as possible, with doses separated by at least 8 hours**.** Avoid eating or drinking grapefruit while on voclosporin.
- Assess eGFR Q2 weeks for the first month, and Q4 weeks thereafter
- Assess blood pressure Q2 weeks for the first month, and as clinically indicated thereafter

Abbreviations: eGFR, estimated glomerular filtration rate; SC, subcutaneous; IV, intravenous; LN, lupus nephritis; Q2, every 2; SLE, systemic lupus erythematosus

[a] This statement was not meant to be a strict cut off for stopping therapy, since FDA reviewers acknowledged that it is important to have room for individualized decision-making by the prescriber regarding treatment duration and potential benefits or harms of continuing or discontinuing treatment.[10] There is an ongoing extension study that will provide more clarification for voclosporin treatment longer than 1 year.[11]

Methods

Background information on the disease characterization, diagnosis, and treatment of lupus nephritis was sought through the following resources:

I. For treatment guidelines we searched websites including
   - Kidney Disease, Improving Global Outcomes: https://kdigo.org/guidelines/
   - American Academy of Rheumatology: https://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines
   - European League Against Rheumatology (EULAR): https://www.eular.org/recommendations_management.cfm
II. Clinicaltrials.gov was referenced to review trial information for these products

III. Professional prescribing information (ie, product labeling) was obtained from the drug sponsor's website for each brand product.

IV. Literature searches for expert reviews on lupus nephritis and the pivotal phase 3 trials were performed in Embase and Cochrane Library. See **Appendix 1** for keywords used.

Background

Lupus pathogenesis is thought to involve impaired clearance of cellular debris (eg, apoptosis material and neutrophil extracellular traps) which leads to over-activation of the immune system and inflammation.[12] Autoantibodies that target nuclear (ie, antinuclear antibodies [ANAs]) and cellular antigens are produced leading to immune complexes that accumulate and cause damage in the glomeruli.[13] Note that antinuclear antibodies are not specific to lupus as this may also be an issue of other diseases (eg, scleroderma, Sjögren's syndrome, polymyositis/dermatomyositis, mixed connective tissue disease, autoimmune hepatitis, juvenile arthritis, Raynaud's, etc).[14] However, anti-dsDNA and anti-Sm antibodies, are more specific to lupus.[15] Due to non-specific symptoms that can present in lupus (eg, fever, fatigue, weight loss, blood clots and hair loss, GI-symptoms, cognitive dysfunction), patients may experience a delay in the diagnosis and many are found to have already progressed to LN upon diagnosis. A delay in LN diagnosis and thus initiation of immunosuppressive treatment is associated with poor outcomes such as end-stage renal disease.[16]

SLE is estimated to affect about 204,000 individuals in the US, based on 2018 registry data from the Centers for Disease Control and Prevention (CDC).[2] About 70% of SLE cases follow a relapsing-remitting disease course, while the other 30% of cases are split, half following prolonged remission and the other half in persistently active disease.[17] More women than men suffer from SLE (about nine times more) and SLE occurs more often in persons of American Indian, Alaska Native, African American, Hispanics, or Asian decent (versus Caucasian).[1,2] SLE is usually diagnosed between the ages of 15 and 45 years. About 38% of those with SLE also have LN, which is the most common severe manifestation resulting from SLE progression and is associated with increased mortality.[3-5] As SLE is more common in women and usually diagnosed during reproductive years, there is treatment need during pregnancy. SLE and LN are associated with poor maternal and fetal outcomes such as premature birth, miscarriage, and intrauterine growth restriction; and additionally hypertension and preeclampsia/eclampsia with LN.[8,9] About 20% of SLE cases are in children.[5,12] Pediatric-onset SLE is usually more active than adult-onset SLE.[7] Thus, pediatric patients with SLE are at high risk of disease-related organ damage, particularly kidney and nervous system damage, and other SLE complications.[7,18] LN is more common in the presentation of childhood SLE vs. adult-onset SLE.[6]

Diagnosis

According to the 2012 guideline by the American College of Rheumatology (ACR), **lupus nephritis in SLE** is defined as "…persistent proteinuria >0.5 g per day or greater than 3+ by dipstick, and/**or** cellular casts including red cell, hemoglobin, granular, tubular or mixed," and if possible (ie, not contraindicated) should be supported by a renal biopsy demonstrating immune complex-mediated glomerulonephritis consistent with LN.[19] A substitute for the 24-hour protein measurement is a spot urine protein to creatinine ratio (UPCR) of >0.5; and a substitute for cellular casts is an active urinary sediment (>5 RBC/high power field [hpf], >5 WBC/hpf in the absence of infection, or cellular casts limited to RBC or WBC casts).[19]

Regarding SLE classification systems: There have been several classification systems published for defining SLE cases for purposes of clinical study enrollment: ACR 1997 criteria[20], 2012 SLICC criteria[21], and the 2019 EULAR/ACR criteria[22] are some examples. If a patient does not fully meet a certain threshold or score on a particular SLE classification system, the ACR has emphasized that this should not be the sole reason to exclude patients *in clinical practice* from therapies a rheumatologist or nephrologist deems appropriate. The ACR has expressed that the "Diagnosis of SLE remains the purview of an appropriately trained physician evaluating an individual patient,"[22] and that a diagnosis of lupus nephritis should be considered valid if deduced by a rheumatologist or nephrologist. Although rationale was not elaborated, it is possible that authors included this statement since there are nuances in the diagnosis of SLE as available classification criteria may not catch all affected SLE cases. Moreover, classification criteria for both LN and SLE are regularly revisited and debated as new biomarkers and definitions are continually added or improved.[22-26] Fanouriakis et al highlight that "Diagnostic criteria [for SLE] are not available and classification criteria are often used for diagnosis, yet with significant caveats."[17]

SLE classification criteria were designed mainly for purposes of enrollment into clinical trials and were not designed nor optimized for diagnosis or treatment decision-making for the clinical practice setting. Although classification criteria exist for research purposes, experts often reiterate that these do not substitute for the expert's clinical judgment when making a diagnosis of SLE.[17,22,27] Moreover, existing SLE criteria perform better in patients with longstanding disease rather than in new-onset disease.[22]

Autoantibody considerations: ANA testing results used in some classifications systems may not always be accurate depending on the performance of testing kits. There is also some subjectivity in the interpretation of ANA results.[28] Moreover, autoantibody positivity status can change throughout the disease, and may not be detected when immunosuppressants have already been initiated.[15] Certain SLE classification systems accepted autoantibody positivity at *anytime* in the patient's history (ie, does not need to be current) to count toward a marker of their disease.[21] Furthermore, "A negative ANA test cannot rule out SLE diagnosis, because up to 20% of patients may be negative (true or false negative) at various stages of the disease, although typically the rate of ANA-negative lupus is much lower."[17] In an updated review by experts (some of which authored recent LN guidelines), authors advise that for patients with suspected SLE but who are ANA-negative, other factors can be considered to indicate SLE such as low complement levels and/or positive anti-phospholipid antibodies.[17] There has been variability in ANA serology observed in SLE cohorts, with as many as 20–30% having a negative ANA result, despite most having a positive result in the past.[29] "One particular biomarker may only reflect one specific aspect of SLE but not be useful for reflecting the state of the disease as a whole."[30] In the 2012 SLICC SLE classification criteria, a patient can have *any* of the following immunologic markers of lupus (plus clinical signs) in order to be classified with SLE: positive ANA, anti-dsDNA, anti-Sm, or antiphospholipid antibody; or low compliment (C3, C4, or CH50); or direct Coombs test positivity (ie, RBC antibodies) in absence of hemolytic anemia.[21] Overall, experts propose putting emphasis on the big picture, including clinical presentation and *past* laboratory findings along with the physician's judgement, to overcome inherent difficulties in serologic testing for autoantibodies.[28]

Regarding renal biopsy: a patient or provider may choose to forgo renal biopsy if in presence of a contraindication, patient refusal or religious belief, thrombocytopenia, significant anemia, skin infection over biopsy approach site, inaccessible biopsy services, or if on chronic anticoagulation.[31,32] Not only may full anticoagulation be indicated for certain co-morbidities, patients may also be indicated for

anticoagulation while they have nephrotic syndrome (NS), especially if they experienced a previous event during NS.[5]

Overview of LN Treatment Approach

The treatment approach for LN, in recent treatment guidelines, is described according to histological classification of LN, using the 2003 LN classification system by the International Society of Nephrology/Renal Pathology Society (ISN/RPS). **Table 2** provides a brief description of the 2003 histological classes of LN and the general treatment approach for active disease. Class V LN is not mutually exclusive from other classes, as some patients may have membranous LN (Class V) in addition to Class III or IV LN. There are also numerous sub-classifications (not shown in the table) such as designations for active and/or chronic lesions in class III and IV. This classification system, however, is in the process of being revised to improve definitions and to apply active and chronic indices for all histologic classes (ie, activity and chronicity of disease are not confined only to class III and IV).[26] Pharmacological treatment for these LN classes will be further described in the *Treatment for Lupus Nephritis* section.

Table 2. General Treatment Approached Based on the Histological Class of Lupus Nephritis

LN Class Description[19,33]	General Treatment Approach[5,6]
Class I: Minimal mesangial LN: normal glomeruli by light microscopy but with minimal mesangial immune deposits by immunofluorescence **Class II**: Mesangial proliferative LN: hypercellularity or matrix expansion with immune deposits confined to mesangium	o Hydroxychloroquine is recommended o In the presence of low level proteinuria, immunosuppressive therapy is **guided by *extra-renal* manifestations** of lupus, which could require agents such as methotrexate, azathioprine, mycophenolate, cyclophosphamide, tacrolimus, and/or belimumab[34] o In the presence of nephrotic syndrome, consider glucocorticoid and another immunosuppressive agent if needed for relapses[5]
Class III: Focal LN: subendothelial immune deposits and lesions or scaring in <50% of glomeruli **Class IV**: Diffuse LN: subendothelial deposits and proliferative glomerular changes in ≥50% of glomeruli **Class V**: Membranous LN: subepithelial immune deposits and membranous thickening of glomerular capillaries; patients present with signs of nephrotic syndrome	**For *active* LN, treat with an immunosuppressive regimen to target renal response** o Standard therapies include glucocorticoids combined with mycophenolate, IV cyclophosphamide, or tacrolimus o Novel drugs, injectable belimumab or oral voclosporin, can be added onto standard therapy, as *initial* therapy of active LN Hydroxychloroquine should be continued as background therapy
Class VI: Advanced sclerosing LN: sclerosis in ≥90% of glomeruli: patients present with slowly progressive kidney dysfunction associated with proteinuria	o Hydroxychloroquine is recommended o Generally requires renal replacement (hemodialysis, peritoneal dialysis, or kidney transplantation) o Immunosuppressive treatment guided by extra-renal lupus manifestations

Abbreviations: IV, intravenous; LN, lupus nephritis

Additional Background Regarding Belimumab

Prior to the recent indication extension to adults with LN for belimumab, this agent was already approved for the treatment of SLE in pediatric and adult patients. Belimumab added to standard therapy reduced SLE disease activity (based on the SLE responder index) and steroid use in several placebo-controlled RCTs; yielded a clinically meaningful improvement in health-related quality of life based on pooled RCT study data; and was associated with minimized long-term organ damage accrual observed in an extension study over 8 years.[35-42] Enrolled patients in SLE phase 3 trials had active disease, despite using standard therapy, and were autoantibody positive (ie, antinuclear antibody (ANA) titer of ≥1:80 or anti-dsDNA antibody ≥30 IU/mL).[35-37,39,43] Excluded patients were those who recently received B-lymphocyte-targeted therapy (eg, rituximab), IV cyclophosphamide, anakinra, prednisone > 100 mg/day, plasmapheresis, or a live vaccine.[35,36] Although these studies excluded patients with severe active LN[†], post-hoc analysis of the 2 trials leading to FDA-approval for SLE (BLISS-52 and BLISS-76) showed a trend of renal improvement (ie, numerical reduction in proteinuria at 53 weeks and significant reduction in renal flares) with belimumab 10 mg/kg in the subgroup of patients with proteinuria at baseline (14–18% of included patients had >2g of proteinuria per 24 hours at baseline).[19,44] This finding motivated the development of belimumab in patients with severe LN.[45]

- In the phase 3 trials supporting approval of IV and SC belimumab for the treatment of SLE, standard therapies allowed as background therapy, in combination with belimumab, included corticosteroids, anti-malarial agents (eg hydroxychloroquine), NSAIDs, and immunosuppressive/immunomodulatory agents (eg azathioprine, mycophenolate, methotrexate, leflunomide, **calcineurin inhibitors** [tacrolimus, cyclosporine], sirolimus, oral cyclophosphamide, 6-mercaptopurine and thalidomide). Most patients (>70%) were taking 2 or more classes of SLE medications. Patients were not allowed to receive other B-cell targeted therapies (eg, rituximab, anti CD20, CD22, or CD52 agents[‡]).[8,46-48]
- In an extension study for belimumab, following the phase 3 RCTs, investigators observed no new safety concerns with up to 8 years on belimumab treatment.[49]

Treatment for Lupus Nephritis

In the recent KDIGO treatment guideline for LN, the place-in-therapy for belimumab and voclosporin is for *initial* treatment of active, class III or IV LN (with or without class V), as add-on treatment.[5] Belimumab, as an add-on therapy, can also be considered for the management of patients with LN, regardless of histologic class, to control extra-renal symptoms when standard therapy alone is insufficient (ie, when there are residual symptoms, inability to taper down glucocorticoid dose, and/or frequent relapses).[17,34] Untreated active class III and class IV LN is associated with significant patient morbidity and high risk of kidney loss and mortality, and 10%–30% of cases with class V LN plus

[†] The full-text of these SLE belimumab studies do not define severe active LN, but authors of the pooled analysis describe that this included patients with proteinuria >6 g/24 hours, serum creatinine >2.5 mg/dl, and those who required hemodialysis or high-dose prednisone within 90 days of study initiation.[44]

[‡] Examples include the following: anti CD20 agents are rituximab, ibritumomab, obinutuzumab, and ofatumumab; anti CD22 agents include inotuzumab and moxetumomab; and ant CD52 agent is alemtuzumab

nephrotic proteinuria would otherwise progress to kidney failure. Thus, initial aggressive treatment is recommended for active class III or IV (with or without class V), and for pure class V in the presence of nephrotic-range proteinuria or nephrotic syndrome.[5] The choice of treatment is patient centered, considering risks vs. benefits of each regimen, quality of life, potential adverse effects of therapies or cumulative toxicities, and patient adherence.

