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Drug Class Update with New Drug Evaluation: Immunosuppressants

Date of Review: February 2022

Date of Last Review: February 2020
Dates of Literature Search: 10/31/2019 - 09/16/2021
Brand Name (Manufacturer):
Lupkynis™ (Aurinia Pharmaceuticals, Inc.)
Saphnelo™ (AstraZenica)
Dossier Received: yes

Generic Name:
Voclosporin
Anifrolumab-fnia

Current Status of PDL Class:
See **Appendix 1**.

Purpose for Class Update:
The purpose of this class update is to evaluate new comparative evidence for efficacy and safety of immunosuppressants, and to evaluate place in therapy belimumab (newly expanded indication for lupus nephritis [LN]), voclosporin (recently approved for lupus nephritis) and anifrolumab-fnia (recently approved for treatment of systemic lupus erythematosus [SLE]).

Research Questions:
1. Is there new comparative evidence that immunosuppressants differ in efficacy or effectiveness?
2. Is their new comparative evidence that immunosuppressants differ in safety?
3. What is the evidence for belimumab and voclosporin in LN?
4. What is the evidence for anifrolumab-fnia in SLE?
5. Are there specific subpopulations (age, race, ethnicity, gender, diagnosis, disease severity, and comorbidity) for which some immunosuppressants have different effectiveness or safety than other immunosuppressants?

Conclusions:
- Five high quality systematic reviews, 4 clinical practice guidelines, 3 new randomized controlled trials, 1 new formulation, 1 new indication, and 1 safety alert were identified after literature review to update evidence for this class.
- High quality guidelines and systematic reviews support the Oregon Health Plan (OHP) fee-for-service (FFS) preferred drug placement for the currently preferred agents.

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- Based on findings from a Drug Effectiveness Review Project report, there is low quality evidence that belimumab is more likely to achieve complete renal response (CRR) or primary efficacy renal response (PERR) than placebo at week 104 in patients with Class III, Class IV, or Class V (in combination with Class III or IV) LN based on 2 randomized controlled trials (RCTs)[1]:
    - CALIBRATE (n=33, background therapy rituximab + cyclophosphamide , moderate risk of bias [RoB]): CRR week 48, belimumab 38.0% vs. placebo 31.8%, 95% confidence interval (CI) -23.4% to 32.5%, P=0.76; CRR week 96, 23.8% vs 18.2%, 95% CI -18.7% to 30.0%, P=0.67.
    - BLISS-LN (n=446, background therapy randomized to cyclophosphamide plus azathioprine, or mycophenolate mofetil [MMF], moderate RoB):
        - PERR week 104, belimumab 43.0% vs. placebo 32.3%, hazard ratio (HR) 1.46, 95% CI 1.07 to 1.98, P=0.02, absolute risk reduction (ARR) 10.8%, number needed to treat (NNT) 10.
        - CRR week 104, belimumab 30.0% vs. placebo 19.7%, relative risk (RR) 1.52, 95% CI 1.09 to 2.12, P=0.01, ARR 10.3%, NNT 10.
    - BLISS-LN cyclophosphamide plus azathioprine background therapy subgroup: no significant differences in reaching PERR or CRR at week 104 with belimumab vs. placebo
    - BLISS-LN MMF background therapy subgroup:
        - PERR at week 104, belimumab 46.3% vs. placebo 34.1%, Odds Ratio (OR) 1.58 95% CI, 1.00 to 2.51
        - CRR at week 104, belimumab 34.1% vs. placebo 20.1%, OR 2.01, 95% CI 1.19 to 3.38
    - Infectious related treatment emergent adverse events (TEAEs) were the most common in all groups. The most frequent infection-related TEAEs in both groups were upper respiratory tract infection (URTI), urinary tract infection (UTI), herpes zoster, bronchitis, and nasopharyngitis.
- Based on findings from a Drug Effectiveness Review Project report, there is low quality evidence that *low dose* voclosporin 23.7 mg twice daily is superior to placebo at achieving CRR at 24 to 52 weeks based on 2 RCT with background therapy of MMF (corticosteroid use varied by protocol) in patients with Class III, Class IV-S or IV-G (A or A/C) or Class V alone or in combination with Class III or IV LN[1]:
    - AURA-LV (n=265, high RoB):
        - CRR week 24, low dose voclosporin 23.7 mg twice daily 32.6% vs. placebo 19.3%, RR 1.69, 95% CI 1.00 to 2.84, P=0.046, ARR 13.3%, NNT 8. High dose voclosporin 39.5 mg twice daily not significant vs. placebo, P=0.22.
        - CRR week 48, low dose voclosporin 49.4% vs. placebo 23.9%, RR 2.07, 95% CI 1.35 to 3.18, P<0.001, ARR 25.6%, NNT 4. High dose voclosporin 39.8% vs. placebo 23.9%, RR 1.67, 95% CI 1.06 to 2.62, P=0.02, ARR 15.9%, NNT 7.
    - AURORA A (n=357, moderate RoB):
        - CRR week 52, low dose voclosporin 40.8% vs. placebo 22.5%, RR 1.81, 95% CI 1.31 to 2.51, P<0.001, ARR 18.3%, NNT 6.
        - CRR week 24, low dose voclosporin 32.4% vs. placebo 19.7%, RR 1.65, 95% CI 1.14 to 2.37, P=0.006, ARR 12.7%, NNT 8.
    - The most frequent TEAEs were infections and infestations, gastrointestinal disorders, nervous system disorders, and renal and urinary disorders.
- There is insufficient evidence from 3 RCTs (one phase 2b, two phase 3) that anifrolumab-fnia 300 mg intravenously (IV) reduces SLE disease activity at 24 to 52 weeks in patients with moderate to severe SLE.[2-4] Evidence was downgraded due to risk of bias, imprecision, and indirectness.
    - MUSE had a statistically significant Systemic Lupus Erythematosus Responder Index (SRI-4) response with glucocorticoid (GC) tapering in the anifrolumab-fnia 300 mg dose group compared to placebo at week 24 (anifrolumab-fnia 300 mg 34.3% vs. placebo 17.6%; OR 2.38, 95% CI 1.19 to 4.77; NNT 6) and at week 52 (anifrolumab-fnia 300 mg 51.5% vs. placebo 25.5%; OR 3.08, 90% CI 1.86 to 5.09, P<0.001). The prespecified use of the high type I interferon (IFN) subpopulation at week 24 showed similar results (anifrolumab-fnia 300 mg 36.0% vs. placebo 13.2%; OR 3.55, 95% CI 1.5 to 7.32; NNT 5). MUSE used a type 1 error rate of 0.1 (two-sided).
    - TULIP-1 failed to find statistical significance for the primary endpoint of SRI-4 response at 52 weeks at either anifrolumab-fnia dose (anifrolumab-fnia 300 mg 36.1% vs. placebo 40.2%; -4.2% difference, 95% CI -14.20 to 5.82, P=0.41). TULIP-1 used BICLA (British Isles Lupus Assessment Groups Index

[BILAG]-based Combined Lupus Assessment) as a secondary endpoint (anifrolumab-fnia 300 mg 37.2% vs. placebo 26.6%; 10.6% absolute difference, 95% CI 0.59 to 19.68).
    - TULIP-2 changed the primary outcome via protocol amendment after TULIP-1 failed to find statistical significance. The change occurred after discussion with the FDA and experts and prior to data unblinding or analysis. TULIP-2 had a statistically significant difference in BICLA response at 52 weeks (anifrolumab-fnia 300 mg 47.8% vs. placebo 31.5%; 16.3% difference, 95% CI 6.3 to 26.3, P=0.001; NNT 7).
    - Complete improvement in a single organ system is needed to achieve SRI-4 response, while partial improvement in multiple affected systems may achieve BICLA response.[5] In real world data comparing these composite endpoints to clinician's global rating of improvement the BICLA was less sensitive than SRI, especially in patients with baseline involvement of multiple organs (**Table 3**).[6]
    - Infections including upper respiratory tract infection and bronchitis are the most common TEAE observed with anifrolumab-fnia. Hypersensitivity and severe infusion related reactions are possible with monoclonal antibody administration.
- Outcome conclusions specific to race and ethnicity are insufficient due to variations of results, lack of statistical significance with many comparisons, and small subgroup sizes. Men are generally underrepresented due to reduced incidence of SLE in men, despite much higher propensity to develop LN.[1] Safety in pregnancy and pediatric patients is unclear for all three drugs.

Recommendations:
- No Oregon Health Plan (OHP) fee-for-service (FFS) preferred drug list (PDL) changes are recommended to the Immunosuppressant class or belimumab based on clinical evidence.
- Update belimumab prior authorization (PA) criteria.
- Implement PA for voclosporin to ensure appropriate use in FDA-approved indications funded by OHP.
- Implement PA for anifrolumab-fnia to ensure appropriate use in FDA-approved indications funded by OHP.
- After evaluation of costs in executive session, no changes were made to the PDL.

Summary of Prior Reviews and Current Policy
- Previous review of evidence found clinical remission in Crohn's disease more effective in patients with infliximab compared to azathioprine, and combination was more effective than infliximab alone. In patients undergoing kidney transplant, mycophenolate mofetil (MMF) was more effective at preserving graft function and preventing acute rejection than azathioprine, but cytomegalovirus (CMV) was more common with MMF.
- High quality guidelines support the OHP FFS preferred drug placement for the treatment of Crohn's disease, kidney transplant, and ulcerative colitis.
- No changes to the PDL were recommended based on the evidence.
- After evaluation of costs in executive session and consideration of high approval percentage of current prior authorization requests, all medications in this class were made PDL preferred.
- Prior Authorization update of belimumab was approved by the Pharmacy and Therapeutics (P & T) committee in August 2021 for the expanded FDA indication for treatment of adults with active LN. Belimumab is in the "Targeted Immune Modulators" class in the OHP FFS PDL (Appendix 1).

Background:
Immunosuppressive agents can be used to treat and manage a wide range of conditions, including patients with graft-versus-host disease, rejection prophylaxis in solid organ transplant recipients, and myasthenia gravis. The primary focus of this review is to evaluate evidence related to new agents for treatment of SLE and its complications, specifically LN.

Systemic lupus erythematosus is a chronic multisystem autoimmune disorder of the connective tissue which causes significant morbidity and mortality in the United States (U.S.) and worldwide. Estimates on prevalence vary based on changing detection methods and case definitions over time. Estimates may also vary based on genetic and environmental differences between countries.[6] Research studies conducted within the past 2 decades have prevalence estimates of 9 to 241 per 100,000 person-years and an incidence of 0.3 to 23.2 per 100,000 person-years.[6] Data from studies conducted within the U.S. population with better designs involving strict case definitions, broad case-finding methodology, and correcting for possible case under-ascertainment show incidence of 4.6 to 6.4 per 100,000 person years and prevalence of 62.2 to 84.8 per 100,000 person years.[6] The Centers for Disease Control and Prevention estimates a U.S. prevalence of 322,000 probable or definite SLE cases.[7] Rates are generally higher among non-Whites, including both Hispanic and Arab ethnicities and those with American Indian, Alaska native, South/East Asian, and African descent.[6] Hispanic and South/East Asian individuals may have more severe disease and organ damage.[1,6] People of African descent are three times more likely to be afflicted with SLE, and have higher rates of renal involvement and mortality than Whites.[6,7] European ancestry is associated with a lower risk of LN.[6] While some of these differences may have genetic components, it has been shown that lower socioeconomic status, educational level, and poverty are associated with the health disparities of higher disease activity, organ damage, and mortality.[6]

Females in their reproductive years are most commonly afflicted with SLE.[1,6] The female-to-male ratio is estimated at 7 to 15:1 in adults and 3 to 5:1 in children. Disease onset in women is usually the 3rd to 5th decade of life; it generally presents later in men in the 5th to 7th decade. While representing about 1 in 10 SLE diagnoses, men tend to develop more severe disease and are 66% more likely to be diagnosed with LN than women based on U.S. Medicaid data.[1]

Smoking, endometriosis, alcohol consumption, and inhalational silica exposure have been strongly associated with SLE.[6] Additionally, psychological stress and environmental triggers such as ultraviolent light, certain drugs (echinacea, trimethoprim/sulfamethoxazole), infections, and mercury have been implicated.[7] The possible role of the gut microbiome is also under investigation.[6]

Systemic lupus erythematosus results from disruption of both the innate and adaptive arms of the immune system.[7] SLE patients have variable presentation, prognosis, and experience remissions and flares over the course of disease.[8] Many different organs are attacked by autoantibodies produced by the body, and this results in variety of complications.[1] Cutaneous lupus presents in nearly 90% of patients, and may manifest in an acute, subacute, or chronic fashion.[7] Non-lupus specific manifestations such as alopecia, vasculitis, livedo reticularis, periungual telangiectasias, and Raynaud's phenomenon may be present.[7] Musculoskeletal involvement is very common and arthralgia and true synovitis occur for almost 90% of patients. Renal disease and central nervous system disease are both associated with significant complications.[7] Kidney disease, present in 50% of patients, is a major cause of morbidity and mortality. The delayed diagnosis of LN is a major risk factor for end-stage-renal disease (ESRD).[7] Prevalence of LN varies within US; among Medicaid beneficiaries LN is two times more common in the South.[1] Childhood-onset of SLE is associated with higher incidence and more severe LN than adult-onset disease.[9] Cognitive impairment is present is nearly 80% of SLE patients.[7] Seizures, psychosis, mononeuritis multiplex, myelitis, peripheral or cranial neuropathy, and acute confusional state are associated with SLE and may assist with diagnosis once other causes are excluded.[7] Patients with SLE are at higher risk of cardiovascular disease, and 10-15% of SLE cases are complicated by antiphospholipid syndrome. Pregnancy in patients with SLE is associated with higher rates of preterm birth, pre-eclampsia, and caesarean section. Prenatal planning and antenatal care are necessary to reduce the risk of complications to both parent and child.[7] Malignant disorders are more common in SLE patients.[6,9] Hospitalization rates due to infection, most commonly pneumonia, are twelve times higher in patient with SLE than those without, though the specific drug classes used for treatment of SLE are further risk factors for infectious complications.[6] Long-term use of steroids can also put SLE patients at risk of bone loss and fractures.[9]

Diagnosis of SLE is made using clinical manifestations and positive serologies.[7,8,10] The European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR) 2019 and Systemic Lupus International Collaborating Clinics (SLICC) 2012 both have classification criteria for SLE.[8,10] The more recent EULAR/ACR criteria are frequently used in practice (**Table 1**). Patients who meet the entry criterion of a positive antinuclear antibody (ANA) proceed to assessment of additive criteria. Patients with at least one clinical criteria without a more likely explanation, and a score of ≥ 10 points meet criteria for SLE diagnosis.[10]

Table 1. European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR) 2019 Diagnostic Criteria[10]

