New Drug Overview

Saphnelo (anifrolumab-fnia)
PDL Category: SLE Agents

Introduction

Disease Background:

- Systemic lupus erythematosus (SLE) is described as a multisystem autoimmune condition of connective tissue denoted by autoantibodies targeting nuclear antigens and described by remissions, flares, and a greatly varying clinical presentation, disease course, and prognosis (*Ramsey-Goldman et al 2026*).
  - It is considered a chronic disease with no known cause that can involve any organ in the body (*Wallace and Gladman 2025*).
  - SLE affects females more than males, especially during childbearing years, and there is a higher prevalence of SLE in Black Americans, American Indians, Alaska natives, and persons of Arab origin (*Ramsey-Goldman et al 2026*).
    - Globally, the incidence of SLE is 1 to 10 per 100,000 person-years and an estimated prevalence of 20 to 70 per 100,000. However, rates may differ dependent on region.
- Main symptoms that occur in most SLE patients at some point during the disease include fatigue, fever, and weight loss. The most frequently reported symptom is fatigue, reported in 80 to 100 percent of patients. Myalgia is also common (*Wallace and Gladman 2025*).
  - Organ involvement may include arthritis and arthralgias, mucocutaneous involvement (skin and mucous membrane lesions), cardiac involvement and vascular manifestations (cardiac disease, Raynaud phenomenon, vasculitis, thromboembolic disease), kidney involvement, gastrointestinal involvement, pulmonary involvement, neurological and neuropsychiatric involvement, hematologic abnormalities, or ophthalmic involvement.
    - Kidney involvement, affecting approximately 50% with SLE, is a significant reason for morbidity and mortality in SLE patients.
- The main goals for managing SLE include prevention of flares and organ damage, as well as improving prognosis and quality of life (*Ramsey-Goldman et al 2026*).
  - Regardless of disease severity, hydroxychloroquine is a first-line treatment for all patients that have non-renal SLE. In addition, glucocorticoids as short-term use can be utilized for control of active disease. Chloroquine may be used as an alternative for those who do not have an adequate response to or have contraindications to hydroxychloroquine (*Narvaez et al 2026*).
- Saphnelo (anifrolumab-fnia) for intravenous infusion was FDA approved in 2021, but Saphnelo for subcutaneous self-administration was FDA approved in 2026.

Pharmacology/Usage

- Saphnelo (anifrolumab-fnia), a type I interferon (IFN) receptor antagonist, is an immunoglobulin G1 kappa (IgG1κ) monoclonal antibody that is produced in mouse myeloma cells by recombinant DNA technology.
  - It binds to subunit 1 of the type I interferon receptor (IFNAR) with high specificity and affinity. This binding inhibits type I IFN signaling, thus blocking the biologic activity of type I IFNs.
  - Anifrolumab-fnia also induces the internalization of IFNAR1, thus reducing the levels of cell surface IFNAR1 available for receptor assembly. Blockade of receptor mediated type I IFN signaling inhibits IFN responsive gene expression as well as downstream inflammatory and immunological processes. Inhibition of type I IFN blocks plasma cell differentiation and normalizes peripheral T-cell subsets.
    - Type I IFNs play a role in the pathogenesis of SLE. About 60-80% of adult patients with active SLE express elevated levels of type I IFN inducible genes.

Indications

Table 1. Food and Drug Administration Approved Indications

Indication	Saphnelo (anifrolumab-fnia)
• For the treatment of adult patients with moderate to severe systemic lupus erythematosus (SLE), who are receiving standard therapy. [a]	✔

[a] Limitations of use: The efficacy of Saphnelo has not been evaluated in patients with severe active lupus nephritis or severe active CNS lupus. Use of Saphnelo is not recommended in these situations.

(Prescribing information: Saphnelo 2026)

- Information on indications, mechanism of action, pharmacokinetics, dosing, safety, and clinical efficacy summary has been obtained from the prescribing information for the individual products, except where noted otherwise.

