▼ This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION

SAPHNELO® (anifrolumab)

concentrated solution for infusion and solution for injection

1 NAME OF THE MEDICINE

Anifrolumab.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Vial

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.

Pre-filled pen

Each pre-filled pen contains 120 mg anifrolumab in 0.8 mL.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Vial

Concentrate for solution for infusion (sterile concentrate).

Pre-filled pen

Solution for injection (injection) in prefilled pen.

Clear to opalescent, colourless to slightly yellow 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 either 300 mg, administered as an intravenous infusion over a 30-minute period, every 4 weeks *Or*

120 mg once weekly, administered as a subcutaneous injection.

Missed dose

Intravenous infusion: If a planned infusion is missed, administer SAPHNELO as soon as possible. A minimum interval of 14-days should be maintained between doses administered by intravenous infusion.

Subcutaneous injection: If a subcutaneous dose is missed, instruct the patient to administer SAPHNELO as soon as they remember. Thereafter, the patient can start a new weekly schedule from the day that the missed dose was administered or resume dosing on their usual day of administration providing that a minimum interval of 3-days is maintained between injections.

Transitioning between routes of administration

If transitioning a patient from intravenous administration to subcutaneous administration, the first subcutaneous injection should be administered approximately 2 weeks after the last intravenous dose.

If transitioning a patient from subcutaneous administration to intravenous administration, the first intravenous infusion should be administered approximately 3 to 4 weeks after the last subcutaneous dose.

Method of administration

Intravenous administration (concentrate for solution for infusion in vial)

The SAPHNELO vial 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.

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

SAPHNELO is supplied as a single-dose vial. The solution for infusion should be prepared and administered by a healthcare provider, 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. Product is for single use in one patient only. 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 Shelf life), allow it to reach room temperature (up 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.

Subcutaneous administration (solution for injection in pre-filled pen)

The SAPHNELO pre-filled pen is for subcutaneous single use.

SAPHNELO solution for injection is supplied in a sterile pre-filled pen for individual use.

Do not shake. Do not freeze. Do not expose to heat. Protect from light.

Prior to administration, remove SAPHNELO from the refrigerator and allow it to come to room temperature for 60 minutes.

Visually inspect SAPHNELO for particulate matter and discolouration prior to administration. SAPHNELO is a clear to opalescent, colourless to slightly yellow solution. Discard the pre-filled pen if the solution is cloudy, discoloured or visible particles are observed.

A patient may self-inject or the patient caregiver may administer SAPHNELO subcutaneously after the healthcare provider determines it is appropriate. The healthcare provider should provide proper training in subcutaneous technique and education about signs and symptoms of hypersensitivity reactions (see Section 4.4 Special warnings and precautions for use).

SAPHNELO is administered as a subcutaneous injection into the thigh or abdomen, except for the 5 cm around the navel. If a healthcare provider or caregiver administers the injection, the upper arm can also be used. It should not be injected into areas where the skin is tender, bruised, erythematous or hardened. When injecting in the same region, patients should be advised to use an injection site at least 3 cm away from the last injection site.

Comprehensive instructions for subcutaneous administration of SAPHNELO using a pre-filled pen are provided in the 'Instructions for Use'.

Special populations

Renal impairment

No specific studies with SAPHNELO have been conducted in patients with renal impairment. Based on population pharmacokinetic analysis no dose adjustment is required in patients with mild (eGFR 60-89 mL/min/1.73 m^2) renal impairment. There is no experience in patients with severe active lupus nephritis, severe renal impairment or end-stage renal disease who were all excluded from the clinical studies (see Section 5.2 Pharmacokinetic properties).

Hepatic impairment

No specific studies have been conducted in patients with hepatic impairment. Based on population pharmacokinetic analysis no dose adjustment is required for patients with mild to moderate hepatic impairment.

Use in the elderly

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

Paediatric use

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

4.3 CONTRAINDICATIONS

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

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Hypersensitivity

Serious hypersensitivity reactions including anaphylaxis have been reported following SAPHNELO administration (see Section 4.8 Adverse effects (Undesirable effects)).

In the placebo-controlled 52-week intravenous 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 intravenous 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 Adverse effects (Undesirable effects). SLE patients also taking immunosuppressants may be at higher risk of herpes zoster infections.