Entry criterion Antinuclear antibodies at a titer of ≥ 1:80 on HEp-2 cells or an equivalent positive test ever in lifetime			
↓			
If absent, do not classify as systemic lupus erythematosus If present, apply additive criteria			
↓			
Additive criteria Do not count a criterion if there is a more likely explanation than systemic lupus erythematosus Occurrence of a criterion on a least one occasion is sufficient SLE classification requires at least one clinical criterion and ≥ 10 points Criteria need not occur simultaneously Within each domain, only the highest weighted criterion is counted toward the total scores.*			
Clinical domains and criteria	**Weight**	**Immunology domains and criteria**	**Weight**
Constitutional • Fever	2	***Antiphospholipid antibodies*** • Anti-cardiolipin antibodies OR • Anti-beta2GP1 antibodies OR • Lupus anticoagulant	2
Hematologic • Leukopenia • Thrombocytopenia • Autoimmune hemolysis	3 4 4	***Complement proteins*** • Low C3 OR low C4 • Low C3 AND low C4	3 4
Neuropsychiatric • Delirium • Psychosis • Seizure	2 3 5	***SLE-specific antibodies*** • Anti-dsDNA antibody† OR • Anti-Smith antibody	6
Mucocutaneous • Non-scarring alopecia	2		

• Oral ulcers • Subacute cutaneous OR discoid lupus • Acute cutaneous lupus	2 4 6	
Serosal • Pleural or pericardial effusion • Acute Pericarditis	 5 6	
Musculoskeletal • Joint involvement	 6	
Renal • Proteinuria >0.5g/24 h • Renal biopsy Class II or V lupus nephritis • Renal biopsy Class III or IV lupus nephritis	 4 8 10	
Total Score: If entry criterion fulfilled and score of 10 or greater should be classified as systemic lupus erythematosus		
* Additional criteria within the same domain will not be counted † Using assay with 90% specificity against relevant disease controls		

Lupus nephritis diagnosis is generally confirmed through kidney biopsy. Serum creatine, urinalysis, spot protein-creatinine ratio, and serology (including anti-dsDNA and complement) are recommended in patients at SLE presentation and times of suspected SLE flare. Evidence of abnormal protein/urine sediment or decreased/decreasing glomerular filtration rate (GFR) should be further evaluated to quantify proteinuria or accuracy of GFR results. Patients with 24-hour proteinuria ≥ 0.5 g/24h or abnormal eGFR with no attributable cause other than SLE should be considered for kidney biopsy.[9]

The International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification system is most commonly used for LN (**Table 2**).[11] Disease classes are based on glomerular pathology ranging from class I, demonstrating minimal mesangial LN, to Class VI, demonstrating advanced sclerosis LN with ≥ 90% of glomeruli globally sclerosed without residual activity. Class III focal lupus nephritis and class IV diffuse lupus nephritis include additional subcategories for the presence of lesions which are active, active and chronic, or inactive and chronic. Additionally, classifications can differentiate segmental versus global lesions. Tubular atrophy, interstitial inflammation and fibrosis, and severity of arteriosclerosis or other vascular lesions should also be graded as mild, moderate, or severe.[8]

Table 2. ISN/RPS Lupus Nephritis Classifications[11]

Status	Description
Class I	Minimal mesangial lupus nephritis: earliest and mildest form of glomerular involvement
Class II	Mesangial proliferative lupus nephritis: excellent prognosis and no specific therapy is indicated
Class III	Focal lupus nephritis: patients present with hematuria and proteinuria, possibly to also have hypertension, decreased renal function and/or nephrotic syndrome. Light microscopy reveals less than 50 percent of glomeruli are affected.
Class IV	Diffuse lupus nephritis: patients present with hematuria and proteinuria and frequently seen with hypertension, decreased renal function and nephrotic syndrome. Light microscopy reveals more than 50 percent of glomeruli are affected.
Class V	Lupus membranous nephropathy: patients present with signs of nephrotic syndrome
Class VI	Advanced sclerosing lupus nephritis: patients present with slowly progressive kidney dysfunction associated with proteinuria

The goal of SLE treatment is to achieve remission or low disease activity.[12] Treatment of SLE for most patients involves use of hydroxychloroquine (HCQ), unless contraindicated, with the addition of GC at the lowest dose needed to enable remission or prevention of flares. Remission is characterized by a Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score of 0 (range 0 to 105)[6] on HCQ and without need for GC.[12] Administration of GC ranges from chronic therapy to high dose pulses for severe flares, and GC should be withdrawn whenever possible for stable disease. Immunosuppressive agents such as methotrexate, azathioprine, and MMF can be added in patients unresponsive to other therapies and those unable to achieve low daily GC doses (e.g. ≤ 7.5 mg/day). Intravenous cyclophosphamide can be considered as a rescue treatment in severe or life-threatening situations when disease is unresponsive to other therapies.[13] The biologic agents belimumab and rituximab have been considered in certain situations; use of rituximab for SLE is off-label, and there have been negative results in certain SLE RCTs.[12,13] Treatment for specific organ complications is dependent on the organ system involved.[12]

Treatment of LN rests in early recognition, followed by induction therapy with MMF or low-dose IV cyclophosphamide.[12] In those with high risk of renal failure, high-dose IV cyclophosphamide may also be considered. Maintenance therapy with MMF or azathioprine should begin after induction.[12] MMF can be combined with a low dose calcineurin inhibitor (CNI) (e.g. cyclosporine or tacrolimus; recommendation preceded FDA approval of voclosporin) in severe nephrotic syndrome or incomplete renal response in certain patients with absence of uncontrolled hypertension, high chronicity index at kidney biopsy and/or reduced GFR.[12]

There remains uncertainty regarding the most appropriate endpoint to use for treatment response in SLE or LN, or clear minimally clinically important differences (MCID). The SLEDAI-2K and British Isles Lupus Assessment Groups Index (BILAG) are both designed to assess disease activity.[5] Systemic Lupus Erythematosus Disease Activity Measure (SLEDAI) is a global index developed in 1986 and has been modified into multiple versions. Scores range from 0 to 105 and those above 5 have a greater than 50% probability of initiating therapy.[14] Score ranges are: no activity (0), mild activity (1-5), moderate activity (6-10), high activity (11-19), and very high activity (≥ 20).[14] A modified version of SLEDAI, the SLEDAI-2K marks 24 manifestations in nine organ systems as present or absent in the previous 30 days.[14] It is a composite global disease activity index. It has been validated and is able to predict major outcomes (e.g. organ damage, mortality). In contrast, BILAG-2004 is a disease activity index using organ-based scales. BILAG scores 9 organ systems as new or recurring, worse, same, improving, or not present during the previous 30 days. Each organ is then assigned a grade of: A (major activity), B (intermediate activity), C (mild or stable disease), D (previous involvement but currently inactive), and E (no previous activity).[5,14] It is not widely used in practice.[6] Additionally, while it is a valid and reliable tool for assessing disease activity, use as a measure of treatment response in the clinical trial setting is an adaptation for which it was not designed.[5] The

Safety of Estrogen in Lupus Erythematosus National Assessment Group (SELENA), SELENA-SLEDAI, is able to count persistent active disease in some cutaneous manifestations.[6] It is a cumulative and weighted index to assess disease activity across 24 domains (e.g., seizure, fever) in individuals with lupus.[5]

SRI-4 and BICLA are composite endpoints used in these studies of potential SLE treatments which include multiple components of disease activity (**Table 3**). Both were developed specifically for clinical trials, SRI based on an exploratory analysis of a phase 2 belimumab trial, and BICLA as part of a phase 2B study for an experimental medication called epratuzumab.[6] Complete improvement in a single organ system is needed to achieve SRI-4 response, while partial improvement in multiple affected systems may achieve BICLA response.[5] In real world data comparing these composite endpoints to clinician's global rating of improvement the BICLA was less sensitive than SRI-4, especially in patients with baseline involvement of multiple organs.[6] These composite indices are also highly complex, which limits applicability to clinical practice, and complicates translation of clinical trial results to individual patients and their disease.[6] For LN, various combinations of "primary efficacy renal response" or "complete renal response" have been used in RCTs, usually including improvement to a specific threshold for urine protein to creatinine ratio (UPCR), percentage improvement in eGFR, and need for rescue therapy, but the values for these component measures are not standardized across RCTs.[1,6] There is no standard eGFR MCID in this population, though studies of graft failure in organ transplant patients have found 5 mL/min/1.73m^2 difference in 12-month eGFR to be associated with almost a 20% increase in death-censored graft failure risk.[1]

Table 3. Disease Activity Composite Endpoint Descriptions for SLE[6]

Composite Endpoint*	Component	Description
SRI-4	SELENA-SLEDAI†	Improvement (≥ 4 point reduction in score)
	BILAG-2004	No new A (active disease) domain score and no more than 1 new B (intermediate activity) domain scores
	PGA	No worsening (<0.3 point decrease on 3 point VAS)
BICLA responder index	BILAG-2004	Improvement with all A scores at baseline improved to B/C/D, and all B scores improved to C/D
	BILAG-2004	No worsening in disease activity with no new A scores and ≤ 1 new B scores
	SLEDAI-2K	No worsening of total score from baseline
	PGA	No worsening (<10% worsening in 100 mm visual analog PGA scale or <0.3 point decrease on 3 point VAS)
	No treatment failure	No new or increased immunosuppression or antimalarials, or increased parenteral corticosteroids, or premature discontinuation from study treatment

*Patients must meet all criteria to be considered a responder to treatment.
†SRI-4 originally designed and used SELENA-SLEDAI in a belimumab clinical trial.[6] SLEDAI-2K was substituted for SELENA-SLEDAI in Anifrolumab clinical trials described in this class update.[5]
Abbreviations: BICLA=BILAG-based Combined Lupus Assessment; BILAG=British Isles Lupus Assessment Groups Index; PGA=Physician Global Assessment; SELENA=Safety of Estrogens in Lupus Erythematosus National Assessment; SLEDAI-2K=Systemic Lupus Erythematosus Disease Activity Index 2000; SRI=Systemic Lupus Erythematosus Responder Index; VAS=visual analogue scale

There are fewer than 60 patients receiving prescriptions for immunosuppressive agents for any indication in the OHP FFS population.

Methods:
A Medline literature search for new systematic reviews and RCTs assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness

Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:

Drug Review Effectiveness Project: Belimumab (Benlysta) and Voclosporin (Lupkynis™) for Active Lupus Nephritis[1]

A review of the use of belimumab and voclosporin was completed by the Drug Review Effectiveness Project (DERP) in Sept 2021.[1] This review targeted belimumab or voclosporin compared to placebo or an active comparator. Belimumab is a B-lymphocyte stimulator (BLyS)-specific inhibitor that was originally approved in 2011 for the intravenous treatment of adults with active, autoantibody-positive SLE on standard therapy.[15] A subcutaneous version became available in 2017 and in 2020 it obtained an expanded FDA indication for the treatment of adults with active lupus nephritis on standard therapy (e.g. cyclophosphamide + azathioprine, or MMF). Voclosporin is a calcineurin-inhibitor which was approved in 2021 for treatment of adults with active lupus nephritis in combination with background immunosuppressive therapy (e.g. MMF).

The review included RCTs published through June 30, 2021 in adults with LN.[1] Two RCTs investigated belimumab compared to placebo or an active treatment and 2 RCTs evaluated voclosporin versus placebo. All trials enrolled participants with at least Class III LN, majority female participants, and included participants from the US. Three studies had moderate RoB, primarily due to extensive pharmaceutical sponsor involvement, while the AURA-LV trial of voclosporin had high RoB due to sponsor involvement and methodologic concerns including high attrition, lack of summary estimates, baseline group imbalances, and lack of blinding.[1] **Table 4** summarizes the RCTs included in the DERP report.[1]

Table 4. Inclusion Criteria of Eligible Randomized Controlled Trials[1]

Author, Year Trial Name Trial Number Locations	Patient Enrollment Inclusion/Exclusion Duration	Participant Characteristics	Treatment Arms; Enrollment	Risk of Bias
Belimumab				
Atisha-Fregoso et al., 2021 **CALIBRATE**[a] NCT02260934 US (14 sites)	• N=43 • Adults aged ≥ 18 years Lupus nephritis of class III, class IV, or class V in combination with class III or IV • No previous treatment with rituximab, belimumab, atacicept (investigational agent), or other biologic B cell therapy • 48 weeks + 48 weeks follow-up	Characteristics • Mean age, years (SD): 33.5 years (10.26) • Female sex, n of N (%): 37 of 43 (86.0%) Race/ethnicity, n (%) • Asian: 5 (11.6) • Black: 18 (41.9) • Hispanic or Latino: 15 (34.9)	• Belimumab + rituximab + CYC; N=21 • Rituximab + CYC; N=22	Moderate

		• Other/unknown: 4 (19.3) • White: 16 (37.2)		
Furie et al., 2020 **BLISS-LN** NCT01639339 US + 20 countries (107 sites)	• N=448 • Adults aged ≥ 18 years • No previous treatment with rituximab, belimumab, atacicept, or other biologic B cell therapy • No receipt of dialysis within previous 12 months • 52 weeks + 52 weeks follow-up	<u>Characteristics</u> • Mean age, years (SD): 33.4 years (10.7) • Female sex, n of N (%): 393 of 446 (88.1) <u>Self-identified race or ethnicity, n (%)</u> • American Indian or Alaska Native: 10 (2.1) • Asian: 223 (49.8) • Black: 61 (13.6) • Multiple races or ethnicities: 4 (0.9) • White: 148 (33.0)	• Belimumab + CYC-AZA; N=60 • Belimumab + MMF; N=164 • Placebo + CYC-AZA; N=59 • Placebo + MMF; N=165	Moderate
Voclosporin				
Rovin et al., 2019 **AURA-LV** NCT02141672 US + 19 countries (79 sites)	• N=265 • Adults aged ≥ 18 to 75 years • Lupus nephritis of class III, class IV, or class V in combination with class III or IV • Not receiving dialysis • Not a kidney transplant recipient • 48 weeks + up to 52 weeks follow-up	<u>Characteristics</u> • Mean age, years (SD): 31.7 years (10.5) • Female sex, n of N (%): 230 of 265 (86.8) <u>Race, n (%)</u> • Asian-Indian subcontinent: 60 (22.6) • Asian-other: 72 (27.2) • Black: 14 (5.3) • Other: 11 (4.2) • White: 108 (40.8)	• Voclosporin, low-dose (23.7 mg twice daily); N=89 • Voclosporin, high-dose (39.5 mg twice daily); N=88 • Placebo, low-dose; N=44 • Placebo, high-dose; N=44	High
Rovin et al., 2021 **AURORA 1** NCT03021499 US + 26 countries (142 sites)	• N=357 • Lupus nephritis of class III, class IV, or class V in combination with class III or IV • 52 weeks	<u>Characteristics</u> • Mean age, years (SD): 31.5 years (18-71) • Female sex, n of N (%): 313 of 357 (87.7) <u>Race, n (%)</u> • Asian: 109 (30.5) • Black: 45 (12.6)	• Voclosporin, 23.7 mg twice daily + MMF; N=179 • Placebo + MMF; N=178	Moderate

		• Other (e.g. American Indian, Alaska native, non-Black mixed race): 74 (20.7) • White: 129 (36.1) Ethnicity, n (%) • Hispanic or Latino: 116 (32.5) • Non-Hispanic or non-Latino: 240 (67.2) • Unknown: 1 (0.3)		
Note: [a]CALIBRATE participants had a 3-week run-in period of prednisolone and methylprednisolone before being randomized. Abbreviations: CYC=cyclophosphamide; CYC-AZA=cyclophosphamide-azathioprine; MMF=mycophenolate mofetil.				