Box 1. Pertinent Definitions from KDIGO[5]

Nephrotic Syndrome *(see chapter 1, page S91 of guideline for more details):*

- In adults: proteinuria (≥ 3.5 g per 24 hours or urine total protein excretion rate ≥3g/g) which may also present with hypoalbuminemia, edema, and/or hyperlipidemia
- In children: proteinuria (≥ 40 mg/m^2/hour per 24 hours, urine total protein excretion rate ≥2g/g, 3+ on urine dipstick or ≥300 mg/dl) which may also present with hypoalbuminemia, edema, and/or hyperlipidemia

Nephrotic-Range Proteinuria

- In adults: proteinuria (≥ 3.5 g per 24 hours or urine total protein excretion rate ≥3g/g), usually with normal albumin, and normal or minor elevation of edema and/or serum lipids
- In children: proteinuria (≥ 40 mg/m^2/hour per 24 hours, urine total protein excretion rate ≥2g/g, 3+ on urine dipstick or ≥300 mg/dl) usually with normal albumin, and normal or minor elevation of edema and/or serum lipids

Non-Nephrotic-Range Proteinuria: Variable levels of proteinuria (0.3 to 3.4 g per 24 hours), with normal albumin, and no clinical symptoms

Hydroxychloroquine (HCQ) is generally recommended for all patients with SLE, including those with LN[§], unless the patient has contraindications.[5] Even some patients with class I or II LN may be selected for immunosuppressive therapy. Immunosuppressive therapy may be employed for extra-renal manifestations of SLE, and in patients with nephrotic syndrome or nephrotic range proteinuria—signs of lupus podocytopathy. Glucocorticoid monotherapy is used to target renal remission or an additional agent such as mycophenolate, azathioprine, or a calcineurin inhibitor (CNI) can be added in patients with insufficient response to glucocorticoids (GCs) alone, or with relapsing disease.[5]

For active **class III or IV (with or without class V)** LN**,** with or without a membranous component (ie, class V), the 2021 KDIGO guideline recommends initial treatment with GCs plus either low-dose intravenous cyclophosphamide or mycophenolate analogs (MAs), based on moderate quality evidence. Alternative recommended *initial* regimens include glucocorticoids in combination with (i) a CNI (eg, tacrolimus for 24 months with low-dose mycophenolate mofetil [MMF; eg, 1 g/d], or **voclosporin** for 1 year with MMF [eg, 2g/d]); or (ii) a B-lymphocyte targeting regimen with **belimumab** added to standard-therapy (ie, induction with MMF [3 g/day] or IV cyclophosphamide). Note that belimumab is continued during maintenance with standard-therapy, usually with MMF [1-3 g/d] or azathioprine. There is no recommendation when to stop belimumab, but the duration of therapy in pivotal clinical studies was 2 years with belimumab and an extension study has been completed out to 8 years in SLE patients and out to 2.5 years in the LN ongoing extension study.[42,50] It should also be noted that the guideline does not require patients to fail a standard regimen first before adding belimumab or voclosporin; rather these are for initial treatment regimens, as they were studied in clinical trials. Rituximab (another B-

[§] Strong recommendation by 2021 KDIGO guideline, based on moderate quality evidence in SLE, but low quality evidence in LN

lymphocyte targeting therapy) as add on therapy, is reserved either for those with persistent disease activity (ie, refractory cases), for those with repeated flares, or for the purposes of minimizing corticosteroid requirements. Further specifics in the KDIGO guideline regarding regimens containing belimumab or voclosporin are as follows:[5]

- Voclosporin (at a dosage of 23.7 mg twice daily for 52 weeks in combination with a mycophenolate analog) was recommended for patients with an eGFR above 45 mL/min/1.73m^2. Authors note, the advantage of a CNI-based regimen is a rapid reduction of proteinuria, but that RCTs of the older CNIs (ie, tacrolimus) are considered to be of low quality. A grading for the evidence supporting voclosporin was not provided, likely because the data was not yet fully published during the guideline's literature review (through June 2020).[5]
- Authors found the evidence supporting renal benefits with belimumab in LN to be of moderate quality, while rituximab evidence is considered very low quality.[5] In the treatment algorithm, authors specify IV belimumab (in combination with a mycophenolate analog, **or** with 6 courses of IV cyclophosphamide 500 mg as initial therapy). Authors do not mention anything regarding the subcutaneous (SC) formulation of belimumab, likely because pharmacokinetic information was not yet available to them at the time of their literature review (through June 2020).[5] The label extension for the subcutaneous product in LN was later included in the December 2020 package insert.[8]

Patients with active, *pure* class V LN plus either worsening proteinuria, complications of proteinuria (thrombosis, dyslipidemia, edema), or nephrotic syndrome should be considered for aggressive immunosuppressive therapy. Authors note more favorable data for combining GCs with a mycophenolate analog, a CNI (agent unspecified), or short-term cyclophosphamide compared to other options (eg, rituximab or azathioprine). Overall, "There is a lack of robust data in the management of Class V LN, especially in patients who present with NS [nephrotic syndrome]."[5] **Table 3** includes more details from the KDIGO guideline.

The **2019 EULAR/ERA–EDTA** LN treatment guideline also recommends intensive immunosuppressant therapy (usually with MMF or IV cyclophosphamide, combined with GCs) for initial therapy of active LN of class III (± class V), IV (± class V) and for certain patients with pure class V LN (presence of nephrotic-range proteinuria or when UPCR exceeds 1000 mg/g despite the optimal use of renin–angiotensin–aldosterone system blockers).[6] Refer to **Table 3** for more detail on the recommended regimens for each LN class. Authors highlighted that therapy should also be optimized to reduce or control disease activity at extra-renal sites, as lupus is often widespread.[6] Because the evidence review for this guideline predated the publication of LN phase 3 trials for belimumab and voclosporin, recommendations do not incorporate these medications for their now known renal benefits. Nonetheless, the EULAR/ERA–EDTA LN guideline did consider the approval/indication of belimumab for the treatment of SLE in general (an earlier approved indication). The guideline recommended that in LN patients, belimumab could be considered as add-on treatment to facilitate a glucocorticoid dose reduction and to control *extra-renal* disease activity and decrease the risk for extra-renal flares.[17] Similarly, in a separate 2019 EULAR guideline for the management of SLE, add-on belimumab treatment was recommended "In patients with inadequate response to standard-of-care (combinations of HCQ and GC with or without immunosuppressive agents), defined as residual disease activity not allowing tapering of glucocorticoids and/or frequent relapses..."[17,34]

Table 3. Recent Guidelines Regarding the Treatment of Lupus Nephritis

2021 KDIGO Clinical Practice Guideline for the Management of Glomerular Disease (Chapter 10: Lupus Nephritis)[5]

Chapter 10 of this guideline provides recommendations for LN patients in general, not necessarily specific to adults. Authors recommend treating pediatric patients with LN using similar regimens as in adults while considering issues and needs relevant to this population: growth and GCs side effects, fertility adverse effects with some drugs (eg, cyclophosphamide), and psychosocial factors.

Kidney biopsy

- kidney biopsy is helpful in confirming the diagnosis of LN and to characterize the activity and chronicity of the disease which also informs treatment decisions and prognosis
- Kidney biopsies should be evaluated by an experienced kidney pathologist and LN classified according to the ISN/RPS classification system

Treatment

- ***Hydroxychloroquine (HDQ)***: All patients with SLE, including those with LN should receive ongoing hydroxychloroquine-equivalent antimalarial unless contraindicated **(1C)**
  - observational studies show that this treatment is associated with lower rates of disease flares, less progressive kidney damage, and fewer vascular complications; the medication also has a favorable safety profile; use in pregnancy was associated with decreased SLE activity and favorable safety profile in both the mother and the fetus
  - Reasons for foregoing use of HDQ may include retinal changes or glucose-6-phosphate dehydrogenase deficiency (due to potential link to hemolysis under stress of infection[51])
    - Patients should have baseline retinal examination and annual monitoring for changes
- **Approach to Class I or II LN**
  - In patients with low-level proteinuria, choose immunosuppressive therapy guided by extra-renal manifestations of SLE
  - Patients with nephrotic syndrome or nephrotic range proteinuria, and class I or II histology, are considered to have lupus podocytopathy; this can be confirmed with electron microscopy showing diffuse podocyte effacement. These patients should be considered for glucocorticoid monotherapy to achieve remission followed by maintenance with low-dose glucocorticoid plus an additional agent such as mycophenolate, azathioprine, or a CNI, especially in patients with a history of relapse.
- **Initial Therapy for Active Class III or Class IV** LN, with or without a membranous component (class V)
  - Authors recommend to treat initially with glucocorticoids plus either low-dose IV cyclophosphamide (500 mg Q2 weeks X 6 doses) or mycophenolate for at least 6 months (2-3g/day MMF or equivalent) (**1B**); this combined regimen is associated with lower relapse rates and improved long-term kidney survival compared to glucocorticoid monotherapy.
    - Mycophenolate-based regimen is usually preferred over cyclophosphamide in patients at high risk of infertility, in those with history of moderate to high prior cyclophosphamide exposure, and for patients of Asian, Hispanic, or African ancestry.
    - A regimen containing IV cyclophosphamide should be used for those who may have difficulty adhering to an oral regimen

  Alternative ***initial*** regimens include the following:
  - In patients with baseline eGFR of at least 45 ml/min/1.73m^2, **voclosporin** can be added to a mycophenolate analog/glucocorticoid (induction/maintenance regimen) **for 1 year**
  - **Belimumab** can be added to standard therapy (eg, MMF or IV cyclophosphamide for induction, and MMF or azathioprine for maintenance) for the treatment of active LN

Table 3. Recent Guidelines Regarding the Treatment of Lupus Nephritis

- Tacrolimus or cyclosporine, with reduced-dose mycophenolate and glucocorticoids is reserved for patients who cannot tolerate standard-dose mycophenolate or who are unfit for or will not use cyclophosphamide-based regimens
- Other therapies (eg, azathioprine or leflunomide combined with glucocorticoids), may be considered if previously mentioned options are not tolerated or are unavailable, but these alternatives may be associated with inferior efficacy and/or increased incidence of drug toxicities
- Rituximab, added to standard therapy, may be considered for patients with persistent disease activity or repeated flares

- **Maintenance Therapy for Active** Class III or Class IV LN
  - After successful initial therapy, MPA for maintenance is recommended (**1B**)
  - Azathioprine is an alternative to MPA for those unable to tolerate MPA, those without access, or who are considering pregnancy. CNIs or mizoribine are third-line alternatives
  - Taper glucocorticoids to lowest possible dose during maintenance, unless higher doses are required for extra-renal lupus manifestations; glucocorticoids can be considered for discontinuation after the patient has maintained complete clinical renal response for *at least* 12 months.
  - Note that if belimumab or voclosporin are stated as initial therapy, added-on to standard therapy, they will also continue concurrently with standard-maintenance therapy
- **The total duration** of immunosuppression (initial therapy plus maintenance) for patients with proliferative LN who have achieved a complete renal response and have no ongoing extra-renal manifestations should be **no less than 36 months**.
- **In pure class V LN with low-level proteinuria or nephrotic syndrome:**
  - Monitor proteinuria and prevent or treatment complications (eg, thrombosis, dyslipidemia, edema)
  - Optimize treatments for renin angiotensin system (ie, ACE or ARB inhibitors), blood pressure, and hydroxychloroquine
  - Employ immunosuppressive treatment for extra-renal manifestations of SLE and/or for renal response to manage worsening proteinuria, complications, and/or nephrotic syndrome
    - Options include glucocorticoid plus the following (mycophenolate analogs, cyclophosphamide, calcineurin inhibitors [particular agents are unspecified], rituximab, or azathioprine)

2019 Guideline Update by the Joint European League Against Rheumatism and European Renal Association–European Dialysis and Transplant Association (EULAR/ERA–EDTA)[6]

Select recommendations regarding screening for LN in patients with SLE

- Candidates for renal biopsy are those with SLE and any sign of kidney involvement (eg, hematuria and/or cellular casts, proteinuria >0.5 g/24hours (or UPCR >500mg/g), or decrease in GFR. However, authors note that some patients may have risk factors that preclude biopsy (eg, increased bleeding risk in selected patients such as those receiving anticoagulation, or other contraindication).
- Recommended that all patients with SLE should be tested for antiphospholipid antibodies (aPL), and testing for anti-dsDNA, anti-C1q (if available); testing for complement levels (C3 and C4) should be considered when LN is suspected.

Therapy Recommendations (based on 2003 ISN/RPS histological classification of LN)

- **Hydroxychloroquine** should be coadministered in all patients with LN unless contraindicated.
- **Belimumab** was recommended for consideration as add-on treatment to facilitate glucocorticoid dose reduction and to control extra-renal disease activity and decrease the risk for extra-renal flares.
  - Note that the FDA's extension of the belimumab indication to LN does not appear incorporated into these guidelines since the evidence review for the guideline predated the approval for this

Table 3. Recent Guidelines Regarding the Treatment of Lupus Nephritis

indication and the publication of the phase 3 evidence for LN. Additionally, voclosporin was not yet approved nor the pivotal trial fully published..