In the placebo-controlled 52-week intravenous 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, 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 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

There is an increased risk of malignancies with the use of immunomodulating agents. The impact of SAPHNELO treatment on the potential development of malignancies is not known. Caution should be exercised when considering anifrolumab therapy for patients with a history of malignancy or when considering continuing treatment in patients who develop malignancy.

In the placebo-controlled 52-week intravenous clinical trials, at any dose, malignant neoplasm (including non-melanoma skin cancers) was reported for 1.2% patients receiving SAPHNELO, compared to 0.6% patients receiving placebo (corresponding to exposure-adjusted incidence rates [EAIRs]: 1.2 and 0.7 events per 100 patient years, respectively). Malignancies excluding non-melanoma skin cancers were observed in 0.7% and 0.6% of patients receiving anifrolumab and placebo, respectively. In patients receiving SAPHNELO, 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.

Concomitant use with B-cell targeted 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.

Use in the elderly

See Section 4.2 Dose and method of administration, Use in the elderly.

Paediatric use

No data available.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No interaction studies have been performed with SAPHNELO.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on 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.

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 61 times the maximum recommended human dose [IV MRHD] on an area under the plasma drug concentration over time curve [AUC] basis) and 60 mg/kg SC once weekly (approximately 51-times the SC MRHD on an AUC basis).

Use in pregnancy – Category C

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 postnatal development study, conducted in cynomolgus monkeys, there were no maternal, embryofetal, or postnatal developmental effects observed for anifrolumab doses 30 or 60 mg/kg administered intravenously from Gestation Day 20, once every 2 weeks thereafter, throughout gestation to 1 month postpartum (approximately Lactation Day 28). Exposures were up to approximately 29 times the exposure at the MRHD on an AUC basis. Anifrolumab could be detected in infant circulation, likely due to placental transfer. A higher risk of certain viral

infections could theoretically occur in infants exposed to anifrolumab during the later stage of the gestational period; however, there is no data to support this.

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

Use in lactation

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.

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.

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 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Summary of the safety profile

The safety of SAPHNELO in adult patients with moderate to severe SLE has been evaluated in three 52-week placebo-controlled intravenous clinical trials (Trials 1, 2 and 3) and one 52-week placebo-controlled subcutaneous clinical trial (Trial 5). The overall safety profile of SAPHNELO administered by intravenous infusion (300 mg every 4 weeks) and subcutaneous injection (120 mg every week) is consistent.

The most commonly reported adverse reactions during anifrolumab treatment in the 3 intravenous and 1 subcutaneous clinical trials were upper respiratory tract infection (31%), bronchitis (10%), infusion-related reaction (9.4%), and herpes zoster (6.0%). The most common serious adverse reaction was herpes zoster (0.4%).

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 Pharmacodynamic properties). 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.

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.

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
Infections and infestations	Upper respiratory tract infection*	Very common
	Bronchitis*	Very common
	Herpes Zoster	Common
	Respiratory tract infection*	Common
Immune system disorders	Hypersensitivity	Common
	Anaphylactic reaction	Uncommon§
Injury, poisoning and procedural complications	Infusion related reaction†	Common

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).
§ See Section 4.4 Special warnings and precautions for use and 'Description of selected adverse reactions' below.
† Applies to intravenous infusion route of administration only.

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.

In the intravenous and subcutaneous clinical trials of 52-week treatment duration, following treatment with anifrolumab, serious hypersensitivity was reported in 0.2% of patients. One event of anaphylactic reaction was reported in the intravenous SLE development program (see Section 4.4 Special warnings and precautions for use).

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 Special warnings and precautions for use).

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 Special warnings and precautions for use).

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.

Adverse events

Adverse events (Trials 1, 2 and 3) 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 placebo-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.

Table 2 presents the most common adverse events regardless of causality occurring in at least ≥3% treated with SAPHNELO 300 mg administered by IV infusion every 4 weeks plus standard of care in the 52-week Phase II and Phase III placebo-controlled trials (Trials 1, 2, and 3).

