Anifrolumab-fnia (SAPHNELO) in Systemic Lupus Erythematosus (SLE) National Drug Monograph January 2022

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA Approval Information

Description / Mechanism of Action

- Anifrolumab-fnia is a human IgG1κ monoclonal antibody to the type I interferon (IFN)-α receptor subunit 1 (IFNAR1).[1] As an IFNAR1 antagonist, it inhibits signaling by all type I IFNs, blocks type I IFN activity, and affects a range of immune cells.[2]
- About 60% to 80% of adults with active systemic lupus erythematosus (SLE) express increased concentrations of type I IFN inducible genes.[1]
- Anifrolumab-fnia is the second drug approved for SLE (after belimumab).

Indication(s) Under Review in This Document

- Treatment of adults with moderate to severe SLE who are receiving standard therapy.
- Limitations of Use: The efficacy of anifrolumab-fnia has not been evaluated in patients with severe active lupus nephritis or severe active central nervous system lupus. Anifrolumab-fnia is not recommended in these situations.

Dosage Regimen and Dosage Form(s) Under Review

- 300 mg IV every 4 weeks
- Injection: 300 mg/2 mL (150 mg/mL) in a single-dose vial

Clinical Evidence Summary

Efficacy Considerations

- The first phase 3, placebo-controlled randomized clinical trial (RCT) of anifrolumab-fnia in moderate to severe SLE (Treatment of Uncontrolled Lupus via the Interferon Pathway-1, TULIP-1 trial) failed to show a significant benefit in the primary outcome measure, the SLE Responder Index of ≥ 4 (SRI-4) (anifrolumab-fnia 36% vs placebo 40%).[3] Several secondary outcome measures suggested a potential treatment benefit; however, they were not formally tested statistically because the primary endpoint was not met. The SRI-4 was selected as the primary outcome measure because it had been used and supported efficacy in belimumab clinical trials.[3]

- A second phase 3 RCT (TULIP-2) used a different primary outcome measure and revised restricted medication rules after the negative TULIP-1 SRI-4 results were partially attributed to unintended and clinically inappropriate misclassification of patients with new or increased use of nonsteroidal antiinflammatory drugs as nonresponders (about 8% of the study population). Prior to unblinding of trial data and after completion of TULIP-1, the study protocol was amended to modify the restricted medications rules and to change the primary outcome measure from SRI-4 to the Week-52 British Isles Lupus Assessment Group (BILAG)-based Composite Lupus Assessment (BICLA) response rate, which was originally a secondary outcome measure and showed numerically better response rates with anifrolumab-fnia (vs placebo) using the revised restricted medication rules in post hoc analyses of the TULIP-1 data.[5] Both BICLA and SRI-4 are considered clinically meaningful end points for assessing treatment effects in SLE.[3] (See outcome definitions in Box 1.) TULIP-2 results showed a significant benefit with anifrolumab-fnia in BICLA response.[4]
- Results of a phase 2b RCT (MUSE / CD1013 trial)[5] and a 3-year open-label extension study[6] of MUSE supported the phase 3 RCTs. The MUSE RCT showed that anifrolumab-fnia achieved a higher SRI-4 response at Week 24 than placebo (34% vs 18%; OR [90% CL] 2.4 [1.3, 4.3]); however, these results were considered nominally significant because the trial was designed for only proof of concept, and multiplicity was not controlled.[3]
- A post hoc analysis of MUSE data showed that the Lupus Low Disease activity State (LLDAS) was a clinically meaningful outcome measure and discriminated between anifrolumab-fnia and placebo.[7]

Box 1 Outcome Definitions

SLE Responder Index of 4 (SRI-4) response requires all of the following:

- A reduction from baseline of ≥ 4 points in the SLE Disease Activity Index-2000 (SLEDAI-2K)
- < 1 new BILAG-2004 A (severe) or < 2 new BILAG-2004 B (moderately severe) organ domain disease activity scores
- < 0.3-point increase in Physician's Global Assessment (PGA) from baseline
- No use of restricted medications exceeding protocolled thresholds
- No discontinuation of study treatment[1]

BILAG-based Composite Lupus Assessment (BICLA) response requires all of the following:

- Reduction of all severe (BILAG-2004 A) or moderately severe (BILAG-2004 B) disease activity at baseline to lower levels
- No worsening in other organ systems, where worsening was defined as ≥ 1 new BILAG-2004 A item or ≥ 2 new BILAG-2004 B items
- No increase from baseline on the SLEDAI-2K score
- No increase of ≥ 0.3 points from baseline on PGA
- No discontinuation of study treatment
- No use of restricted medications beyond protocolled thresholds

The **British Isles Lupus Assessment Group (BILAG)**-2004 score ranges from A / Severe to E / Never Involved for each of nine organ systems assessed.

- Ongoing trials include a phase 3 TULIP SLE long-term extension trial and a phase 3 trial of subcutaneous anifrolumab-fnia in SLE.

TULIP-1 and TULIP-2 Phase 3 RCTs

Methods

- See Appendix A.

