NEW ZEALAND DATA SHEET

1. PRODUCT NAME

SAPHNELO®; 150 mg/mL concentrate for solution for 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.

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

For the full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate).

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

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

SAPHNELO (anifrolumab) is indicated as add on treatment of adult patients with moderate to severe, active systemic lupus erythematosus (SLE), despite standard therapy.

The safety and efficacy of SAPHNELO have not been evaluated in patients with severe active lupus nephritis or severe active central nervous system lupus.

4.2 DOSE AND METHOD OF ADMINISTRATION

Treatment should be initiated and supervised by a physician experienced in the treatment of SLE.

Discontinuation of treatment with SAPHNELO should be considered if there is no improvement in disease control after 6 months of treatment.

Dosage

The recommended dose 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. A minimum interval of 14-days should be maintained between doses.

Special patient populations

Renal impairment

No dose adjustment is required. No specific studies with SAPHNELO have been conducted in patients with renal impairment. There is no experience in patients with severe renal impairment or end-stage renal disease (see section 5.2).

Hepatic impairment

No dose adjustment is required. No specific studies have been conducted in patients with hepatic impairment (see section 5.2).

Use in the elderly

No dose adjustment is required. There is limited information in subjects aged ≥ 65 years (see section 5.2).

Use in paediatric patients

The safety and efficacy of SAPHNELO in children and adolescents (aged < 18 years old) have not yet been established. No data are available.

Method of administration

SAPHNELO is for intravenous (IV) use.

Following dilution with sodium chloride (0.9%) solution for injection, SAPHNELO is administered as an IV infusion over a 30-minute period. Do not administer as an intravenous push or bolus injection. For instructions on the dilution and storage of the medicinal product before administration, see section 6.6.

The infusion rate may be slowed or interrupted if the patient develops an infusion reaction.

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Hypersensitivity

Serious hypersensitivity reactions including anaphylaxis have been reported following SAPHNELO administration (see section 4.8).

In the controlled 52-week clinical trials, serious hypersensitivity events (including angioedema) were reported for 0.6% (3/459) of patients receiving anifrolumab. There was one event of anaphylactic reaction in the SLE development program following the administration of anifrolumab.

If a serious infusion-related or hypersensitivity reaction (e.g., anaphylaxis) occurs, administration of SAPHNELO should be interrupted immediately, and appropriate therapy initiated.

Infections

SAPHNELO increases the risk of respiratory infections and herpes zoster (disseminated herpes zoster events have been observed), see section 4.8.

In the placebo-controlled 52-week clinical trials, serious and sometimes fatal infections have occurred in patients receiving anifrolumab.

In the placebo-controlled long-term extension (LTE), up to an additional 3 years on treatment, the EAIRs of serious infections in patients receiving anifrolumab and placebo were similar to those observed in the 52-week trials.

Due to the mechanism of action, SAPHNELO should be used with caution in patients with a chronic infection, a history of recurrent infections, or known risk factors for infection. Treatment with SAPHNELO should not be initiated 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 therapy, monitor the patient closely and consider interrupting SAPHNELO therapy until the infection resolves.

Studies in patients with a history of primary immunodeficiency have not been conducted.

The placebo-controlled clinical trials excluded patients with a history of active tuberculosis (TB) or latent TB in whom an adequate course of treatment could not be confirmed. Anti-tuberculosis (anti-TB) therapy should be considered prior to initiation of anifrolumab in patients with untreated latent TB. Anifrolumab should not be administered to patients with active TB.

Immunisations

No data are available on the response to live or attenuated vaccines.

Prior to initiating therapy with SAPHNELO, consider completion of all appropriate immunisations according to current immunisation guidelines. Avoid concurrent use of live or attenuated vaccines in patients treated with SAPHNELO.

Malignancy

The impact of SAPHNELO treatment on the potential development of malignancies is not known. Studies in patients with a history of malignancy have not been conducted; however, patients with squamous or basal cell skin cancers and uterine cervical cancer that had been fully excised or adequately treated were eligible for enrolment in the SLE clinical trials.

In controlled 52-week clinical trials, at any dose, malignancies (excluding non-melanoma skin cancers) were observed in 0.7% (5/657) and 0.6% (3/466) of patients receiving SAPHNELO and placebo, respectively. Malignant neoplasm (including non-melanoma skin cancers) was reported for 1.2% (8/657) patients receiving anifrolumab, compared to 3/466 (0.6%) patients receiving placebo (EAIR: 1.2 and 0.7 per 100 patient years, respectively). In patients receiving anifrolumab, breast and squamous cell carcinoma were the malignancies observed in more than one patient.

The EAIRs for malignancy over 4 years (3-year long-term extension combined with the 52-week trials) were 0.8 and 0.7 events per 100 patient years for anifrolumab (at any dose) and placebo, respectively. The types of malignancies reported in the LTE were consistent with the 52-week trials.

Individual benefit-risk should be considered in patients with known risk factors for the development or reoccurrence of malignancy. Caution should be exercised when considering continuing SAPHNELO therapy for patients who develop malignancy.