Table 2 Adverse events that occurred in ≥3% of patients treated with SAPHNELO in Trials 1, 2 and 3

Preferred term	**SAPHNELO (N=459)**	**Placebo (N=466)**
	%	**%**
Nasopharyngitis	16.3	9.4
Upper respiratory tract infection	15.5	9.7
Urinary tract infection	12.0	13.5
Bronchitis	9.8	4.3
Infusion related reaction	9.4	7.1
Headache	8.1	9.7
Herpes zoster	6.1	1.3
Back pain	5.2	4.3
Sinusitis	5.2	5.2
Cough	5.0	3.2
Arthralgia	4.8	1.9
Pharyngitis	4.6	3.6
Vomiting	3.9	2.6
Nausea	3.7	5.4
Oral herpes	3.7	2.6
Pneumonia	3.3	2.8
Diarrhoea	3.1	5.4
Respiratory tract infection	3.1	0.4

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

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

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 information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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 biological 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.

Pharmacodynamic effects

Intravenous administration

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.

Subcutaneous administration

In the subcutaneous study in adult patients with SLE, anifrolumab 120 mg once weekly treatment led to levels of interferon gene signature suppression that were consistent with those observed in the intravenous clinical trials with anifrolumab 300 mg administered every 4 weeks.

Immunogenicity

In the Phase III trials, treatment-emergent anti-drug antibodies were detected in 6 out of 352 patients (1.7%) treated with SAPHNELO at the recommended intravenous 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 intravenous SAPHNELO, no neutralising antibodies were detected.

In the subcutaneous Phase III trial, treatment-emergent anti-drug antibodies were detected in 6 out of 107 patients (5.6%) who received SAPHNELO during the 52-week treatment period, no neutralising antibodies were detected.

Clinical trials

SLE – intravenous administration

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) 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 intravenous infusion, every 4 weeks.

In Trial 1, 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.

The Phase III trials, Trial 2 (N=457) and Trial 3 (N=362), were similar in design, the primary endpoint was improvement in disease activity evaluated at 52 weeks, measured by the composite endpoints SRI-4 and BICLA, respectively. The common secondary efficacy endpoints included in both trials were maintenance of OCS reduction, improvement in cutaneous SLE activity measured by Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI), joint activity and annualised flare rate. 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. 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. The results summarised below are those for the recommended dosing regimen (see Section 4.2 Dose and method of administration).

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. 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). The results are presented in Table 3. For consistency, the results presented for Trial 2 represent the post-hoc analysis using the restricted medication thresholds as defined in Trial 3.

Table 3 Efficacy results in adults with SLE in Trial 2 and Trial 3

	Trial 2		Trial 3	
	SAPHNELO 300 mg	**Placebo**	**SAPHNELO 300 mg**	**Placebo**
BICLA response				
Responder rate, % (n/N)	47.1 (85/180)	30.2 (55/184)	47.8 (86/180)	31.5 (57/182)
Difference (95% CI)	17.0%* (7.2, 26.8)		16.3%* (6.3, 26.3)	
Components of BICLA response:				
BILAG improvement, n (%) †	85 (47.2)	58 (31.5)	88 (48.9)	59 (32.4)
No worsening of SLEDAI-2K, n (%) †	121 (67.2)	104 (56.5)	122 (67.8)	94 (51.6)
No worsening of PGA, n (%) †	117 (65.0)	105 (57.1)	122 (67.8)	95 (52.2)
No discontinuation of treatment, n (%)	145 (80.6)	146 (79.3)	153 (85.0)	130 (71.4)
No use of restricted medication beyond protocol allowed threshold, n (%)	140 (77.8)	128 (69.6)	144 (80.0)	123 (67.6)
SRI-4 response				
Responder rate, % (n/N) †	49.0 (88/180)	43.0 (79/184)	55.5 (100/180)	37.3 (68/182)
Difference (95% CI)	6.0 (-4.2, 16.2)		18.2* (8.1, 28.3)	
Sustained OCS reduction [1]				
Responder rate, % (n/N) †	49.7 (51/103)	33.1 (34/102)	51.5% (45/87)	30.2% (25/83)
Difference (95% CI)	16.6* (3.4, 29.8)		21.2%* (6.8, 35.7)	
Reduction in cutaneous SLE activity (CLASI score) [2]				
Responder rate, % (n/N) †	43.6 (25/58)	24.9 (14/54)	49.0% (24/49)	25.0% (10/40)
Difference (95% CI)	18.7%* (1.4, 36.0)		24.0%* (4.3, 43.6)	
Flare rate				
Annualised flare rate estimate (95% CI)	0.57 (0.43, 0.76)	0.68 (0.52, 0.90)	0.43 (0.31, 0.59)	0.64 (0.47, 0.86)
Rate ratio estimate (95% CI)	0.83 (0.61, 1.15)		0.67* (0.48, 0.94)	
Reduction in joint activity [3]				
Responder rate, % (n/N) †	55.6 (51/93)	36.3 (37/100)	42.2 (30/71)	37.5 (34/90)
Difference (95% CI)	19.3* (5.4, 33.2)		4.7% (-10.6, 20.0)	

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; SRI-4: SLE Responder Index; OCS: oral corticosteroids.