Dosing and administration

Table 2. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Saphnelo (anifrolumab-fnia)	Solution in a single-dose vial for Injection: 300mg/2ml (150mg/ml) for intravenous (IV) infusion. Solution in a single-dose prefilled syringe or single-dose autoinjector (Saphnelo Pen) for Injection: 120mg/0.8ml for subcutaneous (SC) injection.	IV and SC	300mg, administered as an IV infusion over a 30-minute period Q4W; or 120mg, administered as a SC injection once QW. -Patients/caregivers may administer Saphnelo prefilled syringe/Saphnelo Pen after proper training in the SC injection technique and after the healthcare provider determines it is appropriate.	• Saphnelo is intended for use under the guidance of a healthcare provider and may be administered as an IV infusion or as a SC injection. Saphnelo vials are for IV use only and must be diluted prior to IV administration. Saphnelo prefilled syringe and autoinjector (Saphnelo Pen) are for SC use only. • If a planned IV infusion is missed, administer Saphnelo as soon as possible. Maintain a minimum interval of 14 days between infusions. • If a planned SC dose is missed, instruct the patient to administer Saphnelo as soon as it

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				is remembered. Thereafter, instruct the patient to start a new weekly schedule from the day the missed dose was administered or resume dosing on their usual day of administration, providing a minimum interval of 3 days between SC injections. • When transitioning patients from IV administration to SC administration of Saphnelo, administer the first SC injection about 2 weeks after the last IV infusion. • When transitioning patients from SC administration to IV administration of Saphnelo, administer the first IV infusion about 3-4 weeks after the last SC injection.

See the current prescribing information for full details.

Clinical Efficacy Summary

- The safety and efficacy of Saphnelo for IV administration were assessed in three 52-week treatment period, multicenter, randomized, double-blind, placebo-controlled trials (Trial 1, Trial 2, and Trial 3) that included patients diagnosed with SLE per the American College of Rheumatology (ACR; 1982 revised) classification criteria.
  - All patients were ≥18 years of age and had moderate to severe disease, with a SLE Disease Activity Index 2000 (SLEDAI-2K) score ≥6 points, organ level involvement based on the British Isles Lupus Assessment group (BILAG) assessment, and a Physicians Global Assessment (PGA) score ≥1, despite receiving standard SLE therapy consisting of either one or any combination of oral corticosteroids (OCS), antimalarials and/or immunosuppressants at baseline.
  - Patients continued to receive their existing SLE therapy at stable doses during the clinical trials, with the exception of OCS (prednisone or equivalent) where tapering was a component of the protocol.
    - Patients with severe active lupus nephritis and patients who had severe active CNS lupus were excluded.
    - The use of other biologic agents and cyclophosphamide were not permitted during the trials; patients receiving other biologic therapies were required to complete a wash-out period of at least 5 half-lives prior to enrollment.

- Patients received Saphnelo or placebo, administered by IV infusion, Q4W, with all trials conducted in North America, Europe, South America and Asia.