4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

No formal drug-drug interaction studies have been performed with SAPHNELO.

4.6 FERTILITY, PREGNANCY AND LACTATION

Pregnancy

There is a limited amount of data from the use of anifrolumab in pregnant women. The data are insufficient to inform on drug associated risk.

In a pre- and post-natal development study, following IV administration of anifrolumab, no adverse effects on maternal animals or their offspring were observed (see section 5.3).

SAPHNELO should not be used during pregnancy unless the potential benefit justifies the potential risk to the foetus.

Breast-feeding

It is not known whether anifrolumab is excreted in human milk. Anifrolumab was detected in the milk of female cynomolgus monkeys administered 30 or 60 mg/kg intravenously every 2 weeks (see section 5.3).

A risk to the breast-fed child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue SAPHNELO therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the mother.

Fertility

There are no data on the effects of anifrolumab on human fertility.

Animal studies show no adverse effects of anifrolumab treatment on indirect measures of fertility (see section 5.3).

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

SAPHNELO has no or negligible influence on the ability to drive and use machines.

4.8 UNDESIRABLE EFFECTS

Overall summary of the safety profile

The data described in Table 1 reflect the exposure to SAPHNELO 300 mg administered by IV infusion every 4 weeks compared to placebo in 925 patients with moderate or severe SLE, in the 52-week Phase II and Phase III controlled trials (Trials 1, 2, and 3).

Adverse events were reported in 86.9% of patients receiving anifrolumab and 79.4% of patients receiving placebo. The most commonly reported adverse events (≥ 5%) during anifrolumab treatment, irrespective of causality, were nasopharyngitis, upper respiratory tract

infection, urinary tract infection, bronchitis, infusion-related reaction, headache, herpes zoster, back pain, sinusitis and cough.

During the controlled 52-week clinical trials, the proportion of patients with serious adverse events was 11.8% for anifrolumab and 16.7% for placebo.

The proportion of patients who discontinued treatment due to adverse events was 4.1% for anifrolumab and 5.2% for placebo.

Adverse Drug Reactions

Adverse drug reactions (ADRs) are organised by MedDRA System Organ Class (SOC). Within each SOC, preferred terms are arranged by decreasing frequency and then by decreasing seriousness. Frequencies of occurrence of adverse reactions are defined as:

- very common (≥ 1/10);
- common (≥ 1/100 to < 1/10);
- uncommon (≥ 1/1,000 to < 1/100);
- rare (≥ 1/10,000 to < 1/1000);
- very rare (< 1/10,000);
- not known (cannot be estimated from available data).

Table 1. Adverse drug reactions

MedDRA SOC	**MedDRA Preferred Term**	**SAPHNELO (N = 459)**	**Placebo (N = 466)**
Infections and infestations	Upper respiratory tract infection*	Very common (32.9%)	Very common (21.2%)
	Bronchitis*	Very common (10.5%)	Common (4.5%)
	Herpes Zoster	Common (6.1%)	Common (1.3%)
	Respiratory tract infection*	Common (3.1%)	Common (1.3%)
Immune system disorders	Hypersensitivity	Common (2.8%)	Uncommon (0.6%)
	Anaphylactic reaction	Uncommon[§]	-
Injury, poisoning and procedural complications	Infusion related reaction	Common (9.4%)	Common (7.1%)

All patients received standard therapy.

* Grouped terms: 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).

§ Frequency 'uncommon' (0.1%): based on one event of anaphylactic reaction reported in SLE patients who received IV anifrolumab at any dose (N = 837), see section 4.4.

Summary of post-marketing data

The following adverse reactions have been identified during post approval use of SAPHNELO. It is generally not possible to reliably determine the frequency because such reactions have been reported spontaneously from a population of uncertain size and therefore represent reporting rates. The frequency of these adverse reactions is therefore 'not known' (cannot be estimated from available data).

Musculoskeletal and connective tissue disorders: Arthralgia

Long-term safety

Patients who completed Trials 2 and 3 (Phase III feeder trials) through Week 52 were eligible to continue on treatment in a randomised, double-blind, placebo-controlled LTE for an additional 3 years (Trial 4, see section 5.1). The long-term safety of SAPHNELO was assessed in 257 patients who received anifrolumab 300 mg administered by intravenous infusion once every 4 weeks, compared to 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 anifrolumab was consistent with the 52-week trials.

Description of selected adverse reactions

Hypersensitivity and infusion-related reactions

Hypersensitivity reactions were predominantly mild to moderate in intensity and did not lead to discontinuation of anifrolumab. Following treatment with anifrolumab, serious hypersensitivity was reported in 0.6% of patients in the controlled clinical-trials and one event of anaphylactic reaction was reported in the SLE development program (see section 4.4).

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

Respiratory infections (upper respiratory tract infection, respiratory tract infection and bronchitis)

Infections were predominantly non-serious, mild or moderate in intensity and resolved without discontinuation of anifrolumab (see section 4.4).

Herpes zoster

Herpes zoster infections were predominantly of localised cutaneous presentation, mild or moderate in intensity and resolved without discontinuation of anifrolumab. Cases with multidermatomal involvement and disseminated presentation have been reported (see section 4.4).