Table 5. Trial Outcomes of Included Studies[1]

Trial Name	Renal Response, n of n (%)	CRR or PERR Definition	Disease activity SELENA-SLEDAI, n of n (%)
Belimumab			
CALIBRATE Belimumab (n = 21) vs. placebo (n = 22)	Secondary outcomes • CRR at week 48: 8 of 21 (38.0) vs. 7 of 22 (31.8); OR not reported ARR, 4.5% (95% CI, −23.4 to 32.5; *P* = 0.76) • CRR at week 96: 5 of 21 (23.8) vs. 4 of 22 (18.2); OR not reported ARR, 5.6% (95% CI -18.7 to 30.0; *P* = 0.67)	CRR: 1. UPCR < 0.5 AND 2. eGFR no worse than 20% below the pre-flare value *OR* ≥ 120 ml per minute per 1.73 m^2 AND 3. Adherence to the prednisone dosing provisions	N/A
BLISS-LN Belimumab (n = 223) vs. placebo (n = 223)	Primary outcome • **PERR at week 104: 96 of 223 (43.0) vs. 72 of 223 (32.3); HR, 1.46; 95% CI, 1.07 to 1.98; *P* = 0.02** **ARR, 10.8% (95% CI, 1.8 to 19.7; *P* = 0.02); NNT, 10** Secondary outcome	PERR : 1. UPCR ≤ 0.7 AND 2. eGFR no worse than 20% below the pre-flare value *OR* ≥ 60 ml per minute per 1.73 m^2 AND 3. No use of rescue therapy for treatment failure CRR: 1. UPCR < 0.5 AND	N/A

	• **CRR at week 104: 67 of 223 (30.0) vs. 44 of 223 (19.7); RR, 1.52; 95% CI, 1.09 to 2.12; *P* = 0.01** **ARR, 10.3% (95% CI, 2.3 to 18.3; *P* = 0.01); NNT, 10**	2. eGFR no worse than 10% below the pre-flare value *OR* ≥ 90 ml per minute per 1.73 m^2 AND 3. No use of rescue therapy	
Voclosporin			
AURA-LV Voclosporin, low-dose 23.7 mg twice daily (n = 89) vs. voclosporin, high-dose 39.5 mg twice daily (n = 88) vs. placebo (n = 88)	<u>Primary outcome, CRR at 24 weeks</u> • **Voclosporin, low-dose: 29 of 89 (32.6); RR, 1.69 (95% CI, 1.00 to 2.84; *P* = 0.046)** **ARR, 13.3% (95% CI, 0.5 to 26.0; *P* = 0.046); NNT, 8** • Voclosporin, high-dose: 24 of 88 (27.3); RR, 1.41; 95% CI, 0.82 to 2.44; *P* = 0.22 ARR, 7.9% (95% CI, −4.5 to 20.4; *P* = 0.22); • Placebo: 17 of 88 (19.3) <u>Secondary outcome, CRR at 48 weeks</u> • **Voclosporin, low-dose: 44 of 89 (49.4); RR, 2.07; 95% CI, 1.35 to 3.18; *P* < 0.001** • **ARR, 25.6% (95% CI, 11.9 to 39.3; *P* < 0.001); NNT, 4** • **Voclosporin, high-dose: 35 of 88 (39.8); RR, 1.67; 95% CI, 1.06 to 2.62; *P* = 0.02** **ARR, 15.9% (95% CI, 2.3 to 29.5; *P* = 0.02); NNT, 7** • Placebo: 21 of 88 (23.9)	CRR: 1. UPCR to ≤ 0.5 mg/mg AND 2. eGFR no worse than 20% of baseline value <u>OR</u> ≥ 60 ml/min per 1.73 m^2	<u>Score > 6 at 48 weeks,</u> n of n (%): • Voclosporin, low-dose 26 of 89 (29.2) • voclosporin, high-dose 36 of 88 (40.9) • placebo, 47 of 88 (53.4) *P* not reported
AURORA 1 Voclosporin, low-dose (n = 179) vs. placebo (n = 178)	<u>Primary outcome</u> • **CRR at 52 weeks: 73 of 179 (40.8) vs. 40 of 178 (22.5); RR, 1.81; 95% CI, 1.31 to 2.51; *P* < 0.001** **ARR, 18.3% (95% CI, 8.8 to 27.8; *P* < 0.001); NNT, 6** <u>Secondary outcome</u>	CRR: 1. UPCR to ≤ 0.5 mg/mg AND 2. eGFR no worse than 20% of baseline value <u>OR</u> ≥ 60 ml/min per 1.73 m^2	<u>Least squares mean at 24 weeks</u> • Voclosporin (n = 167): -4.5 (95% CI, -5.4 to -3.7) • placebo (n = 172): -4.1 (95% CI, -5.0, -3.2); • mean difference, -0.5 (95% CI, -1.6 to 0.6 *P* = 0.37)

	• **CRR at 24 weeks: 58 of 179 (32.4) vs. 35 of 178 (19.7); RR, 1.65; 95% CI, 1.14 to 2.37; *P* = 0.006** **ARR, 12.7% (95% CI, 3.7 to 21.7; *P* = 0.006); NNT, 8**		<u>Least squares mean at 52 weeks</u> • Voclosporin (n = 150): -6.0 (95% CI, -6.7 to -5.2) • placebo (n = 160): -5.5 (95% CI, -6.3 to -4.7); • mean difference, -0.5 (95% CI, -1.4 to 0.4; *P* = 0.28)
• **Bold** text indicates statistically significant between group differences. • ARRs, RRs, and NNTs were calculated by Drug Effectiveness Review Project. NNTs were rounded for clarity. • Abbreviations: ARR=absolute risk reduction; CI=confidence interval; CRR=complete renal response; eGFR=estimated glomerular filtration rate; HR=hazard ratio; n=number; N/A=not applicable; NNT=number needed to treat; OR=odds ratio; PERR=primary efficacy renal response; RR=risk ratio; SD=standard deviation; SELENA-SLEDAI=Safety of Estrogens in Systemic Lupus Erythematosus National Assessment–Systematic Lupus Erythematosus Disease Activity Index; UPCR=urine protein to creatinine ratio.			

The primary or secondary outcome in all studies was CCR, although the definition of CCR varied slightly across the different RCTs (**Table 5**).[1] The phase 2 CALIBRATE study of belimumab in combination with rituximab + cyclophosphamide did not find statistically significant CCR differences at week 48 or 96 versus rituximab + cyclophosphamide alone. This study included a steroid run-in phase and was the smallest trial evaluated in the DERP report. The BLISS-LN RCT found belimumab versus placebo to be statistically significant for the primary endpoint of PERR (43.0% vs. 32.3%; HR 1.46, 95% CI 1.07 to 1.98, P = 0.02) and secondary endpoint of CRR (30.0% vs. 19.7%, RR 1.52, 95% CI 1.09 to 2.12, P = 0.01) at week 104.[1] When analyzed by concomitant induction therapy (induction therapy received prior to randomization to belimumab or placebo), those taking belimumab with MMF were more likely to achieve PERR (46.3% vs. 34.1%, OR 1.58, 95% CI 1.00 to 2.51) and CRR (34.1% vs. 20.1%, OR 2.01, 95% CI 1.19 to 3.38) than placebo at week 104.[1] Belimumab with cyclophosphamide +azathioprine were not statistically significantly different than placebo.[1] In the AURA-LV RCT, voclosporin was found to be statistically significant for the primary endpoint of CRR at 24 weeks in the low-dose group vs. placebo (32.6% vs. 19.3%; RR 1.69, 95% CI 1.00 to 2.84, P 0.046), but not the high-dose group (27.3% vs. 19.3%; RR 1.41, 95% CI 0.82 to 2.44, P 0.22).[1] At 48 weeks the CRR was statistically significant for both low-dose (49.4% vs. 23.9%; RR 2.07, 95% CI 1.35 to 3.18, P<0.001) and high-dose groups (39.8% vs. 23.9%; RR 1.67, 95% CI 1.06 to 2.62, P=0.02) when compared to placebo.[1] AURORA 1 found low-dose voclosporin to be statistically significantly better than placebo at achieving CRR at both week 52 (40.8% vs. 22.5%; RR 1.81, 95% CI 1.31 to 2.51, P<0.001) and week 24 (32.4% vs. 19.7%; RR 1.65, 95% CI 1.14 to 2.37, P=0.006).[1]

A post-hoc subgroup analysis conducted during the AURORA 1 RCT found that those receiving voclosporin were more likely to have CRR regardless of ethnicity (Hispanic or Latino vs. non-Hispanic or non-Latino).[1] Additional subgroup analyses of BLISS-LN, AURA-LV, and AURORA 1 show varying results of efficacy of the research medications versus placebo, though it is unclear what conclusions may be drawn given the smaller samples sizes provide less power to detect differences.[1]

Adverse event (AE) rates were reported differently across the 4 studies.[1] The CALIBRATE RCT reported 47 serious TEAEs; events were experienced in 19% of those in the belimumab group and 50% of those in the placebo group.[1] BLISS-LN had a more balanced severe adverse event (SAE) rate with 25% belimumab and 29.9% placebo. Four deaths from SAE were reported in the belimumab patients and 3 in patients randomized to placebo during trial intervention. A description of AEs based on induction treatment was not provided. Induction therapy was chosen by investigators up to 60 days before day 1 of trial with randomization stratified by induction treatment. Belimumab reduced the risk of renal related events (including progression to ESRD and increased proteinuria) or death in the BLISS-LN RCT (HR 0.5; 95% CI 0.3-0.8, P=0.001).[1] Discontinuations due to AEs occurred in 13% of patients in both belimumab and placebo treated groups. The

most common side effects were URTI (12% vs. 11%), UTI (7% vs. 6%), herpes zoster (6% vs. 4%), bronchitis (5% vs. 4%), nasopharyngitis (4% both groups), headache (4% vs. 2%), nausea (4% vs. 2%), and rash (3% vs. 2%).[1]

Voclosporin patients in both dosage groups of AURA-LV experienced more SAEs than placebo patients (low-dose, 25 of 89 [28.1%]; high-dose 22 of 88 [25%]; placebo 14 of 88 [15.9%]).[1] There were 12 deaths in the voclosporin groups (10 low-dose, 2 high dose), and 1 in the placebo group. Nine of these occurred in the first 2 months of the study; 7 occurred in 2 study sites in Bangladesh. The most common SAE observed with low-dose voclosporin, high-dose voclosporin, and placebo were infections and infestations (12.4% vs. 13.6% vs. 8.0%), renal and urinary disorders (5.6% vs. 1.1% vs 1.1%), nervous system disorders (4.5% vs. 3.4% vs. 1.1%), reversible posterior leukoencephalopathy syndrome PRES (2.2% vs. 2.3% vs. 0%), GI disorders (2.2% vs. 2.3% vs. 1.1%), vascular disorders (2.2% vs. 2.3% vs. 0%), and hypertension (2.2% vs. 2.3% vs. 0%).[1] In the AURORA 1 RCT, 11% of participants in the voclosporin group and 15% of participants in the placebo arm discontinued treatment early due to AE. Serious adverse effects were equal in each arm (21%). There was 1 voclosporin and 5 placebo patient deaths during the study.[1] The most common AE were infections and infestations (voclosporin 65% vs. placebo 57%), GI disorders (47% vs. 34%), investigations and infestations (34% vs. 17%), nervous system disorders (26% vs. 15%), skin and subcutaneous tissue disorders (24% vs. 17%), musculoskeletal and connective tissue disorders (22% vs. 26%), vascular disorders (21% vs. 13%), general disorders and administration site conditions (20% vs. 18%), blood and lymphatic system disorders (20% vs. 16%), respiratory, thoracic, and mediastinal disorders (15% vs. 10%), renal and urinary disorders (15% vs. 21%), and metabolism and nutritional disorders (14% vs. 21%).[1]

There is currently one ongoing study, AURORA 2, a continuation study of AURORA 1, to evaluate the long-term safety, effectiveness, and quality of life (QoL) of voclosporin compared to placebo. DERP was unable to identify any ongoing studies of belimumab which met search criteria.[1]

Cochrane-Interventions for Idiopathic Steroid-Resistant Nephrotic Syndrome in Children[16]

A 2019 Cochrane report reviewed the benefits and harms of interventions used in children 3 months to 18 years with nephrotic syndrome who do not achieve remission after a minimum of 4 weeks of GC therapy. Randomized controlled trials and quasi-randomized controlled trials were included to compare different immunosuppressants. Studies enrolling both children and adults, where the data could not be separated, were included in the analysis with all patients.[16] The reported results focus on the available comparative evidence between agents in the immunosuppressant class.

