NEW DRUG APPROVAL

Brand Name	Saphnelo™
Generic Name	anifrolumab-fnia
Drug Manufacturer	AstraZeneca AB

New Drug Approval

FDA Approval Date: July 30, 2021

Review Designation: N/A

Type of Review: Biologic License Application (BLA): 761123

Dispensing restrictions: Speciality

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Systemic Lupus Erythematosus (SLE) is an autoimmune disease in which the immune system attacks healthy tissue in the body. It is a chronic and complex disease with a variety of clinical manifestations that can impact many organs and can cause a range of symptoms including pain, rashes, fatigue, swelling in joints and fevers. More than 50% of patients with SLE develop permanent organ damage, caused by the disease or existing treatments, which exacerbates symptoms and increases the risk of mortality. At least five million people worldwide have a form of lupus.

SLE, the most common form of lupus affecting up to 300,000 people in the US, disproportionately affects the African-American, Hispanic and Asian populations.

Efficacy

The safety and efficacy of Saphnelo™ were evaluated in three 52-week treatment period, multicenter, randomized, double-blind, placebo-controlled studies (Trial 1 [NCT01438489], Trial 2 [NCT02446912] and Trial 3 [NCT02446899]). Patients were diagnosed with SLE according to the American College of Rheumatology (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 BILAG assessment, and a Physician's 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 received anifrolumab-fnia or placebo, administered by intravenous infusion, every 4 weeks.

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).

Trial 1 randomized 305 patients (1:1:1) who received anifrolumab-fnia, 300 mg or 1000 mg, or placebo 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 457 patients who received anifrolumab-fnia 150 mg, 300 mg or placebo (1:2:2). Trial 3 randomized 362 patients (1:1) who received anifrolumab-fnia 300 mg or placebo. The primary endpoints were improvement in disease activity evaluated 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 studies were the maintenance of OCS reduction, improvement in cutaneous SLE activity, and flare rate. During Weeks 8-40,

patients with a baseline OCS ≥10 mg/day were required to taper their OCS dose to ≤7.5 mg/day, unless there was worsening of disease activity. Both studies evaluated the efficacy of anifrolumab-fnia 300 mg versus placebo; a dose of 150 mg was also evaluated for dose response in Trial 2.

Table 3 BICLA Response Rate at Week 52

	Trial 1*,†		Trial 2*,†		Trial 3ǂ	
	Anifrolumab-fnia 300 mg (N=99)	Placebo (N=102)	Anifrolumab-fnia 300 mg (N=180)	Placebo (N=184)	Anifrolumab-fnia 300 mg (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)
Difference in Response Rates (95% CI)	28.8 (15.7, 41.9)		17.0 (7.2, 26.8)		16.3 (6.3, 26.3) p-value = 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 (65.0)	105 (57.1)	122 (67.8)	95 (52.2)

The response rates and associated difference and 95% CI are calculated using a Cochran-Mantel-Haenszel approach adjusted for stratification factors. The reported percentages for the components are unadjusted.
* Not formally tested in a pre-specified testing scheme and findings should be interpreted with caution.
† Based on post hoc analysis.
ǂ Primary endpoint.
§ In all 3 trials, patients who discontinued investigational product or initiated restricted medications beyond the protocol-specified thresholds are considered non-responders. For consistency, the results presented for Trial 2 represent the post-hoc analysis using the restricted medication thresholds as defined in Trial 3.

Safety

ADVERSE EVENTS

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

Table 1 Adverse Reactions Occurring in ≥2% of Patients on SAPHNELO 300 mg (Trials 1, 2 and 3) at 52 weeks

Adverse Reaction	SAPHNELO (N=459) %	Placebo (N=466) %
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

All patients received standard therapy
* Upper respiratory tract infections (including Upper respiratory tract infections, Nasopharyngitis, Pharyngitis)
† Bronchitis (including Bronchitis, Bronchitis viral, Tracheobronchitis)
‡ Respiratory tract infection (including Respiratory tract infection, Respiratory tract infection viral, Respiratory tract infection bacterial)

WARNINGS & 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 benefitrisk if using in patients with severe or chronic infections. Consider interrupting therapy with Saphnelo™ if patients develop a new infection during treatment.
- Hypersensitivity Reactions Including Anaphylaxis: Serious hypersensitivity reactions including anaphylaxis and angioedema have been reported.
- Malignancy: Consider the individual benefit-risk in patients with known risk factors for malignancy prior to prescribing Saphnelo™.
- Immunization: Avoid use of live or live-attenuated vaccines in patients receiving Saphnelo™.
- Not Recommended for Use with Other Biologic Therapies.

CONTRAINDICATIONS

Saphnelo™ is contraindicated in patients with a history of anaphylaxis with anifrolumab-fnia.

Clinical Pharmacology

MECHANISMS OF ACTION

Anifrolumab-fnia is a human IgG1κ monoclonal antibody that binds to subunit 1 of the type I interferon receptor (IFNAR) with high specificity and affinity. This binding inhibits type I IFN signaling, thereby blocking the biologic activity of type I IFNs. Anifrolumab-fnia also induces the internalization of IFNAR1, thereby 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. Approximately 60-80% of adult patients with active SLE express elevated levels of type I IFN inducible genes.

Dose & Administration

ADULTS

The recommended dosage is 300 mg as an intravenous infusion over 30-minute period every 4 weeks.

PEDIATRICS

The safety and efficacy of Saphnelo™ in pediatric patients less than 18 years of age have not been established.

GERIATRICS

Refer to adult dose.

RENAL IMPAIRMENT

No specific clinical studies have been conducted to investigate the effect of renal impairment on anifrolumab-fnia. Based on population PK analyses, anifrolumab-fnia clearance was comparable in SLE patients with mild (60-89 mL/min/1.73 m^2) and moderate (30-59 mL/min/1.73 m^2) decrease in eGFR values and patients with normal renal function (≥90 mL/min/1.73 m^2). There were no SLE patients with a severe decrease in eGFR or end stage renal disease (<30 mL/min/1.73 m^2); anifrolumab-fnia is not cleared renally.

HEPATIC IMPAIRMENT

No specific clinical studies have been conducted to investigate the effect of hepatic impairment on anifrolumab-fnia. IgG1 monoclonal antibodies are predominantly eliminated via catabolism and are not expected to undergo hepatic metabolism; changes in hepatic function are not expected to influence anifrolumab-fnia clearance. Based on population PK analyses, baseline hepatic function biomarkers (ALT and AST ≤2.0 × ULN, and total bilirubin) had no clinically relevant effect on anifrolumab-fnia clearance.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

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