In the LTE, the EAIR of herpes zoster in patients treated with SAPHNELO declined over time relative to the 52-week trials. By year 4 on treatment the EAIR of herpes zoster in patients treated with SAPHNELO and placebo were similar.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions via https://pophealth.my.site.com/carmreportnz/s/.

4.9 OVERDOSE

In clinical trials, doses of up to 1000 mg have been administered intravenously in patients with SLE with no evidence of dose limiting toxicities.

There is no specific treatment for an overdose with anifrolumab. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Immunosuppressants, Monoclonal antibodies, ATC code: L04AG11.

Mechanism of action
Anifrolumab is a human immunoglobulin G1 kappa monoclonal antibody that binds to subunit 1 of the type I interferon receptor (IFNAR1) with high specificity and affinity. This binding inhibits type I IFN signalling, thereby blocking the biologic activity of type I IFNs. Anifrolumab also induces the internalisation of IFNAR1, thereby reducing the levels of cell surface IFNAR1 available for receptor assembly. Blockade of receptor mediated type I IFN signalling inhibits IFN responsive gene expression, as well as downstream inflammatory and immunological processes. Inhibition of type I IFN blocks plasma cell differentiation and normalises peripheral T-cell subsets, restoring the balance between adaptive and innate immunity that is dysregulated in multiple autoimmune disorders.

Type I IFNs play an important role in the pathogenesis of SLE. Most adult patients with SLE (approximately 60-80%) express elevated levels of type I IFN inducible genes, which are associated with increased disease activity and severity.

Pharmacodynamics

In adult patients with SLE, administration of anifrolumab at doses ≥300 mg, via IV infusion every 4 weeks, demonstrated consistent neutralisation (≥80%) of a 21-gene type I interferon pharmacodynamic (PD) signature in blood. This suppression occurred as early as 4 weeks post-treatment and was either maintained or further suppressed over the 52-week treatment period. Anifrolumab 150 mg IV, showed < 20% suppression of the gene signature at early timepoints, that reached a maximum of < 60% by the end of the treatment period.

Neutralisation (≥70%) of the type I IFN PD signature has also been observed in skin tissue as shown in a Phase I trial in patients with scleroderma (anifrolumab ≥1.0 mg/kg).

Following withdrawal of anifrolumab at the end of the 52-week treatment period in the SLE clinical trials, the type I IFN PD signature in blood samples returned to baseline levels within 8 to 12 weeks.

In the Phase III trials in SLE patients positive for anti-dsDNA antibodies at baseline, treatment with anifrolumab 300 mg led to numerical reductions in anti-dsDNA antibodies over time (median change from baseline at Week 52: -14.82 U/mL anifrolumab vs -5.37 U/mL placebo). At Week 52, 7.8% (13/167) of patients treated with anifrolumab and 5.8% (9/155) of patients receiving placebo had converted to anti-dsDNA negative.

In patients with low C3 levels at baseline, treatment with anifrolumab 300 mg led to greater numerical increases in C3 over the 52-week treatment period (mean change from baseline at Week 52: 0.13 g/L anifrolumab vs 0.04 g/L placebo). For patients with an abnormal C4 level at baseline, small increases were observed over the 52 weeks in both treatment groups (mean change from baseline at Week 52: 0.02 g/L anifrolumab vs 0.02 g/L placebo). In patients with low complement levels at baseline, normalisation of C3 and C4 was observed in 16.2% (21/130) and 22.6% (19/84) of patients receiving anifrolumab and in 9.5% (13/137) and 7.1% (6/85) of patients receiving placebo, respectively, at Week 52.

Treatment with anifrolumab 300 mg led to significantly ($p < 0.05$) increased numbers of T-cell subsets in patients with a high interferon gene signature. Normalised T-cell subset counts were observed as early as Week 12 and through Week 52.

Compared with placebo, anifrolumab 300 mg inhibited the production of proteins involved in B cell survival and recruitment (CXCL13, BAFF). Inhibition was observed as early as Week 12 and maintained through Week 52, which is consistent with the down regulation of certain autoantibody levels by anifrolumab.

Immunogenicity

In the Phase III trials, treatment-emergent anti-drug antibodies were detected in 6 out of 352 (1.7%) patients treated with SAPHNELO at the recommended dosing regimen during the 60-week study period. A total of 0.3% (1/351) of patients treated with SAPHNELO developed *in-vitro* detected neutralising antibodies. Anti-anifrolumab antibodies were not associated with increased clearance of anifrolumab or loss of pharmacodynamic activity compared to anti-drug antibody negative patients. No evidence of an association of anti-drug antibodies with efficacy or safety was observed.

In the LTE (years 2 through 4 on treatment), treatment-emergent anti-drug antibodies were detected in an additional 5 patients treated with SAPHNELO, no neutralising antibodies were detected.