All patients received standard therapy.

† Patients who discontinued treatment or used restricted medications beyond protocol allowed threshold are considered non-responders.

* Nominal p-value <0.05

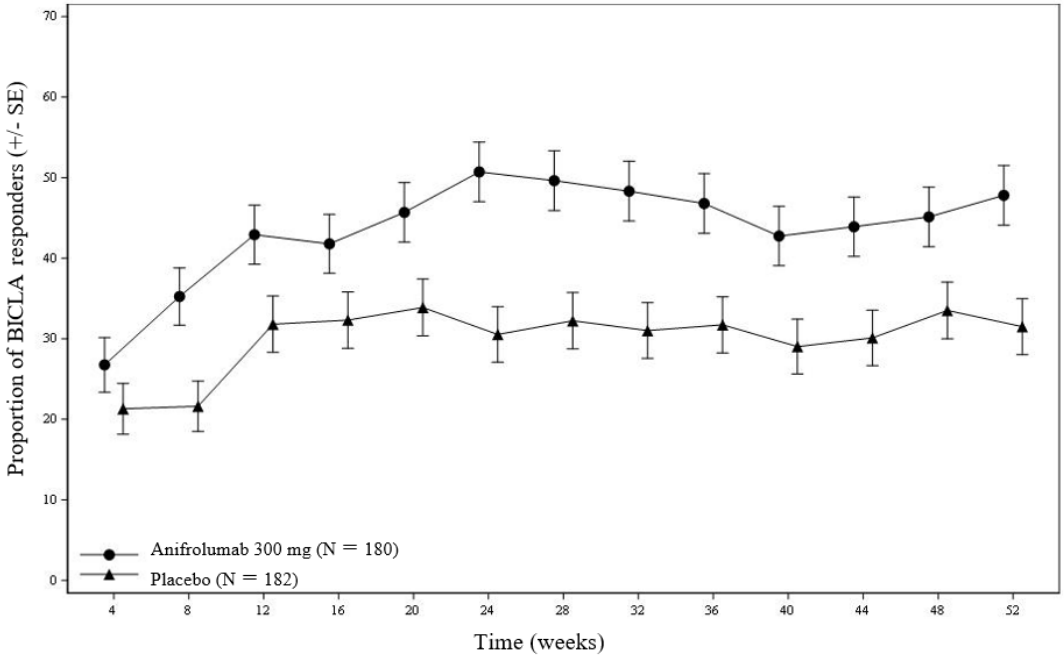
[1] Subgroup of patients with OCS ≥10 mg/day at baseline. Responders were defined as patients with OCS reduction to ≤7.5 mg/day at Week 40, maintained through Week 52.

[2] Subgroup of patients with CLASI activity ≥10 at baseline. Responders were defined as patients with an at least 50% reduction in CLASI activity score compared to baseline, at Week 12.

[3] Subgroup of patients ≥6 swollen and ≥6 tender joints at baseline. Responders were defined as patients with ≥50% improvement in swollen/tender joint count at Week 52.