Patient Characteristics

- Across the MUSE, TULIP-1, and TULIP-2 RCTs, patients had multi-organ involvement at baseline, most commonly mucocutaneous, musculoskeletal, and immunologic. Across the anifrolumab 300 mg and placebo treatment groups,

- 95% to 100% of patients had active skin disease (CLASI activity score > 0) with 22.0% to 32.2% of patients having moderate to severe skin disease.
- 93% to 98% of patients had active joint disease, with median swollen joint counts of 5.0 to 7.0 and median tender joint counts of 7.0 to 11.0.
- 74.5% to 83.3% of patients were classified as type I IFN gene signature test high.

- The baseline demographic and clinical characteristics of patients in the phase 3 RCTs are shown in Table 1.

Table 1 Patient Characteristics at Baseline

Characteristic	TULIP-1	TULIP-2
N	457	362
Age, mean (y)	41	42
Male (%)	8	7
Race: White / Black / Asian (%)	71 / 15 / 6	60 / 11 / 17
Country: US or Canada (%)	41	36
Time from initial SLE diagnosis, median (mos)	85	86
Physicians Global Assessment score, mean	1.8	1.7
High type IFN gene signature (%)	82	83
Baseline treatment for SLE		
Glucocorticoid (%)	83	80
Antimalarial (%)	75	70
Immunosuppressant† (%)	48	48

† Immunosuppressants included azathioprine, methotrexate, and mycophenolate in TULIP-1 and TULIP-2. TULIP-2 also included mizoribine.

Results

- Efficacy data are summarized in Table 2 and Table 3.

Table 2 Efficacy results from phase 3 clinical trials

Outcome	Time (Wk)	TULIP Trial	ANI-fnia 300	PBO	Relative Risk (95% CL)	NNT (95% CL)
Primary Outcome Measure						
SRI-4[†], n/N (%)	52	1	65/180 (36)	74/184 (40)	0.9 (0.7, 1.2)	25 (NSD)
BICLA Response, n/N (%)	52	2	86/180 (47.8)	57/182 (31.5)	2.5 (1.2, 2.0)	7 (4, 16)
Selected Key Secondary Outcome Measures						
Sustained GC reduction to target dose‡ (exploratory[§]), n/N (%)	40 to 52	1	42/103 (40.8)	33/102 (32.4)	1.3 (0.9, 1.8)	—
Sustained GC reduction to target dose,[‡] n/N (%)	40 to 52	2	45/87 (51.5)	25/83 (30.2)	1.7 (1.2, 2.5)	5 (3, 14)
Other Secondary Outcome Measures						
BICLA response (exploratory[§])	52	1	67/180 (37.2)	49/184 (26.6)	1.4 (1.0, 1.9)	10 (5, 93)
SRI-4, n/N (%)	52	2	100/180 (55.5)	68/182 (37.3)	1.5 (1.2, 1.9)	6 (4, 13)

Sources: Morand (2020),[4] AMCP Dossier[2]; FDA Multi-discipline Review[3]

BICLA, British Isles Lupus Assessment Group (BILAG)-based Composite Lupus Assessment; **CFB**, Change from baseline; **GC**, Glucocorticoid; **Q**, GRADE quality of evidence; **SRI-4**, SLE Response Index of ≥ 4

† Prespecified analysis results. After amendment of the protocol to reclassify patients who had new or increased NSAID use from nonresponders to responders, the post hoc SRI-4 analysis with amended rules for restricted medications showed anifrolumab-fnia 84/180 (47%) vs placebo 79/184 (43%) with nonsignificant nominal p-value.

‡ Target dose was ≤ 7.5 mg daily of prednisone or equivalent

§ All secondary outcomes in TULIP-1 were exploratory and inconclusive with nominal p-values because the primary endpoint was not met.

Table 3 Anticipated absolute effects based on pooled phase 3 RCT results (TULIP-1 and TULIP-2)

Outcome	ANI-fnia 300	PBO	Relative Risk (95% CL)	Absolute Risk Difference per 1,000 patients (95% CL)	Q
BICLA Response, n/N (%)	153/360 (42.5)	106/366 (29.0)	1.5 (1.2, 1.8)	145 (58, 232) more	H
Sustained GC reduction to target dose, n/N (%)	87/190 (45.8)	58/185 (31.4)	1.5 (1.1, 1.9)	157 (31, 282) more	M[α]
SRI-4, n/N (%)	165/360 (45.8)	142/366 (38.8)	1.2 (1.0, 1.4)	78 more (0 fewer to 155 more)	M[α]

[α] Downgraded for inconsistency between trials.

- Other secondary efficacy results are briefly summarized in Table 4. All secondary outcomes in TULIP-1 were exploratory and inconclusive with nominal p-values because the primary endpoint was not met.

Table 4 Summary of secondary outcome results for anifrolumab-fnia vs placebo

Outcome	TULIP-1	TULIP-2
SRI-4 response		
At Wk 24	Numerically similar†	—
Subgroup with high IFN gene signature	Numerically worse	—
Subgroup with low IFN gene signature	—	—
BICLA response		
Subgroup with high IFN gene signature	—	Significantly better
Subgroup with low IFN gene signature	—	Nonsignificantly better
CFB in PGA at Wk 52	Numerically better	—
CLASI-50 response at Wk 12	Numerically better	Significantly better
STJ-50 at Wk 52	Numerically better	Nonsignificantly better
Annualized flare rate through Wk 52	Numerically better	Nonsignificantly better

† Treatment difference was ≤ 1.0 percentage points.