- Efficacy of Saphnelo was established based on assessment of clinical response using the composite endpoints, the British Isles Lupus Assessment Group based Composite Lupus Assessment (BICLA) and the SLE Responder Index (SRI-4).
  - BICLA response at week 52 was defined as improvement in all organ domains with moderate or severe activity at baseline:
    - Reduction of all baseline BILAG A to B/C/D and baseline BILAG B to C/D, and no BILAG worsening in other organ systems, as defined by ≥1 new BILAG A or ≥2 new BILAG B;
    - No worsening from baseline in SLEDAI-2K, where worsening is defined as an increase from baseline of >0 points in SLEDAI-2K;
    - No worsening from baseline in patients' lupus disease activity, where worsening is defined by an increase ≥0.30 points on a 3-point PGA visual analogue scale (VAS);
    - No discontinuation of treatment;
    - No use of restricted medication beyond the protocol-allowed threshold.
  - SRI-4 response was defined as meeting each of the following criteria at week 52 compared with baseline:
    - Reduction from baseline of ≥4 points in the SLEDAI-2K;
    - No new organ system affected as defined by 1 or more BILAG A or 2 or more BILAG B items compared to baseline;
    - No worsening from baseline in the patients' lupus disease activity defined by an increase ≥0.30 points on a 3-point PGA VAS;
    - No discontinuation of treatment;
    - No use of restricted medication beyond the protocol-allowed threshold.
- *Trial 1* randomized patients (N=305) who received Saphnelo 300mg or 1000mg or placebo once Q4W for up to 52 weeks.
  - The primary endpoint was a combined assessment of the SRI-4 and the sustained reduction in OCS (<10mg/day and ≤OCS dose at week 1, sustained for 12 weeks) measured at week 24.
- *Trial 2 and 3* were similar in design.
  - Trial 2 randomized patients (N=457) who received Saphnelo 150mg, 300mg once Q4W or placebo.
  - Trial 3 randomized patients (N=362) who received Saphnelo 300mg once Q4W or placebo.
    - The primary endpoints were improvement in disease activity assessed at 52 weeks, measured by SRI-4 in Trial 2 and BICLA in Trial 3 (defined above).
    - The common secondary efficacy endpoints included in both trials were the maintenance of OCS reduction, improvement in cutaneous SLE activity, and flare rate.
    - During weeks 8-40, patients with a baseline OCS ≥10mg/day were required to taper their OCS dose to ≤7.5mg/day, unless there was worsening of disease activity.
- Baseline characteristics included a mean age of 40 in Trial 1, 41 in Trial 2, and 42 in Trial 3. In addition, 93%, 92%, and 93%, respectively were female and 42%, 71%, and 60%, respectively were White. The mean baseline SLEDAI-2K score was 10.9, 11.3, and 11.5, respectively.
- While other IV Saphnelo dosages were studied in Trials 1 and 2, only data for the approved IV Saphnelo dosage of 300mg Q4W are presented below.
  - The reduction in disease activity seen in the BICLA and SRI-4 was related mainly to improvement in the mucocutaneous and musculoskeletal organ systems.
  - Flare rate was reduced in Saphnelo patients compared to placebo patients but the difference was not statistically significant.
  - BICLA was the primary endpoint in Trial 3 and results suggested that Saphnelo 300mg once Q4W demonstrated statistically significant and clinically meaningful efficacy in overall disease activity compared with placebo, with

greater improvements in all components of the composite endpoint. In Trial 1 and 2, BICLA was a pre-specified analysis.

- BICLA results are presented in the table below, which was adapted from the prescribing information.

Table 3. Efficacy results

	Trial 1		Trial 2		Trial 3	
	Saphnelo (N=99)	**Placebo (N=102)**	**Saphnelo (N=180)**	**Placebo (N=184)**	**Saphnelo (N=180)**	**Placebo (N=182)**
BICLA Response Rate						
Responder, n (%)	54 (54.6%)	27 (25.8%)	85 (47.1%)	55 (30.2%)	86 (47.8%)	57 (31.5%)
Differences in Response Rates	28.8		17.0		16.3; p=0.001	
Components of BICLA Response						
BILAG improvement, n (%)	54 (54.5%)	28 (27.5%)	85 (47.2%)	58 (31.5%)	88 (48.9%)	59 (32.4%)
No worsening of SLEDAI-2K, n (%)	73 (73.7%)	61 (59.8%)	121 (67.2%)	104 (56.5%)	122 (67.8%)	94 (51.6%)
No worsening of PGA, n (%)	76 (76.8%)	62 (60.8%)	117 (65%)	105 (57.1%)	122 (67.8%)	95 (52.2%)

- SRI-4 was the primary endpoint in Trial 2, and results suggested that treatment with Saphnelo did not result in statistically significant improvements over placebo. In Trials 1 and 3, SRI-4 was a pre-specified analysis.
  - The SRI-4 results are presented in the table below, which was adapted from the prescribing information.