Clinical Efficacy and Safety

The safety and efficacy of SAPHNELO were evaluated in three 52-week treatment period, multicentre, randomised, double-blind, placebo-controlled trials (Trial 1 [MUSE], Trial 2 [TULIP 1] and Trial 3 [TULIP 2]). Patients were diagnosed with SLE according to the American College of Rheumatology (1997 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 clinical trials; patients receiving other biologic therapies were required to complete a wash-out period of at least 5 half-lives prior to enrolment. All three trials were conducted in North America, Europe, South America and Asia. Patients received anifrolumab or placebo, administered by IV infusion, every 4 weeks.

Phase II

In Trial 1 (*NCT01438489*) 305 patients were randomised (1:1:1) and received anifrolumab 300 mg or 1000 mg, or placebo. The primary endpoint was a combined assessment of the SLE Responder Index (SRI-4, a composite endpoint) and the sustained reduction in OCS (< 10 mg/day and ≤ OCS dose at week 1, sustained for 12 weeks) measured at Week 24; a significantly higher proportion of anifrolumab 300 mg-treated patients achieved SRI-4 response and sustained OCS reduction (anifrolumab: placebo 34.3% vs 17.6%). Pre-specified analysis of disease activity measured by the British Isles Lupus Assessment Group based Composite Lupus Assessment (BICLA) was 53.5% for anifrolumab and 25.1% for placebo, at Week 52. The dose-response modelling and benefit-risk profile supported the evaluation of the 300 mg dose in the subsequent trials; the 1000 mg dose is not recommended.

Phase III

Trial 2 and 3 were similar in design, the primary endpoint was improvement in disease activity evaluated at 52 weeks, measured by SRI-4 and BICLA, respectively. The common secondary efficacy endpoints included in both trials were the response rate in the interferon gene signature test-high subgroup (using the primary endpoint measure), maintenance of OCS reduction, improvement in cutaneous SLE activity measured by Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) and annualised flare rate. An assessment of improvement in joint activity was included as a secondary endpoint in Trial 3. Both trials 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 were generally similar in both trials; the median age was 41.3 and 42.1 years (range 18-69), 4.4% and 1.7% were ≥65 years of age, 92% and 93% were female, 71% and 60% were White, 14% and 12% were Black/African American, and 5% and 17% were Asian, in Trials 2 and 3 respectively. In both trials, 72% of patients had high disease activity (SLEDAI-2K score ≥10). In Trials 2 and 3 respectively, 48% and 49% had severe disease (BILAG-A) in at least 1 organ system and 46% and 47% of patients 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 mucocutaneous (Trial 2: 87%, Trial 3: 85%) and musculoskeletal (Trial 2: 89%, Trial 3: 88%) systems; 7.4% and 8.8% of patients had cardiorespiratory, and 7.9% and 7.5% had renal manifestations at baseline, in Trials 2 and 3 respectively.

In Trials 2 and 3, 90% of patients (both trials) were seropositive for anti-nuclear antibodies (ANA), and 45% and 44% for anti–double-stranded DNA (anti-dsDNA) antibodies; 34% and 40% of patients had low C3, and 21% and 26% had low C4.

Patients were tested prospectively for overexpression of four type I interferon-inducible genes in whole blood samples at a central laboratory using a polymerase chain reaction (PCR)-based method (QIAGEN therascreen® IFIGx RGQ RT-PCR). In both trials, the majority of patients were classified as interferon gene signature test-high at baseline (Trial 2: 82%, Trial 3: 83%).

Baseline concomitant standard therapy medications included oral corticosteroids (Trial 2: 83%, Trial 3: 81%), antimalarials (Trial 2: 73%, Trial 3: 70%) and immunosuppressants (Trial 2: 47%, Trial 3: 48%; including azathioprine, methotrexate, mycophenolate and mizoribine). For those patients taking OCS (prednisone or equivalent) at baseline, the mean daily dose was 12.3 mg in Trial 2 and 10.7 mg in Trial 3. 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.

Randomisation 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).

Trial 2 (NCT02446912)

In Trial 2, 457 patients were randomised (1:2:2) and received anifrolumab 150 mg or 300 mg, or placebo. The primary endpoint, 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 subjects' 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 thresholds.

For the primary endpoint (SRI-4 at Week 52), treatment with anifrolumab did not result in statistically significant improvements over placebo (p-value = 0.455). The secondary endpoints were not formally tested; however, clinically meaningful improvements in BICLA response, sustained OCS dose reduction, CLASI response, flare rate and joint response were observed for patients receiving anifrolumab 300 mg compared to those receiving placebo. The BICLA responder rate was 47.1% (85/180) for anifrolumab 300 mg versus 30.2% (55/184) for placebo (difference 17.0%, 95% CI 7.2, 26.8, nominal p-value < 0.001). There was no consistent pattern of efficacy across the endpoints or over time in patients receiving anifrolumab 150 mg. The 150 mg dose is not recommended.

Trial 3 (NCT02446899)

In Trial 3, 362 patients were randomised (1:1) and received anifrolumab 300 mg or placebo. The primary endpoint, 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 subjects' 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 thresholds.

The primary endpoint was met; anifrolumab 300 mg demonstrates statistically significant and clinically meaningful efficacy in overall disease activity compared with placebo. Greater improvements in all components of the BICLA composite endpoint were observed for anifrolumab compared to placebo (Table 2).

