

FULL PRESCRIBING INFORMATION

1 NAME OF THE MEDICINAL PRODUCT

SAPHNELO® 300 mg concentrate for solution for intravenous infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of concentrate for solution for infusion contains 150 mg of anifrolumab.

One vial of 2.0 mL of concentrate contains 300 mg of anifrolumab (150 mg/mL).

Anifrolumab is a human, immunoglobulin G1 kappa (IgG1κ) monoclonal antibody produced in mouse myeloma cells (NS0) by recombinant DNA technology.

For a full list of excipients, see section 11.

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate) in a single dose vial.

Clear to opalescent, colourless to slightly yellow, pH 5.9 solution.

4 INDICATIONS AND USAGE

SAPHNELO is indicated for the treatment of adult patients with moderate to severe systemic lupus erythematosus (SLE), who are receiving standard therapy. [see [Clinical Studies \(14\)](#)].

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.

5 DOSAGE AND ADMINISTRATION

5.1 Dosage Recommendations

SAPHNELO must be diluted prior to intravenous administration [see [Dosage and Administration \(5.2\)](#)].

The recommended dosage of SAPHNELO is 300 mg, administered as an intravenous infusion over a 30-minute period, every 4 weeks.

Missed dose

If a planned infusion is missed, administer SAPHNELO as soon as possible. Maintain a minimum interval of 14 days between infusions.

5.2 Instructions for Preparation and Administration

SAPHNELO is supplied as a single-dose vial. Prepare the diluted infusion solution using aseptic technique, by the following procedure:

1. Visually inspect the vial for particulate matter and discoloration. SAPHNELO is a clear to opalescent, colorless to slightly yellow, solution. Discard the vial if the solution is cloudy, discolored or visible particles are observed. Do not shake the vial.
2. Withdraw and discard 2 mL of solution from a 50 mL or 100 mL 0.9% Sodium Chloride Injection, infusion bag.
3. Withdraw 2 mL of solution from the vial of SAPHNELO and add it to the infusion bag. Mix the solution by gentle inversion. Do not shake.
4. Each vial is intended for one time use only. Discard any unused portion remaining in the vial.
5. Administer the infusion solution immediately after preparation.
6. If the infusion solution is not administered immediately, store the diluted solution of SAPHNELO at room temperature (15°C to 25°C) for up to 4 hours, or refrigerated (2°C to 8°C) for up to 24 hours. Do not freeze. Protect from light. If refrigerated, allow the diluted SAPHNELO solution to reach room temperature prior to administration.
7. Administer the infusion solution intravenously over a 30-minute period through an infusion line containing a sterile, low-protein binding 0.2 to 15 micron in-line or add-on filter.
8. To ensure the complete dose of SAPHNELO has been administered, flush the entire infusion line with 25 mL of 0.9% Sodium Chloride Injection at the end of the infusion.
9. Do not co-administer other medicinal products through the same infusion line.
10. Dispose of any unused medicinal product or waste material in accordance with local requirements.

6 CONTRAINDICATIONS

SAPHNELO is contraindicated in patients with a history of anaphylaxis with anifrolumab [see [Warnings and Precautions \(7.2\)](#)].

Hypersensitivity to the active substance or to any of the excipients listed in section 11.

7 WARNINGS AND PRECAUTIONS

7.1 Serious Infections

Serious and sometimes fatal infections (including COVID-19) have occurred in patients receiving immunosuppressive agents, including SAPHNELO. Overall, the incidence of serious infections in controlled trials was similar in patients receiving SAPHNELO compared with placebo, whereas fatal infections occurred more frequently in patients receiving SAPHNELO [see [Adverse Reactions \(8.1\)](#)].

In controlled trials, SAPHNELO increased the risk of respiratory infections and herpes zoster (disseminated herpes zoster events have been reported) [see [Adverse Reactions \(8.1\)](#)].

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. Avoid initiating treatment with SAPHNELO in patients with any clinically significant active infection until the infection resolves or is adequately treated. Instruct patients to seek medical advice if signs or symptoms of clinically significant infection occur. If a patient develops an infection, or is not responding to standard anti-infective therapy, monitor the patient closely and consider interrupting SAPHNELO therapy until the infection resolves.