Table 4. Efficacy results

	Trial 1		Trial 2		Trial 3	
	Saphnelo (N=99)	**Placebo (N=102)**	**Saphnelo (N=180)**	**Placebo (N=184)**	**Saphnelo (N=180)**	**Placebo (N=182)**
SRI-4 Response Rate						
Responder, n (%)	62 (62.8%)	41 (38.8%)	88 (49.0%)	79 (43.0%)	100 (55.5%)	68 (37.3%)
Difference in Response Rates	24.0		6.0		18.2	
Components of SRI-4 Response						
SLEDAI-2K Improvement, n (%)	62 (62.6%)	41 (40.2%)	89 (49.4%)	80 (43.5%)	101 (56.1%)	71 (39%)
No worsening of BILAG, n (%)	75 (75.8%)	61 (59.8%)	119 (66.1%)	105 (57.1%)	125 (69.4%)	94 (51.6%)
No worsening of PGA, n (%)	76 (76.8%)	62 (60.8%)	117 (65%)	105 (57.1%)	122 (67.8%)	95 (52.2%)

- In Trial 3, among the 47% of patients with a baseline OCS use ≥10mg/day, Saphnelo demonstrated a statistically significant difference in the proportion of patients able to reduce OCS use by at least 25% to ≤7.5mg/day at week 40 and maintain the reduction through week 52 (p=0.004); 52% of the Saphnelo group versus 30% of the placebo group achieved this level of steroid reduction (difference 21%).
  - Consistent trends in favor of Saphnelo compared to placebo, on effect of reduction of OCS use, were observed in Trial 1 and 2, but the difference was not statistically significant.
- The safety and efficacy of Saphnelo administered subcutaneously were assessed in a 52-week treatment period, multicenter, randomized, double-blind, placebo-controlled trial (Trial 5).
  - All patients were ≥18 years of age, diagnosed with SLE per the ACR (1997 revised) classification criteria, and had moderate to severe disease, with a SLEDAI-2K score ≥6 points, organ level involvement based on BILAG assessment, and a PGA score ≥1, despite receiving standard SLE therapy consisting of either one or any combination of OCS, antimalarials and/or immunosuppressants at baseline. Patients continued to receive their existing SLE therapy at stable doses during the trial, with the exception of OCS (prednisone or equivalent) where tapering was a component of the protocol.
    - Patients who had severe active lupus nephritis or severe active CNS lupus were excluded.
  - Patients were randomized to receive Saphnelo 120mg plus standard therapy or placebo plus standard therapy by SC injection QW.
  - A prespecified interim analysis was conducted when the first 220 randomized patients completed week 52 or had withdrawn from the trial.
    - Of these, 89% were female, 78% were white, and the mean age was 43 years. At baseline, the mean SLEDAI-2K score was 10.9 and 67% had high disease activity (SLEDAI-2K score ≥10), 45% had severe disease (BILAG A) in at least 1 organ system, and 50% had moderate disease (BILAG B) in at least 2 organ systems. The most commonly affected organ systems (BILAG A or B at baseline) were the musculoskeletal (95%) and mucocutaneous (92%) systems; 2% cardiorespiratory and 2% renal organ domain involvement. At baseline, 95% had abnormal ANA, 40% were positive for anti-dsDNA antibodies; 33% had abnormal C3, and 24% abnormal C4.
    - Background SLE standard therapy included OCS (82%; mean daily dose, prednisone or equivalent, 9.8mg), immunosuppressants (56%), and anti-malarial agents (80%). During weeks 8-40, patients with a baseline OCS ≥10mg/day were required to taper their OCS dose to ≤7.5mg/day, unless there was worsening of disease activity.
    - The primary endpoint was BICLA response rate measured at week 52.
      - At the interim analysis, Saphnelo by SC administration demonstrated a statistically significant and clinically meaningful reduction of overall disease activity compared with placebo.
      - Results are presented in the table below, which was adapted from the prescribing information.