Table 2. Trial 3: BICLA response rate at Week 52

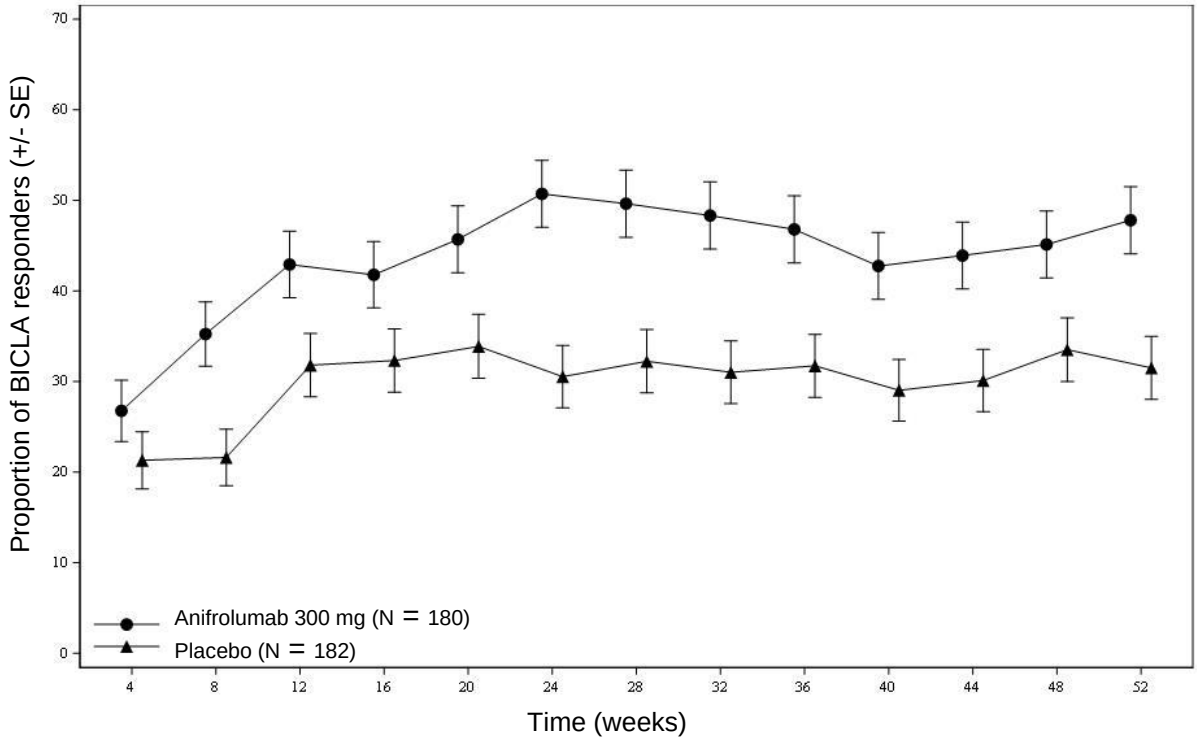
	Anifrolumab 300mg (N = 180)	**Placebo (N = 182)**
BICLA response rate		
Responder, n (%)	86 (47.8)	57 (31.5)
Difference in Response Rates (95% CI)	16.3% (6.3, 26.3)	
p-value (2-sided)	0.0013	
Components of BICLA response		
BILAG improvement, n (%) †	88 (48.9)	59 (32.4)
No worsening of SLEDAI-2K, n (%) †	122 (67.8)	94 (51.6)

	Anifrolumab 300mg (N = 180)	Placebo (N = 182)
No worsening of PGA, n (%) †	122 (67.8)	95 (52.2)
No discontinuation of treatment, n (%)	153 (85.0)	130 (71.4)
No use of restricted medication beyond protocol allowed threshold, n (%)	144 (80.0)	123 (67.6)

All patients received standard therapy.
BICLA: British Isles Lupus Assessment Group-based Composite Lupus Assessment, BILAG: British Isles Lupus Assessment Group, PGA: Physician's Global Assessment, SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index 2000.
† Patients who discontinued treatment or used restricted medications beyond protocol allowed threshold are considered non-responders.