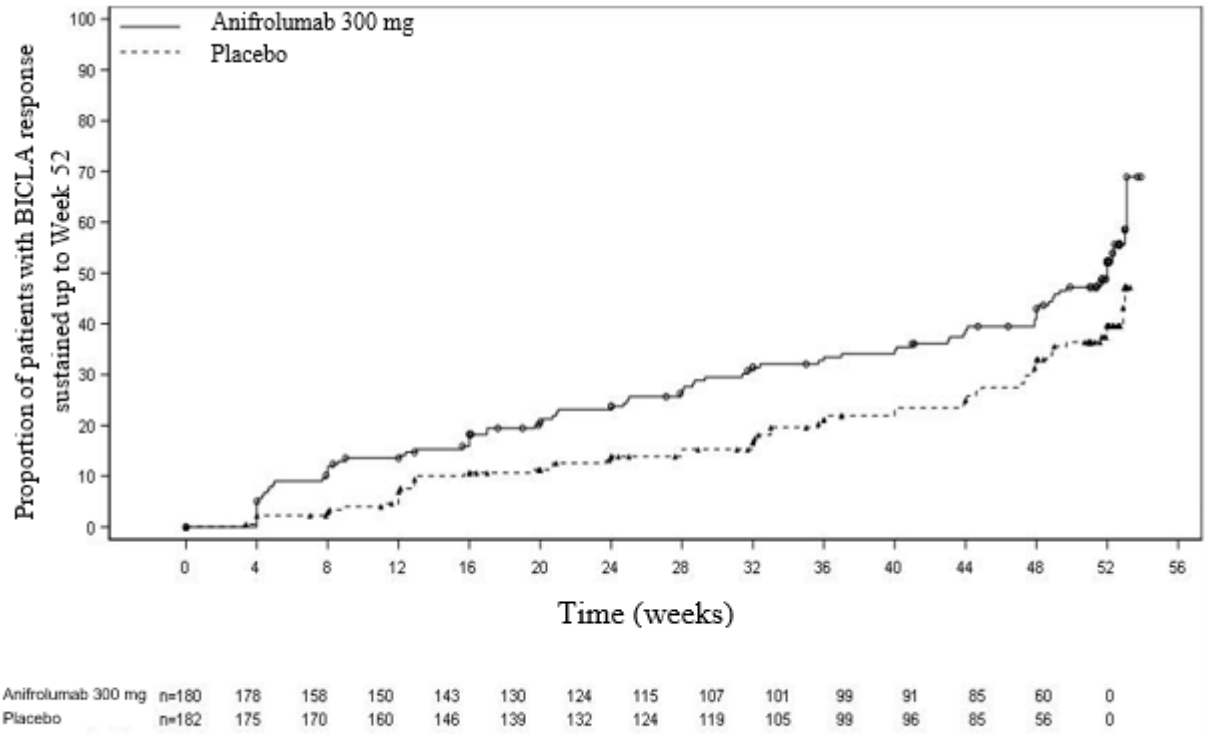
In Trial 3, clinically meaningful differences in BICLA response rate were observed as early as Week 8 and were maintained through to Week 52 (Figure 1). Similar findings were seen in Trial 2.

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 Trial 3, patients treated with anifrolumab were 55% more likely to achieve a sustained BICLA response, relative to patients receiving placebo (hazard ratio [HR] =1.55, 95% CI 1.11, 2.18). Separation between the treatment arms began at approximately Week 4 (Figure 2). Similar findings were seen in Trial 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, as measured by BICLA response, was consistent across subgroups (by age, gender, race, ethnicity, disease severity [SLEDAI-2K at baseline] and baseline OCS use).

In patients with a baseline OCS use ≥10 mg/day, the cumulative OCS dose was lower in patients treated with anifrolumab. The median (min, max) cumulative OCS dose at Week 52 was 3229 mg (718, 9893) versus 3697 mg (988, 11988) in Trial 2 and 3197 mg (309, 13265) versus 3640 mg (1745, 10920) in Trial 3 for the anifrolumab and placebo groups, respectively.

In patients with moderate to severe skin disease (CLASI score ≥10 at baseline), the improvement in cutaneous SLE lesions measured at Week 12 (Table 2) was maintained through Week 52. At any time during the treatment period, respectively in Trials 2 and 3, patients receiving anifrolumab were 91% and 55% more likely to achieve a sustained CLASI response (defined as a ≥50% reduction in CLASI activity score, in the subgroup of subjects with baseline CLASI activity score ≥10, that was attained at any time during the study and subsequently sustained at all visits through to Week 52), relative to patients receiving placebo (Trial 2 HR = 1.91, 95% CI 1.14, 3.27; Trial 3 HR = 1.55, 95% CI 0.87, 2.85).

In Trials 2 and 3, respectively, 63.9% (115/180) and 68.9% (124/180) of patients receiving anifrolumab experienced no SLE flares compared to 56.5% (104/184) and 57.7% (105/182) of patients receiving placebo, during the 52-week treatment period. 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 (Trial 2 HR = 0.76, 95% CI 0.55, 1.06; Trial 3 HR = 0.65, 95% CI 0.46, 0.91).