Induction Therapy

For initial treatment (ie, induction) for **active class III (± V) or IV (± V) LN** (patient may also have chronic renal lesions but should have active lesions for induction initiation)

- **First-line**: mycophenolate mofetil (MMF) **or** low-dose IV cyclophosphamide, in combination with glucocorticoids
  - MMF target dose of 2 to 3 g/day, or MPA at equivalent dose
  - Low dose IV cyclophosphamide is 500 mg every 2 weeks for a total of 6 doses
- **Alternative Options**:
  - Combination of MMF (1 to 2 g/day, or MPA at equivalent dose) and a CNI, especially tacrolimus. This regimen is especially recommended for those with nephrotic-range proteinuria. At the time of this guideline writing, voclosporin was not yet approved nor was the phase 3 study fully published.
  - High-dose IV cyclophosphamide (0.5–0.75 g/m2 monthly) for 6 months may also be considered for patients at high risk for kidney failure (reduced GFR, presence of crescents or fibrinoid necrosis, or severe interstitial inflammation)
- For reduction of cumulative glucocorticoid dose: intravenous pulses methylprednisolone, followed by oral prednisone can be considered
- Add-on rituximab can be considered for non-responders

For initial treatment (ie, induction) of **pure class V** LN in patients with nephrotic-range proteinuria or proteinuria >1 g/24 hours despite optimal use of renin–angiotensin–aldosterone (RAS) system blockers:

- **First line:** MMF (2 to 3 g/day, or MPA at equivalent) in combination with pulse IV methylprednisolone followed by oral prednisone
- **Alternative options**: IV cyclophosphamide; or CNIs (especially tacrolimus) as monotherapy, or in combination with MMF/MPA for patients with nephrotic-range proteinuria. Add-on rituximab to standard therapy can be also be considered for non-responders.

Maintenance

- Upon improvement following initial treatment, continue lower dose MMF/MPA (1 to 2 g/day), especially if used as initial treatment, **or** use azathioprine (AZA) (2 mg/kg/day), which is preferred if pregnancy is contemplated, both in combination with low-dose prednisone (2.5–5 mg/day) if needed
- Gradual withdrawal of treatment (glucocorticoids first, then immunosuppressive drugs) can be attempted after at least 3 to 5 years maintenance therapy usually only upon complete clinical response. Continue hydroxychloroquine long-term.
  - Duration of immunosuppressive therapy should be individualized based on the patient's response and duration of flare-free maintenance, extra-renal activity and patient preferences.
- Continuation, switching to or addition of CNIs (especially TAC) can be considered in pure class V nephritis at the lowest effective dose and after considering nephrotoxicity risks.

Specific populations

- **ESKD/dialysis:** Tailor immunosuppressant therapy to target extra-renal manifestations in ESKD and dialysis
- **LN in pregnancy:** Compatible medications such as hydroxychloroquine, prednisone, AZA and/or CNIs (especially TAC) should be continued at safe dosages throughout pregnancy and lactation. LN flares

Table 3. Recent Guidelines Regarding the Treatment of Lupus Nephritis

during pregnancy can be managed with these aforementioned medications in addition to pulses of intravenous mycophenolic acid, depending on flare severity.

- **Pediatric patients:** Diagnosis, management and monitoring of LN in children are similar to that of adults

Other Adjunctive Therapies include

(a) apply ACEI or ARB in patients with UPCR>500 mg/g or arterial hypertension (or proteinuria ≥0.5 g/24 hr per 2012 ACR guideline); this reduces proteinuria and delays doubling of SCr and progression to ESRD[19]; but dose adjust and use judiciously with impaired renal clearance
(b) use a statin based on 10-year cardiovascular disease risk using Systematic Coronary Risk Evaluation or other validated tool
(c) calcium/vitamin D supplementation and/or antiresorptive agents; and immunization with non-live vaccines can help reduce disease-related osteoporosis and infections, respectively
(d) consider acetyl-salicylic acid in the presence of antiphospholipid antibodies, and anticoagulation for patients with nephrotic syndrome plus serum albumin of <20g/L
(e) NSAIDs should be avoided in LN

Monitoring

- Ideally, visits should occur at least every 4 weeks during the first 2–4 months after diagnosis or flare
- At each visit measure body weight, blood pressure, GFR, serum albumin, proteinuria; urine red cell count or sediment, and complete blood cell count when nephritis is active and less frequently if stable
- Monitor serum C3/C4 and anti-dsDNA antibody levels periodically
- Consider repeat kidney biopsy with worsening of kidney variables, non-responsiveness to treatment, or at relapse, to determine histologic class transition or change in chronicity and activity (for prognostic information and detection of other pathologies).

Abbreviations: AZA, azathioprine: CNIs, calcineurin inhibitors; CY, cyclophosphamide; eGFR, estimated glomerular filtration rate; GC, glucocorticoid; HDQ, hydroxychloroquine; ISN/RPS, International Society of Nephrology/ Renal Pathology Society; IV, intravenous; LN, lupus nephritis; MMF, mycophenolate mofetil; MPA, mycophenolic analog; SLE, systemic lupus erythematosus; UPCR, urine protein-to-creatine ratio

KDIGO Grade for Quality of Evidence and Grade of Recommendation

- 1B= **strong recommendation** that most patients (but excluding a small proportion) should undergo the recommended course of action; based on **moderate quality of evidence** to suggest that the true effect is likely to be close to the estimated effect but there is possibility of substantial difference between the two
- 1C= **strong recommendation** that most patients (but excluding a small proportion) should undergo the recommended course of action; based on **low quality of evidence** to suggest that the true effect could be substantial different from the estimated effect

Treatment Goals

Aims of treatment for active LN are to induce remission and slow or prevent progression of organ damage by suppressing the disordered, overly active immune system. Proteinuria at 12 months after treatment initiation is thus far the best individual surrogate marker for predicting progression of LN to end-stage renal disease.[6] Proteinuria is incorporated into clinical-decision-making regarding treatment initiation and response assessment, in addition to key clinical trial endpoints. The treatment goal described by the EU guideline in LN is to control and target proteinuria to <0.5–0.7 g/24 hours and preserve or improve kidney function (ie, achieve near-baseline GFR) by month 12 of therapy; achieving this target is usually termed '*complete clinical response*.'[6,52] Authors note that while a significant amount

of patients do not meet this target, they may at least have long-term stabilized kidney function with treatment. If complete renal response is unattainable, the goal should be at least *partial remission,* defined as ≥50% reduction in proteinuria to sub-nephrotic levels and serum creatinine within 10% from baseline by 6–12 months.[34] A shorter-term loose goal includes improvement in proteinuria (with GFR normalization or stabilization) by month 3. **However, the goal timelines for partial/complete responses in those with nephrotic-range proteinuria at baseline are extended by 6–12 months since slower improvements are expected**.[6]

The 2021 KDIGO guideline emphasizes that while key endpoints in LN clinical trials generally involve specified time-points for improving proteinuria and stabilization or improvement in kidney function, there is a lack of universal or standardized criteria for the level of improvement required in clinical practice or in clinical trials.[5] Furthermore there is a lack of consensus on the time point when response should be assessed/expected. While clinical trials may assess at 6 to 12 months for logistical/economic reasons, rates of improvement vary between individuals and improvements in proteinuria and/or eGFR are generally continuous over time.[5] **Ultimately, KDIGO recommends that in the clinical practice setting, patients should be allowed 18–24 months to achieve a complete response[**] on the selected regimen if they are generally showing continued clinical improvement.** Other markers that may indicate favorable kidney outcomes are normalization of complement levels with at least a 25% reduction of proteinuria. Moreover, a repeat kidney biopsy can be useful in confirming renal response, especially to help decide whether discontinuation of immunosuppression is appropriate.[5] An older guideline of 2012 by the American College of Rheumatology expressed that most patients should be followed for 6 months after initiation of induction treatment before making major changes in treatment other than alteration of glucocorticoid doses, unless there is clear evidence of worsening at 3 months (eg, 50% or more worsening of proteinuria or serum creatinine).[19]

Box 2. Response Definitions from KDIGO[5]

Complete renal response (see chapter 1, page S82 of guideline for more information):

- In adults: reduction in proteinuria <0.5g/g measured as the protein creatinine ratio from a 24-h urine collection, and stabilization or improvement in kidney function (±10%-15% of baseline), within 6-12 months of starting therapy but could take more than 12 months

Partial response: reduction in proteinuria by at least 50% and to <3g/g measured as the protein creatinine ratio from a 24-h urine collection, and stabilization or improvement in kidney function (±10%-15% of baseline), within 6-12 months of starting therapy

No kidney response**:** Failure to achieve a partial or complete response within 6-12 months of starting therapy

[**] *Complete renal response* in adults in the KDIGO guideline is defined as a reduction in proteinuria <0.5g/g measured as the PCR from a 24-h urine collection, and stabilization or improvement in kidney function (±10%-15% of baseline), within 6-12 months of starting therapy but could take more than 12 months (eg, 24 months).

Pediatric Population

LN occurs in 50-60% of patients with childhood-onset SLE.[53] Since pediatric SLE and pediatric LN are rare diseases overall, there are limited approved drugs for this population. There are no medications with an approved indication specifically for pediatric LN, and only belimumab is approved for pediatric SLE (for children ≥5 years of age). Nonetheless, treatment of LN follows a similar approach as that in adults.[5,6,19,53] The 2021 KDIGO guideline recommended that pediatric patients should be treated with similar immunosuppressive regimens as those used in adults, while considering the following issues relevant to this age group:

- adherence difficulties may favor IV medications
- growth concerns may favor limiting glucocorticoid use
- fertility concerns may favor limiting cyclophosphamide exposure

Since disease activity is usually more aggressive in childhood-onset lupus, "Timely recognition of renal involvement and appropriate treatment are essential to prevent renal damage."[53] While renal biopsy is a standard in the classification of LN class, as in adults, there may be scenarios that preclude a renal biopsy (eg, during critical clinical condition or lack of resources). In that case, the 2017 EU guideline for pediatric LN states that that patients with SLE plus nephrotic syndrome, hypertension, and impaired renal function should be treated as if it were class IV LN.[53] The KDIGO guideline recommends that pediatric patients should ideally be co-managed by pediatric nephrologists and rheumatologists with expertise in lupus.[5] **Table 4** includes recommendations from the 2017 European guideline that was dedicated to addressing pediatric LN, whereas other guidelines available only briefly discuss pediatric LN. The newer medications, belimumab and voclosporin, are not among this guideline since its literature review (up to July 2013) predated their initial approvals and availability.

Table 4. 2017 Treatment Recommendations for Childhood-Onset Lupus Nephritis from the SHARE Initiative [53]

- Recommendations are provided based on the histological classification of LN, per the 2003 ISN/RPS classification system. It is recommended that an experienced renal pathologist be involved in the evaluation/determination of renal biopsies and LN classification.
    - If biopsy is not possible (eg, during critical clinical condition or lack of resources) authors describe that SLE patients with nephrotic syndrome, hypertension, and impaired renal function should be treated as if it were class IV LN
- Treatment goal in LN is complete renal response (ie, with UPCR<50 mg/mmol and normal or near-normal renal function (within 10% of normal GFR)
    - Class I LN: treatment should be guided by extra-renal symptoms
    - Class II LN: initial treatment should usually be low-dose prednisone, adding a disease-modifying anti-rheumatic drug after 3 months of persistent proteinuria or prednisone dependency
    - **Class III/IV LN**
        - Induction treatment: mycophenolate or intravenous cyclophosphamide combined with corticosteroids is first-line
        - Maintenance treatment should be MMF or azathioprine for at least 3 years
        - For treatment flares or refractory cases the following can be considered: increase the corticosteroid dose, switch to a different DMARD, or add rituximab; may also consider calcineurin inhibitors

Table 4. 2017 Treatment Recommendations for Childhood-Onset Lupus Nephritis from the SHARE Initiative [53]

- **Pure class V LN**
  - Induction with MMF plus low dose prednisone
  - Maintenance treatment with MMF or AZA
  - Consider the following for induction non-responders: cyclophosphamide, calcineurin inhibitors (cyclosporine or tacrolimus), or rituximab

Adverse Events with Standard Therapies

Standard therapies for active flaring LN have included high dose corticosteroids plus other immunosuppressants (eg, azathioprine, cyclophosphamide, mycophenolate mofetil (MMF), methotrexate, and rituximab).[12] Patients also often require analgesics for pain due to painful SLE-caused co-morbidities. Drug-class side effects with common standard initial immunosuppressants used for severe active LN include the following:

- **Immunosuppressants** in general carry risk of treatment-associated infections.
- **Glucocorticoids** (GCs), especially at high doses can lead to osteoporosis (and diminished growth in children), hypertension, dyslipidemia, atherosclerosis, weight gain, glaucoma, and cataracts.[5,12,54] Facture risk and eye health should be monitored in patients on GCs, and supplementation with vitamin D and calcium should be considered, along with treatment with bisphosphonates if clinically indicated. Nonetheless, glucocorticoids are helpful for active LN since they aid in reducing disease flare while waiting out the lag in effect with additive agents (eg, cyclophosphamide, MPA, CNIs, or B cell–directed therapies).[5,12]
- **Cyclophosphamide** may increase risk of malignancy, infertility, and leukopenia. The patient's individual cancer risk and/or burden may preclude the use of this agent.[5] Moreover, the cumulative lifetime dosage of cyclophosphamide should not exceed 36 g. Cyclophosphamide is generally avoided in pregnancy due to its embryo-fetal toxicity risk.[5]
- **Mycophenolate**-based regimens for active proliferative LN are usually preferred over cyclophosphamide, especially in patients at high risk of infertility, in those with history of moderate to high prior cyclophosphamide exposure, and for patients of Asian, Hispanic, or African ancestry. However, mycophenolate can cause significant gastrointestinal toxicity that may be intolerable (an enteric-coated formulation *may* help reduce symptoms). Mycophenolate is avoided in pregnancy (has black box warning regarding increased risks of first trimester pregnancy loss and congenital malformations).[5,55]
- **Older calcineurin inhibitors,** tacrolimus (TAC) and cyclosporine (CSA) are "…commonly associated with metabolic side effects, including hypertension (CSA > TAC), hyperlipidemia (CSA > TAC), and diabetes (TAC> CSA)."[5]