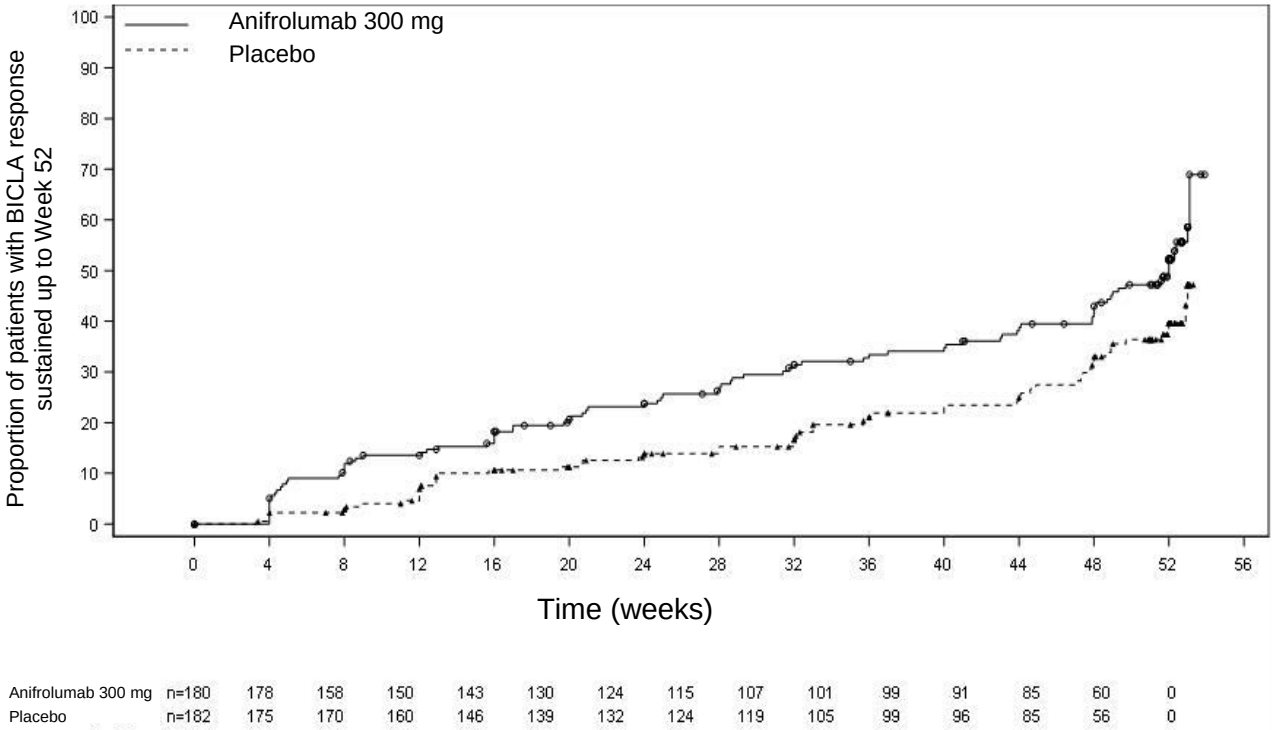
Clinically meaningful differences in BICLA response rate was observed as early as Week 8 and were maintained through to Week 52 (Figure 1).

Figure 1. Trial 3: Proportion of BICLA responders by visit



Treatment with anifrolumab reduced the time to the first visit at which BICLA response was attained and subsequently sustained up to, and including, Week 52. At any time during the study, patients treated with anifrolumab were 55% more likely to achieve a sustained BICLA response, relative to patients receiving placebo (hazard ratio = 1.55, 95% CI 1.11, 2.18). Separation between the treatment arms began at approximately Week 4 (Figure 2).

Figure 2. Trial 3: Kaplan-Meier curve for time to BICLA response sustained up to Week 52



Anifrolumab 300 mg	n=180	178	158	150	143	130	124	115	107	101	99	91	85	60	0
Placebo	n=182	175	170	160	146	139	132	124	119	105	99	96	85	56	0

Patients without a BICLA response sustained up to Week 52 were censored at the date of treatment discontinuation, or Week 52, whichever occurred earlier.

The treatment effect of anifrolumab relative to placebo was consistent across subgroups (by age, gender, race, ethnicity, disease severity [SLEDAI-2K at baseline] and baseline OCS use).

Pre-specified analysis of disease activity measured by SRI-4 was consistent with the response measured by BICLA (SRI-4 responder rate; anifrolumab 55.5% vs placebo 37.3%; difference 18.2% [95% CI 8.1, 28.3]).

Effect on Concomitant Steroid Treatment: In the 47% of patients with a baseline OCS use ≥ 10 mg/day, anifrolumab demonstrated a statistically significant and clinically meaningful reduction in OCS use to ≤7.5 mg/day at Weeks 40 maintained through to Week 52 (p-value = 0.0135); 51.5% (45/87) of patients in the anifrolumab group versus 30.2% (25/83) in the placebo achieved this level of steroid reduction (difference 21.2% [95% CI 6.8, 35.7]). In patients with a baseline OCS use ≥ 10 mg/day, the cumulative OCS dose was lower in patients treated with anifrolumab compared to placebo. The median (min, max) cumulative OCS dose at Week 52 was 3197 mg (309, 13265) in the anifrolumab group compared to 3640 mg (1745, 10920) for the placebo group.

Effect on cutaneous SLE activity: In patients with moderate to severe skin disease at baseline (CLASI activity score ≥ 10; n = 89), anifrolumab demonstrated statistically significant and clinically meaningful improvements in cutaneous lupus activity (CLASI response defined as, at least 50% reduction in CLASI activity score compared to baseline) at Week 12 (responder rate 49.0% [24/49] and 25.0% [10/40] for the anifrolumab and placebo group, respectively; observed difference 24.0% [95% CI 4.3, 43.6], p-value = 0.017). Compared to placebo, the treatment benefit of anifrolumab was maintained through Week 52. At any time during the study, patients treated with anifrolumab were 55% more likely to achieve a sustained CLASI response (defined as a CLASI response attained at any time during the study and

subsequently sustained at all visits through to Week 52), relative to patients receiving placebo (hazard ratio = 1.55, 95% CI 0.87, 2.85).