7.2 Hypersensitivity Reactions Including Anaphylaxis

Serious hypersensitivity reactions (including anaphylaxis) have been reported following SAPHNELO administration [see [Contraindication \(6\)](#)]. Events of angioedema have also been reported [see [Adverse Reactions \(8.1\)](#)].

Other hypersensitivity reactions and infusion-related reactions have occurred following administration of SAPHNELO [see [Adverse Reactions \(8.1\)](#)]. 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 (e.g., anaphylaxis) occurs, immediately interrupt the administration of SAPHNELO and initiate appropriate therapy.

7.3 Malignancy

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.

7.4 Immunizations

Update immunizations, according to current immunization guidelines, prior to initiating SAPHNELO therapy. Avoid concurrent use of live or live-attenuated vaccines in patients treated with SAPHNELO.

7.5 Not Recommended for Concomitant Use with Other Biologic Therapies

SAPHNELO has not been studied in combination with other biologic therapies, including B-cell-targeted therapies. Therefore, use of SAPHNELO is not recommended for use in combination with biologic therapies.

8 ADVERSE REACTIONS

The following clinically significant adverse reactions are also discussed elsewhere in the labeling:

- Serious Infections [see [Warnings and Precautions \(7.1\)](#)]
- Hypersensitivity Reactions Including Anaphylaxis [see [Warnings and Precautions \(7.2\)](#)]
- Malignancy [see [Warnings and Precautions \(7.3\)](#)]

8.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of SAPHNELO was assessed through 52 weeks in patients with moderate to severe SLE who received anifrolumab 300 mg by intravenous infusion every 4 weeks (N=459), compared to placebo (N=466) in controlled clinical trials (Trials 1, 2 and 3) [see [Clinical Studies \(14\)](#)]. The population studied had a mean age of 41 years (range: 18 to 69), of which 93% were female, 60% White, 13% Black/African American, and 10% Asian.

In the controlled-clinical trials, adverse reactions, irrespective of causality, were reported in 87% of patients receiving SAPHNELO and 79% of patients receiving placebo.

Adverse reactions that occurred at greater than or equal to 2% incidence are shown in Table 1.

Table 1 Adverse Reactions Occurring in \geq 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)

Long-term Safety

Patients who completed Trials 2 and 3 (Phase III feeder trials) were eligible to continue on treatment in a randomized, double-blind, placebo-controlled long-term extension (LTE) study, for an additional 3 years. The long-term safety of SAPHNELO was assessed in 257 patients who received anifrolumab 300 mg and 112 patients who received placebo in both a feeder trial and the LTE. Of these, 177 patients who received

SAPHNELO (68.9%) and 52 patients who received placebo (46.4%) completed a total of 4 years on treatment. The overall long-term safety profile of SAPHNELO was consistent with Trials 1, 2 and 3.

Specific Adverse Reactions

Infections

In the 52-week controlled-clinical trials, infections were reported in a greater proportion of patients while on treatment with SAPHNELO compared to placebo (69.7% [320/459] versus 55.4% [258/466]), corresponding to exposure-adjusted incidence rates (EAIR) of 141.8 and 99.9 per 100 patient years (PY), respectively.

Serious Infections

In the 52-week controlled-clinical trials, the incidence of serious infections while on treatment was 4.8% (22/459) in patients treated with SAPHNELO compared with 5.6% (26/466) in patients receiving placebo, corresponding to EAIR of 5.4 and 6.6 per 100 PY, respectively. The most frequent serious infection was pneumonia.

In the 52-week controlled-clinical trials, fatal infections occurred in 0.4% of patients receiving SAPHNELO and 0.2% of the patients receiving placebo.

During the LTE study, the most common serious infections were COVID-19 and pneumonia.

Herpes Zoster

In the 52-week controlled-clinical trials, the incidence of herpes zoster in patients while on treatment with SAPHNELO was 6.1% (28/459) and 1.3% (6/466) in patients on placebo, corresponding to EAIRs of 6.9 and 1.5 per 100 PY, respectively. Cases with multidermatomal involvement and disseminated presentation have been reported. Of the 28 SAPHNELO-treated patients with herpes zoster, 2 experienced disseminated disease requiring hospitalization compared to none among patients who received placebo.