Little or no difference was found between tacrolimus and cyclosporine in the number of patients who achieve complete or partial remission (2 studies, 58 participants: RR 1.05, 95% CI 0.87 to 1.25, low certainty evidence) or in the number of patients with worsening hypertension (2 studies, 58 participants: RR 0.41, 95% CI 0.08 to 2.15, low certainty evidence).[16] There is likely little or no difference between cyclosporine compared with MMF plus dexamethasone in the number of patients who achieve complete or partial remission (1 study, 138 participants: RR 2.14, 95% CI 0.87 to 5.24, moderate certainty evidence), deaths (1 study, 138 participants: RR 2.14, 95% CI 0.87 to 5.24), or patients with 50% reduction in glomerular filtration rate (GFR) (1 study, 138 participants: RR 2.29, 95% CI 0.46 to 11.41, low certainty evidence).[16] Among those with complete remission, tacrolimus compared with MMF may increase the number who maintain complete or partial response for 12 months (1 study, 60 children: RR 2.01, 95% CI 1.32 to 3.07, low certainty evidence).[16]

Cochrane- Interventions for Renal Vasculitis in Adults[17]

A 2020 Cochrane report reviewed steroid and non-steroid medication treatments and plasma exchange in the treatment of renal vasculitis, it was an update of a previous 2008 and 2015 Cochrane review to answer questions such as dose and duration of therapy and role of new therapies. Overall, availability of direct comparative data of oral immunosuppressant (the focus of this summary) was limited by few trials and small sample sizes.[17] Risk of any relapse was statistically significantly lower for azathioprine maintenance therapy (n=76) compared to MMF (n=80) (MMF 55.3% vs. azathioprine 37.5%, RR 1.47, 95% CI 1.04 to 2.09).[17]

Comparison of major relapses and minor relapses between the two agents did not yield statistically significant results.[17] Other outcomes such as death were not reported for this comparison, and there were no statistically significant differences in any adverse event (MMF 28.9% vs. azathioprine 35%, RR 0.83, 95% CI 0.52 to 1.31).[17]

Cochrane- Belimumab for Systemic Lupus Erythematosus[18]

A 2021 Cochrane report reviewed the benefits and harms of belimumab in SLE. Six RCTs (n=2917) ranging from 84 days to 76 weeks were included in the analysis and participants were 22 to 80 years old and primarily female. Bias was low with the exception of attrition bias, which was rated as high in 67% of RCTs.[18] Background therapy varied across trials.[18] There is moderate to high-certainty evidence that more patients on belimumab compared to placebo at 52 weeks had at least a 4 point improvement on the SELENA-SLEDAI scale at the FDA approved 10 mg/kg dose (belimumab 52.2% vs. placebo 39.4%, RR 1.33, 95% CI 1.22 to 1.45, I^2=0%, high certainty evidence).[18] The change in health related quality of life assessed by the Short Form-36 Physical Component Summary Score improvement indicates there was probably little to no clinical difference between groups (mean difference 1.6 points, 95% CI 0.30 to 2.90; n=401 belimumab vs. n=400 placebo, I^2= 0%, 2 RCTs, moderate-certainty evidence).[18] More patients treated with belimumab had a GC dose reduction of greater than 50% compared to placebo (30.1% belimumab vs. 19.4% placebo, RR 1.59, 95% CI 1.17 to 2.15, I^2= 0%, 2 RCTs; high-certainty evidence).[18]

Evidence on harms was inconclusive between belimumab and placebo treatment. Those experiencing one or more serious adverse reaction was similar between groups (14% belimumab vs. 17% placebo, RR 0.87, 95% CI: 0.68 to 1.11, I^2= 48%, 5 RCTs, low-certainty evidence).[18] One or more serious infection (3.4% belimumab vs. 4.2% placebo, RR 1.01, 95% CI: 0.66 to 1.54, I^2= 0%, 4 RCTs, moderate-certainty evidence) and withdrawals due to adverse events (6.6% belimumab vs. 7.9% placebo, RR 0.82, 95% CI: 0.63 to 1.07, I^2= 0%; 5 RCTs; moderate-certainty evidence) were also similar.[18] Mortality was infrequent in both groups (9/1714 belimumab vs. 6/1203 placebo, Peto odds ratio 1.15, 95% CI 0.41 to 3.25, I^2= 4%; 6 RCTs; low-certainty evidence).[18]

Cochrane-Non-Corticosteroid Immunosuppressive Medications for Steroid-Sensitive Nephrotic Syndrome in Children[19]

A 2020 Cochrane report reviewed the benefits and harms of non-corticosteroid immunosuppressive medications in steroid-sensitive nephrotic syndrome in children who experience a relapsing course or during their first episode of nephrotic syndrome. Studies were searched through March of 2020 for RCTs and quasi-RCTs to update a previously published report. Forty-three studies (n=2428) were included.[19] Risk of relapse at 12 months was not significantly higher for MMF compared to cyclosporine (10 events vs. 7 events, RR 1.9, 95% CI 0.66 to 5.46, n=82, I^2=30.23%, low certainty evidence).[19] Gum hypertrophy and hypertrichosis were less likely with MMF compared to cyclosporine (gum hypertrophy, RR 0.09, 95% CI 0.02 to 0.47, n=144, low certainty evidence; hypertrichosis, RR 0.23, 95% CI 0.10 to 0.50, n=140, low certainty evidence).[19] There was no statistical difference in rates of hypertension, lymphopenia, or reduced GFR between cyclosporine and MMF (low certainty evidence).[19]

After review, 88 systematic reviews were excluded due to poor quality (e.g., indirect network-meta analyses), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

New Guidelines:

High Quality Guidelines:

Joint American Academy of Dermatology-National Psoriasis Foundation guidelines of care for the management and treatment of psoriasis in pediatric patients[20]

In 2020 guidelines for the treatment of psoriasis in pediatric patient were published. Recommendations related to oral immunosuppressant agents are limited to cyclosporine. Evidence was graded on a 3 point scale of I (good quality patient-oriented evidence), II (limited-quality patient oriented evidence) and III (Other evidence, including consensus guidelines, expert opinion, case studies, or disease-oriented evidence). Recommendations were ranked as A (based on consistent

and good quality patient oriented evidence), B (based on inconsistent or limited-quality patient oriented evidence) or C (based on consensus, expert opinion, case studies, or disease-oriented evidence.
The recommendations related to oral cyclosporine use in the treatment of pediatric psoriasis were:

- Cyclosporine is recommended as an effective systemic therapy for moderate to severe plaque psoriasis in children. (Level of Evidence II-III, Strength of Recommendation B)
- Cyclosporine is recommended as an effective systemic therapy for moderate to severe pustular psoriasis in children. (Level of Evidence III, Strength of Recommendation B)
- Cyclosporine is recommended for short-term crisis management of severe or unstable plaque, erythrodermic, or pustular psoriasis until the patient can be transitioned to a medication appropriate for long-term use. (Level of Evidence III, Strength of Recommendation C)
- Routine blood pressure clinical and laboratory monitoring is recommended during therapy with cyclosporine. (Level of Evidence III, Strength of Recommendation A)
- Modified cyclosporine (for microemulsion in capsules or solution) is recommended for use and is not interchangeable with unmodified forms of cyclosporine. (Level of Evidence III, Strength of Recommendation C)

2019 Update of the European League Against Rheumatism (EULAR) Recommendations for the Management of Systemic Lupus Erythematosus[12]
In 2019, EULAR updated the previous 2008 guidelines for the treatment of SLE. The systematic literature search included publications from January 2008 to December 2017. Levels of evidence were based on the Oxford Centre and grading of recommendations used GRADE methods (**Table 6**), and task force members were asked to rate their level of agreement from 0 to 10 (full agreement being 10) with final recommendation/statements after the committee had reached consensus. Agreement was reported numerically. Recommendations with the management of SLE are summarized in **Table 7**.

Table. 6 EULAR Guidelines Levels of Evidence and Grading of Recommendations[12,21]

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (LoE)		
LoE	**Therapy/Prevention/Etiology/Harm**	**Risk factors/Prognosis**
1a	Systematic reviews of RCT	Systematic review of inception cohort studies
1b	Individual, high-quality RCT	Individual inception cohort study (high quality)
2a	Systematic reviews of cohort studies	Systematic review of retrospective cohort studies or data from RCT
2b	Cohort study or low quality RCT	Retrospective cohort study or data from RCT
2c	"Outcomes" research studies	"Outcomes" research studies

3a	Systematic review of case-control studies	
3b	Case-control studies	
4	Case-series (and poor-quality cohort and case-control studies)	Case-series (and poor-quality prognostic cohort) studies)
5	Expert opinion	Expert opinion
	Grading of recommendations, assessment, development and evaluations (GRADE)	
A	Consistent level 1 studies	
B	Consistent level 2 or 3 studies; or extrapolations from level 1 studies	
C	Level 4 studies; or extrapolations from level 2 or 3 studies	
D	Level 5 evidence; or very inconsistent or inconclusive studies of any level	

Table 7. EULAR Recommendations for Management of Systemic Lupus Erythematosus[12]

Recommendation/Statement	**Level of Agreement (SD)**
1. Goals of treatment	
1.1 Treatment in SLE should aim at remission or low disease activity (2b/B) and prevention of flares (2b/B) in all organs, maintained with the lowest possible dose of glucocorticoids.	10.0 (0)
1.2 Flares of SLE can be treated according to the severity of organ(s) involvement by adjusting ongoing therapies (glucocorticoids, immunomodulating agents) to higher doses, switching or adding new therapies (2b/C).	9.95 (0.22)
2. Treatment of SLE	
2.1 HCQ	
2.1.1 HCQ is recommended for all patients with SLE (1b/A), unless contraindicated, at a dose not exceeding 5 mg/kg/real BW (3b/C).	9.65 (1.11)
2.1.2 In the absence of risk factors for retinal toxicity, ophthalmological screening (by visual fields examination and/or spectral domain-optical coherence tomography) should be performed at baseline, after 5 years, and yearly thereafter (2b/B).	9.75 (0.70)
2.2 GC	
2.2.1 GC can be used at doses and route of administration that depend on the type and severity of organ involvement (2b/C).	9.95 (0.22)
2.2.2 Pulses of intravenous methylprednisolone (usually 250–1000 mg per day, for 1–3 days) provide immediate therapeutic effect and enable the use of lower starting dose of oral GC (3b/C).	9.85 (0.36)

2.2.3 For chronic maintenance treatment, GC should be minimized to less than 7.5 mg/day (prednisone equivalent) (1b/B) and, when possible, withdrawn.	9.65 (0.65)
2.2.4 Prompt initiation of immunomodulatory agents can expedite the tapering/discontinuation of GC (2b/B).	9.90 (0.30)
2.3 Immunosuppressive therapies	
2.3.1 In patients not responding to HCQ (alone or in combination with GC) or patients unable to reduce GC below doses acceptable for chronic use, addition of immunomodulating/immunosuppressive agents such as methotrexate, (1b/B) azathioprine (2b/C) or mycophenolate (2a/B) should be considered.	9.85 (0.48)
2.3.2 Immunomodulating/immunosuppressive agents can be included in the initial therapy in cases of organ-threatening disease (2b/C).	9.85 (0.48)
2.3.3 Cyclophosphamide can be used for severe organ-threatening or life-threatening SLE as well as 'rescue' therapy in patients not responding to other immunosuppressive agents (2b/C).	9.90 (0.30)
2.4 Biologics	
2.4.1 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).	9.20 (0.81)
2.4.2 In organ-threatening disease refractory or with intolerance/contraindications to standard immunosuppressive agents, rituximab can be considered (2b/C).	9.85 (0.48)
3 Specific manifestations	
3.1 Skin disease	
3.1.1 First-line treatment of skin disease in SLE includes topical agents (GC, calcineurin inhibitors) (2b/B), antimalarials (HCQ, quinacrine) (1a/A) and/or systemic GC (4/C).	10.0 (0)
3.1.2 In non-responsive cases or cases requiring high-dose GC, methotrexate (3a/B), retinoids (4/C), dapsone (4/C) or mycophenolate (4/C) can be added.	9.85 (0.48)
3.2 Neuropsychiatric disease	
3.2.1 Attribution to SLE—as opposed to non-SLE—related neuropsychiatric manifestations, is essential and can be facilitated by neuroimaging, investigation of cerebrospinal fluid, consideration of risk factors (type and timing of the manifestation in relation to the onset of lupus, patient age, non-neurological lupus activity, presence of aPL) and exclusion of confounding factors (2b/C).	9.65 (0.85)
3.2.2 Treatment of SLE-related neuropsychiatric disease includes glucocorticoids/immunosuppressive agents for manifestations considered to reflect an inflammatory process (1b/A), and antiplatelet/anticoagulants for atherothrombotic/aPL-related manifestations (2b/C).	9.85 (0.48)
3.3 Hematological disease	
3.3.1 Acute treatment of lupus thrombocytopenia includes high-dose GC (including pulses of intravenous methylprednisolone) (4/C) and/or intravenous immunoglobulin G (4/C).	9.95 (0.22)
3.3.2 For maintenance of response, immunosuppressive/GC-sparing agents such as mycophenolate (2b/C), azathioprine (2b/C) or cyclosporine (4/C) can be used.	9.75 (0.62)

3.3.3 Refractory cases can be treated with rituximab (3a/C) or cyclophosphamide (4/C).	9.65 (0.73)
3.4 Renal disease	
3.4.1 Early recognition of signs of renal involvement and—when present—performance of a diagnostic renal biopsy are essential to ensure optimal outcomes (2b/B).	9.95 (0.22)
3.4.2 Mycophenolate (1a/A) or low-dose intravenous cyclophosphamide (2a/B) are recommended as initial (induction) treatment, as they have the best efficacy/toxicity ratio.	9.85 (0.36)
3.4.3 In patients at high risk for renal failure (reduced glomerular filtration rate, histological presence of fibrous crescents or fibrinoid necrosis, or tubular atrophy/interstitial fibrosis], similar regimens may be considered but high-dose intravenous cyclophosphamide can also be used (1b/A).	9.45 (0.80)
3.4.4 For maintenance therapy, mycophenolate (1a/A) or azathioprine (1a/A) should be used.	9.75 (0.62)
3.4.5 In cases with stable/improved renal function but incomplete renal response (persistent proteinuria >0.8–1 g/24 hours after at least 1 year of immunosuppressive treatment), repeat biopsy can distinguish chronic from active kidney lesions (4/C).	9.85 (0.48)
3.4.6 Mycophenolate may be combined with low dose of a calcineurin inhibitor in severe nephrotic syndrome (2b/C) or incomplete renal response (4/C), in the absence of uncontrolled hypertension, high chronicity index at kidney biopsy and/or reduced GFR.	9.50 (0.81)
4 Comorbidities	
4.1 Antiphospholipid syndrome	
4.1.1 All patients with SLE should be screened at diagnosis for aPL (1a/A).	10.0 (0)
4.1.2 Patients with SLE with high-risk aPL profile (persistently positive medium/high titers or multiple positivity) may receive primary prophylaxis with antiplatelet agents (2a/C), especially if other atherosclerotic/thrombophilic factors are present, after balancing the bleeding hazard.	9.45 (0.80)
4.1.3 For secondary prevention (thrombosis, pregnancy complication/loss), the therapeutic approach should be the same as for primary antiphospholipid syndrome (1b/B).	10.0 (0)
4.2 Infectious diseases	
4.2.1 Patients with SLE should be assessed for general and disease-related risk factors for infections, such as advanced age/frailty (–/D), diabetes mellitus (–/D), renal involvement (2b/B), immunosuppressive/biological therapy (1b-2b/B-C) and use of GC (1a/A).	9.85 (0.65)
4.2.2 General preventative measures (including immunizations) and early recognition and treatment of infection/sepsis are recommended (–/D).	9.90 (0.44)
4.3 Cardiovascular disease	
4.3.1 Patients with SLE should undergo regular assessment for traditional (1b/B-C) and disease-related risk factors for cardiovascular disease, including persistently active disease (1b/B), increased disease duration (1b/A), medium/high titers of aPL (1b/A), renal involvement (1b/B) (especially, persistent proteinuria and/or GFR <60 mL/min) and chronic use of GC (1b/B).	9.85 (0.65)

4.3.2 Based on their individual cardiovascular risk profile, patients with SLE may be candidates for preventative strategies as in the general population, including low-dose aspirin (2b/D) and/or lipid-lowering agents (2b/D).	9.85 (0.48)
Abbreviations: aPL=antiphospholipid antibodies; GC=glucocorticoids; GFR=glomerular filtration rate; HCQ=hydroxychloroquine; SD=standard deviation; SLE=systemic lupus erythematosus.	