Effect on SLE Flares: Disease flare was defined as severe disease activity (BILAG-A) in one, or more, new organ system, or moderate disease activity (BILAG-B) in 2 or more new organ systems compared to the previous visit. In Trial 3, 68.9% (124/180) of patients receiving anifrolumab experienced no SLE flares compared to 57.7% (105/182) of patients receiving placebo, during the 52-week treatment period. Treatment with anifrolumab led to a clinically meaningful 33% reduction of the annual flare rate versus placebo (annualised rate 0.43 and 0.64 for the anifrolumab and placebo group, respectively; rate ratio 0.67 [95% CI 0.48, 0.94], p-value = 0.020); this difference was not statistically significant following adjustment for multiple comparisons. The time to first flare was longer in the anifrolumab group, at any time during the study patients had a 35% lower risk of experiencing a first flare relative to patients receiving placebo (hazard ratio = 0.65; 95% CI 0.46, 0.91).

Effect on joint activity: At baseline, 44% of patients had ≥ 6 swollen and ≥ 6 tender joints. Response was defined as ≥ 50% improvement in swollen/tender joint count at Week 52. There was no notable difference in joint response between treatment groups (response rate 42.2% [30/71] and 37.5% [34/90] for the anifrolumab and placebo group, observed difference 4.7% [95% CI -10.6, 20.0], p-value = 0.547).

Health-Related Outcomes: The proportion of patients who reported improvement in fatigue, as measured by FACIT-F responder rate (improvement from baseline at Week 52 of > 3 points), was 33.2% for anifrolumab and 24.7% for placebo (difference 8.5%, 95% CI -0.9, 17.9).

Phase III long-term extension (NCT02794285)

Patients who completed Trials 2 and 3 (feeder trials) were eligible to continue on treatment in a randomised, double-blind, placebo-controlled, 3-year LTE (Trial 4). Patients who had received anifrolumab, either 150 mg or 300 mg, in Trials 2 and 3 received anifrolumab 300 mg in Trial 4. Patients who had received placebo in Trials 2 and 3 were re-randomised 1:1 to receive either anifrolumab 300 mg or placebo, giving an approximate anifrolumab 300 mg: placebo ratio of 4:1 in Trial 4.

The long-term efficacy of anifrolumab was evaluated in patients who received anifrolumab 300 mg or placebo in both a feeder trial and the LTE. The long-term data for patients receiving anifrolumab 300 mg indicate a sustained reduction in disease activity over time, as measured by mean SLEDAI-2K. In Trial 4, investigators were permitted to change a patients' use of OCS according to best clinical judgment and there was no protocol mandated OCS taper; during Trial 4 the overall use of OCS continued to decrease in the anifrolumab 300 mg group, compared to placebo.

During Trial 4, the EAIR of adverse events leading to discontinuation was 1.9 and 2.1 per 100 patient years for patients receiving anifrolumab and placebo, respectively. The EAIR of serious adverse events was 8.6 per 100 patient years for anifrolumab and 11.4 per 100 patient years for placebo.

5.2 PHARMACOKINETIC PROPERTIES

The pharmacokinetics (PK) of anifrolumab was studied in adult patients with SLE following IV doses ranging from 100 to 1000 mg, once every 4 weeks, and healthy volunteers following a single dose.

Anifrolumab exhibits nonlinear PK in the dose range of 100 mg to 1000 mg. PK exposure decreased more rapidly at doses lower than 300 mg every 4 weeks (the recommended dosage).

Absorption

SAPHNELO is administered by intravenous infusion.

Distribution

Based on population pharmacokinetic analysis, the estimated central and peripheral volumes of distribution for anifrolumab were 2.93 L (with 26.9% CV inter-individual variability) and 3.3 L, respectively for a 69.1 kg patient.

Biotransformation

Anifrolumab is a protein, therefore specific metabolism studies have not been conducted.

SAPHNELO is eliminated by target IFNAR mediated elimination pathway and reticuloendothelial system where SAPHNELO is expected to be degraded, into small peptides and individual amino acids, by proteolytic enzymes that are widely distributed in the body.

Elimination

There was a greater-than-dose-proportional increase in drug exposure due to IFNAR1-mediated drug clearance.

From population PK modelling, the estimated typical systemic clearance (CL) was 0.193 L/day with a 33.0% CV inter-individual variability. The median CL decreases slowly over time, with 8.4% after 1 year of treatment. Following long-term observations, the clearance of anifrolumab was found to be stable in years 2 through 4 on treatment.

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

Special 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.

Elderly patients (≥ 65 years old)

Based on the population PK analysis, age (range 18 to 69 years) did not impact the clearance of anifrolumab; there were 20 (3%) patients ≥ 65 years of age. No overall differences in safety or effectiveness were observed between older and younger patients who received anifrolumab in clinical trials.