BICLA, BILAG-based Composite Lupus Assessment; **CFB**, Change from baseline; **CLASI-50**, At least 50% reduction in the cutaneous lupus erythematosus disease area and severity index; **PGA**, Physicians Global Assessment measured on a visual analogue scale (range from 0 / No Disease Activity to 3 / Severe Disease); **SRI-4**, SLE Response Index of ≥ 4; **STJ-50**, At least 50% reduction in the swollen and tender joint count

- Prevention of Flares: Post Hoc Analysis of Pooled Data from TULIP-1 and TULIP-2
  - A flare was defined as either ≥ 1 new BILAR-2004 A or ≥ 2 new BILAG-2004 B domain scores relative to the prior visit.
  - Anifrolumab-fnia 300 mg was superior to placebo in reducing annualized flare rates through Week 52 (0.51 [95% CL 0.41, 0.62] vs 0.67 [0.55, 0.82]; rate ratio 0.75 [95% CL 0.60, 0.96]).[8] However, there was inconsistency in this outcome measure between TULIP-1 (rate ratio 0.83 [0.61, 1.15]; nonsignificant nominal p-value) and TULIP-2 (0.67 [0.48, 0.94]; nominal p-value 0.020).
  - Anifrolumab-fnia was also better than placebo in
    - total number of flares (132 vs 198, respectively);

        - median time to first flare (140 days, range 24–376 vs 119 days, range 21–370 days, respectively; hazard ratio 0.70 [95% CL 0.55, 0.89]; and
        - percentage of flare-free patients (66.5% vs 57.1%, respectively).[8]

- Subgroup Analyses by Biologic Experience
    - In a post hoc pooled analysis of TULIP-1 and TULIP-2 data reported only as a conference presentation, anifrolumab-fnia was shown to be efficacious regardless of whether patients were biologic experienced or biologic-naive.[9] The most common prior biologics used that are available in the US were belimumab (n = 70) and rituximab (n = 14). Other common biologics were epratuzumab (n = 49) and tabalumab (n = 18).
- The FDA did not perform pooled analyses of efficacy data.[3]
- Gaps in outcome measures
    - Remission
    - Survival / Mortality
    - Hospitalization or readmission
    - Health-related Quality of Life
    - Functional ability / Disability
    - Patient Satisfaction

Network Meta-analyses (Indirect Comparative Efficacy)

- No network meta-analyses involving anifrolumab were found.
- A meta-analysis of 9 RCTs evaluating type I IFN inhibitor monoclonal antibodies in the treatment of adults with SLE did not indirectly compare anifrolumab with other IFN inhibitors (not available in the US).
    - In the analysis of the phase 2 and phase 3 trials of anifrolumab (MUSE, TULIP-1, and TULIP-2), anifrolumab was superior to placebo in achieving SRI-4 (235/459 [51.2%] vs 173/468 [37.0%]; OR [95% CL] 1.91 [1.11, 3.28] and in achieving BICLA response (222/459 [48.4%] vs 137/467 [29.3%]; OR 2.25 [1.72, 2.95]).[10]

Safety Considerations

- **Boxed Warnings**: None.
- **Contraindications**: History of anaphylaxis to anifrolumab-fnia.
- **Other Warnings / Precautions**:
    - Serious infections including disseminated herpes zoster.
    - Hypersensitivity reactions including anaphylaxis and infusion-related reactions. Consider pre-medication before infusions for patients with a history of these reactions.
    - Malignancy: Immunosuppressants increase the risk of malignancies. Risk of developing malignancy on anifrolumab-fnia is unknown.
    - Immunization: Update immunizations prior to initiating therapy. Avoid live or live attenuated vaccines during anifrolumab-fnia therapy.
    - Not recommended for concomitant use with other biologic therapies.
- **Deaths and Serious Adverse Events** (anifrolumab-fnia vs placebo, respectively):
    - Fatal infections: 0.4% vs 0.2% to Week 52.[3] Beyond 52 weeks, fatal infections occurred in 7 anifrolumab-fnia patients vs no placebo patients.[3]
    - Serious infections: 4.8% vs 5.6% (corresponding to 5.4 vs 6.6 per 100 patient-years [PY]).[3]