Table 5. Efficacy results

	Saphnelo SC N=109	**Placebo N=11**
BICLA Response		
Responder, n (%)	64 (58.5%)	48 (43.2%)
Difference in Response Rates, %	15.3; p=0.0231	
Components of BICLA Response		
BILAG Improvement, n (%)	64 (58.5%)	48 (43.3%)

	Saphnelo SC N=109	Placebo N=11
No worsening of SLEDAI-2K, n (%)	80 (73.4%)	77 (68.9%)
No worsening of PGA, n (%)	80 (73.5%)	78 (70%)

- Subgroup analysis by disease severity (based on baseline SLEDAI-2K, <10 points, ≥10 points) and baseline OCS use (<10mg/day, ≥10mg/day) did not identify differences in response to Saphnelo.

Clinical guidelines

- **2025 American College of Rheumatology (ACR) Guideline for the treatment of systemic lupus erythematosus** (*Sammaritano et al 2025).*
  - The goal of treatment for SLE includes optimal control of disease to enhance long-term clinical outcomes.
  - A general treatment strategy includes that if numerous organ systems are involved at onset or during a SLE flare, treatment should be directed to all manifestations but prioritize areas at the largest risk for damage that is irreversible.
  - For ongoing moderate to severe cutaneous lupus that is refractory to topical and antimalarial treatments, and/or oral glucocorticoid requiring escalation of treatment, the authors conditionally recommend adding methotrexate, MPAA (mycophenolic acid analogs, including mycophenolate mofetil [MMF] and mycophenolic acid [MPA]), anifrolumab, and/or belimumab.
  - For persistent or recurrent active SLE arthritis on hydroxychloroquine, regardless of prior or current NSAID use or short-term glucocorticoid treatment, the authors conditionally recommend initial treatment with methotrexate, MPAA, or azathioprine, with a low threshold to add or substitute with belimumab or anifrolumab for inadequate response over initial biologic treatment.
  - For vasculitis associated with active SLE, the authors conditionally recommend initial treatment with pulse or high-dose glucocorticoid taper and conventional (IV cyclophosphamide, MPAA, azathioprine) or biologic (anti-CD 20 therapy, belimumab, anifrolumab) immunosuppressive treatment rather than glucocorticoid monotherapy.
  - Refer to the guideline for additional information.

Safety summary

- **Contraindications:**
  - In patients with a history of anaphylaxis with anifrolumab-fnia

- **Box Warning:** None.

- **Warnings and precautions:**
  - Serious and sometimes fatal infections (including COVID-19) have occurred in patients receiving immunosuppressive agents, including Saphnelo. In controlled trials, fatal infections occurred more frequently in patients receiving Saphnelo. In controlled trials, Saphnelo increased the risk of respiratory infections and herpes zoster.
    - Avoid starting Saphnelo treatment in patients with any clinically significant active infection until the infection is resolved or adequately treated. Consider the benefit and risk of administering Saphnelo in patients with a chronic infection, a history of recurrent infections, or known risk factors for infection.

- Instruct patients to seek medical advice if signs or symptoms of a clinically significant infection occur. If a patient develops an infection or is not responding to standard anti-infective therapy while on Saphnelo, monitor the patient closely and consider interrupting Saphnelo until the infection resolves.
- Serious hypersensitivity reactions (including anaphylaxis) have been reported following Saphnelo administration. Events of angioedema have also been reported.
  - Other hypersensitivity reactions and infusion-related reactions have occurred following administration of Saphnelo.
    - Consider pre-medication before infusion of Saphnelo for patients with a history of these reactions.
    - Saphnelo should be administered by healthcare providers prepared to manage hypersensitivity reactions, including anaphylaxis, and infusion-related reactions. If a serious infusion-related or hypersensitivity reaction occurs, immediately interrupt the administration of Saphnelo and start appropriate therapy.
- There is an increased risk of malignancies with the use of immunosuppressants. The impact of Saphnelo treatment on the potential development of malignancies is not known.
  - Consider the individual benefit-risk in patients with known risk factors for the development or reoccurrence of malignancy prior to prescribing Saphnelo. In patients who develop malignancies, consider the benefit-risk of continued treatment with Saphnelo.
- Update immunizations, per current immunization guidelines, prior to starting Saphnelo therapy.
  - Avoid concurrent use of live or live-attenuated vaccines in patients treated with Saphnelo.
- Saphnelo has not been studied in combination with other biologic therapies, including B-cell-targeted therapies. Thus, use of Saphnelo is not recommended for use in combination with biologic therapies.