Hypersensitivity Reactions Including Anaphylaxis

During the SLE development program, there was one report of an anaphylactic reaction in a patient who received 150 mg anifrolumab, and 4 reports of angioedema after 300 mg. In general, the hypersensitivity reactions were predominantly mild or moderate in intensity and did not lead to discontinuation of SAPHNELO.

In the 52-week controlled-clinical trials, hypersensitivity reactions occurred in 2.8% (13/459) of patients while on treatment with SAPHNELO and 0.6% (3/466) of patients on placebo, corresponding to EAIR of 3.2 and 0.7 per 100 PY, respectively. Serious hypersensitivity reactions were reported for 0.6% (3/459) of patients receiving SAPHNELO, including angioedema (n=2).

Infusion-related Reactions

Infusion-related reactions were mild to moderate in intensity; the most common symptoms were headache, nausea, vomiting, fatigue, and dizziness.

In the 52-week controlled-clinical trials, the incidence of infusion-related reactions while on treatment was 9.4% (43/459) in patients while on treatment with SAPHNELO and 7.1% (33/466) in patients on placebo, corresponding to EAIRs of 11.1 and 8.7 per 100 PY, respectively.

Malignancies

In 52-week controlled-clinical trials, malignancies (excluding non-melanoma skin cancers) were observed in 0.7% (3/459) and 0.6% (3/466) of patients receiving SAPHNELO and placebo, corresponding to EAIR of 0.7 and 0.7 per 100 PY, respectively. Malignant neoplasm (including non-melanoma skin cancers) was reported for 1.3% (6/459) patients receiving SAPHNELO, compared to 0.6% (3/466) patients receiving placebo (EAIR: 1.3 and 0.7 per 100 PY, respectively). The malignancies that were reported in more than one patient treated with SAPHNELO included breast cancer and squamous cell carcinoma.

8.2 Postmarketing Experience

The following adverse reaction has been identified during post-approval use of SAPHNELO. Because the reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Arthralgia.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: <https://sideeffects.health.gov.il>

9 DRUG INTERACTIONS

No formal drug interaction studies have been conducted.

10 USE IN SPECIFIC POPULATIONS

10.1 Pregnancy

Risk Summary

The limited human data with SAPHNELO use in pregnant women are insufficient 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; therefore, anifrolumab exposure to the fetus may be greater during the third trimester of pregnancy.

In an enhanced pre- and post-natal development study with pregnant cynomolgus monkeys that received intravenous administration of anifrolumab, there was no evidence of embryotoxicity or fetal malformations with exposures up to approximately 28-times the exposure at the maximum recommended human dose (MRHD) on an Area Under Curve (AUC) basis (*see Data*).

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk: Pregnant women with SLE are at increased risk of adverse pregnancy outcomes, including worsening of the underlying disease, premature birth, miscarriage, and intrauterine growth restriction. Maternal lupus nephritis increases the risk of hypertension and preeclampsia/eclampsia. Passage of maternal autoantibodies across the placenta may result in adverse neonatal outcomes, including neonatal lupus and congenital heart block.

Data

Animal Data: In an enhanced pre- and post-natal development study, pregnant cynomolgus monkeys received anifrolumab at intravenous doses of 30 or 60 mg/kg once every 2 weeks from confirmation of pregnancy at Gestation Day 20, throughout the gestation period, and continuing until 1-month post-partum (approximately Lactation Day 28). There was no evidence of anifrolumab related maternal toxicity, embryo-fetal toxicity, or post-natal developmental effects. No anifrolumab related effect on T-cell-dependent antibody response in the infants was noted up to Day 180 after birth. The no observed adverse effect level (NOAEL) for maternal and developmental toxicity was identified as 60 mg/kg (approximately 28-times the MRHD on an AUC basis). In the infants, mean serum concentrations of anifrolumab on Day 30 after birth increased with dose and were approximately 4.2% to 9.7% of the respective maternal concentrations. The anifrolumab concentrations in the infant serum were up to approximately 22-times the concentrations in the maternal milk, suggesting that anifrolumab had transferred via the placenta.