2019 Update of the Joint European League Against Rheumatism and European Renal Association-European Dialysis Transplant Association (EULAR/ERA-EDTA) Recommendations for the Management of Lupus Nephritis[21]

In 2019, EULAR/ERA-EDTA updated the previous 2012 guidelines for the management of lupus nephritis. The systematic literature search included publications from January 2012 to December 2018. Levels of evidence were based on the Oxford Centre and grading of recommendations used GRADE methods (**Table 6**), and task force members were asked to rate their level of agreement from 0 to 10 (full agreement being 10) with final recommendation/statements after the committee had reached consensus. Agreement was reported numerically.

Goals of treatment should be optimization (preservation or improvement) of kidney function, accompanied by a reduction in proteinuria of at least 25% by 3 months (2b/C), 50% by 6 months (2a/B), and a UPCR target below 500–700 mg/g by 12 months (complete clinical response)(2a/B). Patients with nephrotic-range proteinuria at baseline may require an additional 6–12 months to reach complete clinical response; in such cases, prompt switches of therapy are not necessary if proteinuria is improving. (2a/C).

General recommendations include the use of immunosuppressive agents, administered in combination with glucocorticoids, in class III (A) and class IV (A/C) (±V) nephritis (2a/A). In pure class V nephritis, glucocorticoids and immunosuppression are recommended in cases of nephrotic-range proteinuria (2b/B), or when UPCR exceeds 1000 mg/g despite the optimal use of renin–angiotensin–aldosterone system blockers (5/D). Additionally for adjunctive treatment, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers are recommended for all patients with UPCR > 500 mg/g or arterial hypertension (5/D). More specific recommendations for initial and subsequent drug therapy are below in **Table 8**. Strategies for refractory and adjunct therapy are available but generally have low levels of evidentiary support.

Table 8. EULAR/ERA-EDTA recommendations for Initial and Subsequent management of Lupus Nephritis[21]

Recommendation/Statement	**Level of Agreement (SD)**
Initial Treatment	
For patients with class III or IV (±V) LN, MMF (target dose: 2 to 3 g/day, or MPA at equivalent dose) (1a/A) or low-dose intravenous CYC (500 mg every 2 weeks for a total of 6 doses) (1a/A) in combination with glucocorticoids, are recommended as they have the best efficacy/toxicity ratio.	9.84 (0.37)
Combination of MMF (target dose: 1 to 2 g/day, or MPA at equivalent dose) with a CNI (especially TAC) is an alternative, particularly in patients with nephrotic-range proteinuria. (1a/B)	9.32 (0.93)
Patients at high risk for kidney failure (reduced GFR, histological presence of crescents or fibrinoid necrosis or severe interstitial inflammation) can be treated as in 4.3–4.4 (2b/B), but high-dose intravenous CYC (0.5–0.75 g/m2 monthly for 6 months) can also be considered. (1a/B)	8.88 (1.56)

To reduce cumulative glucocorticoid dose, the use of intravenous pulses methylprednisolone (total dose 500–2500 mg, depending on disease severity) is recommended, followed by oral prednisone (0.3–0.5 mg/kg/day) for up to 4 weeks, tapered to ≤7.5 mg/day by 3 to 6 months. (2b/C)	9.48 (0.90)
In pure class V nephritis, MMF (target dose 2 to 3 g/day; or MPA at equivalent dose)(2a/B), in combination with pulse intravenous methylprednisolone (total dose 500–2500 mg, depending on disease severity) followed by oral prednisone (20 mg/day, tapered to ≤5 mg/day by 3 months) (2b/C) is recommended as initial treatment due to best efficacy/toxicity ratio.	9.28 (0.96)
Alternative options for class V nephritis include intravenous CY (2b/B), or CNIs (especially TAC) in monotherapy (2b/B) or in combination with MMF/MPA, particularly in patients with nephrotic-range proteinuria (1b/B).	9.28 (0.92)
HCQ should be coadministered (2a/B), at a dose not to exceed 5 mg/kg/day and adjusted for the GFR (3b/C).	9.28 (1.40)
Subsequent Treatment	
If improvement after initial treatment is achieved, subsequent immunosuppression is recommended with either MMF/MPA (dose: 1 to 2 g/day)—especially if it was used as initial treatment (1a/A)—or azathioprine (2 mg/kg/day)—preferred if pregnancy is contemplated—in combination with low-dose prednisone (2.5–5 mg/day) when needed to control disease activity (1a/A).	9.80 (0.49)
Gradual withdrawal of treatment (glucocorticoids first, then immunosuppressive drugs) can be attempted after at least 3 to 5 years therapy in complete clinical response. HCQ should be continued long-term (2b/C).	9.40 (0.75)
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 (2b/B).	9.28 (1.15)
Abbreviations: aPL=antiphospholipid antibodies; CNI=calcineurin inhibitor; CYC=cyclophosphamide; ESKD=end- stage kidney disease; GFR=glomerular filtration rate; HCQ=hydroxychloroquine; LN=lupus nephritis; MMF=mycophenolate mofetil; MPA=mycophenolic acid; RTX=rituximab; SLE=systemic lupus erythematosus; TAC=tacrolimus; UPCR=urine protein–creatine ratio.	

KDIGO 2021 Clinical Practice Guidelines for the Management of Glomerular Diseases[9]

In 2021 Kidney Disease: Improving Global Outcomes (KDIGO) group published updated guidelines. Strength of recommendations were given grades of Level 1 (Strong, "we recommend") and Level 2 (Weak, "we suggest"). Quality of supporting evidence is shown as Grade A (High), Grade B (Moderate), Grade C (Low), and Grade D (Very Low).

Graded recommendations specific to treatment of lupus nephritis are:

- We recommend that patients with SLE, including those with LN, be treated with hydroxychloroquine or an equivalent antimalarial unless contraindicated (1C).
- We recommend that patients with active Class III or IV LN, with or without a membranous component, be treated initially with glucocorticoids plus either low-dose intravenous cyclophosphamide or mycophenolic acid analogue (1B).
- We recommend that after completion of initial therapy, patients with class III or class IV LN should be placed on mycophenolic acid analogue for maintenance (1B).

After review, 7 guidelines were excluded due to poor quality or lack of applicability to research topic.

New Formulations or Indications:

Methotrexate (Reditrex®), new formulation of SC auto injector indicated for arthritis (adults and pediatrics) and psoriasis (adults) (11/27/2019)[22]

Tacrolimus (Prograf®), expanded indication for use in combination with other immunosuppressant drugs to prevent organ rejection in adults and pediatric patients receiving lung transplantation (7/14/21)[23]

New FDA Safety Alerts:

Table 9. Description of New FDA Safety Alerts[24,25]

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Mycophenolate mofetil	Cellcept	10/22/21	Warnings and Precautions	• Addition of Acute Inflammatory Syndrome • Addition of increased risk of COVID-19 infection

Randomized Controlled Trials:
A total of 356 citations were manually reviewed from the initial literature search. After further review, 356 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

NEW DRUG EVALUATION: Anifrolumab-fnia (SAPHNELO)

See **Appendix 4** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:
Anifrolumab-fnia, a human immunoglobulin G1 kappa monoclonal antibody,[5] is a type I IFN receptor antagonist indicated for the treatment of adult patients with moderate to severe SLE, who are receiving standard therapy.[26] Approval was based on data from 3 clinical studies (MUSE, TULIP-1, and TULIP-2).[2-5]

MUSE was a multi-center, double-blind, randomized, placebo-controlled, phase 2b trial, while TULIP-1 and TULIP-2 were phase 3 trials with similar design. All trials included adult patients with SLE diagnosis based on the American College of Rheumatology (1982 revised) classification criteria, and moderate to severe disease. Patients in all 3 studies had a score of 6 points or greater on the SLEDAI-2K, organ level involvement according to a BILAG assessment, and a Physician Global Assessment (PGA) score of at least 1 on a 3 point scale where 0 indicates no disease activity and a score of 3 indicates severe disease. Patients were receiving standard therapy of 1 or multiple agents (e.g., GC, antimalarials, immunosuppressants) under specified dosage maximums and these therapies were

continued during the studies. Use of oral glucocorticoids (GC), tapering, and steroid bursts varied between MUSE and the phase 3 studies. Patients with severe active lupus nephritis or neuropsychiatric SLE were excluded, as were those at risk of opportunistic infections or certain viral illnesses (**Table 12**). MUSE included 3 treatment arms (anifrolumab-fnia 300 mg, anifrolumab-fnia 1000 mg, or placebo; each given IV every 4 weeks), TULIP-1 included 3 treatment arms (anifrolumab-fnia 300 mg, anifrolumab-fnia 150 mg, or placebo; each given IV every 4 weeks), while TULIP-2 included 2 treatment arms (anifrolumab-fnia 300 mg or placebo; each given IV every 4 weeks).[2,4,5] The 300 mg dose alone received FDA approval due to lack of efficacy seen with other doses, and will be the primary focus of this summary. Randomization in all studies was stratified by SLEDAI-2K score (<10 or ≥ 10), baseline GC dose (<10 mg/day or ≥ 10 mg/day prednisone or equivalent), and type I IFN gene signature (high or low). All trials lasted 52 weeks, with the MUSE primary endpoint at week 24 and a secondary endpoint at week 52.[2,4,5] The phase 3 primary endpoints were assessed at week 52. Each study included use of composite endpoints for the primary outcome (see **Table 3** for details). Additional trial specific restrictions regarding investigational products, restricted medications, and corticosteroid use and doses are included below.

The phase 2B Muse study used a primary composite endpoint of SRI-4 in addition to GC tapering at week 24 in both the total population and the Type I IFN high subgroup. Details of the composite include[5]:

- Reduction in baseline SLEDAI-2K disease activity score of ≥ 4 points
- No worsening from baseline in subjects' lupus disease activity, where worsening is defined by an increase ≥ 0.30 points on a 3-point physician global assessment (PGA) visual analogue scale (VAS)
- No worsening in BILAG-2004 defined as ≥ 1 new A or ≥ 2 new B items compared to baseline
- No discontinuation of investigational product
- Patients who need a burst of GC need to satisfy the following:
    - No increase in dose of antimalarials or disease modifying anti-rheumatic above Day 1 levels or added new antimalarials/disease modifying anti-rheumatic between Day 1 and Day 169
    - No IV corticosteroid between Day 1 and Day 169
    - No increase in oral GC above Day 1 dose or intramuscular/intraarticular (IM/IA) injection of corticosteroid after Day 71 and up to Day 169
    - No more than one course of burst of corticosteroid between Day 1 and Day 71. One course of burst is defined as burst of oral GC above Day 1 dose (up to a maximum dose of 40 mg/day prednisone or equivalent and no increase in oral GC dose for > 14 days above Day 1 dose) or 1 IM injection of corticosteroids (≤ 160 mg methylprednisolone or equivalent) or 2 IA injections of corticosteroids
    - Reduce oral GC to < 10mg/day and ≤ Day 1 dose of prednisone or equivalent by Day 85 and maintain oral GC dose < 10mg/day and ≤ Day 1 dose until Day 169 (Note: this criterion applies to subjects with oral GC ≥ 10 mg/day at baseline)

TULIP-1 used SRI-4, without the GC tapering, as the composite primary endpoint at week 52[5]:

- Reduction from baseline of ≥ 4 points in the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) score
- No new organ system clinical manifestations as defined by British Isles Lupus Assessment Group (BILAG) grade
- No worsening from baseline in subjects' lupus disease activity, where worsening is defined by an increase ≥ 0.30 points on a 3-point PGA VAS
- No discontinuation of investigational product
- No use of restricted medications beyond the protocol-allowed threshold before assessment

TULIP-2 used the British Isles Lupus Assessment Group-based Composite Lupus Assessment (BICLA), as a primary endpoint at week 52. BICLA is a composite of:[5]

- Reduction in severity of all baseline clinical manifestations and no worsening in other organ systems, as defined by BILAG grade
- No worsening from baseline in SLEDAI-2K score
- No worsening from baseline in subjects' lupus disease activity, where worsening is defined by an increase ≥ 0.30 points on a 3-point PGA VAS
- No discontinuation of investigational product
- No use of restricted medications beyond the protocol-allowed threshold before assessment

The MUSE study had a statistically significant SRI-4 response with GC tapering in the anifrolumab-fnia 300 mg dose group compared to placebo for the primary endpoint at week 24 (anifrolumab-fnia 300 mg 34.3% vs. placebo 17.6%; OR 2.38, 95% CI 1.19 to 4.77; NNT 6) and secondary endpoint at week 52 (anifrolumab-fnia 300 mg 51.5% vs. placebo 25.5%; OR 3.08, 90% CI 1.86 to 5.09, P<0.001).[2] The prespecified use of the high type I IFN subpopulation at week 24 showed similar results (anifrolumab-fnia 300 mg 36.0% vs. placebo 13.2%; OR 3.55, 95% CI 1.5 to 7.32; NNT 5).[2] Statistical analyses for MUSE were conducted using a type 1 error rate of 0.1 (two-sided).[2] The FDA review included a 0.05 alpha value in its statistical calculations.[5] The TULIP-1 study failed to find statistical significance for the primary endpoint of SRI-4 response at 52 weeks at either anifrolumab-fnia dose (anifrolumab-fnia 300 mg 36.1% vs. placebo 40.2%; -4.2% difference, 95% CI -14.20 to 5.82, P=0.41).[5]

The TULIP-2 study changed the primary outcome via protocol amendment after TULIP-1 failed to find statistical significance.[4,5] TULIP-1 used BICLA as a secondary endpoint (anifrolumab-fnia 300 mg 37.2% vs. placebo 26.6%; 10.6% absolute difference, 95% CI 0.59 to 19.68).[5] The change occurred after discussion with the FDA and experts and prior to data unblinding or analysis.[5] TULIP-2 showed a statistically significant difference in BICLA response at 52 weeks (anifrolumab-fnia 300 mg 47.8% vs. placebo 31.5%; 16.3% difference, 95% CI 6.3 to 26.3, P=0.001; NNT 7).[4,5] SRI-4 response results are provided as a secondary endpoint, however "results are not multiplicity adjusted and no formal inferences can be drawn from them."[27]

Limitations of these studies include differing GC use and differing composite endpoints used for efficacy assessment, making interpretation results and applicability of results to clinical practice difficult. Lack of dose response to different doses studied, uneven attrition across studies, and conflicts of interest among authors and sponsor involvement in trial designs and interpretation further increase risk of bias. Men were underrepresented given 10:1 female to male prevalence and more likelihood that men have severe disease. Non-White representation in demographics was reasonably present in MUSE and TULIP-2, less so in TULIP-1. It is unclear how exclusion of participants with active LN or need for stable treatment prior to enrollment may have reduced enrollment of men and non-White patients who tend to experience more severe disease and health disparities in treatment of SLE.