- **Withdrawals Due to Adverse Events (WDAEs)**: In pooled data from MUSE, TULIP-1, and TULIP-2, WDAEs were similar between anifrolumab-fnia and placebo (19/459 [4.1%] vs 24/466 [5.2%], respectively), corresponding to 4.5 vs 6.0 per 100 PY.
- **Common Adverse Events (≥ 5%)**: Nasopharyngitis, upper respiratory tract infections, bronchitis, infusion related reactions, herpes zoster, and cough.
- **Adverse Events of Special Interest**
    - **Infections / Herpes zoster / Tuberculosis (TB)**. Infections that occurred more often on anifrolumab-fnia than placebo included nasopharyngitis (16.3% vs 9.4%, respectively), upper respiratory infection (15.5% vs 9.7%), bronchitis (9.8% vs 4.3%), herpes zoster (6.1% vs 1.3%), influenza (2.6% vs 1.9%) and latent TB (0.9% vs 0.2%).[3] The exposure-adjusted incidence rate risk difference for herpes zoster was 5.4 (95% CL 2.8, 8.4).[11]
        - There were no cases of active TB. (Study entry criteria required no evidence of active TB or latent TB and no untreated latent TB.)
        - Opportunistic infections developed in 2 patients on anifrolumab-fnia (mycobacterium avium complex and ophthalmic herpes simplex) and 3 placebo patients (oropharyngeal candidiasis, cryptococcal meningitis, and respiratory moniliasis).
        - There was no mention of development or reactivation of viral hepatitis (e.g., hepatitis B or C) in the FDA review, trial publications, and prescribing information. However, patients positive for hepatitis B or C or HIV were excluded from the trials.
    - **Anaphylaxis**. One patient developed anaphylaxis after Dose 2 of anifrolumab-fnia 150 mg IV.[3]
    - **Malignancy**. The risk of malignancy was similar between anifrolumab-fnia and placebo: 6 patients (1.3%; 1.3 per 100 PY) vs 3 patients (0.6%; 0.7 per 100 PY), respectively.[3]
    - **Non-SLE Vasculitis**. No cases of non-SLE vasculitis were observed in patients.[3] (Focal arteritis had been noted in a nonclinical study.)
    - **Major Acute Cardiovascular Events (MACE).** One anifrolumab-fnia patient vs 3 placebo patients.[3]
- **Safety signals** suggested potential increased risk of the following adverse events[3]:
    - Herpes zoster when anifrolumab-fnia is used with immunosuppressive therapies.
    - Pneumonia with concomitant use of glucocorticoids
    - Fatal infections
    - Nervous system disorders
    - Chemistry abnormalities (e.g., increased serum glucose and gamma glutamyl transferase)

Drug-Drug Interactions

- No formal drug interaction studies were conducted.[1]
- The pharmacokinetics of anifrolumab-fnia were not affected by concomitant use of oral glucocorticoids, antimalarials, immunosuppressants (azathioprine, methotrexate, mycophenolate mofetil, mycophenolic acid, and mizoribine), NSAIDs, ACE inhibitors, and HMG-CoA reductase inhibitors.[1]

Other Considerations

- **Renal Impairment**: Anifrolumab-fnia is not cleared renally. SLE clinical trials did not include patients with severe renal impairment or end stage renal disease (< 30 mL/min/1.73 m^2) and patients with urine protein-to-creatinine ratio (UPCR) > 2 mg/mg. Population pharmacokinetic analyses showed that increased UPCR did not significantly affect anifrolumab-fnia clearance.
- **Hepatic Impairment**: Anifrolumab-fnia clearance is not expected to be affected by changes in hepatic function.

- **Antidrug Antibodies**: Antidrug antibodies were detected in 25 anifrolumab-fnia patients vs 35 placebo patients. There was no apparent evidence of correlation with adverse events including hypersensitivity or anaphylaxis; however, data is insufficient to draw conclusions about the clinical impact of antidrug antibodies.

Other Therapeutic Options

- Standard therapy for SLE consists of an antimalarial (e.g., hydroxychloroquine) and glucocorticoids with or without conventional synthetic immunomodulators or immunosuppressives such as azathioprine, methotrexate, or mycophenolate. An antimalarial, typically hydroxychloroquine, is indicated in all patients with SLE regardless of extent or degree of disease activity.

Standard Therapy for SLE		
Glucocorticoids	**Antimalarials**	**Immunosuppressives**
Methylprednisolone Prednisone Others	Chloroquine Hydroxychloroquine	Azathioprine Methotrexate Mycophenolate

- In severe or life-threatening SLE (e.g., renal or central nervous system involvement), a short course (pulse) of high-dose glucocorticoids may be needed to induce clinical control and prevent tissue injury.
- For maintenance therapy, discontinuation or tapering of glucocorticoids to the lowest possible dose (≤ 7.5 mg/d of prednisone or equivalent) should be a goal of therapy.[13]
- Targeted immunomodulators can be added for patients with an inadequate response to standard therapy.
- NSAIDs may be used in combination with conventional immunosuppressants and targeted immunomodulators.
- Alternative non-glucocorticoid treatments for moderate to severe SLE are summarized in Table 5.

Table 5 Non-glucocorticoid Immunomodulatory Treatments for Nonrenal SLE

Drug / Dose	Formulary	FDA-approved SLE-related Indications	Place in Therapy	Safety Considerations	Other Considerations
Type 1 Interferon Receptor Antagonist					
Anifrolumab-fnia (ANI) 300 mg IV every 4 wks No dosage adjustment recommendations for renal or hepatic impairment.	TBD	Moderate to severe SLE; added to standard tx. Not recommended in patients with severe active NPSLE or severe active LN.	Uncertain. May prevent flares; is GC sparing.	WP: Hypersensitivity reactions, infections, infusion reactions, malignancy.	Not indirectly differentiable from BEL in SRI-4 response. Indirectly better than BEL in GC sparing effects. Unlike BEL, ANI is not approved for active LN.
Antigen Processing Inhibitor[12]					
Hydroxychloroquine (HCQ) ≤ 5 mg/kg TBW/d, usually 300–400 mg/d. Consider tapering to 200 mg/d for pts in remission.	Yes (tab)	Treatment of chronic discoid erythematosus and SLE in adults.	1st-line tx. Recommended for all pts with SLE of any degree and type of disease activity.[13,14]	Retinopathy. Routine eye exams should be done at baseline and every 3 mos. May be used during pregnancy. WP: QT prolongation, TdP,	Multiple benefits and well tolerated. May reduce flares, thrombotic events, organ damage, and