Belimumab and Voclosporin for Lupus Nephritis

Pharmacology

Belimumab is an antibody that blocks the binding of B lymphocyte stimulator (BLyS) to its receptor on B cells (ie, a BLyS-specific inhibitor).[8] Patients with active SLE have elevated BLyS levels which promote B cell activation and differentiation. Elevated BLyS levels are also associated with increased autoantibody-secreting plasma cells.[56-58] Antagonizing BLyS reduces B-cell survival and total circulating B cells (naive and activated B-cells, including the SLE B-cell subset).[8] Yung et al describe, "The pathogenic role of B cells is not just limited to autoantibody production but extends to antigen presentation, T cell activation and polarization, modulation of dendritic cell maturation, and cytokine secretion."[59] In patients with SLE or LN, belimumab is known to reduce autoantibodies, CD19+, and CD20+; and increase complement protein levels (C3 and C4) in patients with low levels at baseline).[8] In active LN, decreases in serum IgG as early as week 4 were followed by an increase in serum IgG levels and decreased proteinuria.[8]

Since belimumab is a monoclonal antibody, no direct pharmacokinetic interactions with the CYP pathway or co-administered small molecular weight drugs are expected.[48] Results from population PK analyses showed that co-administration of drugs commonly used to treat SLE patients (eg, NSAIDs, statins, anti-malarial medications, angiotensin pathway antihypertensives and immunosuppressants such as azathioprine, methotrexate and mycophenolate) did not affect belimumab's PK profile.[3]

- Pharmcokinetic parameters[8]
  - $T_{1/2}$: 19.4 days with **IV** dosing
  - $T_{1/2}$: 18.3 days with **SC** dosing, and T_{max} of 2.6 days with 200 mg weekly via SC
  - In adults with LN, the average steady-state concentration from subcutaneous administration (200 mg weekly) is expected to be similar to that from IV administration (as 10 mg/kg IV Q4 weeks).

It is unclear exactly how voclosporin modulates active SLE, but it is thought to improve SLE-related inflammation though its immunosuppressant activity.[9] As a calcineurin inhibitor, the medication decreases (a) intracellular calcium concentrations and calcium binding to the calcineurin regulatory site, (b) activation of calmodulin binding catalytic subunit, and (c) activation of Nuclear Factor of Activated T-Cell Cytoplasmic (NFATc) transcription factor. These pathways normally lead to proliferation of lymphocytes, T-cell cytokine production, release of interleukin 2 (IL-2), and expression of T-cell activation surface antigens.[5,9] Animal models also suggest that voclosporin may have a non-immunological role in SLE where inhibition of calcineurin increases podocyte integrity in glomeruli.[5,9] Voclosporin has a more predictable pharmacokinetic profile than traditional CNIs such as cyclosporine and tacrolimus. Voclosporin does not require therapeutic drug monitoring, as is required for other CNIs, and it appears to have a more favorable effect on lipids and glucose than older CNIs.[5,60] These advantages stem from its higher binding affinity to calcineurin and lower drug metabolite concentrations, respective to traditional CNIs used for SLE.[5,60,61]

- Pharmcokinetic parameters[9]
  - Steady state is achieved after 6 days, with twice daily dosing
  - Median T_{max} is 1.5 hours (1 to 4 hours), on an empty stomach. Food decreases the rate and extent of absorption (with either low- or high-fat meals)

- Mean terminal half-life ($T_{1/2}$) is approximately 30 hours (24.9 to 36.5 hours).
- Primarily metabolized by **CYP3A4**; the parent molecule is the main active component, while the major metabolite is about 8-fold less potent than the parent molecule
- Excretion: 92.7% of dose recovered in feces (5% as unchanged voclosporin), and 2.1% was recovered in urine (0.25% as unchanged voclosporin)

Efficacy in the Lupus Nephritis Population, Phase 3 Clinical Trials

Phase 3 clinical trials were designed to establish the efficacy and safety of belimumab or voclosporin *added onto standard immunosuppressants,* to reduce renal decline in patients with active, flaring LN. Despite use of standard of care agents, Rovin et al describe that up to 60% of patients are unable to attain targeted reductions in proteinuria (eg, 25% or 50% reductions by month 3 and 6 of therapy initiation, respectfully; or proteinuria ratio of <0.5–0.7 mg/mg in the first year of treatment).[60]

Eligible adult patients for these studies had SLE, based on the 1982/1997 ACR criteria for SLE (see Appendix B), and biopsy-proven class III, IV, or V (alone or in combination with class III or IV) lupus nephritis per 2003 ISN/RPS classification, within the past 2 years for VOC study, or within 6-8 months for the BEL study.[60,62] Of note is that the ISN/RPS classification is in the process of being revised and the ACR criteria for SLE has been updated.[22,26] Patients had to have active LN (based on different UPCR thresholds and definitions depending on the study). Only the belimumab study required patients to have a positive autoantibody result for study entry (either antinuclear antibodies or anti–double-stranded DNA antibodies); this requirement was motivated after an insignificant benefit with belimumab was found in the subpopulation without autoantibodies from a phase 2 study in SLE.[15] For the phase 3 LN studies, patients were ineligible if on dialysis, or if eGFR was ≤45 mL/min per 1.73m² for the voclosporin study or ≤30 mL/min per 1.73 m² for the belimumab study.[60,62]

Belimumab Phase 3 Clinical Trial in LN (BLISS-LN)

In 2021, the indication for belimumab was expanded to include lupus nephritis following supportive results from the 2 year, randomized, double-blind placebo-controlled trial (Trial 5; NCT #01639339, phase 3 study[62]). Prior trials that led to the initial approval of belimumab for SLE did not include patients with severe active lupus nephritis.[8] In the trial for LN, belimumab (10 mg/kg IV route on days 1, 15, 29, and then every 28 days thereafter) was added to standard induction therapy (eg, **corticosteroids** with either oral **MMF** [for induction and maintenance], or **IV cyclophosphamide** [for induction] + oral azathioprine [for maintenance], started within 60 days prior to day 1 on belimumab)[††]. Additional standard of care agents were allowed (immunosuppressants such as methotrexate, hydroxychloroquine, etc) if they were started prior to baseline.

[††] Background immunosuppressant therapy was either (a) IV cyclophosphamide (500 mg every 2 weeks [±3 days] for 6 infusions) for induction + maintenance with azathioprine (target dose, 2 mg/kg per day; ≤200 mg per day) initiated 2 weeks after the last dose of cyclophosphamide; or (b) MMF for induction (target dose, 3 g per day) and maintenance with 1 to 3 g per day of MMF until trial end. In the protocol, authors note that the study objective was to assess belimumab added onto standard of care therapies. Dose adjustments of protocol directed treatments were allowed based on tolerability.

Included adults met the following key criteria:[4,52,63]

- ✓ **autoantibody-positive SLE,** with the diagnosis of SLE meeting American College of Rheumatology 1982/1997 criteria. Antibody positivity was defined as antinuclear antibody titers ≥1:80 antibodies (based on Hep-2 immunofluorescence assay or equivalence by enzyme immunoassay assay) and/**or** positive anti-dsDNA serum antibody test of ≥ 30 IU/mL based on ELISA assay
- ✓ **biopsy-proven**, class III, IV, or V active proliferative and/or membranous lupus nephritis, based on the 2003 ISN/RPS classification, up to 6 months before screening. Note that screening could be initiated up to 60 days prior to starting belimumab (ie, biopsy proven LN up to 8 months prior to initiating belimumab)[63]
- ✓ **urinary protein to creatine ratio (UPCR)** of ≥1.0
- ✓ active renal disease that required **standard immunosuppressive therapy**

Excluded patients were those on dialysis within the last year or those with severe renal impairment (estimated glomerular filtration rate [eGFR] less than 30 ml/minute/1.73 m^2). Prohibited therapies included anti-TNF agents (eg, adalimumab, etanercept, infliximab), other biologics (eg, abatacept, anakinra, rituximab), intravenous immunoglobulin, or plasmapheresis.[52]

A total of 448 adults were enrolled, with the mean age being 33 years, and the majority female (88%). The median duration of LN in the study population was 0.2 years (interquartile range, 0.1 to 3.3), with 58% classified as class III or IV LN at baseline, 26% as class III or IV coexisting with class V LN, and 16% with pure class V LN. The baseline biomarker characteristics were as follows (provided as the proportion of the total study population): antinuclear antibodies (88%), anti-dsDNA antibodies (77%), Anti-C1q antibodies (79%), Anti-Sm antibodies (33%), Complement C3 <90mg/dl (60%), Complement C4 <10mg/dl (28%).[62]

The primary endpoint was primary efficacy renal response (PERR), defined as having a UPCR≤0.7, an eGFR no more than 20% below pre-flare value (or ≥60 ml/minute/1.73m^2), and no use of glucocorticoid rescue therapy for treatment failure. Additionally, patients who were unable to titrate down to 10 mg of prednisone/day or less by week 24 were considered a treatment failure. More belimumab-treated patients achieved PERR at week 104 compared with placebo (in combination with standard therapy): 43% vs. 32%, odds ratio of 1.6 (95% CI 1.0 to 2.3; P = 0.03); a significant difference in favor of belimumab was also shown at week 52 and as early as week 24. Key secondary endpoints also favored belimumab treatment, including longer time to first severe flare, more likely to have low lupus disease activity (<4 on SLEDAI-2K), higher proportion achieving a complete renal response[‡‡] at week 104, and lower risk for the composite of renal-related event[§§] or death (hazard ratio, 0.51; 95% CI, 0.34 to 0.77; P=0.001).[62,64]

- Primary efficacy renal response (PERR) at week 104 in favor of belimumab (BEL): 43%, vs. 32%; Odds Ratio 1.6 (95% CI 1.0, 2.3; P=0.03)
- PERR at week 52 in favor of BEL: 47%, vs. 35% of PLA arm; Odds Ratio: 1.6 (95% CI 1.1, 2.4)

[‡‡] Complete renal response (CRR) was defined as UPCR < 0.5, an eGFR no worse than 10% below the pre-flare value (or ≥90 ml/minute/1.73 m^2), and no use of rescue therapy

[§§] Renal-related events included end-stage kidney disease, doubling of serum creatinine, increased proteinuria, impaired kidney function, kidney disease-related treatment failure

- Complete renal response (CRR) at week 104, in favor of BEL: 30% vs. 20%; Odds Ratio: 1.7 (95% CI 1.1, 2.7)
- Time to renal-related event or death, in favor of BEL: Hazzard Ratio: 0.5 (95% CI 0.3 to 0.8)

"The safety profile for belimumab plus standard therapy was similar to that of standard therapy alone."[62] The proportion of patients with any adverse event (AE), treatment-related AEs, or serious AEs were similar between study arms. In belimumab or placebo arms, AEs occurring in 5% or more patients were upper respiratory infection (12% vs. 11%), urinary tract infection (7% vs. 6%), herpes zoster (6% vs.4%), and bronchitis (5% vs. 4%). The most common treatment-related serious adverse events in either group were pneumonia (1% vs. 2%) and herpes zoster (1% vs. 1%).[62]

Limitations of this study included the limited induction and background maintenance regimens permitted (calcineurin inhibitors were not among background therapy) and that patient-reported outcomes were not measured.[62]

Investigators of a 6 month extension study with completers of BLISS-LN reported, in a conference abstract, increased proportions of PERR and CRR responders in both belimumab-naïve patients (ie, patients who were in the placebo arm of the original RCT) and in the belimumab-experienced patients. Additionally, there were no new safety signals.[50]

Voclosporin Phase 3 Clinical Trial in LN (AURORA1)

One of the two phase 3, RCTs for voclosporin has been completed and published, supporting the approval of the medication. Voclosporin was studied over 52 weeks at a daily dosage of 23.7 mg twice daily (given as three 7.9 mg capsules, and dose adjusted based on eGFR and blood pressure if needed).[9] In the active and placebo arms, patients received background induction therapy with MMF (2 g/day target dose) and IV boluses of corticosteroid (eg, methylprednisolone 500 mg/dose) on days 1 and 2, followed by oral prednisone, stared at 20-15 mg per day, tapered to 2.5 mg/day by week 16, and adjusted by investigator discretion from thereforward.[9,60,65] Included adults met the following key criteria:[9]

- ✓ SLE diagnoses according to ACR criteria (1997)
- ✓ **biopsy-proven,** up to 2 years prior to screening, class III, IV, and/or V LN, with active disease[***] (see footnote for UPCR requirement per LN class and timing of biopsy)
- ✓ patient requires high-dose corticosteroids and immunosuppressive therapy

Excluded patients were those with eGFR of 45 mL/min per 1.73 m^2 or less, or on dialysis. To minimize confounding factors, immunosuppressants other than the study drugs were prohibited during the study. This included but was not limited to cyclophosphamide, other calcineurin inhibitors (cyclosporine,

[***] Active, biopsy proven LN was defined as any of the following: (a) kidney biopsy result within **2 years** prior to screening indicating ISN/RPS (2003) class III, IV-S, IV-G (alone or in combination with Class V), or Class V LN, with at least a doubling increase in UPCR within the last 6 months to **≥1.5 mg/mg** for Class III/IV, or to **≥2 mg/mg** for Class V; (b) kidney biopsy result within 6 months prior to screening showing Class III, IV-S or IV-G (alone or in combination with Class V) LN with a UPCR of **≥1.5 mg/mg** at screening; or (c) kidney biopsy result within 6 months prior to screening showing Class V LN and a UPCR **of ≥2 mg/mg** at screening.