10.2 Lactation

Risk Summary

No data are available regarding the presence of SAPHNELO in human milk, the effects on the breastfed child, or the effects on milk production. Anifrolumab was detected in the milk of female cynomolgus monkeys administered anifrolumab. Due to species-species differences in lactation physiology, animal data may not reliably predict drug levels in humans. Maternal IgG is known to be present in human milk. If anifrolumab is transferred into human milk, the effects of local gastrointestinal exposure and limited systemic exposure in the breastfed infant to anifrolumab are unknown.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for anifrolumab and any potential adverse effects on the breast-fed child from anifrolumab or from the underlying maternal condition.

10.3 Pediatric Use

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

10.4 Geriatric Use

Of the 664 patients with SLE exposed to anifrolumab in clinical trials, 3% (n=20) were 65 and over. The number of patients aged 65 years of age and older was not sufficient to determine whether they respond differently from younger adult patients.

11 DESCRIPTION

Anifrolumab is a type I interferon (IFN) receptor antagonist, immunoglobulin G1 kappa (IgG1k) monoclonal antibody that is produced in mouse myeloma cells (NS0) by recombinant DNA technology. The molecular weight is approximately 148 kDa.

SAPHNELO (anifrolumab) injection is a sterile, preservative-free, clear to opalescent, colorless to slightly yellow, solution for intravenous use. SAPHNELO contains anifrolumab at a concentration of 150 mg/mL in a single-dose vial.

Each vial contains 300 mg (150 mg/mL) of anifrolumab, trehalose dihydrate (98 mg), L-lysine hydrochloride (18 mg), L-histidine hydrochloride monohydrate (6 mg), L-histidine (3 mg), polysorbate 80 (1 mg) and Water for Injection, USP. The pH is 5.9.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Anifrolumab is a human IgG1k 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 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.

12.2 Pharmacodynamics

In patients with SLE, following the administration of anifrolumab at 300 mg dose, via intravenous infusion every 4 weeks for 52 weeks, neutralization ($\geq 80\%$) of a type I IFN gene signature was observed from Week 4 to Week 52 in blood samples of patients with elevated levels of type I IFN inducible genes and returned to baseline levels within 8 to 12 weeks following withdrawal of anifrolumab at the end of the 52-week treatment period. However, the clinical relevance of the type I IFN gene signature neutralization is unclear.

In SLE patients with positive anti-dsDNA antibodies at baseline (Trials 2 and 3), treatment with anifrolumab 300 mg led to numerical reductions in anti-dsDNA antibodies over time through Week 52.

In patients with low complement levels (C3 and C4), increases in complement levels were observed in patients receiving anifrolumab through Week 52.

12.3 Pharmacokinetics

The PK of anifrolumab was studied in adult patients with SLE following intravenous doses ranging from 100 to 1000 mg once every 4 weeks, and healthy volunteers following a single intravenous dose at 300 mg. Anifrolumab exhibits non-linear PK in the dose range of 100 mg to 1000 mg with more than dose-proportional increases in the exposure as measured by AUC. Following the 300 mg every 4 weeks intravenous

administrations of anifrolumab, steady-state was reached by Day 85. The accumulation ratio was approximately 1.36 for C_{max} and 2.49 for C_{trough} .

Distribution

Based on population PK analysis, the estimated volume of distribution at steady state for a typical patient with SLE (69.1 kg) is 6.23 L.

Elimination

From population PK analysis, anifrolumab exhibited non-linear PK due to IFNAR1-mediated drug clearance.

Following the administration of anifrolumab at a dose of 300 mg via intravenous infusion every 4 weeks, the estimated systemic clearance (CL) for anifrolumab was 0.193 L/day.

Based on population PK analysis of patients who received SAPHNELO for one year, serum concentrations of anifrolumab were below detection in 95% of patients approximately 16 weeks after the last dose.

Specific Populations

There was no clinically meaningful difference in systemic clearance based on age, race, ethnicity, region, gender, IFN status or body weight, that requires dose adjustment.

Age: Based on population PK analyses, age (range 18 to 69 years) did not affect anifrolumab clearance. Limited PK data are available for elderly patients; 3% (n=20) of the patients included in the PK analysis were 65 years or older [see [Use in Specific Populations \(11.5\)](#)].