Drug / Dose	Formulary	FDA-approved SLE-related Indications	Place in Therapy	Safety Considerations	Other Considerations
Adjust dosage in CKD and hepatic impairment.				cardiomyopathy, severe hypoglycemia, CNS effects including seizures, cytopenias. Use caution in pts with G6PD deficiency.	mortality.[13,14] Efficacy established with dose of 6.5 mg/kg/d. Efficacy of the recommended lower dose is unproven.
Purine Synthesis Inhibitor					
Azathioprine (AZP) 2–3 mg/kg/d in 2–3 divided doses. Consider tapering to < 2 mg/d for pts in remission. Adjust dosage in CKD.	Yes (inj, tab)	Off label	Consider as add-on tx in pts with mild SLE refractory to HCQ ± GC, 1st-line tx of moderate SLE.[13,15] Prevents flares, is GC sparing.[13,15]	Compatible with pregnancy at doses ≤ 2 mg/kg/d.[16] WP: GI toxicity; myelotoxicity, hepatotoxicity, infections, malignancy. Consider testing for TPMT or NUDT15 deficiency (myelotoxicity).	Recommended for maintenance tx of LN.
Dihydrofolate Reductase Inhibitor					
Methotrexate (MTX) 10–25 mg/wk in 1–2 doses. Adjust dosage in CKD.	Yes (inj, tab) Oral soln is NonF.	Off label	Consider as add-on tx in pts with mild SLE refractory to HCQ ± GC or 1st-line tx of moderate SLE.[13,15] Prevents flares, is GC sparing.[13,15]	BW: Multiple issues including secondary malignancy, infections, myelotoxicity, pneumonitis, hepatotoxicity, GI toxicity. CI: Pregnancy,[16] alcohol use disorder, alcoholic liver disease or other chronic liver disease, immunodeficiency syndromes, preexisting blood dyscrasias. WP: Include DDIs with NSAIDs, PPIs, vaccines, folate.	Has stronger evidence than AZP.[15]
Inosine Monophosphate Dehydrogenase Inhibitor					
Mycophenolate Mofetil (MMF) Severe SLE or initial tx in LN: 3 g/d in 2 divided doses. Mild–moderate SLE or	Yes (cap, inj, tab) Oral susp is NonF.	Off label	Consider for 1st-line tx of moderate or severe SLE or as add-on tx for refractory moderate SLE.[13] Prevents flares, is	Teratogenic BW: Infections, lymphoma and skin malignancy CI: Pregnancy.[16] Pts allergic to	Also used for refractory SLE skin disease and maintenance tx of hematologic SLE. Recommended

Drug / Dose	Formulary	FDA-approved SLE-related Indications	Place in Therapy	Safety Considerations	Other Considerations
continuation tx in LN: 1–2 g/d in 2 divided doses. Adjust dosage in CKD.			GC sparing.[13,15]	polysorbate 80 (Tween). WP: Viral reactivation / infections, neutropenia, PRCA.	as initial and maintenance tx for LN.
Mycophenolate Sodium (MPS) For LN: Initiate tx with 720 mg twice daily for ~6 mos, then maintain response with 360 mg twice daily.[17] Adjust dosage in CKD. Doses not equivalent to MMF doses.	Yes (tab, EC)	Off label	Consider for pts intolerant to MMF.[15]	BW: Same as for MMF. CI: Pregnancy.[16] WP: Same as for MMF.	EC MPS was better than AZP in achieving remission and reducing flares.[18]
Regulatory T-cell Inhibitor (low doses)					
Cyclophosphamide (CYC) Severe SLE: 0.75–1 g/m^2 BSA IV once monthly for 6 mos (NIH regimen). Initial tx in LN: 500 mg IV at Wks 0, 2, 4, 6, 8 and 10 (Euro-Lupus regimen). Adjust dosage in CKD and hepatic impairment.	Yes (cap, inj) Tab is NonF.	Off label	Consider as 1st-line tx for severe SLE including NPSLE, severe SLE refractory to ISTs, or as rescue therapy for non-severe disease refractory to standard ISTs.[13,15] Prevents flares, is GC sparing.[13,15]	CI: Pregnancy[16] WP: Myelotoxicity, cardiotoxicity, hepatotoxicity, hyponatremia, infections, pulmonary toxicity, secondary malignancies, urinary / renal toxicity (hemorrhagic cystitis). Gonadotoxic.	Recommended in low doses for initial and maintenance tx of LN. May be considered for pts at high risk for renal failure.
B-lymphocyte Stimulator Inhibitor					
Belimumab (BEL) IV: 10 mg/kg on Wks 0, 2, 4, then q4wks. SC: 200 mg once weekly. No dosage adjustment in CKD.	No (lyphl inj and soln inj) No CFU; 2012 NDM PIT.	Treatment of adults with active, autoantibody-positive SLE who are receiving standard therapy. Treatment of adults with active LN who are receiving standard therapy.	Consider as add-on tx for extrarenal moderate or severe SLE inadequately responding to HCQ + GC + standard IST.[13,15] Prevents flares,[15] reduces cumulative GC dosage.[19]	WP: Hypersensitivity / infusion reactions, serious and fatal infections, malignancy, PML, psychiatric events (including depression and suicide ideation and behavior). Pregnancy: Use selectively with caution, weighing risk-benefits. Some dosage forms contain polysorbate 80, which may cause hypersensitivity	NNT (95% CL) for SRI-4 response at Wk 52: 8 (5, 17) with SC inj[20]; 8 (5, 17) and 11 (6, 60) with IV.[21,22] Black patients had lower response rates. Unlike ANI-fnia, (1) BEL did not significantly improve the percentage of pts able to taper GC to ≤ 7.5 mg/d[20,21,22]; and (2) BEL is approved for