tacrolimus), and biologic immunosuppressants (eg, abatacept, belimumab, rituximab infliximab, adalimumab, etanercept).[66] The primary endpoint was complete renal response at week 52. Complete renal response was defined as follows: UPCR of 0.5 mg/mg or less, eGFR ≥ 60 or decrease from baseline eGFR of no more than 20%, and no administration of rescue medication. Non-responders were those who received more than 10 mg prednisone for ≥3 consecutive days or for ≥7 days in total during weeks 44 through 52.[60]

A total of 357 patients were enrolled (median age 31 years, 88% women). The mean duration of LN in study population was about 4 ½ years with about 60% classified as class III or IV LN at baseline, 25% as class III or IV coexisting with class V LN, and 14% with pure class V LN. Baseline biomarker characteristics were as follows (provided as the proportion of the total study population): anti-dsDNA antibodies (66-74%), Complement C3 <90mg/dl (about 60%), Complement C4 <10mg/dl (about 27%); antinuclear antibodies were not reported.[60]

More voclosporin-treated patients achieved a complete renal response at both week 24 (32.4% vs 19.7%; odds ratio [OR] 2.2, 95% CI 1.3 to 3.7) and at week 52 (40.8% vs 22.5%; OR 2.7, 95% CI 1.6 to 4.3) compared to the placebo arm. The effects were similar between men and women, and between white and Asian patients.[60]

- Complete renal response (CRR) at week 52, in favor of voclosporin (VOC): 41% vs. 23%, OR 2.7 (95% CI 1.6, 4.3)
- CRR at week 24, in favor of VOC: 32% vs. 20%, P=0.002
- Partial renal response (ie, ≥50% reduction from baseline UPCR) at week 52, in favor of VOC: 70% vs. 52%, P<0.001
- Time to UPCR≤ 0.5 mg/mg, in favor of VOC: 169 day vs. 372 days, P<0.001
- Time to 50% reduction in UPCR, in favor of VOC: 29 days vs. 63 days, P<0.001

Regarding safety issues that are common with older CNIs like tacrolimus, voclosporin did not appear to have a negative metabolic affect. Rather, greater decreases in total cholesterol and LDL occurred by week 52 with voclosporin treatment vs. placebo.[60] Hemoglobin A1c was stable in each study arm over the trial, and new onset diabetes occurred in 1 patient of the placebo group. Magnesium and potassium concentrations remained stable and within the normal range in both study arms. While the mean systolic blood pressure (sBP) in the voclosporin arm was slightly elevated from baseline at week 2 (increased by 3.9 mmHg), mean sBP returned to baseline by week 8 and by the study end, there was an improvement from baseline in the both arms. Similarly, there was an eGFR decrease of 1.5 mL/min per 1.73 m^2 at week 2 in the voclosporin group, but the mean eGFR was recovered near baseline by week 4 and was stabilized throughout the study.[60]

Limitations of this study were that voclosporin was not studied in combination with cyclophosphamide, results were limited to 1 year on treatment, and results were not stratified by new onset LN vs. relapsed LN. An ongoing extension study is assessing the efficacy and safety of an additional 2 years of voclosporin treatment (versus placebo), continued with mycophenolate and low-dose steroids.[60] This study was recently completed (NCT03597464). The full publication is not yet available but the sponsor has announced positive results with ongoing voclosporin (eg, no new safety signals, similar safety profile to AURORA1; and sustained reduction in proteinuria).[67]

Potential Emerging Indications

- Phase 3 studies for belimumab include uses for vasculitis, antiphospholipid syndrome, and myositis.
- Phase 3 studies for voclosporin include uses for dry eye syndrome, uveitis, plaque psoriasis, and renal transplant.
- Refer to **Appendix D** for a fuller list of phase 2 and 3 studies registered in clinicaltrials.gov (ie, off-label uses under investigation for these therapies).

Safety

Adults receiving belimumab by SC route should receive proper training on injection technique and be educated about signs and symptoms of hypersensitivity reactions. Prior to administration, after removing the medication from storage in the fridge, the patient must allow the contents to sit at room temperature for 30 minutes to warm; warming must not be carried out any other way than this.

Common side effects occurring in greater than 3% of patients in clinical studies were the following:

- *For belimumab (BEL):* based on data from the SLE population, with BEL administered by IV route, AEs included nausea, diarrhea, pyrexia, nasopharyngitis, bronchitis, insomnia, pain in extremity, depression, hypersensitivity/infusion reactions, migraine, pharyngitis, cystitis, leukopenia, viral gastroenteritis. Prescribing information notes that the adverse event (AE) profile in the lupus nephritis populaiton was consistent with the SLE population; additionally the AE safety profile was noted to be similar in pediatric pateints compared to adults; and with SC route compared to IV route. Injection site reactions are also common with subcutaneous administration (occuring in 6.1% of patients on BEL vs. 2.5% on placebo in clinical study). Injection site reactions are usually mild.
- *For voclosporin*: kidney toxicity (decreased eGFR, acute kidney injury), hypertension, GI symptoms, headache, anemia, cough, urinary tract infection, alopecia, fatige, tremor, and decreased appetite.

Main warnings and precautions for belimumab and voclosporin are listed in **Table 5**.

Table 5. Warnings and Precautions for Belimumab and Voclosporin[8,9]

Warnings for both medications	
• Immunosuppression/risk for serious infection (black box warning with voclosporin) • Immunosupressants may increase risk of malignancy (black box warning with voclosporin) • Contraindication: hypersensitivity to the active ingredient • Immunization: Avoid live vaccines while on these therapies (eg, give live vaccine at least 30 days before the first dose of immunosuppressant). Inactivated vaccines may not be sufficiently immunogenic during treatment with the immunosuppressant.	
Unique warnings	
Belimumab	Voclosporin
Infusion reaction with IV administration, and/or hypersensitivity reactions, including anaphylaxis	Use with strong CYP3A4 inhibitors is contraindicated
Psychiatric worsening: depression/suicidality	Neurotoxicity

Table 5. Warnings and Precautions for Belimumab and Voclosporin[8,9]

Belimumab *continued*	Voclosporin *continued*
Use in combination with other biologics has not been studied and is not recommended	Use in combination with cyclophosphamide has not been studied and is not recommended
Development of anti-drug antibodies	Nephrotoxicity
PML, progressive multifocal leukoencephalopathy	Hyperkalemia
	Hypertension
	QTc prolongation
	PRC, pure red cell aplasia

As these agents are systemic immunosuppressants, their use **increases the risk of developing serious infections**.[8,9] This is a warning with belimumab and a black box warning with voclosporin. Patients should be monitored for the development of infection while on these therapies and therapy interruption should be considered upon development of a new infection. Labeling notes that providers can weigh the benefits vs. risks for the individual patient with respect to initiating therapy. The use of live vaccines must be avoided while taking these medications and for at least 30 days before therapy initiation.[8,9]

- Although the incidence of serious infections in controlled trials was similar between belimumab versus placebo, fatal infections were numerically more frequent with belimumab in 3 studies: 0.3%-0.45% vs. 0.1%-0.15% in 2 SLE studies by IV route; and 0.5% vs. 0% in an SLE study by SC route.[8]
- Similar rates of serious infections occurred between placebo (12.0 per 100 patient-years) vs. voclosporin 23.7 BID (11.9 per 100 patient-years), most frequently being pneumonia, gastroenteritis, or urinary tract infections. Case reports of opportunistic viral infections included cytomegalovirus and herpes zoster.[9]

Both agents are **contraindicated** if the patient experienced prior **hypersensitivity** to the active ingredient. The warning is elaborated for belimumab since serious and fatal reactions have been reported, usually within 3 hours of belimumab administration. Even patients who previously tolerated therapy may develop reactions during subsequent administrations. While premedication in an effort to avoid hypersensitivity may be used, it is not yet clear if this significantly reduces frequency or severity of reactions. Patients self-administering belimumab by SC route should also be warned of signs of hypersensitivity and have a plan of action. A provider administering the medication by IV route should have the capacity/resources to respond to an anaphylactic reaction.[8]

Immunosuppressants **may increase the risk of malignancies** (including lymphoma with voclosporin). This is a black box warning for voclosporin and a warning for belimumab. While the mechanism of action of belimumab could theoretically increase the risk of malignancies, based on low rates of events and similar rates to placebo in clinical trials, it is not clear that belimumab increases risk.[8,9]

Additional Warnings for Belimumab[8]

- **Progressive multifocal leukoencephalopathy** (PML): Cases of PML, particularly John Cunningham (JC) virus associated, have been reported in patients taking immunosuppressants including belimumab. Patients with new-onset or deteriorating neurological symptoms while on

belimumab should be assessed for PML and the drug should be discontinued if PML is confirmed.

- **Depression and suicidality**: There were more frequent psychiatric events, primarily of depression, insomnia, and anxiety, in adults on IV belimumab compared to placebo. Patients should be assessed for depression and risk of suicide before initiation of treatment and monitored during treatment for new or worsening psychiatric condition/events.
- Since belimumab is a large molecule protein, it may induce the development of antibodies directed against the drug. **Antidrug antibodies**, some neutralizing, were detected among few patients in clinical studies. The highest incidence (4.8%) was in the arm of belimumab 1mg/kg, rather than 10 mg/kg (0.7%) which suggests that the frequency is underestimated at higher dosages "…due to lower assay sensitivity in the presence of high drug concentrations."[8]
- Concomitant use with other immunosuppressant **biologics** has not been studied and therefore is not recommended.

Regarding belimumab use in combination with other biologics:

I. The labeling recommends against the use of biologics while on belimumab, while the LN study protocol and FDA review documents name more *specifically* biologic immunomodulators that were not allowed while on belimumab.[47,52] The exclusion criteria do not seem to go as far to exclude patients on biologics that do not target the immune system (eg, insulin, dulaglutide, onabotulinumtoxinA, alirocumab, etc). There are many biologics that do not target the immune system, and special consideration should be made for patients that also require such therapy for other co-occurring conditions they may have.

II. Labeling for belimumab highlights that belimumab has not been studied in combination with other biologics, including rituximab (RTX), a monoclonal antibody that targets CD20 antigen on B-lymphocytes and mediates B-cell lysis; RTX is currently recommended for treatment refractory SLE and LN.[6,17] However, we are aware of a phase 3 study (BLISS-BELIEVE, NCT03312907, N= 292) assessing treatment with 52 weeks of belimumab plus 2 doses of rituximab for the treatment of **SLE**. Investigators note that this trial targets patients who maintain some degree of disease activity despite treatment with belimumab.[68] Although the study is not yet published in full, results presented at a conference showed no significant benefits in disease control or clinical remission with this regimen compared to belimumab plus matching placebo. There were also numerically more patients in the belimumab/rituximab arm with severe infections vs. the comparator arms of belimumab/placebo or belimumab/standard therapy.[69]

    In a small phase 2 study (N=43) of patients with refractory **LN**, a regimen of rituximab plus cyclophosphamide, administered in weeks 0 and 2, followed by belimumab (10 mg/kg IV at weeks 4, 6, 8, and every 4 weeks thereafter) appeared tolerable and safe over 48 weeks and trended to improve partial or complete renal response among those with baseline nephrotic proteinuria (vs. the control arm of rituximab/cyclophosphamide without belimumab).[70] A phase 3 trial, powered for efficacy outcomes is needed to confirm benefits with this regimen in particular LN patients; though, it is unclear if/when one will be carried out.

Additional Warnings for Voclosporin[9]

- **Nephrotoxicity:** CNIs may cause acute and/or chronic nephrotoxicity especially if given with other medications associated with nephrotoxicity. In clinical trials, serious renal adverse reactions were reported at 3.7 per 100 patient-years on placebo vs. 5.6 per 100 patient-years on voclosporin 23.7 mg BID.[4]
- **Neurotoxicity:** CNIs may cause neurotoxicity; serious manifestations include posterior reversible encephalopathy syndrome (PRES), delirium, seizure, and coma. Serious nervous system symptoms were reported at 0.9 per 100 patient-years with placebo and 3.9 per 100 patient-years with voclosporin 23.7 mg twice a day (eg, headache, migraine, seizure, and posterior reversible encephalopathy syndrome).[4]
- **Hyperkalemia:** serious hyperkalemia may develop while on treatment and may require treatment (rate was 0.8 vs. 2.1 per 100 patient-years with placebo vs. voclosporin 23.7 mg, respectively). Use caution when used in combination with other agents associated with hyperkalemia.[4]
- **Hypertension**: Treatment with voclosporin is not recommended with baseline BP >165/105 mmHg or with hypertensive emergency. Blood pressure should be monitored every 2 weeks during the first month of treatment, and as clinically indicated thereafter. Since hypertension is a common adverse reaction (19% with BEL vs. 9% on standard therapy only), patients may require antihypertensive therapy or dose increase of their current antihypertensive agent.
- **QTc Prolongation:** voclosporin was found to prolong the QTc interval in a dose-dependent manner at higher than the recommended dosing (0.5–4.5 mg/kg representing up to 9-fold coverage of the therapeutic exposure). Use caution during combined use with other agents that also pose risk for QTc interval prolongation.[4]
    - "The maximum mean placebo-adjusted changes of QTc from baseline after LUPKYNIS 0.5 mg/kg, 1.5 mg/kg, 3.0 mg/kg, and 4.5 mg/kg dose were 6.4 msec, 17.5 msec, 25.7 msec, and 34.6 msec, respectively."[4]
    - "…an absence of large mean increases (i.e., >20 msec) was observed following 7 days of treatment with LUPKYNIS at 0.3, 0.5 and 1.5 mg/kg twice daily (approximately 6-fold coverage of the therapeutic exposure)."[4]
- **Pure Red Cell Aplasia:** Cases of pure red cell aplasia (PRCA) have been reported in patients treated with another CNI immunosuppressant.
- **Drug-Drug Interactions**: Avoid co-administration of voclosporin and strong CYP3A4 inhibitors or with strong or moderate CYP3A4 inducers (labeled contraindication).[†††] Reduce the dosage to 15.8 mg in AM and 7.9 mg in PM, when co-administered with moderate CYP3A4 inhibitors (eg, verapamil, fluconazole, diltiazem). Should reduce dose of certain P-gp substrates with narrow

[†††] Examples of strong CYP3A4 inhibitors include ketoconazole, itraconazole, and clarithromycin; and strong or moderate CYP3A4 inducers include carbamazepine, rifampin, and efavirenz.

therapeutic index (eg, digoxin, cyclosporine) if used in combination with voclosporin which is a P-gp inhibitor.