Renal Impairment: No specific clinical studies have been conducted to investigate the effect of renal impairment on anifrolumab. Based on population PK analyses, anifrolumab clearance was comparable in SLE patients with mild (60-89 mL/min/1.73 m²) and moderate (30-59 mL/min/1.73 m²) decrease in eGFR values and patients with normal renal function (≥ 90 mL/min/1.73 m²). There were no SLE patients with a severe decrease in eGFR or end stage renal disease (< 30 mL/min/1.73 m²); anifrolumab is not cleared renally.

Patients with UPCR > 2 mg/mg were excluded from the clinical trials. Based on population PK analyses, increased urine protein/creatinine ratio (UPCR) did not significantly affect anifrolumab clearance.

Hepatic Impairment: No specific clinical studies have been conducted to investigate the effect of hepatic impairment on anifrolumab. 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 clearance. Based on population PK analyses, baseline hepatic function biomarkers (ALT and AST $\leq 2.0 \times$ ULN, and total bilirubin) had no clinically relevant effect on anifrolumab clearance.

Drug Interactions

No formal drug-drug interaction studies have been conducted.

Based on population PK analysis, concomitant use of oral corticosteroids, anti-malarials, immunosuppressants (azathioprine, methotrexate, mycophenolate mofetil, mycophenolic acid, and mizoribine), NSAIDs, ACE inhibitors, and HMG-CoA reductase inhibitors did not significantly affect the PK of anifrolumab.

12.6 Immunogenicity

The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies

in the studies described below with the incidence of anti-drug antibodies in other studies, including those of anifrolumab.

In Trials 2, 3, and the long-term extension, treatment emergent anti-anifrolumab antibodies were detected in 9 of 350 (ADA incidence 2.6%) patients who received SAPHNELO at the recommended dosing regimen for up to 4 years.

Because of the low occurrence of anti-drug antibodies, the effect of these antibodies on the pharmacokinetics, pharmacodynamics, safety, and/or effectiveness of anifrolumab products is unknown.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic and genotoxic potential of anifrolumab have not been evaluated. In rodent models of IFNAR1 blockade, increased carcinogenic potential has been observed. The clinical relevance of these findings is unknown.

Effects on male and female fertility have not been directly evaluated in animal studies. No anifrolumab-related adverse effects on indirect measures of male or female fertility, based on semen analysis, spermatogenesis staging, menses cycle, organ weights and histopathological findings in the reproductive organs were observed in 9-month repeat-dose toxicity studies in cynomolgus monkeys at doses up to 50 mg/kg intravenous once weekly (approximately 58-times the MRHD on an AUC basis).

14 CLINICAL STUDIES

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 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 who had severe active lupus nephritis and patients who had severe active central nervous system 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. All three studies were conducted in North America, Europe, South America and Asia. Patients received anifrolumab 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).

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 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 visual analogue scale (VAS);
- No discontinuation of treatment;
- No use of restricted medication beyond the protocol-allowed threshold.

Trial 1 randomized 305 patients (1:1:1) who received anifrolumab, 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 (<10 mg/day and \leq 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 150 mg, 300 mg or placebo (1:2:2). Trial 3 randomized 362 patients (1:1) who received anifrolumab 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 300 mg versus placebo; a dose of 150 mg was also evaluated for dose-response in Trial 2.

Patient demographics and disease characteristics were generally similar and balanced across treatment arms (Table 2).

Table 2 Demographics and Baseline Characteristics

	Total Population		
	Trial 1 (N = 305)	Trial 2 (N = 457)	Trial 3 (N = 362)
Mean Age (years)	40	41	42