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 m^2) and moderate decrease in eGFR (30-59 mL/min/1.73 m^2) values and patients with normal renal function (≥ 90 mL/min/1.73 m^2). SLE patients with a severe decrease in eGFR or end-stage renal disease (< 30 mL/min/1.73 m^2) were excluded from the clinical trials; 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.

As an IgG1 monoclonal antibody, anifrolumab is principally eliminated via catabolism and is not expected to undergo metabolism via hepatic enzymes, as such changes in hepatic function are unlikely to have any effect on the elimination of anifrolumab. Based on population pharmacokinetic analyses, baseline hepatic function biomarkers (ALT and AST ≤2.0 × ULN, and total bilirubin) had no clinically relevant effect on anifrolumab clearance.

Drug-Drug Interaction

No formal drug interaction studies have been conducted with anifrolumab. An effect of anifrolumab on the pharmacokinetics of co-administered medications is not expected.

Based on population PK analyses, concomitant use of oral corticosteroids, antimalarials, immunosuppressants [including azathioprine, methotrexate, mycophenolate and mizoribine], NSAIDS, ACE inhibitors, HMG-CoA reductase inhibitors did not significantly influence the PK of anifrolumab.

5.3 PRECLINICAL SAFETY DATA

Non-clinical

Non-clinical data reveal no special hazards for humans based on conventional studies of safety pharmacology or repeated dose toxicity studies in cynomolgus monkeys.

Mutagenicity and carcinogenicity

Anifrolumab is a monoclonal antibody, as such genotoxicity and carcinogenicity studies have not been conducted.
In rodent models of IFNAR1 blockade, increased carcinogenic potential has been observed. The clinical relevance of these findings is unknown.

Reproductive toxicity

Developmental toxicity

In a pre- and post-natal development study, conducted in cynomolgus monkeys, there were no maternal, embryo-foetal, or post-natal developmental effects observed for anifrolumab doses 30 or 60 mg/kg administered intravenously (exposures up to approximately 28-times the exposure at the maximum recommended human dose [MRHD] on an AUC basis) from Gestation Day 20, once every 2 weeks thereafter, throughout gestation to 1 month postpartum (approximately Lactation Day 28).

Fertility

Effects on male and female fertility have not been directly evaluated in animal studies. In the 9-month repeat dose study, there were 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, in cynomolgus monkeys at doses up to 50 mg/kg IV once weekly (approximately 58-times the MRHD on an AUC basis).

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

- L-Histidine
- L-Histidine hydrochloride monohydrate
- L-Lysine hydrochloride
- Trehalose dihydrate
- Polysorbate 80
- Water for injection

6.2 INCOMPATIBILITIES

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 SHELF LIFE

Unopened vial

36 months.

Diluted solution for infusion

If not used immediately, chemical and physical in-use stability has been demonstrated from the time of vial puncture to the start of administration for no more than:

- 4 hours at room temperature up to 25°C.
- 24 hours in a refrigerator (2 to 8°C).

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Unopened vial

Store in a refrigerator (2 to 8°C).
Store in the original package in order to protect from light.
Do not freeze.

Diluted solution for infusion

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 NATURE AND CONTENTS OF CONTAINER

2.0 mL of concentrate in a 2R clear type I glass vial closed by a Teflon faced elastomeric stopper sealed with an aluminium overseal.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

SAPHNELO is supplied as a single-dose vial. The solution for infusion should be prepared and administered by a healthcare professional, using aseptic technique as follows:

Preparation of solution

1. Visually inspect the vial for particulate matter and discolouration. SAPHNELO is a clear to opalescent, colourless to slightly yellow solution. Discard the vial if the solution is cloudy, discoloured or visible particles are observed. Do not shake the vial.
2. Withdraw and discard 2.0 mL from an infusion bag containing 50 mL or 100 mL of sodium chloride 9 mg/mL (0.9%) solution for injection.
3. Withdraw 2.0 mL from the vial of SAPHNELO and add it to the infusion bag. Mix the solution by gentle inversion. Do not shake.
4. The concentrate does not contain any preservatives. Any concentrate remaining in the vial must be discarded.

Administration

1. It is recommended that the solution for infusion be administered immediately after preparation. If the solution for infusion has been stored in a refrigerator (see section 6.3), allow it to reach room temperature (15 to 25°C) prior to administration.
2. Administer the infusion solution intravenously over 30 minutes through an IV line containing a sterile, low-protein binding 0.2 to 15 micron in-line or add-on filter.
3. To ensure the complete dose of SAPHNELO has been administered, flush the infusion set with 25 mL sodium chloride 9 mg/mL (0.9%) solution for injection at the end of the infusion.
4. Do not co-administer other medicinal products through the same infusion line.

Disposal

Return unused and expired medicines to your local pharmacy for disposal.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

AstraZeneca Limited
PO Box 87453
Meadowbank
Auckland 1742.
Telephone: 0800 684 432

9. DATE OF FIRST APPROVAL

21 August 2025

10. DATE OF REVISION OF THE TEXT

21 August 2025

SAPHNELO is a registered trademark of the AstraZeneca group of companies.

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
N/A	New product