For contrast, common AEs (≥15%) listed for systemic tacrolimus (Progard*;* an older calcineurin inhibitor option for LN) include, among others, diabetes mellitus, hyperglycemia, hyperkalemia, hypomagnesemia, and hyperlipidemia. These were not *common* AEs observed with voclosporin in clinical studies. Nonetheless, hyperkalemia may occur with voclosporin infrequently so it remains a labeled warning. Voclosporin does not have a warning regarding onset of diabetes mellitus as does tacrolimus, an agent also know to commonly elevate lipids and blood glucose.[5] Both agents have warnings in common regarding lymphoma/other malignancy, serious infections, nephrotoxicity, neurotoxicity, hypertension, hyperkalemia, interactions with CYP3A4 inhibitors and inducers, QT prolongation, and pure red cell aplasia.[9,71]

Specific Populations

Pregnancy

Human evidence with either belimumab or voclosporin is insufficient to conclude whether there is a drug-associated risk for major birth defects or miscarriage.[8,9] Labeling advises to avoid use of voclosporin during pregnancy as a precautionary measure due to dehydrated alcohol being a part of the formulation. Immunosuppressants in general pose infection risk to the fetus, and both of these molecules cross the placenta. Yet, possible/theoretical drug-related risks are juxtaposed with the known serious risks, to the mother and fetus, of untreated SLE or LN. Active SLE increases the risk of adverse pregnancy outcomes such premature birth, miscarriage, and intrauterine growth restriction. Lupus nephritis increases the risk of hypertension and preeclampsia/eclampsia.[8,9] Moreover, autoantibodies that induce SLE disease in the mother cross the placenta and can result in acquisition of neonatal lupus and congenital heart block.[8,9] Several standard therapies used in SLE and LN are avoided during pregnancy including mycophenolate and cyclophosphamide— narrowing patients' options. The 2021 KDIGO guideline states "Only glucocorticoids, hydroxychloroquine, azathioprine, and CNIs are considered safe immunosuppressive treatments during pregnancy."[5]

- Belimumab is a monoclonal antibody that is actively transported across the placenta during the third trimester of pregnancy and *may* affect immune response of the utero-exposed infant. Fetal harm in animal models was not demonstrated upon supra-therapeutic exposure about 9 or 20 times the exposure to humans at the maximum recommended dose by IV or SC route, respectively. Fetal reduction of B-cell counts, and reduction in the density of lymphoid tissue B-lymphocytes in the spleen and lymph nodes was observed in animal studies.[8]
- Voclosporin: The usual voclosporin regimen yields exposure of up to 129.4 mg per day of alcohol. Since the safe level of alcohol exposure is unknown for pregnancy and there are alcohol-associated fetal risks (eg, central nervous system abnormalities, behavioral disorders and impaired intellectual development), labeling recommends avoidance of the medication during pregnancy. Treatment-related fetal malformations were minimal in animal studies when voclosporin was given at 1 to 15 times the exposure of the maximum recommended human dose; adverse events noted were reduced fetal body weights and dystocia.[9]

Lactation

Belimumab passes into the milk of monkeys; it is possible this also occurs in human milk but with insufficient clinical data, the risk to an infant during lactation is unclear. Labeling advises to weigh the developmental/health benefits of breastfeeding plus benefits of therapy to the mother, against potential/theoretical adverse effects of therapy on the child.[8]

Since voclosporin passes into milk of lactating rats, it is likely that this will also occur in human milk. Labeling recommends avoidance of breastfeeding while on this therapy (or for 7 days following the last dose) since there are serious adverse events that can occur similar to those in the mother (eg, increased risk of serious infections).[9]

Pediatric Use

Voclosporin use has not been established in the pediatric population. Regarding belimumab, safety and effectiveness have not been established in patients younger than 5 years of age. The medication is approved for use, by IV route only, for pediatric patients 5 years or older who have active, autoantibody-positive SLE and are taking standard therapy.[9]

Refer to related information from guidelines regarding the management of LN in the pediatric population on page 17. Since this is a rare disease, approved medications for this population are minimal, leaving off-label use of agents to accommodate the treatment need. Belimumab is the only agent with a pediatric indication, approved for pediatric SLE (autoantibody positive).

Geriatric Use

It is unclear if response to belimumab or voclosporin differs in older patients (>65 years of age) versus younger subjects. However, they should be use with caution in elderly patients. Labeling for voclosporin recommends to initiate therapy at the low end of the dosage range in elderly patients, since elderly are likely to have decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.[9]

Renal Impairment

Clinical experts of LN do not see it appropriate to have a rigid eGFR cutoff for exclusion of patients for these therapies since renal function should be viewed in the context of renal histology.[72] While there is not a specific contraindication for these medications with renal impairment there are dose adjustments recommended for voclosporin and a labeled warnings:

- Voclosporin has a labeled warning that use is not recommended in patients with baseline eGFR ≤45 mL/min/1.73 m^2 unless benefit outweighs the risk, since these patients may be at risk of nephrotoxicity. If used in patients with pre-treatment severe renal impairment, a lower initial dose of 15.8 mg twice daily is recommended. Prior to starting treatment, eGFR should be measured, along with every 2 weeks during the first month of therapy, and every 4 weeks thereafter. If eGFR is reduced during treatment, the following adjustments are recommended [9]:
    - For eGFR <60 mL/min/1.73 m^2 and reduced from baseline by 20% to 30%, reduce the dose by 7.9 mg twice a day. Re-assess eGFR within 2 weeks; if eGFR is still reduced from baseline by>20%, reduce the dose again by 7.9 mg twice a day.

- If eGFR <60 mL/min/1.73 m^2 and reduced from baseline by ≥30%, discontinue. Re-assess eGFR within 2 weeks; consider re-initiating voclosporin at a lower dose (7.9 mg twice a day) when eGFR has returned to ≥80% of baseline.
- For those using a decreased dose due to eGFR, consider increasing the dose by 7.9 mg twice a day for each eGFR measurement that is ≥80% of baseline; do not exceed the starting dose.

No dosage adjustment for belimumab is recommended in patients with renal impairment.[8] A case series (reported in a meeting abstract) showed that belimumab was relatively safe for reducing SLE disease activity in patients with advanced CKD and ESRD on dialysis; though, some patients contracted infections while on treatment.[73] Infection risk remains a challenge with all immunosuppressants used for SLE/LN.

Hepatic Impairment

- For mild and moderate hepatic impairment (Child-Pugh A and Child-Pugh B), reduce the dosage of voclosporin to 15.8 mg twice daily. Avoid use in severe hepatic impairment.[9]
- Labeling for belimumab notes that the effects of hepatic impairment on the pharmacokinetics of belimumab are unknown and that dosage adjustment is not recommended at this time for use during hepatic impairment.[8]

Utah Medicaid Fee-for-Service (FFS) Utilization

Over the last year, from December 2020 through November 2021, there have been less than 5 patients total who have recieved belimumab or voclosporin. All utilization during this period has been in adults and all patients have ICD 10 diagnosis coding indicating lupus disease (M32.XX). Half the belimumab utilizers and all voclosporin utilizers had diagnosis coding for glomerular disease in SLE (M32.14). Utlization appears to be in line with the indicated disease states of these products.

Table 6. Utah Medicaid FFS Claims (Dec. 2020 through Nov. 2021)

Generic	Product	Claims	Patients
Pharmacy			
Belimumab	BENLYSTA INJ 200MG/ML	12	<5
Voclosporin	LUPKYNIS CAP 7.9MG	<5	<5
Medical			
Belimumab	BENLYSTA INJ 400MG	15	<5

Prior Authorization Considerations

The following criteria can be considered for belimumab and voclosporin, keeping in mind that these are the only medications with FDA approval for lupus nephritis on the market; belimumab is the first/only agent with FDA approval for pediatric SLE[7]; and these medications added onto standard therapy outperformed standard therapy alone for inducing a renal response in LN.[4,60] While both medications are indicated for active LN, belimumab has additional place-in-therapy for the management of SLE extra-renal symptoms (regardless of the histological class of LN[6]). Pivotal trials for these agents had different inclusion criteria, one difference being that the voclosporin phase 3 trial did not require autoantibody positivity, while this was a pre-requisite for the belimumab phase 3 studies.[‡‡‡] Nonetheless, for the *LN indication*, FDA-indication wording does not require autoantibody positivity for belimumab nor do guidelines for the management of LN specify withholding belimumab until autoantibody positivity is demonstrated. Labeling for belimumab regarding the treatment of SLE, *does* specify requirement for autoantibody positivity— likely related to failure, of a phase 2 SLE trial, to meet the primary endpoint when autoantibody negative patients were included in the study population with SLE (but who were without severe LN).[15,74]

Potential criteria are as follows, with additional considerations listed below the table:

Voclosporin	Belimumab
✓ Not to exceed maximum recommended labeled dosage	
✓ For use in adult patients (based on FDA-approval)	✓ For use in patients at least 5 years of age (based on FDA-approval for SLE). Note that the SC formulation is intended for adults only at this point, and the IV form is for pediatric or adult patients.
✓ Provider attestation that patient has **active LN** (ideally a nephrologist or rheumatologist, or in consultation) and that the medication will be used as add-on therapy to a background immunosuppressive regimen - If considering adding the requirement to have class III, IV, or V LN, consider the caveats in those without biopsy under current provider, patients with biopsy contraindication, patients without prompt access to biopsy, and less favorable outcomes with unregulated disease flare due to treatment delays	✓ Provider attestation that patient has either **active LN** (ideally a nephrologist or rheumatologist, or in consultation) or **autoantibody positive SLE** and that the medication will be used as add-on therapy to a background immunosuppressive regimen - Since SLE can be widespread, affecting many organ systems, a variety of specialists may treat lupus (eg, dermatologist, cardiologist, nephrologist, rheumatologist, neurologist, etc) - Consider the caveats of requiring current autoantibody positivity in patients already started on a standard immunosuppressant, and/or who have already demonstrated positivity while under a previous provider

[‡‡‡] Antibody positive defined as antinuclear antibody titers ≥1:80 antibodies (based on Hep-2 immunofluorescence assay or equivalence by enzyme immunoassay assay) **AND/OR** positive anti-dsDNA serum antibody test of ≥ 30 IU/mL based on ELISA assay

Voclosporin	Belimumab
- Consider provider attestation or educational note that this agent should not be combined with cyclophosphamide, strong CYP3A4 inhibitors, or strong/moderate CYP3A4 inducers [per FDA-labeling]	- Consider provider attestation or educational note that this agent will not to be used concurrently with *immunosuppressive* biologics (eg, anti-TNF therapy, abatacept, anakinra or other B-cell targeting biologics) - The medication is also not intended for **severe active** central nervous system lupus per labeling

Supporting Information for Proposed Criteria and Additional Considerations

- Consider allowing coverage of **belimumab** for patients with SLE, with or without LN, and regardless of LN class; thus, the provider may attest that patient has either **active LN** (FDA approval) or **autoantibody positive SLE** (FDA approved indications)
  - According to guidelines, belimumab, added-on to standard therapy, can be considered for
    - patients **with SLE** inadequately responding to standard-of-care (ie, disease activity not allowing tapering of glucocorticoids and/or frequent relapses)[17,34]
    - ***initial* therapy** for active class III or IV (with or without class V) LN to achieve a renal response;[5] and in LN patients, regardless of histologic class, for the management of persistent *extra-renal* activity/flares despite standard therapy **or** for purposes of minimizing glucocorticoids.[6]
    - Note that the LN guidelines do not state that belimumab must be withheld until the patients demonstrate autoantibody positivity. This might be because authors recognize the caveats, as autoantibodies can be influenced by the immunosuppressants the patient may already be taking for maintenance therapy or initiated for organ-threatening disease flare. Both ANA and anti-dsDNA autoantibodies can be suppressed while on standard treatments.[28] It could cause harm (disease progression and less favorable outcomes) to force a patient off all immunosuppressants in order to catch their autoantibody levels uninfluenced by any therapy. The labeled indication for belimumab specifies autoantibody positivity requirement for SLE patients, but *does not* make this requirement for LN patients in the indication.
  - The pivotal LN clinical study leading to label extension for belimumab included patients with severe LN (active class III or IV [with or without class V], or active pure class V LN).[63] While the earlier belimumab SLE studies excluded patients with severe LN, it is not evident that the exclusion criteria applied to class I or II LN, and certainly some patients had renal involvement at baseline in these SLE phase 3 studies (14–18% of included patients had >2g of proteinuria per 24 hours at baseline).[19,44]

- Consider allowing coverage of **voclosporin**, for patients with **active LN** (based on FDA indication)
  - Labeling for voclosporin states the indication is for **active LN** generally
  - The 2021 KDIGO guideline places this medication among *initial* regimen options, as add-on therapy, for active LN class III, or IV (with/or without class V)[5]
  - The phase 3 LN clinical trial leading to drug approval included patients with active class III or IV LN (with or without class V), and active pure class V LN.[60]
- A **diagnosis of SLE and LN** by nephrologist or rheumatologist should be considered valid according to guidelines.[19]
  - Experts advise that patients with LN should not be withheld from treatment based on failure to meet a particular SLE classification criteria thresholds (intended for clinical studies) since these thresholds were not designed/optimized for clinical practice.[19] Since there are nuances in the disease where criteria thresholds can fail to capture some patients with SLE,[25] experts reiterate that "Fulfilment of the classification criteria is not necessary for the diagnosis for SLE."[17]
  - If a patient already had **biopsy-proven LN** demonstrated up to 2 years beforehand, it is not clinically appropriate to require repeat biopsies for the sole purpose of providing newer results to the payer.[72] This is because biopsy is not without risks; patients may have co-morbidities that can increase risks of complications with biopsy.[32,72] There are other markers that indicate LN activity (eg, worsening proteinuria) in patients with prior biopsy proven disease.[72] We may also consider whether patients have access to a prompt renal biopsy services (or if services are delayed/constrained) and if the provider views that withholding coverage to the intended therapy will lead to poorer outcomes.