Clinical Safety:
Safety data of anifrolumab-fnia is derived from use in moderate to severe SLE over 52 weeks, pooled from the 3 studies detailed in **Table 12**.[2-4,26] The most common adverse events were included in **Table 10**. Average age of treatment population was 41 years (age 18 to 69 years), primarily female (93%), with a racial identity of 60% White, 13% Black, and 10% Asian. Those 65 years and older represented only 3% of the trial population. Given exclusion criteria, those who are immunocompromised or who had certain viral illnesses were not represented in research studies, as well as patients with active, severe lupus nephritis or neuropsychiatric lupus, and uncontrolled diabetes with a HbA1c of >8%.[26] Pregnant women were excluded. Pregnancy in women with SLE is associated with increased risk of adverse pregnancy outcomes.

Special interest adverse events included serious infections, opportunistic infections, anaphylaxis, cancer, herpes zoster, tuberculosis, influenza, non-SLE related vasculitis, and adjudicated major cardiovascular events (**Table 9**). Serious adverse reactions included hypersensitivity, which included 1 case of anaphylactic reaction and 2 cases of angioedema in patients randomized to treatment, compared with no cases in patients randomized to placebo. Most infusion reactions

were mild to moderate. Serious infections, most commonly pneumonia, occurred in 4.8% of anifrolumab-fnia and 5.6% of placebo treated patients. Fatal infections occurred in 0.4% of patients on active treatment versus 0.2% of those on placebo. Discordant rates of herpes zoster also occurred (**Table 10**), with 2 anifrolumab-fnia patients having disseminated disease requiring hospitalization compared to none on placebo. During year 1 of a 3 year open-label extension study, 30 of 218 patients (13.8%) reported a grade 3 or higher severe AE.[26] The most frequent were bronchitis (3 patients; 1.4%), gastroenteritis (2 patients; 0.9%), pharyngitis (2 patients; 0.9%), osteonecrosis (2 patients; 0.9%), and SLE flares (2 patients; 0.9%). Infections and infestations occurred in 138 of 218 patients (63.3%) throughout the extension study. Herpes zoster infections occurred in 5% of patients, 2 of 11 were disseminated and neither serious.[28]

Table 10: Adverse reactions occurring in at least 2% of patients[2-4,26]

Adverse Reaction	**Anifrolumab-fnia (300 mg Q4 weeks at 52 weeks) %**	**Placebo %**
Upper respiratory tract infection	34	23
Bronchitis	11	5.2
Infusion-related reactions	9.4	7.1
Herpes zoster	6.1	1.3
Cough	5.0	3.2
Respiratory tract infection	3.3	1.5
Hypersensitivity	2.8	0.6

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Reduction in disease activity
2) Clinical response or remission
3) Quality of Life
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:

1) SRI-4 responder at week 24 or 52
2) BICLA responder at week 52

Table 11. Pharmacology and Pharmacokinetic Properties[26]

Parameter	
Mechanism of Action	Type 1 interferon (INF) receptor antagonist binds to subunit 1 of type 1 interferon receptor (IFNAR1) inducing internalization and reducing cell surface levels, ultimately reducing downstream signaling of inflammatory and immunological processes.
Oral Bioavailability	Not applicable
Distribution and Protein Binding	6.23 liters (L) in typical 69.1 kg systemic lupus erythematosus patient
Elimination	Non-linear, 0.193 L/day
Half-Life	Not reported, steady state achieved at Day 85
Metabolism	IFNAR1-mediated drug clearance

Table 12. Comparative Evidence Table.[2-5,26]

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/NNH	Risk of Bias/ Applicability
1. Study 1 NCT01438489 MUSE FDA trial ID: CD-IA-MEDI-546-**1013** MC, R, DB, PC Phase 2b	1. Anifrolumab 300 mg IV Q4wk x 48 weeks 2. Anifrolumab 1000 mg IV Q4wk x 48 weeks 3. Placebo IV Q4wk 52 weeks duration 1:1:1 randomized Stratified by: SLEDAI-2K score (<10 or ≥ 10), baseline GC dose (<10 mg/day or ≥ 10 mg/day pred or equivalent), and type I interferon gene signature (high or low) GC tapering encouraged but at investigator discretion, allowed post-randomization but not within 8 weeks of primary (week 24) and secondary (week 52) assessments. Two GC bursts allowed (once between weeks 1	<u>Demographics</u>: Mean age 39 years Female 93.4% White 1. 35 (35.4%) 2. 51 (49.0%) 3. 41 (40.2%) Black 1. 19 (19.2%) 2. 10 (9.6%) 3. 12 (11.8%) Asian 1. 3 (3.0%) 2. 6 (5.8%) 3. 13 (12.7%) Other 1. 38 (38.4%) 2. 36 (34.6%) 3. 36 (35.3%) Hispanic 42% GC use 1. 79 (79.8%) 2. 91 (87.5%) 3. 88 (86.3%) MTX Use 1. 19 (19.3%) 2. 25 (24.5%) 3. 16 (15.7%) <u>Key Inclusion Criteria</u>: -18 to 65 years old - ≥ 40 kg -ACR classification criteria for SLE (≥ 4 of 11 criteria) -≥ 6 points (≥ 4 in clinical components) SLE by SLEDAI-2K, excluding lupus headache or organic brain syndrome	<u>mITT</u>: 1. 99 2. 104 3. 102 <u>Attrition</u>: 1. 12 (12.1%) 2. 28 (26.9%) 3. 31 (30.4%)	<u>Primary Endpoint</u>: SRI-4 at week 24 with sustained GC reduction week 12 to 24 Whole population: 1. 34 (34.3%) 2. 30 (28.8%) 3. 18 (17.6%) 1 vs. 3 OR 2.38 (90% CI 1.33 to 4.26) P=0.014 (95% CI 1.19 to 4.77) 2 vs. 3 OR 1.94 (90% CI 1.08 to 3.49) P=0.063 (95% CI 0.96 to 4.77) Type 1 High IFN subgroup: 1. 27 (36.0%) 2. 22 (28.2%) 3. 10 (13.2%) 1 vs. 3 OR 3.55 (90% CI 1.72 to 7.32) P=0.004 (95% CI 1.5 to 8.4) 2 vs. 3 OR 2.65 (90% CI 1.27 to 5.53) P=0.029 (95% CI 1.11 to 6.36) <u>Key Secondary Endpoints</u>: SRI-4 at week 52 with sustained GC reduction week 40 to 52 1. 51 (51.5%) 2. 40 (38.5%)	16.7%/6 11.2%/9 22.8%/5 15.0%/7	<u>Any AE:</u> 1. 84 (84.8%) 2. 90 (85.7%) 3. 78 (77.2%) <u>Serious AE:</u> 1. 16 (16.2%) 2. 18 (17.1%) 3. 19 (18.8%) <u>Death:</u> 1. 0 2. 1 (1.0%) 3. 0 <u>Special interest AE:</u> 1. 10 (10.1%) 2. 15 (14.3%) 3. 12 (11.9%)	N/A	**Risk of Bias (low/high/unclear)**: <u>Selection Bias</u>: (High) Stratified 1:1 randomization, method not described. Some unbalance in Race (White, Black, Asian), GC and MTX use between groups, and disease duration. <u>Performance Bias</u>: (Low) Training and certification provided to investigators and designated site personnel. When possible, evaluation performed by single assessor. <u>Detection Bias</u>: (Low) Training and certification provided to investigators and designated site personnel. When possible, evaluation performed by single assessor. Used Type I error rate 0.1, 2-sided while FDA review included 95% CI for 0.05 error rate. <u>Attrition Bias</u>: (High) Missing data used LOCF, withdrawal without week 20 data treated as nonresponders for responder analyses, unbalanced attrition between groups, high overall attrition. <u>Reporting Bias</u>: (Low) Prespecified outcomes reported <u>Other Bias:</u> (High) Multiple CoI among authors. Industry funded (MedImmune) and publication contingent on sponsor. **Applicability**: <u>Patient</u>: Male underrepresented given normal prevalence relative to female and risk of severe disease. Patients with severe lupus nephritis or neuropsychiatric disease were excluded. <u>Intervention</u>: Appropriate based on previous studies <u>Comparator</u>: Placebo comparison appropriate <u>Outcomes</u>: Complex composite outcomes with differing GC protocols difficult to interpret clinically <u>Setting</u>: 79 sites in 15 countries; 36.8% Latin America, 30.9% North America, 25.4% Eastern Europe, 6.8% Asia

	& 10, once between weeks 24 & 40) if needed for increased SLE disease activity	-organ domain score ≥ 1A or ≥ 2B BILAG-2004 -PGA 1 or higher on VAS -antinuclear, anti-dsDNA, or anti-Smith antibody seropositive -stable treatment with at least one: pred or equivalent, antimalarial agent, azathioprine, mycophenolate mofetil, mycophenolic acid, or MTX <u>Key Exclusion Criteria</u>: -active, severe lupus nephritis -neuropsychiatric SLE - >1 prescribed NSAID at anti-inflammatory dose within 2 weeks -Primary immunodeficiency, certain infectious diseases-HIV, active HBV, HCV, hx severe HSV, unresolved HSV within 12 weeks, any clinically significant active infection, any infection requiring hospitalization or IV anti-infectives within 60 days -cancer history (except certain squamous or basal		3. 26 (25.5%) 1 vs. 3 OR 3.08 (90% CI, 1.86 to 5.09) P<0.001 2 vs. 3 OR 1.84 (90% CI, 1.11 to 3.04) P=0.063 BICLA responder week 52 1. 53 (53.5%) 2. 42 (41.2%) 3. 26 (25.7%) 1 vs. 3 OR 3.42 (90% CI, 2.06 to 5.68) P<0.001 2 vs. 3 OR 2.06 (90% CI, 1.25 to 3.42) P=0.018				

		cell carcinomas or cervical cancer)						
2. Study 2 NCT02446912 TULIP-1 FDA trial ID: D3461C-000**05** MC, R, DB, PC, phase 3	1. Anifrolumab 300 mg IV Q4wk x 48 weeks 2. Anifrolumab 150 mg IV Q4wk x 48 weeks 3. Placebo IV Q4wk 52 weeks duration 2:1:2 randomization Stratified by: SLEDAI-2K score (<10 or ≥ 10), baseline GC dose (<10 mg/day or ≥ 10 mg/day pred or equivalent), and type I interferon gene signature (high or low) Patients with baseline pred ≥ 10 mg/day (or equivalent) had required taper attempt to ≤ 7.5 mg/day pred between week 8 and week 40.	<u>Demographics</u>: -Age (yr) 1. 42.0±12.0 3. 41.0±12.3 -Female 92.3% -Race White 1. 69.4% 3. 74.5% Black 1. 29 (16.1%) 3. 23 (12.5%) Asian 1. 11 (6.1%) 3. 5 (2.7%) Other 9.3% Ethnicity Hispanic/Latino NR US/Canada 40.4% <u>Key Inclusion Criteria</u>: See TULIP-2 <u>Key Exclusion Criteria</u>: See TULIP-2	<u>ITT</u>: 1. 180 2. 93 3. 184 <u>Attrition</u>: NR	<u>Primary Endpoint</u>: SRI-4 at week 52 1. 65 (36.1%) 2. 35 (37.6%) 3. 74 (40.2%) 1 vs. 3 -4.2% difference (95% CI -14.20 to 5.82) P=0.41 2 vs. 3 -2.6% difference (95% CI -14.71 to 9.60) P=0.68 <u>Secondary Endpoints</u>: BICLA response at week 52 1. 67 (37.2%) 2. 27 (29.0%) 3. 49 (26.6%) 1 vs. 3 10.1%[5] difference (95% CI 0.59 to 19.68) P NR 2 vs. 3 2.4% difference (95% CI -9.03 to 13.87) P NR	N/A 10.6/10 NS	NR	N/A	**Risk of Bias (low/high/unclear)**: *Note: Tulip-1 results have only been published as post-hoc analysis of pooled data with Tulip-2. Full study methods are not available and risk of bias cannot be fully assessed.* <u>Selection Bias</u>: See TULIP-2 <u>Performance Bias</u>: Unable to assess. Allocation concealment using blinded identical investigational product kit. <u>Detection Bias</u>: Unable to assess. Double-blind with adequate allocation concealment <u>Attrition Bias</u>: Unable to assess. Nonresponder imputation method for missing data. <u>Reporting Bias</u>: (High) Tulip-1 results only published as post-hoc analysis of pooled data with Tulip-2 outside of FDA review. Protocol available online. <u>Other Bias:</u> Unable to assess. Funded by AstraZenica **Applicability**: <u>Patient</u>: Male underrepresented given normal prevalence relative to female and risk of severe disease. Results may not be applicable to patients with mild disease and patients with severe lupus nephritis or neuropsychiatric disease were excluded. <u>Intervention</u>: unable to assess <u>Comparator</u>: placebo appropriate to evaluate efficacy, dose appropriate given phase 2b results with lack of efficacy of 1000 mg dose <u>Outcomes</u>: unable to assess <u>Setting</u>: 146 sites in 18 countries; Descending order US, Europe, Latin America, Asia-Pacific, Other
3. Study 3 NCT02446899	1. Anifrolumab 300 mg IV Q4wk x 48 weeks	<u>Demographics</u>: -Age (yr) 1. 41.1±11.5 2. 43.1±12.0	<u>mITT</u>: 1. 180 2. 182	<u>Primary Endpoint</u>: Proportion with BICLA response at week 52	16.3%/7	<u>Serious AE:</u> 1. 15 (8.3%) 2. 31 (17%)		**Risk of Bias (low/high/unclear)**: <u>Selection Bias</u>: (Low) Block 1:1 randomization with interactive voice/web response system,