Drug / Dose	Formulary	FDA-approved SLE-related Indications	Place in Therapy	Safety Considerations	Other Considerations
		Not recommended in severe active CNS SLE or in combination with other biologics.		reactions.	active LN.
Calcineurin Inhibitors					
Cyclosporine (CSA) 1–3 mg/kg/d or 100–400 mg/d in 2 divided doses. Avoid in CKD.	Yes (cap, oral soln)	Off label	Consider as 1st-line tx for moderate SLE or as add-on to HCQ + GC + BEL for refractory moderate SLE[13]; for moderate or severe SLE.[15] GC sparing.[15] May also be used for cytopenias and to prevent flares.[13,15]	CI: Renal impairment, uncontrolled HTN, malignancies, co-use with MTX or other IS txs. WP: See TAC. Pregnancy: Weigh risk-benefits.[16]	May be considered for LN.13 2 open-label RCTs.
Tacrolimus (TAC) 0.05–0.1 mg/kg/d or 2–4 mg/d in 2 divided doses. Titrate to target blood concentration 12 h post-dose of 4–6 ng/mL. Adjust dosage in CKD.	Yes (cap, inj) SA Cap and oral granules for susp are NonF.	Off label	Consider as 1st-line tx for moderate SLE or as add-on to HCQ + GC + BEL for refractory moderate SLE[13]; for moderate or severe SLE.[15] GC sparing.[15]	WP include QT prolongation, TdP, HTN, hyperkalemia, infections, malignancy, nephrotoxicity, neurotoxicity. Pregnancy: Selective use allowable.[16]	May be considered for LN.[13] No RCTs for nonrenal SLE.
B-Lymphocyte CD20 Inhibitor					
RiTUXimab (RTX) / Biosimilar 1 g IV on Days 1 and 15 (1 cycle); repeat cycle every 6 mos or on demand. No dosage adjustment in CKD.	Yes (rituximab-pvvr inj)	Off-label	Can be considered for severe renal or extrarenal (mainly hematologic or neuropsychiatric) SLE refractory to generally ≥ 2 standard ISTs and/or BEL.[13] Can be considered for refractory moderate SLE.[15]	WP include bowel obstruction / perforation, CV effects, cytopenias, HBV reactivation, infections, infusion-related reactions, mucocutaneous reactions. Pregnancy: Use selectively with caution, weighing risk-benefits.[16]	Role is uncertain. RCTs have shown no significant benefits.[13]

Sources: FDA Multi-discipline Review,[3] UpToDate[14,16]
Severe SLE refers to organ-threatening disease activity.
BW, Boxed Warning; **CI**, Contraindications; **CV**, Cardiovascular; **EC**, Enteric coated; **GC**, Glucocorticoid; **HBV**, Hepatitis B virus; **IST**, Immunosuppressive therapy (e.g., azathioprine, hydroxychloroquine, methotrexate, mycophenolate); **LN**, Lupus nephritis; **Lyphl**, Lyophilized; **NDM**, National drug monograph; **NPSLE**, Neuropsychiatric systemic lupus erythematosus; **NUDT15**, Nudix hydrolase 15; **PIT**, Place in therapy; **PRCA**, Pure red cell aplasia; **SA**, Sustained action (extended release); **Soln**, Solution; **Susp**, Suspension; **TdP**, Torsades de pointes; **TPMT**, Thiopurine S-methyltransferase; **WP**, Warnings and Precautions