Additional Considerations

- Consider allowing providers to decide the most appropriate LN regimen based on the patient-specific needs as these regimens can outperform standard therapy alone for renal response[60,62], they can reduce glucocorticoid burden,[75] with belimumab there is greater likelihood of low SLE activity vs. standard therapy at week 104,[75] and voclosporin may pose less metabolic AEs over alternative off-label CNI options. Additionally, we should consider that patients may qualify for belimumab for the treatment of SLE extra-renal disease activity alone.
  - Pivotal trials for these new medications in LN did not require patients to fail standard induction therapy first or for patients to be treatment resistant to standard therapy. Rather, patients were excluded if they had previously failed both cyclosporine and mycophenolate for the belimumab study, and patients had to be able/willing to take mycophenolate for the voclosporin study.
  - ICER (Institute for Clinical and Economic Review) conclusions/recommendations for belimumab or voclosporin policy:
    - In patients *with LN*, there is high certainty in the evidence of at least small health benefits and moderate certainty of a substantial health benefit with belimumab or voclosporin added to standard care. Additionally, authors noted that "there is no other treatment

that could be considered a first-step treatment prior to eligibility [for these medications in lupus nephritis]."[72] **ICER advised avoiding policy that narrows FDA indications.** They also advised using peer-to-peer consultation by a physician knowledgeable in LN **before a coverage denial** for either of these medications, to understand fully the patient's clinical characteristics and therapy needs.[72]

- **Concomitant therapy**
  - In the pivotal **LN** clinical trial, belimumab was studied in combination with glucocorticoid plus MMF or cyclophosphamide for induction therapy, followed by its combination with mycophenolate (73%) or azathioprine (27%) for maintenance. Prohibited therapies included other B-cell targeting agents, anti-TNF agents (eg, adalimumab, etanercept, infliximab), other immunosuppressive biologics (eg, abatacept, anakinra), and intravenous immunoglobulin.[52] In the trials of belimumab for the treatment of **SLE,** patients were allowed standard therapies while on belimumab including the following: corticosteroids, anti-malarial agents (eg hydroxychloroquine), NSAIDs, and immunosuppressive/immunomodulatory agents (eg azathioprine, mycophenolate, methotrexate, leflunomide, **calcineurin inhibitors** [tacrolimus, cyclosporine], sirolimus, oral cyclophosphamide, 6-mercaptopurine and thalidomide.[46-48] Patients were not allowed to receive other B-cell targeted therapies (eg, rituximab, anti CD20, CD22, or CD52 agents).[46-48]
    - The labeling recommends against the use of biologics while on belimumab, while the LN study protocol and FDA review documents name more *specifically* biologic immunomodulators that were not allowed while on belimumab.[47,52] The exclusion criteria do not seem to go as far to exclude patients on biologics that do not target the immune system (eg, insulin, dulaglutide, onabotulinumtoxinA, alirocumab, etc). There are many biologics that do not target the immune system, and special consideration should be made for patients who also require such therapy for other co-occurring conditions they may have.
  - Voclosporin has not been studied in combination with other CNIs, rituximab, or belimumab. Additionally, it is not clear how the medication works in combination with cyclophosphamide, as this was not studied in clinical trials. Use in combination with cyclophosphamide is not recommended according to the product labeling.[9] In clinical studies, voclosporin was combined with glucocorticoid plus mycophenolate therapy.
- **Other limitations**:
  - These agents have not been studied for central nervous system lupus. The package insert advises not to use belimumab in this situation.[8]
  - The subcutaneous (SC) dosage form of belimumab is currently only labeled for adults (intravenous form can be used in pediatric and adult patients). There is a recruiting study that will address SC belimumab in pediatric patients with dosing based on weight (NCT04179032): for those ≥50kg, the dosage will be 200 mg/mL SC belimumab weekly; those ≥30kg to <50 kg, 200 mg/mL SC belimumab every 10 days, and for patients <30 kg, 200 mg/mL SC belimumab every 2 weeks.[76]

- **Treatment response in LN**
    - In the most recent LN clinical guideline of 2021 by KDIGO, authors describe that a partial renal response (50% reduction in proteinuria, and stabilization or improvement in kidney function (±10%-15% of baseline) could take as long as 12 months; and complete renal response could take over a year.[5] This is further highlighted in the 2019 EULAR/ERA-EDTA LN guideline where authors note that slower responses are expected in patients with nephrotic-range proteinuria at baseline. The 2021 KDIGO guideline recommends that patients should be allowed 18–24 months to achieve a complete response[§§§] on the selected regimen if they are generally showing continued clinical improvement. Additionally, immunosuppressive treatment need should also be considered with respect to targeting remission or low disease activity extra-renally as well.[6]
    - The labeling for voclosporin advised considering its discontinuation if the patient does not experience therapeutic benefit **by 24 weeks** (ie, 6 months).[9]
        - There are no universally established criteria for the level of improvement required in LN before discontinuing or switching therapies, however, the provider's attestation for general improvement in proteinuria and/or stabilization or improvement in kidney function by 6 months after starting therapy can be considered.
    - Since belimumab may be initiated for SLE extra-renal symptoms as well, general improvements in SLE disease activity should be considered.

[§§§] *Complete renal response* in adults in the KDIGO guideline is defined as a reduction in proteinuria <0.5g/g measured as the protein creatinine ratio from a 24-h urine collection, and stabilization or improvement in kidney function (±10%-15% of baseline), within 6-12 months of starting therapy but could take more than 12 months[5]

Summary

Treatment guidelines recommend intensive immunosuppressant therapy (usually with mycophenolate mofetil [MMF] or IV cyclophosphamide, combined with glucocorticoids) for **active class III or IV LN** (with or without class V LN),[5] and for certain patients with **pure** class V LN (eg, nephrotic-range proteinuria, or worsening proteinuria despite the optimal use of renin–angiotensin–aldosterone system blockers).[6] Belimumab, a B-cell targeted, subcutaneous/intravenous therapy, and voclosporin, an oral calcineurin inhibitor (CNI), are also among *initial* regimen options listed in the 2021 KDIGO guideline for active class III or IV (±V) LN.[5] KDIGO guideline authors note, "An advantage of a CNI-based regimen is the more rapid reduction of proteinuria."[5] Relative to older CNIs (tacrolimus and cyclosporine) that are used off-label for SLE and LN, voclosporin offers the advantage of not requiring pharmacokinetic monitoring and may have a more favorable effect on serum lipids and glucose.[5] Belimumab not only can be used for active class III, IV, and/or V LN, but it is also recommended for extra-renal disease activity in SLE patients (who may not have LN) but are inadequately responding to standard-of-care for SLE,[34] or for patients with LN in general, in order to decrease the risk of flares and/or help minimize glucocorticoid dosages.[6] Belimumab is the only medication approved for pediatric SLE, as an intravenous treatment in children ages 5 or older. Voclosporin's indication only covers adults who have progressed to active LN.

Pivotal phase 3 trials **in severe active LN** for belimumab and voclosporin required active, biopsy-proven **class III, IV, or V LN** for study entry**.** For the belimumab LN phase 3 trial, patients were also required to have antinuclear antibodies and/or anti- dsDNA antibodies at screening;[28] this was not required for the voclosporin study. In the phase 3 LN trials, belimumab was added to a standard regimen, either mycophenolate- or cyclophosphamide-based plus glucocorticoid; and voclosporin was studied in combination with MMF and glucocorticoid therapy only. Significantly more belimumab-treated patients achieved a primary efficacy renal response compared to the standard therapy alone, starting at week 24 with the effect maintained through the end of the trial at week 104. Results for key secondary endpoints, complete renal response and the risk of renal event or death, also favored belimumab treatment. Compared to standard therapy alone, add-on voclosporin resulted in a higher proportion of patients achieving a complete renal response at week 24 and the difference maintained to the end of study at week 52.[60]

Warnings and precautions for these agents are summarized in Table 5 on page 24. Like other strong immunosuppressants, these agents have labeled warnings regarding the risk of serious infection with their use. Immunosuppressants may also increase the risk of malignancy. Unique warnings with belimumab include the possibility for hypersensitivity reaction, numerically higher rates of depression/suicidality vs. placebo, and rare cases of progressive multifocal leukoencephalopathy. When using voclosporin, the prescriber should be cognizant of possible drug interactions via CYP3A4 and consider QTc prolongation risk factors. Like other calcineurin inhibitors such as tacrolimus, voclosporin has similar warnings regarding the potential for neurotoxicity, nephrotoxicity, hypertension, hyperkalemia, and pure red cell aplasia.

Prior authorization criteria considerations are provided on page 31, taking into account the labeled indication(s) wording, pivotal LN clinical trial key inclusion criteria, and recommendations regarding limitations (eg, combination therapies not studied). Belimumab and voclosporin currently are the only medications FDA-indicated for LN, a common complication of SLE that is associated with increased morbidity and mortality. The most recent LN guideline (2021 KDIGO) recommends these therapies

among *initial* regimen options for patients with severe active LN; patients are not required to fail a previous treatment for LN in the guideline, nor was this required in pivotal studies.[5] Belimumab has additional place-in-therapy for extra-renal SLE manifestations and is the only agent on the market approved for pediatric patients with lupus.[6,34]

Appendix A: Literature Searches

Embase (searched November 2nd, 2021)

('voclosporin'/exp OR voclosporin OR 'belimumab'/exp OR belimumab) AND ('lupus nephritis'/exp OR 'lupus nephritis') limited to 2019-2021 => 228 results

Cochrane Library (searched November 2nd, 2021):

Cochrane Reviews

- lupus-nephritis or belimumab or voclosporin [Title, abstract, keyword]
  - 4 Cochrane Reviews

Cochrane Trials Database (limited to 2017-2021)

- lupus-nephritis AND (belimumab or voclosporin) [Title, abstract, keyword]
  - 65 results

Wiley online Library:

Lupus [Title] AND Arthritis and Rheumatology (Journal of the American College of Rheumatology)

- 164 results on October 20th, 2021

Guidelines referenced for preparation of this report

- 2021 KDIGO guideline, chapter 10 for the management of lupus nephritis[5]
- 2019 EULAR/ERA–EDTA, Recommendations for the Management of Lupus Nephritis[6]
- 2019 EULAR Recommendations for the Management of Systemic Lupus Erythematosus[34]
- 2017 Recommendations for the Diagnosis and Treatment of Childhood-Onset Lupus Nephritis: the SHARE Initiative[53]
- 2021 ACR Guideline: Screening, Case Definition, Treatment and Management of Lupus Nephritis[19]

Appendix B: Additional SLE Background Information

SLE symptoms vary between individuals and can be localized or widespread, inconsistent (ie, may come and go), can range from mild to severe, and additional symptoms can develop over time.[1] Symptoms can include fever, fatigue, rashes (eg, malar, discoid), sun sensitivity, hair loss, sores in nose or mouth, changing color of fingers and toes, swelling of glands, legs, or around eyes, GI symptoms, weight loss, headaches, dizziness, and pain that can stem from inflammation and damage to tissues or organs.[1,77] Inflammation can occur in joints, skin, kidneys, lining of the heart and lungs, brain, and blood cells which can progress to compounded comorbidities such as arthritis, lupus nephritis, depression, cognitive dysfunction, seizures, heart damage to valve, pericarditis or myocarditis, vasculitis, and blood clots.[1,12,78] SLE itself, along with treatments for SLE, can cause low RBC, WBC, and platelets, leaving the patient more prone to infection.