TULIP-2 FDA trial ID: D3461C-000**04** MC, R, PC, DB, phase 3	2. Placebo IV Q4wk 52 weeks duration 1:1 randomization Stratified by: SLEDAI-2K score (<10 or ≥ 10), baseline GC dose (<10 mg/day or ≥ 10 mg/day pred or equivalent), and type I interferon gene signature (high or low) Patients with baseline pred ≥ 10 mg/day (or equivalent) had required taper attempt to ≤ 7.5 mg/day pred between week 8 and week 40. GC doses required to be stable during final 12 wks of trial. Other treatments stable throughout whole trial period.	-Female 93.4% -Race White 59.9% Black 1. 25 (13.7%) 2. 17 (9.4%) Asian 16.6% Other 11.9% Ethnicity Hispanic/Latino 29.8% US 37.6% <u>Key Inclusion Criteria</u>: -18 to 70 years old -ACR classification criteria for SLE -moderate to severe SLE by SLEDAI-2K -severe dz activity ≥ 1 organ or moderate in ≥ 2 organs by BILAG-2004 -PGA 1 or higher -antinuclear, anti-dsDNA, or anti-Smith antibody seropositive -stable treatment with at least one with dose below specified thresholds: pred or equivalent, antimalarial agent, azathioprine, mizoribine (Japan only), mycophenolate mofetil, mycophenolic acid, or MTX	<u>Attrition</u>: 1. 15.0% 2. 28.6%	1. 86 (47.8%) 2. 57 (31.5%) Difference 16.3% (95% CI 6.3 to 26.3%) P=0.001 <u>Secondary Endpoints</u>: BICLA response by subpopulation at week 52 High interferon gene signature (301/362) 1. 72/150 (48.0%) 2. 46/151 (30.7%) Difference 17.3% (95% CI 6.5 to 28.2) P=0.002 Low Interferon gene signature (61/362) 1. (46.7%) 2. (35.5%) Difference 11.2% (95% CI -13.5 to 35.8) P NR Reduction in GC dose to ≤ 7.5 mg/day sustained wk 40 to 52 among baseline GC ≥ 10 mg/day (170/362) 1. 45/87 (51.5%) 2. 25/83 (30.2%) Difference 21.2% (95% CI 6.8 to 35.7) P=0.01 Reduction ≥ 50% in CLASI at week 12 1. 24/49 (49.0%) 2. 10/40 (25.0%) Difference 24.0% (95% CI 4.3 to 43.6) P=0.04	17.3%/6 N/A 21%/5 24%/5	<u>Death</u>: 1. 1 (0.6%) pneumonia 2. 0 (0%) <u>Special interest AE</u>: 1. 25 (13.9%) 2. 18 (9.9%)		multiple stratifications. Baseline characteristics balanced. <u>Performance Bias</u>: (Low) Allocation concealment using blinded identical investigational product kits <u>Detection Bias</u>: (Low) Double-blind with adequate allocation concealment. <u>Attrition Bias</u>: (High) LOCF used for missing data in responder analysis (nonresponder if week 48 missing), multiple imputation for intermittent missing data used in sensitivity analysis, unbalanced attrition <u>Reporting Bias</u>: (High) SRI-4 used as primary outcome for belimumab for SLE and in TULIP-1. Primary endpoint changed for TULIP-2 to BICLA response after failure of SRI-4 in TULIP-1 (protocol amended prior to TULIP-2 data unblinding/analysis) <u>Other Bias:</u> (High) Industry sponsor designed, participated in collection, analysis, and interpretation of data, and paid for professional writing assistance. Confidentiality agreements were in place between authors and AstraZeneca. **Applicability**: <u>Patient</u>: Male underrepresented given normal prevalence relative to female and risk of severe disease. Results may not be applicable to patients with mild disease and patients with severe lupus nephritis or neuropsychiatric disease were excluded. <u>Intervention</u>: Appropriate based on previous studies <u>Comparator</u>: placebo comparison appropriate <u>Outcomes</u>: Complex composite outcomes with differing GC protocols difficult to interpret clinically, outcome changed due to lack of efficacy of a different composite outcome in other research study <u>Setting</u>: 113 sites in 16 countries; Descending order US, Europe, Latin America, Asia-Pacific, Other

		Key Exclusion Criteria: -active, severe lupus nephritis -neuropsychiatric SLE -suicidal ideation within 6 mo or suicidal behavior within 12 mo -HbA1c >8% (diabetic subjects only) -regular use of >1 NSAID -certain infectious diseases-HIV, active HBV, HCV, hx severe HSV, unresolved HSV/CMV/EBV, opportunistic infection requiring hospitalization within 3 years -cancer history (except certain squamous or basal cell carcinomas or cervical cancer)		Reduction of ≥ 50% in swollen/tender joints at week 52 1. 34/90 (37.5%) 2. 30/71 (42.2%) Difference 4.7% (95% CI -10.6 to 20.0) P=0.55 Annualized flare rate through week 52 1. 0.64 2. 0.43 Rate Ratio 0.67 (95% CI 0.48 to 0.94) P=0.08	NS N/A			

Abbreviations: ACR = American College of Rheumatology; AE = adverse event; anti-dsDNA = anti-double-stranded DNA; ARR = absolute risk reduction; BICLA = British Isles Lupus Assessment Group-based composite lupus assessment; BILAG-2004 = British Isles lupus assessment group 2004 index; CLASI = cutaneous lupus erythematosus disease area and severity index; CI = confidence interval; CMV = cytomegalovirus; CoI = conflict of interest; DB = double-blind; dz = disease; EBV = Epstein-Barr virus; FDA = Food and Drug Administration; GC = glucocorticoid; HbA1c = glycosylated hemoglobin; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HSV = *herpes zoster*; IV = intravenous; LOCF = last observation carried forward; MC = multi-center; mg = milligram; mITT = modified intention to treat; mo = months; MTX = methotrexate; N = number of subjects; NSAID = non-steroidal anti-inflammatory drug; N/A = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; OR = odds ratio; PC = Placebo-controlled; PGA = Physician Global Assessment; PP = per protocol; pred = prednisone; Q = every; R = randomized; SLE = Systemic Lupus Erythematosus; SLEDAI-2K = SLE disease activity index 2000; SRI = Systemic Lupus Erythematosus Responder Index; TULIP = treatment of uncontrolled lupus via the interferon pathway; US = United States; VAS = visual analogue scale; wk = week; yr = year.

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Appendix 1: Current Preferred Drug List

Immunosuppressants

Generic	Brand	Route	Form	PDL
azathioprine	AZASAN	ORAL	TABLET	Y
azathioprine	AZATHIOPRINE	ORAL	TABLET	Y
azathioprine	IMURAN	ORAL	TABLET	Y
cyclosporine	CYCLOSPORINE	ORAL	CAPSULE	Y
cyclosporine	SANDIMMUNE	ORAL	CAPSULE	Y
cyclosporine	SANDIMMUNE	ORAL	SOLUTION	Y
cyclosporine, modified	CYCLOSPORINE MODIFIED	ORAL	CAPSULE	Y
cyclosporine, modified	GENGRAF	ORAL	CAPSULE	Y
cyclosporine, modified	NEORAL	ORAL	CAPSULE	Y
cyclosporine, modified	CYCLOSPORINE MODIFIED	ORAL	SOLUTION	Y
cyclosporine, modified	GENGRAF	ORAL	SOLUTION	Y
cyclosporine, modified	NEORAL	ORAL	SOLUTION	Y
everolimus	EVEROLIMUS	ORAL	TABLET	Y
everolimus	ZORTRESS	ORAL	TABLET	Y
mycophenolate mofetil	CELLCEPT	ORAL	CAPSULE	Y
mycophenolate mofetil	MYCOPHENOLATE MOFETIL	ORAL	CAPSULE	Y
mycophenolate mofetil	CELLCEPT	ORAL	SUSP RECON	Y
mycophenolate mofetil	MYCOPHENOLATE MOFETIL	ORAL	SUSP RECON	Y
mycophenolate mofetil	CELLCEPT	ORAL	TABLET	Y
mycophenolate mofetil	MYCOPHENOLATE MOFETIL	ORAL	TABLET	Y
mycophenolate sodium	MYCOPHENOLIC ACID	ORAL	TABLET DR	Y
mycophenolate sodium	MYFORTIC	ORAL	TABLET DR	Y
sirolimus	RAPAMUNE	ORAL	SOLUTION	Y
sirolimus	SIROLIMUS	ORAL	SOLUTION	Y
sirolimus	RAPAMUNE	ORAL	TABLET	Y
sirolimus	SIROLIMUS	ORAL	TABLET	Y
tacrolimus	ASTAGRAF XL	ORAL	CAP ER 24H	Y
tacrolimus	PROGRAF	ORAL	CAPSULE	Y
tacrolimus	TACROLIMUS	ORAL	CAPSULE	Y
tacrolimus	PROGRAF	ORAL	GRAN PACK	Y
tacrolimus	ENVARSUS XR	ORAL	TAB ER 24H	Y
anifrolumab-fnia	SAPHNELO	IV	VIAL	N
belumosudil mesylate*	REZUROCK	ORAL	TABLET	N
voclosporin	LUPKYNIS	ORAL	CAPSULE	N
Belimumab†	BENLYSTA	IV	VIAL	N

Belimumab†	BENLYSTA	IV	SYRINGE	N
Belimumab†	BENLYSTA	SC	AUTO INJCT	N

*This medication is prior authorized under the orphan drug policy and was excluded from this review.
†This medication is categorized in the Targeted Immune Modulator class

Appendix 2: Abstracts of Comparative Clinical Trials
None

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to November Week 3 2014, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations Sept 16th, 2021

# ▲	Searches	Results	Type	Actions
1	Azathioprine/ae, tu [Adverse Effects, Therapeutic Use]	11769	Advanced	Display Results | More
2	Cyclosporine/ae, tu [Adverse Effects, Therapeutic Use]	16148	Advanced	Display Results | More
3	Everolimus/ae, tu [Adverse Effects, Therapeutic Use]	1277	Advanced	Display Results | More
4	Mycophenolic Acid/ae, tu [Adverse Effects, Therapeutic Use]	5556	Advanced	Display Results | More
5	Sirolimus/ae, tu [Adverse Effects, Therapeutic Use]	6450	Advanced	Display Results | More
6	Tacrolimus/ae, tu [Adverse Effects, Therapeutic Use]	9070	Advanced	Display Results | More
7	1 or 2 or 3 or 4 or 5 or 6	41522	Advanced	Display Results | More
8	limit 7 to (english language and humans)	33679	Advanced	Display Results | More
9	limit 8 to yr="2019 -Current"	2293	Advanced	Display Results | More
10	limit 9 to (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or guideline or meta analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review")	591	Advanced	Display Results | More
11	Stents/	71237	Advanced	Display Results | More
12	10 not 11	581	Advanced	Display Results | More
13	12 not eluting.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	490	Advanced	Display Results | More

1	Azathioprine/ae, tu [Adverse Effects, Therapeutic Use]	11769	Advanced	Display Results | More	
2	Cyclosporine/ae, tu [Adverse Effects, Therapeutic Use]	16148	Advanced	Display Results | More	
3	Everolimus/ae, tu [Adverse Effects, Therapeutic Use]	1277	Advanced	Display Results | More	
4	Mycophenolic Acid/ae, tu [Adverse Effects, Therapeutic Use]	5556	Advanced	Display Results | More	
5	Sirolimus/ae, tu [Adverse Effects, Therapeutic Use]	6450	Advanced	Display Results | More	
6	Tacrolimus/ae, tu [Adverse Effects, Therapeutic Use]	9070	Advanced	Display Results | More	
7	1 or 2 or 3 or 4 or 5 or 6	41522	Advanced	Display Results | More	
8	limit 7 to (english language and humans)	33679	Advanced	Display Results | More	
9	limit 8 to yr="2019 -Current"	2293	Advanced	Display Results | More	
10	limit 9 to (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or guideline or meta analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review")	591	Advanced	Display Results | More	
11	Stents/	71237	Advanced	Display Results | More	
12	10 not 11	581	Advanced	Display Results | More	
13	12 not eluting.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	490	Advanced	Display Results | More	
14	anifrolumab.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	74	Advanced	Display Results | More	
15	voclosporin.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	67	Advanced	Display Results | More	
16	14 or 15	135	Advanced	Display Results | More	
17	limit 16 to (english language and humans)	85	Advanced	Display Results | More	
18	limit 17 to (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or guideline or meta analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review")	26	Advanced	Display Results | More	

Appendix 4: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use LUPKYNIS™ safely and effectively. See full prescribing information for LUPKYNIS.

LUPKYNIS (voclosporin) capsules, for oral use
Initial U.S. Approval: 2021

WARNING: MALIGNANCIES AND SERIOUS INFECTIONS
See full prescribing information for complete boxed warning.

Increased risk for developing serious infections and malignancies with LUPKYNIS or other immunosuppressants that may lead to hospitalization or death. (5.1, 5.2)

----------INDICATIONS AND USAGE----------
LUPKYNIS is a calcineurin-inhibitor immunosuppressant indicated in combination with a background immunosuppressive therapy regimen for the treatment of adult patients with active lupus nephritis (LN). (1, 14)

Limitations of Use: Safety and efficacy of LUPKYNIS have not been established in combination with cyclophosphamide. Use of LUPKYNIS is not recommended in this situation.

----------DOSAGE AND ADMINISTRATION----------
Administration:
- LUPKYNIS must be swallowed whole on an empty stomach. (2.1)
- Administer consistently as close to a 12-hour schedule as possible, and with at least 8 hours between doses. (2.1)
- If a dose is missed, instruct the patient to take it as soon as possible within 4 hours after missing the dose. Beyond the 4-hour time frame, instruct the patient to wait until the usual scheduled time to take the next regular dose. Instruct the patient not to double the next dose. (2.1)
- Instruct patients to avoid eating grapefruit or drinking grapefruit juice while taking LUPKYNIS. (2.1, 7.1)

Dosage Recommendations:
- Before initiating LUPKYNIS, establish an accurate baseline estimated glomerular filtration rate (eGFR) and check blood pressure (BP).
  - Use of LUPKYNIS is not recommended in patients with a baseline eGFR ≤45 mL/min/1.73 m^2 unless the benefit exceeds the risk; these patients may be at increased risk for acute and/or chronic nephrotoxicity. (2.2, 5.3)
  - Do not initiate LUPKYNIS in patients with baseline BP >165/105 mmHg or with hypertensive emergency. (2.2, 5.4)
- Recommended starting dose: 23.7 mg orally, twice a day. (2.3)
- Use LUPKYNIS in combination with mycophenolate mofetil (MMF) and corticosteroids. (2.3)
- Modify the LUPKYNIS dose based on eGFR (2.3, 5.3):
  - Assess eGFR every two weeks for the first month, and every four weeks thereafter.
  - If eGFR <60 mL/min/1.73 m^2 and reduced from baseline by >20% and <30%, reduce the dose by 7.9 mg twice a day. Re-assess eGFR within two 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 LUPKYNIS. Re-assess eGFR within two weeks; consider re-initiating LUPKYNIS at a lower dose (7.9 mg twice a day) only if eGFR has returned to ≥80% of baseline.
  - For patients that had a decrease in 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.
- Monitor blood pressure every two weeks for the first month after initiating LUPKYNIS, and as clinically indicated thereafter. For patients with BP >165/105 mmHg or with hypertensive emergency, discontinue LUPKYNIS and initiate antihypertensive therapy. (2.3, 5.4)
- If the patient has not experienced therapeutic benefit by 24 weeks, consider discontinuation of LUPKYNIS. (2.3)
- Consider the risks and benefits of LUPKYNIS treatment beyond one year in light of the patient's treatment response and risk of worsening nephrotoxicity. (2.3, 5.3)

Dosage Adjustments:
- Patients with severe renal impairment: the recommended dose is 15.8 mg twice daily. (2.4, 8.6)
- Patients with mild and moderate hepatic impairment: the recommended dose is 15.8 mg twice daily. (2.4, 8.7)

----------DOSAGE FORMS AND STRENGTHS----------
Capsules: 7.9 mg (3)

----------CONTRAINDICATIONS----------
- Patients concomitantly using strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin). (4)
- Known serious or severe hypersensitivity reaction to LUPKYNIS or any of its excipients. (4)