Projected Place in Therapy

- **Epidemiology and Prevalence of SLE**. SLE is a chronic, potentially fatal, multisystem, immune-mediated disorder with multifactorial causes that develops in patients mainly aged 16 to 55 years. The prevalence of SLE is 20 to 150 cases per 100,000 in the US and is higher in women than men, and in Asians, African Americans, African Caribbeans, and Hispanic Americans than White people.[23] Incidence rates have been estimated to range from 1 to 25 per 100,000 in North American, South America, Europe, and Asia.[23]
- **Place in Therapy Based on Medical Society Guidelines**. No recent society guidelines on the management of SLE include anifrolumab-fnia.
- **Potential Place in Therapy Based on the Evidence**. Anifrolumab-fnia added on to standard therapy was superior to standard therapy in improving composite clinical end points in patients with moderate to severe, seropositive SLE. Standard therapy was comprised of one or any combination of oral glucocorticoid, antimalarial, and/or conventional synthetic immunosuppressant (azathioprine, mycophenolate, or methotrexate). There was high certainty evidence that anifrolumab-fnia added to standard therapy produced a small but clinically meaningful improvement in BICLA response over standard therapy (plus placebo). In addition, there was moderate certainty evidence that anifrolumab-fnia has a glucocorticoid sparing effect. In post hoc analyses of pooled data from the phase 3 RCTs, anifrolumab-fnia also reduced flares vs placebo. Anifrolumab-fnia monotherapy was not evaluated. The comparative efficacy and safety of adjunctive anifrolumab-fnia relative to other biologics in the treatment of SLE is uncertain because there have been no active-controlled trials. The efficacy and safety of anifrolumab-fnia in patients on concomitant cyclophosphamide or other biologics (e.g., rituximab or belimumab) or patients with severe lupus nephritis or central nervous system disease were not evaluated and use of anifrolumab-fnia in these situations is not recommended. There is no reported information about concomitant use of calcineurin inhibitors (e.g., tacrolimus, cyclosporine). There is insufficient evidence of the relative safety and efficacy of anifrolumab-fnia in males, patients ≥ 65 years of age, and non-White patients. The FDA reviewer stated that a high suspicion of TB and planned monitoring for active and latent TB should be considered, particularly in SLE patients from endemic countries and with high cumulative exposure to glucocorticoids.[3]
- **Potential Place in Therapy in VHA**. Adjunctive anifrolumab-fnia therapy may be useful for improving global, skin, and joint symptoms, glucocorticoid-sparing effects, and reducing flares in patients with active, moderate to severe SLE despite standard therapy, excluding patients who have severe lupus nephritis or central nervous system disease. Patients treated with anifrolumab-fnia should not take cyclophosphamide or targeted biologic or synthetic immunomodulators concomitantly. Relative to belimumab, anifrolumab-fnia has less clinical experience, is less preferable in patients with active lupus nephritis, and lacks the convenience of at-home subcutaneous administration, but may be more preferable for tapering glucocorticoids to ≤ 7.5 mg/d prednisone equivalent. Before starting anifrolumab-fnia therapy, update vaccinations; avoid live vaccines during therapy. Although the prescribing information does not recommend pretreatment screening for hepatitis B and C, HIV, or TB, anifrolumab-fnia has not been studied in patients who tested positive for these infections. Patients should be under the care of a VA or VA Community Care rheumatologist or locally designated SLE expert.

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Appendix A. TULIP-1 and TULIP-2 Trial Methods

Method Category	TULIP-1	TULIP-2
Study Design	52-week, multinational, multicenter, double-blind, placebo-controlled RCT. Randomization was stratified by SLE Disease Activity Index 2000 (SLEDAI-2K, < 10 points vs ≥ 10 points); oral glucocorticoid dose (< 10 mg/d vs ≥ 10 mg/d prednisone or equivalent), and type 1 IFN test results (high vs low). At Week 52, patients could either enroll in the long-term extension study (anifrolumab-fnia 300 mg every 4 weeks) or continue in the current study for another 8 weeks to complete a 12-week safety follow-up after the last dose of investigational treatment at Week 48.	Same as TULIP-1.
Key Inclusion Criteria	Adults 18–70 years old who met the American College of Rheumatology classification criteria for SLE with diagnosis for ≥ 24 weeks. Moderate to severe SLE as measured by a score of ≥ 6 on the SLEDAI-2K (score range 0–105) and a score ≥ 4 on the clinical SLEDAI-2K. Either severe disease activity in ≥ 1 organ or moderate activity in ≥ 2 organs as measured by scores of ≥ 1 A item or ≥ 2 B items, respectively, on the BILAG 2004 index. Score of ≥ 1 on the Physician Global Assessment (PGA) visual analogue scale (score range: 0 / No Disease Activity to 3 / Severe Disease). Seropositive for antinuclear antibodies, anti–double-stranded DNA (anti-dsDNA), or anti-Smith antibodies Stable treatment with at least one of either prednisone or equivalent, an antimalarial, azathioprine, mizoribine, mycophenolate mofetil or mycophenolic acid, or methotrexate.	Adults 18–70 years old who met the American College of Rheumatology classification criteria for SLE. Moderate to severe SLE as measured by a score of ≥ 6 on the SLEDAI-2K (score range 0–105) and a score ≥ 4 on the clinical SLEDAI-2K. Either severe disease activity in ≥ 1 organ or moderate activity in ≥ 2 organs as measured by scores of ≥ 1 A item or ≥ 2 B items, respectively, on the BILAG 2004 index. Score of ≥ 1 on the Physician Global Assessment (PGA) visual analogue scale (score range: 0 / No Disease Activity to 3 / Severe Disease). Seropositive for antinuclear antibodies, anti–double-stranded DNA (anti-dsDNA), or anti-Smith antibodies Treatment with at least one of the following: an oral glucocorticoid for ≥ 2 weeks at a stable dose (prednisone ≤ 40 mg/d or equivalent), an antimalarial agent for ≥ 12 weeks and ≥ 8 weeks at a stable dose (e.g., chloroquine, hydroxychloroquine, or quinacrine), or slow-acting immunosuppressant for ≥ 12 weeks and ≥ 8 weeks at a stable dose (azathioprine ≤ 200 mg/d, mizoribine ≤ 150 mg/d, mycophenolate mofetil ≤ 2 g/d, mycophenolic acid ≤ 1.44 g/d, or oral, subcutaneous, or intramuscular methotrexate ≤ 25 mg/week). If the patient was not taking an oral glucocorticoid, at least 1 antimalarial or slow-acting immunosuppressant was required. Pap smear within the past 2 years showing no malignancy or adenocarcinoma in situ. No active tuberculosis (TB) or untreated latent TB. TB testing had to be done within the prior 3 months. (For patients with negative TB test at baseline and no symptoms of active TB, TB tests were repeated at Week 52.)
Selected Exclusion Criteria	Active severe or unstable neuropsychiatric SLE SLE-driven renal disease requiring intense treatment Immunodeficiency (e.g., HIV, primary immunodeficiency) History of cancer Clinically significant infection (e.g., HBV, HCV, severe herpes, unresolved herpes zoster or CMV or EBV, or any other infection that is chronic, requires hospitalization, or IV anti-infectives)	Active severe lupus nephritis (LN) Neuropsychiatric SLE Serum creatinine > 2.0 mg/dL Urine protein / creatinine ratio (UPCR) > 2.0 mg/mg B cell-depleting therapy (e.g., epratuzumab, ocrelizumab, rituximab) ≤ 52 weeks prior or if administered > 52 weeks prior, absolute B cell less than the lower limit of normal or the baseline value before B-cell depleting therapy. Live or attenuated vaccine ≤ 8 weeks prior. Bacillus Calmette-Guerin (BCG) vaccine ≤ 1 year prior. History of a primary immunodeficiency or other condition