The 1982/1997 American College of Rheumatology (ACR) SLE classification criteria were used for belimumab and voclosporin clinical studies; however, updated criteria have been published more recently in 2019.[22] Criteria from SLICC (Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus) were also published in 2012, grouping clinical and immunological signs differently compared to the 1982/1997 ACR criteria. For patients not fully meeting SLE criteria or a threshold score, the ACR has emphasized that this should not be the sole reason to exclude patients from therapies a rheumatologist or nephrologist deems appropriate. Criteria that have been developed over the years are continually being improved and do not capture all SLE patients. Classification criteria were designed mainly for enrollment into clinical trials. The criteria were not designed nor optimized for diagnosis or treatment decision making. Authors emphasize that these criteria are not intended to exclude patients who do not fully meet a particular threshold from receiving appropriate therapies. The ACR states, "Diagnosis of SLE remains the purview of an appropriately trained physician evaluating an individual patient."[22]

American College of Rheumatology 1982 SLE Criteria with 1997 Update[79]

For clinical studies, authors advised that a person should have **at least 4** of the 11 criteria present "…serially or simultaneously, during any interval of observation." The 11 criteria are based on presence of the following features (refer to full document for definitions of each and specification for meeting criteria):

1. Malar rash
2. Discoid rash
3. Photosensitivity
4. Oral ulcers
5. Arthritis
6. Serositis: pleuritis or pericarditis
7. Renal disorder (ie, lupus nephritis): persistent proteinuria > 0.5 g/day OR > 3+ if quantitation not performed; **OR** cellular casts (eg, red cell, hemoglobin, granular, tubular, or mixed)
8. Neurologic disorder: seizures or psychosis not otherwise cause by other non SLE conditions or drugs
9. Hematologic disorder: hemolytic anemia, leukopenia, lymphopenia, or thrombocytopenia

10. Immunologic disorder: anti-DNA abnormal titer (ie, antibody to native DNA) **OR** anti-Sm (presence of antibody to Sm nuclear antigen), **OR** positive antiphospholipid antibodies based on IgG or IgM anticardiolipin antibodies, +lupus anticoagulant, or a false positive syphilis result)
11. Antinuclear antibody

Treatment for SLE, 2019 Guidance by EULAR[34]

Goals: remission of disease (or low disease activity), prevention of organ damage accrual, minimize drug side-effects, and improve of quality of life

- Because complete remission of SLE disease (ie, absence of clinical activity without use of GC and immunosuppressants) is infrequently attainable, low disease activity is a subsequent goal (ie, SLEDAI score ≤3 on antimalarials, or alternatively SLEDAI ≤4, PGA≤1 with GC ≤7.5 mg of prednisone and well tolerated immunosupressive) since this goal also decreases organ damage accrual.
- Similarly, rather than complete renal remission in LN, the subsequent goal for LN is to achieve at least partial remission (ie, ≥50% reduction in proteinuria to subnephrotic levels and SCr within 10% of baseline) by 6–12 months

Treatment

- All patients with lupus are to receive hydroxychloroquine (HCQ) (up to 5 mg/kg) unless there is a contraindication
- Additional treatment of **non-renal SLE** includes the following
  - For **mild disease** activity: PO or IM glucocorticoids(GC); add MTX or AZA if inadequately responding to GC/HCQ;
    - Mild disease is considered as constitutional symptoms/mild arthritis/rash ≤ 9% BSA/PLTs 50 to 100x 103 /mm^3 ; SLEDAI **≤ 6**; or BILAG C or ≤ 1 BILAG B manifestation
  - For **moderate diseases** activity: PO or IV glucocorticoids; add mycophenolate, MTX, or AZA if inadequately responding to GC/HCQ; however, immunomodulating/ immunosuppressive agents can be started immediately with organ-threatening disease.
    - Moderate disease is considered: RA-like arthritis/rash 9-18% BSA/ cutaneous vasculitis ≤ 18% BSA; PLTs 20 to 50x103/mm^3 /serositis; SLEDAI 7 to 12[a]; or ≥ 2 BILAG B manifestations
  - For **severe disease** activity: PO or IV glucocorticoids plus mycophenolate, cyclophosphamide, or rituximab
    - Severe disease is any of the following: major organ-threatening disease (nephritis, cerebritis, myelitis, pneumonitis, mesenteric vasculitis); thrombocytopenia with platelets < 20x103/mm3; TTP-like disease or acute hemophagocytic syndrome; SLEDAI > 12; ≥ 1 BILAG A manifestations
  - "In patients with inadequate response to standard-of-care (combinations of HCQ and GC with or without immunosuppressive agents), defined as residual disease activity not allowing tapering of glucocorticoids and/or frequent relapses, add-on treatment with **belimumab** should be considered (1a/A)."
    - Factors associated with greater likelihood of response to belimumab include "…high disease activity (eg, SLEDAI >10), prednisone dose >7.5 mg/day and serological activity

(low C3/C4, high antidsDNA titres), with cutaneous, musculoskeletal and serological manifestations responding the most."

- Considerations for specific disease locations:
  - **Skin disease**: first line includes topical treatment with GC and calcineurin inhibitors, antimalarials, and/or systemic GC. In nonresponsive skin disease, the following can be considered, high-dose GC, MTX, retinoids, dapsone, mycophenolate as add-on therapy
  - **Lupus thrombocytopenia**: may require intravenous additional treatment with IV immunoglobulin G. For maintenance of response, mycophenolate, azathioprine, or cyclosporine are favorable.
- Maintenance treatment: minimize glucocorticoids to <7.5mg/day (prednisone equivalent) and, if possible, discontinue. Initiation of immunomodulatory agents (methotrexate, azathioprine, mycophenolate) can expedite the tapering/discontinuation of glucocorticoids.

Abbreviations: AZA, azathioprine; C3/C4, compliment 3 and 4; SLEDAI, SLE Disease Activity Index; GC, glucocorticoids; IV, intravenous; LN, lupus nephritis; MTX, methotrexate

[a] Note that other guidelines such as the British Society of Rheumatology guideline classifies moderate SLE disease severity as SLEDAI 6- 12 rather than 7-12 as in the EULAR guideline;

Appendix C: Additional Clinical Trial Information in LN

Table 1. Phase 3 Clinical Studies in Lupus Nephritis for Belimumab[4] and Voclosporin[60,67]

Study	Characteristics	Interventions
Bliss LN: Efficacy and Safety of **Belimumab** in Patients With Active Lupus Nephritis (NCT01639339)	**Phase 3,** Completed, N=448 • Randomized, parallel intervention model; quadruple blinded (participant, provider, investigator, outcomes assessor)	Belimumab vs. Placebo plus standard therapy, either (a) IV cyclophosphamide (500 mg every 2 weeks [±3 days] for 6 infusions) for induction + maintenance with azathioprine (target dose, 2 mg/kg per day; ≤200 mg per day) initiated 2 weeks after the last dose of cyclophosphamide; or (b) MMF for induction (target dose, 3 g per day) and maintenance with 1 to 3 g per day of MMF until trial end.
AURORA1; Aurinia Renal Response in Lupus With **Voclosporin** (NCT03021499, First posted on clinicaltrials.gov in Jan 2017)	**Phase 3,** Completed, N=358 • Randomized, parallel intervention model; quadruple blinded (participant, provider, investigator, outcomes assessor)	Voclosporin vs. Placebo, both with mycophenolate and corticosteroid background therapy: induction therapy with MMF (2 g/day target dose) and IV boluses of corticosteroid (eg, methylprednisolone 500 mg/dose) on days 1 and 2, followed by oral prednisone, stared at 20-15 mg per day, tapered to 2.5 mg/day by week 16, and adjusted by investigator discretion from thereforward
AURORA2; Aurinia Renal Response in Lupus With **Voclosporin**, Assessment 2 (NCT03597464)	**Phase 3,** Completed, N=216 (not published yet) • Randomized, parallel intervention model; quadrupal blinded (participant, provider, investigator,outcomes assessor) Included patients completers AURORA1. Those with temporary interruption and successful restart of study drug during the AURORA 1 were also allowed	Voclosporin vs. Placebo Both with mycophenolate and corticosteroid background therapy

Key Inclusion and Exclusion Criteria for Completed Phase 3 Studies in Lupus Nephritis

Belimumab, BLISS-LN (NCT01639339)

Key Inclusion Criteria[4,52,63]

- Non-pregnant adults (≥18 years) with diagnosis of SLE per 1982/1997 American College of Rheumatology criteria
- Biopsy confirmed active lesions consistent with LN, and LN classified according to the **2003** International Society of Nephrology and Renal Pathology Society as **class III** (focal lupus nephritis) or **IV** (diffuse lupus nephritis) **with or without coexisting class V** (membranous lupus nephritis), or **pure class V** lupus nephritis within 6 months before, or during screening
- Autoantibody-positive (ie, antinuclear antibody titers ≥1:80 antibodies (based on Hep-2 immunofluorescence assay or equivalence by enzyme immunoassay assay) **AND/OR** positive anti-dsDNA serum antibody test of ≥ 30 IU/mL based on ELISA assay)
- Clinically active lupus renal disease at screening requiring /receiving induction therapy with Standard of Care medications (eg, with high dose corticosteroids plus either IV cyclophosphamide or mycophenolate mofetil (IV or oral). Active LN is characterized as the following:
    - Ratio of urinary protein to creatinine of 1 or more **and**
        - urinary sediment: *at least 1* of the following (in absence of menses and genitourinary tract infection)
            - > 5 red blood cell (RBC)/high power field (hpf) or above reference range
            - > 5 white blood cell (WBC)/hpf or above the laboratory reference range
            - Presence of cellular casts (RBC or WBC)
        - **OR** at least 1 of the following criteria for those without urinary sediment:
            - Confirmatory biopsy within 3 months meeting the second inclusion criteria bullet above
            - Have proteinuria ≥ 3.5 grams/day (or urinary protein:creatinine ratio≥ 3.5)
- In the protocol, authors note that the study objective was to assess belimumab added onto standard of care therapies (SOC). Additional SOC agents were allowed (immunosuppressants such as methotrexate, hydroxychloroquine, etc) if they were started prior to baseline, in addition to the protocol planned agents (cyclophosphamide, mycophenolate, azathioprine, and glucocorticoids.)

Key Exclusion Criteria[4,52,63]

- History of failure to **both** cyclophosphamide and mycophenolate mofetil induction
- estimated glomerular filtration rate (eGFR) of< 30 ml per minute per 1.73 m2 of body surface area
- Receiving dialysis, belimumab, B-cell targeted therapy, anti-TNF therapy (eg, adalimumab, etanercept, infliximab), other biologics (eg, abatacept, interleukin-1 receptor antagonist [anakinra]), intravenous immunoglobulin, or plasmapheresis.
- Severe active central nervous system (CNS) lupus
- Acute or chronic infections requiring treatment within the past 60 day, or positive for HIV, hepatitis B, or hepatitis C.
- Current drug or alcohol abuse or dependence

Voclosporin, AURORA (NCT03021499)

Key Inclusion Criteria[80]

- Nonpregnant adults 18-75 years of age with diagnosis of SLE per 1982/1997 American College of Rheumatology criteria
- Patient requires high-dose corticosteroids and immunosuppressive therapy for active LN and is willing to take oral mycophenolate mofetil (MMF) for the duration of the study,
- Biopsy proven, **active nephritis**, defined as follows:
    - Kidney biopsy result within 2 years prior to screening indicating a histologic lupus nephritis (according to the 2003 International Society of Nephrology/Renal Pathology Society classification) as **Class III, IV-S, IV-G** (alone or in combination with Class V), or **Class V** LN, with at least a doubling increase in urine protein creatinine ratio (UPCR) within the last 6 months to ≥1.5 mg/mg for Class III/IV, or to ≥2 mg/mg for Class V
      OR
    - Kidney biopsy result within 6 months prior to screening showing Class III, IV-S or IV-G (alone or in combination with Class V) LN with a UPCR of ≥1.5 mg/mg at screening
      OR
    - Kidney biopsy result within 6 months prior to screening showing Class V LN and a UPCR of ≥2 mg/mg at screening

Exclusion Criteria[80]

- Estimated glomerular filtration rate (eGFR) of ≤45 mL/minute at screening (by Chronic Kidney Disease Epidemiology Collaboration equation). On **renal dialysis** (hemodialysis or peritoneal dialysis) or expected to require dialysis during the study period. Previous or planned kidney transplant
- Congenital or acquired immunodeficiency
- Clinically significant drug or alcohol abuse within 2 years prior to screening
- Malignancy within 5 years of screening, with the exception of basal and squamous cell carcinomas treated by complete excision; Lymphoproliferative disease or previous total lymphoid irradiation
- Severe viral infection, known HIV infection, active tuberculosis (TB), or known history of TB/evidence of old TB if not taking prophylaxis with isoniazid.
- Clinically significant active medical conditions: eg, severe cardiovascular disease, liver dysfunction, COPD or asthma requiring oral steroids, or other autoimmune condition if the condition or its related treatment can affect the study assessments or outcomes

Appendix D: List of Clinical Trials for Emerging Indications for Belimumab and Voclosporin

Voclosporin clinical trials for conditions other than lupus nephritis (phase 2 or 3 studies), located from ClinicalTrials.gov[81]

Completed studies for

- De novo renal transplant (phase 2, PROMISE, NCT00270634)
- Dry eye syndrome, keratoconjunctivitis sicca (phase 2/3, AUDREY, NCT04147650; phase 2 NCT03597139)
- Active, non-infectious Uveitis (phase 3, NCT01243983)
- Plaque Psoriasis (phase 3, SPIRIT NCT00244842, NCT00244842; ESSENCE, NCT00408187)

Recruiting studies for

- Antiviral effect in Covid-19 positive kidney transplant patients (phase 2; NCT04701528)

Terminated or withdrawn studies in the following conditions:

- Renal transplantation (phase 3, withdrawn, NCT01586845)
- Focal Segmental Glomerulosclerosis (phase 2, terminiated due to difficulties enrolling enough patients with this rare disease; NCT03598036)

Belimumab clinical trials for conditions other than lupus nephritis and SLE (phase 2 or 3 studies), located from ClinicalTrials.gov[82,83]

Completed studies for

- Vasculitis (phase 3, NCT01663623)
- Systemic sclerosis (phase 2, NCT01670565)
- Sjogren's syndrome (phase 2, NCT01160666, NCT01008982, NCT02631538)
- Blomerulonephritis membranous (phase 2, NCT01610492)
- Prevention for organ transplant rejection (phase 2, NCT01536379)
- Myasthaenia gravis (phase 2, NCT01480596)
- Rheumatoid arthritis (phase 2, NCT00071812)
- Prevention for renal transplant rejection (phase 1/2, NCT02500251)

Recruiting or may be about to recruit for

- Antiphospholipid syndrome (phase 2/3, NCT05020782)
- Myositis (phase 2/3, NCT02347891)
- COPD/emphysema (phase 2, NCT03244059)
- Vasculitis, cryoglobulinemia (phase 2, NCT04629144)
- ANCA associated vasculitis or granulomatosis with polyangiitis (phase 2, NCT03967925)
- Membranous nephropathy, nephrotic syndrome (phase 2, NCT03949855)
- Symptomatic Waldenstroms Macroglobulinaemia (phase 2, NCT01142011)
- Chronic lymphoid leukemia relapse (phase 2, NCT05069051)
- Systemic sclerosis (phase 2, NCT03844061)
- Multiple sclerosis (phase 2, NCT04767698)

Terminated or withdrawn studies in the following conditions:

- Desensitization in patients awaiting kidney transplant (phase 2, NCT01025193)
- Rheumatoid arthritis (phase 2, NCT00583557)

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