- **Common adverse drug reactions**:
  - Listed % incidence for adverse drug reactions= reported % incidence for drug (Saphnelo IV) minus reported % incidence for placebo. Please note that an incidence of 0% means the incidence was the same as or less than comparator.
    - The most frequently reported adverse events included upper respiratory tract infection (11%), bronchitis (5.8%), infusion-related reactions (2.3%), herpes zoster (4.8%), cough (1.8%), respiratory tract infection (1.8%), and hypersensitivity (2.2%).
    - The safety profile observed for Saphnelo administered SC was consistent with the known safety profile of Saphnelo administered IV.

- **Drug interactions:**
  - No formal drug interaction trials have been conducted.

- **Special populations:**
  - There is no pregnancy category for this medication; however, the risk summary indicates that the limited human data with Saphnelo use in pregnant women are not sufficient to inform on drug-associated risk for major birth defects, miscarriage, or adverse maternal or fetal outcome.
    - Monoclonal IgG antibodies are known to be actively transported across the placenta as pregnancy progresses; thus, anifrolumab-fnia exposure to the fetus may be greater during the third trimester of pregnancy.
    - There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to Saphnelo during pregnancy. For more information about the registry or to report a pregnancy while on Saphnelo, healthcare providers should contact AstraZeneca at 1-877-693-9268 or visiting online.
    - There are clinical considerations discussed in the prescribing information.
  - The safety and efficacy of use in the pediatric population have not been established.

Conclusion

- Systemic lupus erythematosus (SLE) is described as a multisystem autoimmune condition of connective tissue denoted by autoantibodies targeting nuclear antigens and described by remissions, flares, and a greatly varying clinical presentation, disease course, and prognosis (*Ramsey-Goldman et al 2026*).
- Saphnelo is a type l interferon (IFN) receptor antagonist indicated for the treatment of adult patients with moderate to severe SLE, who are receiving standard therapy.
  - A limitation of use includes that the efficacy of Saphnelo has not been assessed in patients with severe active lupus nephritis or severe active CNS lupus. Use of Saphnelo is not recommended in these situations.
- Avoid starting treatment with Saphnelo in patients with any clinically significant active infection until the infection is resolved or adequately treated.
- There is an increased risk of malignancies with the use of immunosuppressants. The impact of Saphnelo treatment on the potential development of malignancies is not known.
  - Consider the individual benefit-risk in patients with known risk factors for the development or reoccurrence of malignancy prior to prescribing Saphnelo. In patients who develop malignancies, consider the benefit-risk of continued treatment with Saphnelo.
- Avoid concurrent use of live or live-attenuated vaccines in patients treated with Saphnelo.
- The efficacy of Saphnelo for IV administration was assessed in three 52-week treatment period, multicenter, randomized, double-blind, placebo-controlled trials.
  - Efficacy of Saphnelo was established based on assessment of clinical response using the composite endpoints, the BICLA and the SRI-4.
    - The reduction in disease activity seen in the BICLA and SRI-4 was related mainly to improvement in mucocutaneous and musculoskeletal organ systems. Flare rate was reduced in Saphnelo patients compared to placebo, although the difference was not statistically significant.
- The safety and efficacy of Saphnelo administered SC was assessed in a 52-week treatment period, multicenter, randomized, double-blind, placebo-controlled trial.
  - The primary endpoint was BICLA response rate measured at week 52.
    - At the interim analysis, Saphnelo by SC administration demonstrated a statistically significant and clinically meaningful reduction of overall disease activity compared with placebo.
- Guidelines for SLE treatment do include anifrolumab.

- There is no evidence to suggest that Saphnelo is safer or more effective than other currently preferred, more cost-effective medications. It is therefore recommended that Saphnelo remain non-preferred and require prior authorization and be available to those who are unable to tolerate or who have failed on preferred medications.

- **PDL Placement:**
  - ☐ Preferred
  - ☒ Non-Preferred

References

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