	Total Population		
	Trial 1 (N = 305)	Trial 2 (N = 457)	Trial 3 (N = 362)
Female (%)	93	92	93
White (%)	42	71	60
Black/African American (%)	13	14	12
Asian (%)	7	5	17
Hispanic or Latino (%)	42	19	30
Baseline SLEDAI-2K score			
Mean (SD)	10.9 (4.1)	11.3 (3.72)	11.5 (3.76)
≥10 points, n (%)	182 (60)	328 (72)	260 (72)
BILAG organ system scoring (Overall)			
At least one A, n (%)	152 (50)	217 (48)	176 (49)
No A and at least 2 Bs, n (%)	134 (44)	211 (46)	169 (47)
Positive Anti-dsDNA levels, n (%)	185 (77)	207 (45)	159 (44)
Abnormal ANA, n (%)	299 (98)	412 (90)	325 (90)
Abnormal Complement C3 level, n (%)	119 (39)	157 (34)	144 (40)
Abnormal Complement C4 level, n (%)	74 (24)	95 (21)	95 (26)
Baseline SLE treatment			
OCS, n (%)	258 (85)	381 (83)	292 (81)
Antimalarials, n (%)	219 (72)	334 (73)	252 (70)
Immunosuppressants, n (%)	150 (49)	214 (47)	174 (48)

Randomization was stratified by disease severity (SLEDAI-2K score at baseline, <10 vs ≥10 points), OCS dose on Day 1 (<10 mg/day vs ≥10 mg/day prednisone or equivalent) and interferon gene signature test results (high vs low).

The reduction in disease activity seen in the BICLA and SRI-4 was related primarily to improvement in the mucocutaneous and musculoskeletal organ systems. Flare rate was reduced in patients receiving SAPHNELO compared to patients who received placebo although the difference was not statistically significant.

BICLA responder analysis: BICLA was the primary endpoint in Trial 3; anifrolumab 300 mg 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. The BICLA results are presented in Table 3.

Table 3 BICLA Response Rate at Week 52

	Trial 1*†		Trial 2*†		Trial 3‡	
	Anifrolumab 300 mg (N=99)	Placebo (N=102)	Anifrolumab 300 mg (N=180)	Placebo (N=184)	Anifrolumab 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)

	Trial 1*†		Trial 2*†		Trial 3‡	
	Anifrolumab 300 mg (N=99)	Placebo (N=102)	Anifrolumab 300 mg (N=180)	Placebo (N=184)	Anifrolumab 300 mg (N=180)	Placebo (N=182)
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.

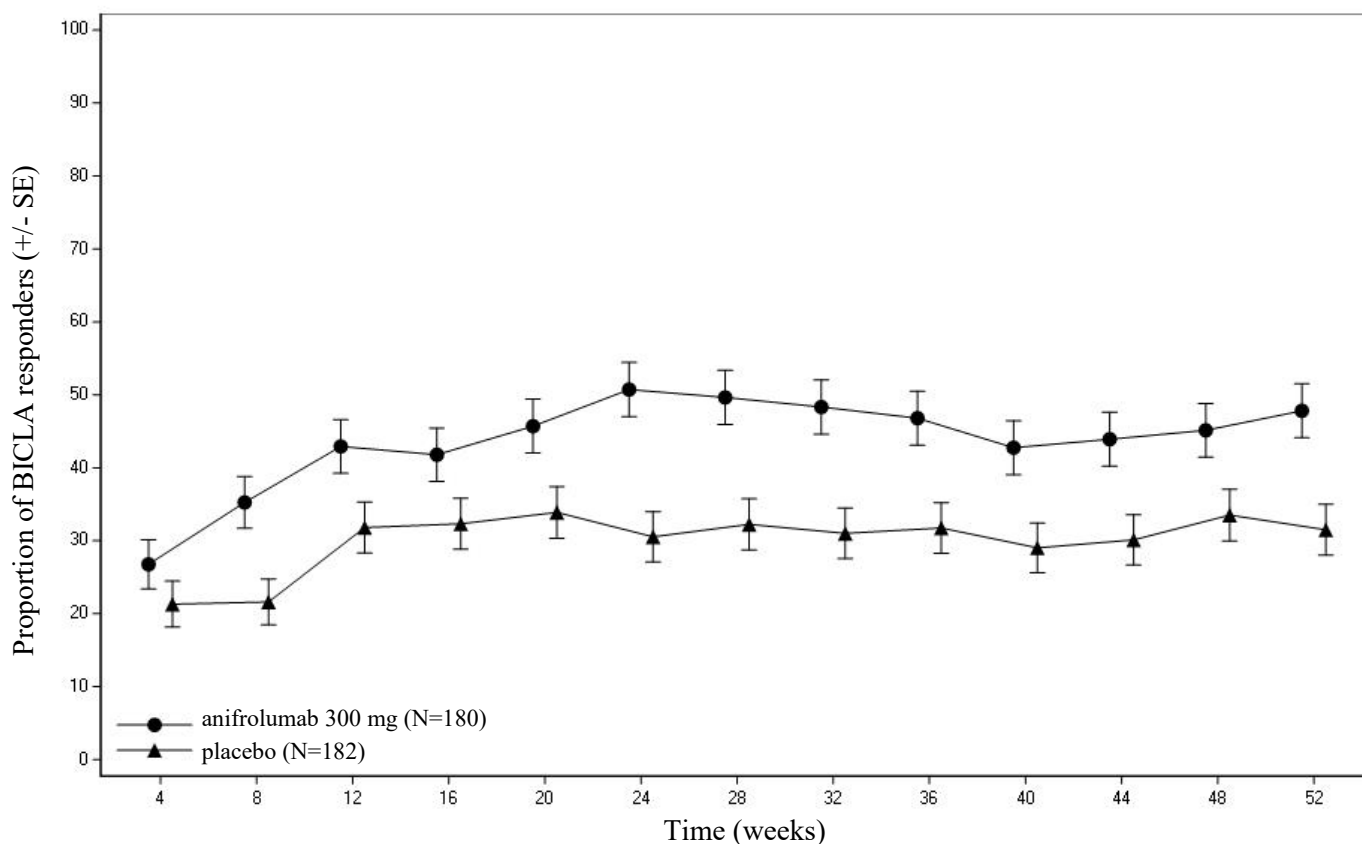
‡ Primary endpoint.