----------WARNINGS AND PRECAUTIONS----------
- Nephrotoxicity (acute and/or chronic): May occur due to LUPKYNIS or concomitant nephrotoxic drugs. Monitor renal function; consider dosage reduction. (5.3)
- Hypertension: May require antihypertensive therapy; monitor relevant drug interactions. (5.4)
- Neurotoxicity: Including risk of posterior reversible encephalopathy syndrome (PRES); monitor for neurologic abnormalities; reduce dosage or discontinue LUPKYNIS. (5.5)
- Hyperkalemia: Risk may be increased with other agents associated with hyperkalemia; monitor serum potassium levels. (5.6)
- QT Prolongation: Consider obtaining electrocardiograms and monitoring electrolytes in patients at high risk. (5.7)
- Immunizations: Avoid live vaccines. (5.8)
- Pure Red Cell Aplasia: Consider discontinuation. (5.9)

----------ADVERSE REACTIONS----------
The most commonly reported adverse reactions (≥3%) were: glomerular filtration rate decreased, hypertension, diarrhea, headache, anemia, cough, urinary tract infection, abdominal pain upper, dyspepsia, alopecia, renal impairment, abdominal pain, mouth ulceration, fatigue, tremor, acute kidney injury, and decreased appetite. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Aurinia Pharmaceuticals at 1-833-672-0028 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Moderate CYP3A4 inhibitors: Reduce LUPKYNIS daily dosage to 15.8 mg in the morning and 7.9 mg in the evening. (2.5, 7.1, 12.3)
- Strong and moderate CYP3A4 inducers: Avoid co-administration. (7.1, 12.3)
- Certain P-gp substrates: Reduce dosage of certain P-gp substrates with a narrow therapeutic window when co-administered with LUPKYNIS. (7.2, 12.3)

----------USE IN SPECIFIC POPULATIONS----------
- Pregnancy: May cause fetal harm. (8.1)
- Lactation: Advise not to breastfeed. (8.2)
- Renal Impairment: Use of LUPKYNIS is not recommended in patients with a baseline eGFR ≤45 mL/min/1.73 m^2 unless the benefit exceeds the risk. If used in patients with severe renal impairment at baseline, LUPKYNIS should be used at a reduced dose. (2.4, 8.6)
- Hepatic Impairment:
  - Mild and moderate hepatic impairment: Dose reduction is required.
  - Severe hepatic impairment: Avoid LUPKYNIS use. (2.4, 8.7)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 01/2021

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SAPHNELO™ safely and effectively. See full prescribing information for SAPHNELO.

SAPHNELO (anifrolumab-fnia) injection, for intravenous use
Initial U.S. Approval: 2021

INDICATIONS AND USAGE

SAPHNELO is a type I interferon (IFN) receptor antagonist indicated for the treatment of adult patients with moderate to severe systemic lupus erythematosus (SLE), who are receiving standard therapy. (1)

Limitations of Use: The efficacy of SAPHNELO has not been evaluated in patients with severe active lupus nephritis or severe active central nervous system lupus. Use of SAPHNELO is not recommended in these situations. (1)

DOSAGE AND ADMINISTRATION

The recommended dosage is 300 mg as an intravenous infusion over a 30-minute period every 4 weeks. For complete dilution and intravenous administration instructions see Full Prescribing Information. (2.1)

DOSAGE FORMS AND STRENGTHS

Injection: 300 mg/2 mL (150 mg/mL) in a single-dose vial. (3)

CONTRAINDICATIONS

SAPHNELO is contraindicated in patients with a history of anaphylaxis with anifrolumab-fnia. (4)

WARNINGS AND PRECAUTIONS

- Serious Infections: Serious and sometimes fatal infections have occurred in patients receiving SAPHNELO. SAPHNELO increases the risk of respiratory infections and herpes zoster. Avoid initiating treatment during an active infection. Consider the individual benefit-risk if using in patients with severe or chronic infections. Consider interrupting therapy with SAPHNELO if patients develop a new infection during treatment. (5.1)
- Hypersensitivity Reactions Including Anaphylaxis: Serious hypersensitivity reactions including anaphylaxis and angioedema have been reported. (5.2)
- Malignancy: Consider the individual benefit-risk in patients with known risk factors for malignancy prior to prescribing SAPHNELO. (5.3)
- Immunization: Avoid use of live or live-attenuated vaccines in patients receiving SAPHNELO. (5.4)
- Not Recommended for Use with Other Biologic Therapies. (5.5)

ADVERSE REACTIONS

Most common adverse drug reactions (incidence ≥5%) are nasopharyngitis, upper respiratory tract infections, bronchitis, infusion related reactions, herpes zoster and cough. (6)

To report SUSPECTED ADVERSE REACTIONS, contact AstraZeneca at 1-800-236-9933 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA approved patient labeling.

Revised: 07/2021

Appendix 5: Key Inclusion Criteria

Population	Patients with SLE, patients with LN
Intervention	Appendix 1
Comparator	Other appendix 1 medications, placebo for new products/indications, standard of care (NSAIDS, antimalarials)
Outcomes	Renal response, disease activity scores, hospitalizations, need for dialysis, quality of life, adverse events
Timing	Not applicable
Setting	Outpatient
Abbreviations: LN= lupus nephritis; NSAIDS=non-steroidal anti-inflammatory drugs; SLE=systemic lupus erythematosus	

Belimumab (Benlysta®)

Goal(s):

- Promote use that is consistent with national clinical practice guidelines and medical evidence.

Length of Authorization:

- 6 months

Requires PA:

- Benlysta® (belimumab) pharmacy or physician administered claims.

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD-10 code.	
2. Is the diagnosis funded by OHP?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by the OHP.
3. Does the patient have severe active central nervous system lupus?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #4
4. Is this a request for continuation of therapy previously approved by fee-for-service (FFS)?	**Yes**: Go to **Renewal Criteria**	**No:** Go to #5

Approval Criteria		
5. Is the patient diagnosed with lupus nephritis or systemic lupus erythematosus (SLE)?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness
6. Is belimumab dosed appropriately and with an approved formulation for patient's age as outlined in Table 1?	**Yes:** Go to # 7	**No:** Pass to RPh. Deny; medical appropriateness
7. Is the patient currently on other targeted immune modulators?	**Yes:** Pass to RPh. Deny; medical appropriateness. Belimumab has not been studied in combination with other targeted immune modulators	**No:** Go to # 8
8. Is the drug being prescribed by or in consultation with a rheumatologist, nephrologist, or a provider with experience treating SLE or lupus nephritis?	**Yes:** Go to # 9	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
9. Does the patient have active autoantibody-positive SLE or lupus nephritis and is a baseline assessment of SLE disease activity available using one of the following functional assessment tools: • SLE Index Score (SIS) • British Isles Lupus Assessment Group (BILAG) • Systemic Lupus Activity Measure (SLAM) • Systemic Lupus Erythematosus Disease Activity Score (SLEDAI or modified versions, e.g. SLEDAI-2K, SELENA-SLEDAI) • Physicians Global Assessment (PGA) • Systemic Lupus International Collaborating Clinic (SLICC) Damage Index • Urinary protein to creatinine ratio • Most recent estimated Glomerular Filtration Rate (eGFR)	**Yes:** Go to # 10. Document baseline assessment _____.	**No:** Pass to RPh. Deny; medical appropriateness
10. Is the patient currently taking or have a contraindication to BOTH of the following: • Hydroxychloroquine • Glucocorticoids (e.g. prednisone)	**Yes:** Go to #11	**No:** Pass to RPh. Deny; medical appropriateness. Belimumab has not been studied as monotherapy in patients with SLE.
11. Does the patient have lupus nephritis AND a urine protein: creatinine ratio of >500 mg/g?	**Yes:** Go to #12	**No:** Approve for 6 months

Approval Criteria		
12. Is the patient currently taking, or have a contraindication to, either an angiotensin-converting enzyme inhibitor (ACEI) OR an angiotensin II receptor blocker (ARB)?	**Yes:** Approve for 6 months	**No:** Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
1. Is the patient currently on another therapeutic immune modulator ? Note: Belimumab has not been studied in combination with other therapeutic immune modulators.	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #2
2. Has the patient's SLE disease activity improved or stabilized as assessed by one of the following functional assessment tools: • SLE Index Score (SIS) • British Isles Lupus Assessment Group (BILAG) • Systemic Lupus Activity Measure (SLAM) • Systemic Lupus Erythematous Disease Activity Score (SLEDAI or modified versions, e.g. SLEDAI-2K, SELENA-SLEDAI) • Physicians Global Assessment (PGA) • Systemic Lupus International Collaborating Clinic (SLICC) Damage Index • Urinary protein to creatinine ratio • eGFR	**Yes:** Approve for 6 months.	**No:** Pass to RPh; Deny; medical appropriateness.

Table 1: FDA approved ages

Indication	Approved formulation	
	Intravenous (IV) powder for solution	**Subcutaneous (SC) Injection**
Systemic Lupus Erythematosus (SLE)	5 years and older	18 years and older
Lupus Nephritis	18 years and older	18 years and older
IV (usual dosage): **SLE or Lupus Nephritis:** 10 mg/kg IV infusion over 1 hour every 2 weeks for the first 3 doses, then every 4 weeks thereafter **SC** (usual dosage): **SLE**: 200 mg SC once weekly **Lupus Nephriti**s:400 mg (two 200-mg injections) SC once weekly into abdomen or thigh for 4 doses, then 200 mg SC once weekly thereafter		

P&T/DUR Review: *02/22 (SF);8/21 (DM) 2/20, 5/18*
Implementation: *4/1/22; 3/1/2020; 7/1/18*

Voclosporin

Goal(s):
- Promote use that is consistent with medical evidence.

Length of Authorization:
- Up to 12 months

Requires PA:
- Voclosporin pharmacy claims

Covered Alternatives:
- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this an FDA approved indication?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the diagnosis funded by OHP?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; not funded by the OHP.
4. Is this a request for continuation of therapy previously approved by fee-for-service (FFS)?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #5
5. Does the patient have Class III, Class IV, or Class V lupus nephritis AND is a baseline assessment with one of the following: • Urinary protein to creatinine ratio • eGFR	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness
6. Is the drug being prescribed by or in consultation with a rheumatologist, nephrologist, or a provider with experience treating lupus nephritis?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness
7. Is the patient currently on cyclophosphamide? Note: Voclosporin safety and efficacy has not been established in combination with cyclophosphamide and use is not recommended.	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #8

Approval Criteria		
8. Is the patient currently taking or have a contraindication to ALL of the following: • Mycophenolate OR Azathioprine • Glucocorticoids (e.g. prednisone) • Hydroxychloroquine	**Yes:** Go to #9	**No:** Pass to RPh. Deny; medical appropriateness
9. Does the patient have proteinuria with a urine protein: creatinine ratio of >500 mg/g?	**Yes:** Go to #10	**No:** Go to #11
10. Is the patient currently taking, or have a contraindication to, either an angiotensin-converting enzyme inhibitor (ACEI) OR an angiotensin II receptor blocker (ARB)?	**Yes:** Go to #11	**No:** Pass to RPh. Deny; medical appropriateness.
11. Is the patient of childbearing potential?	**Yes:** Go to #12	**No:** Approve for 6 months
12. Is the patient pregnant or actively trying to conceive?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #13
13. Is there documentation that the provider and patient have discussed the teratogenic risks of the drug if the patient were to become pregnant?	**Yes:** Approve for 6 months	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Does the patient have an eGFR within past 60 days? Note: Should be monitored monthly per package labeling.	**Yes:** Go to #2 Record eGFR value & date _____	**No:** Pass to RPh. Deny; medical appropriateness
2. Has the voclosporin dose been adjusted appropriately based on baseline eGFR and current eGFR? • If eGFR <60 mL/min/1.73 m2 and reduced from baseline by >20% and <30%, reduce the dose by 7.9 mg twice a day. Reassess eGFR within two 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 m2 and reduced from baseline by ≥30%, discontinue LUPKYNIS. Re-assess eGFR within two weeks; consider re-initiating LUPKYNIS at a lower dose (7.9 mg twice a day) only if eGFR has returned to ≥80% of baseline. • For patients that had a decrease in 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.	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Has the patient's lupus nephritis improved or stabilized as assessed by one of the following: • Urinary protein to creatinine ratio • eGFR	**Yes:** Approve for 12 months.	**No:** Pass to RPh; Deny; medical appropriateness.

Anifrolumab-fnia

Goal(s):

- Promote use that is consistent with medical evidence.

Length of Authorization:

- Up to 6 months

Requires PA:

- Anifrolumab-fnia physician administered and pharmacy claims

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD-10 code.	
2. Is this an FDA approved indication?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the diagnosis funded by OHP?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; not funded by the OHP.
4. Does the patient have severe active central nervous system lupus or severe, active lupus nephritis?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #5
5. Is this a request for continuation of therapy previously approved by fee-for-service (FFS)?	**Yes**: Go to **Renewal Criteria**	**No:** Go to #6
6. Is the patient currently on other biologic therapy?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to # 7

Approval Criteria		
7. Is the drug being prescribed by or in consultation with a rheumatologist, nephrologist, or a provider with experience treating SLE?	**Yes:** Go to # 8	**No:** Pass to RPh. Deny; medical appropriateness
8. Does the patient have a baseline assessment of SLE disease activity available using one of the following functional assessment tools: • SLE Index Score (SIS) • British Isles Lupus Assessment Group (BILAG) • Systemic Lupus Activity Measure (SLAM) • Systemic Lupus Erythematosus Disease Activity Score (SLEDAI or modified versions, e.g. SLEDAI-2K, SELENA-SLEDAI) • Physicians Global Assessment (PGA) • Systemic Lupus International Collaborating Clinic (SLICC) Damage Index	**Yes:** Go to # 9. Document baseline assessment _____.	**No:** Pass to RPh. Deny; medical appropriateness
9. Is the patient currently taking ALL of the following or have a documented contraindication: • Hydroxychloroquine • Glucocorticoids (e.g. prednisone) • Methotrexate OR Azathioprine OR Mycophenolate	**Yes:** Approve for 6 months.	**No:** Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
1. Is the patient currently on other biologic therapy?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #2

Renewal Criteria		
2. Has the patient's SLE disease activity improved or stabilized as assessed by one of the following functional assessment tools: • SLE Index Score (SIS) • British Isles Lupus Assessment Group (BILAG) • Systemic Lupus Activity Measure (SLAM) • Systemic Lupus Erythematous Disease Activity Score (SLEDAI or modified versions, e.g. SLEDAI-2K, SELENA-SLEDAI) • Physicians Global Assessment (PGA) • Systemic Lupus International Collaborating Clinic (SLICC) Damage Index	**Yes:** Approve for 6 months.	**No:** Pass to RPh; Deny; medical appropriateness.

P&T/DUR Review: 2/22 (SF)
Implementation: 4/1/22