Method Category	TULIP-1	TULIP-2
		that predisposes to infection (e.g., HIV or splenectomy). Positive for hepatitis B surface antigen (HBSAg) or positive for both hepatitis B core antibody (anti-HBc) and hepatitis B virus (HBV) DNA (> 169 copies/mL). Patients positive for anti-HBc at baseline were tested every 3 months for HBV DNA. Positive for hepatitis C antibody Any history of severe herpes infection (ever) not limited to disseminated herpes, herpes encephalitis, ophthalmic herpes, or recurrent herpes zoster (≥ 2 episodes within 2 years). Opportunistic infection ≤ 3 years prior Clinically significant chronic infection within 8 weeks prior except for chronic nail infection were allowed. Any infection requiring hospitalization or treatment with IV anti-infectives including antivirals ≤ 2 weeks prior History of cancer excluding squamous or basal cell carcinoma of the skin successfully treated with curative therapy ≥ 3 months prior and cervical cancer in situ successfully treated with curative therapy ≥ 1 year prior.
Interventions (Added to standard therapy)	Anifrolumab-fnia 300 mg IV every 4 weeks to Week 48 (13 doses) Anifrolumab-fnia 150 mg IV every 4 weeks to Week 48 (13 doses) Placebo	Anifrolumab-fnia 300 mg IV every 4 weeks to Week 48 (13 doses) Placebo
Selected Allowed Co-therapies	Premedication with an antihistamine and/or acetaminophen was allowed for patients with documented prior infusion-related reaction. GC premedication was not allowed.	Only one glucocorticoid dose burst and taper could be administered for an increase in SLE disease activity or non-SLE related disease from Week 0 to Week 12. IM glucocorticoid (methylprednisolone ≤ 80 mg/d or equivalent) for increase in SLE disease activity from Week 0 to Week 12, instead of burst and taper oral glucocorticoid. Glucocorticoid tapering to ≤ 7.5 mg/d prednisone or equivalent, starting at Week 8 and ending by Week 40, must have been attempted in all patients with a baseline dose of ≥ 10 mg/d unless there was worsening of disease activity, new organ system involvement, moderate to severe skin disease, or moderate to severe arthritis. Glucocorticoid tapering was protocolled. Topical therapies for cutaneous lupus. Premedications: Same as TULIP-1.
Selected Prohibited Co-therapies	No information available.	Cyclophosphamide Interferon therapy Biologic immunomodulators Immunoglobulin therapy Intravenous glucocorticoids > 1 g methylprednisolone or equivalent
Primary Efficacy Measure	The primary efficacy outcome was the difference in proportion of patients who achieved an SLE responder index of 4 (SRI-4) at Week 52. SRI-4 response is defined as meeting all of the following criteria:	The primary outcome measure was the difference in the proportion of patients achieving BICLA response at Week 52. BICLA response was defined as meeting all of the following criteria:

Method Category	TULIP-1	TULIP-2
	• ≥ 4-point reduction in SLEDAI-2K • < 1 new BILAG-2004 A or < 2 new BILAG-2004 B organ domain scores • < 0.3-point increase in PGA from baseline • No discontinuation of study treatment • No use of restricted medications as per protocol.	• Reduction of all baseline BILAG-2004 (from A to B/C/D or B to C/D) and no worsening in other organ systems (i.e., ≥ 1 new BILAG-2004 A items or ≥ 2 new BILAG-2004 B items). • No worsening from baseline by > 0 points in SLEDAI-2K. • No worsening from baseline by ≥ 0.3 points in lupus disease activity as measured on a 3-point PGA VAS. • No discontinuation of study treatment. • No use of restricted medications as per protocol. Time to BICLA response sustained up to Week 52 was assessed as a supportive measure to the primary outcome.