§ 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.

In Trial 3, examination of subgroups by age, race, gender, ethnicity, disease severity [SLEDAI-2K at baseline], and baseline OCS use did not identify differences in response to anifrolumab.

Figure 1 shows the proportion of BICLA responders through the 52-week treatment period in Trial 3.

Figure 1 Trial 3: Proportion (%) of BICLA Responders by Visit*



* The same patients may not have responded at each timepoint.

SRI-4 responder analysis: SRI-4 was the primary endpoint in Trial 2; treatment with anifrolumab 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 Table 4.

Table 4 SRI-4 Response Rate at Week 52

	Trial 1*		Trial 2†		Trial 3*	
	Anifrolumab 300 mg (N=99)	Placebo (N=102)	Anifrolumab 300 mg (N=180)	Placebo (N=184)	Anifrolumab 300 mg (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 (95% CI)	24.0 (10.9, 37.2)		6.0 (-4.2, 16.2)		18.2 (8.1, 28.3)	
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 (39.0)

	Trial 1*		Trial 2†		Trial 3*	
	Anifrolumab 300 mg (N=99)	Placebo (N=102)	Anifrolumab 300 mg (N=180)	Placebo (N=184)	Anifrolumab 300 mg (N=180)	Placebo (N=182)
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 (65.0)	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.

† Primary endpoint.

‡ In all 3 studies, 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. The most commonly involved SLEDAI-2K organ domains were mucocutaneous, musculoskeletal and immune.

Effect on Concomitant Steroid Treatment: In Trial 3, among the 47% of patients with a baseline OCS use ≥ 10 mg/day, anifrolumab demonstrated a statistically significant difference in the proportion of patients able to reduce OCS use by at least 25% to ≤ 7.5 mg/day at Week 40 and maintain the reduction through Week 52 (p-value = 0.004); 52% (45/87) of patients in the anifrolumab group versus 30% (25/83) in the placebo achieved this level of steroid reduction (difference 21% [95% CI 6.8, 35.7]). Consistent trends in favor of anifrolumab compared to placebo, on effect of reduction of OCS use, were observed in Trial 1 and 2, but the difference was not statistically significant.

15 HOW SUPPLIED/STORAGE AND HANDLING

SAPHNELO is available in a carton containing one single-dose vial.

Store in a refrigerator at 2°C to 8°C in the original carton to protect from light.

Do not freeze. Do not shake.

The expiry date of the product is indicated on the packaging materials

License number: 169-50-37020-00

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