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 35.4% versus 28.4% in Trial 2 (difference 7.1%, 95% CI -2.6, 16.7) and 33.2% versus 24.7% in Trial 3 (difference 8.5%, 95% CI -0.9, 17.9) for the anifrolumab and placebo groups, respectively.

Phase III long-term extension

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.

SLE – subcutaneous administration

Trial 5 (TULIP subcutaneous, NCT04877691) evaluated the efficacy and safety of subcutaneous anifrolumab in a 52-week treatment period, multicentre, randomised, double-blind, placebo-controlled study. All patients were ≥ 18 years of age, diagnosed with SLE according to the American College of Rheumatology (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 central nervous system lupus were excluded. Patients were randomised (1:1) to receive 120 mg anifrolumab or placebo by subcutaneous injection once every week.

A pre-specified interim analysis was conducted when 220 randomised patients completed Week 52 or had withdrawn from the trial. Of these, 89% were female, 78% White, 7% Asian, and 4% Black/African American. The median age was 43 years (range: 19-70). At baseline, 67% had high disease activity (SLEDAI 2K score ≥ 10), 45% severe disease (BILAG A) in at least one organ system and 50% moderate disease (BILAG B) in at least two 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% were seropositive for ANA and 40% for anti-dsDNA antibodies; 33% of patients had low C3, and 24% low C4. Background SLE standard therapy included OCS (82%; mean daily dose (prednisone or equivalent) 9.8 mg), immunosuppressants (56%), and anti-malarials (80%). 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 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 primary analyses assessed reduction in overall disease activity, as measured by BICLA response, at Week 52. At the interim analysis, anifrolumab 120 mg by subcutaneous administration demonstrated a statistically significant and clinically meaningful reduction of overall disease activity compared with placebo (Table 4).

Table 4 Trial 5 Interim Analysis: BICLA response rate at Week 52

	Anifrolumab 120 mg (N = 109)	Placebo (N = 111)
BICLA response rate		
Responder, n (%)[†]	65 (59.4)	49 (43.9)
Difference in Response Rates (95% CI)	15.5% (2.3, 28.6)	
p-value (2-sided)	0.0211	
Components of BICLA response		
BILAG improvement, n (%)	65 (59.5)	49 (44.1)
No worsening of SLEDAI-2K, n (%)	81 (74.3)	80 (71.6)
No worsening of PGA, n (%)	81 (74.4)	82 (73.7)

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 received restricted medications beyond protocol allowed thresholds, discontinued treatment, or died are considered non-responders.

5.2 PHARMACOKINETIC PROPERTIES

The pharmacokinetics (PK) of anifrolumab were studied in adult patients with SLE following IV doses ranging from 100 to 1000 mg, once every 4 weeks, subcutaneous weekly doses of 120 mg, and in healthy volunteers following a single intravenous or subcutaneous 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 intravenous dosage).

Absorption

Following subcutaneous administration, the bioavailability of anifrolumab was approximately 73%. Steady-state exposure was reached after approximately 16 weeks of subcutaneous administration. The estimated maximum serum concentration (C_{max}) of anifrolumab at steady state was 63.7 µg/mL.

Distribution

Based on population pharmacokinetic analysis, the estimated central and peripheral volumes of distribution for anifrolumab were 3.46 L and 1.70 L, respectively for a 68 kg patient.

Metabolism

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

Anifrolumab is expected to be degraded, into small peptides and individual amino acids, by proteolytic enzymes that are widely distributed in the body and not restricted to hepatic tissues.

Excretion

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 0.146 L/day. 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

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 interaction studies

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

Genotoxicity

Anifrolumab is a monoclonal antibody, as such genotoxicity studies have not been conducted. As a large protein molecule, anifrolumab is not expected to interact directly with DNA or other chromosomal material.

Carcinogenicity

Anifrolumab is a monoclonal antibody, as such 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.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Histidine, histidine hydrochloride monohydrate, lysine hydrochloride, trehalose dihydrate, polysorbate 80, and water for injections.

6.2 INCOMPATIBILITIES

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

6.3 SHELF LIFE

Vial/Pre-filled pen

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

Vial-Diluted solution for infusion

To reduce microbiological hazard, use as soon as practicable after dilution. If storage is necessary, hold at 2 to 8°C for not more than 24 hours or up to 25°C for not more than 4 hours.

Pre-filled pen

If needed, SAPHNELO pre-filled pen may be kept at room temperature up to 25°C for a maximum of 7 days protected from light. Once SAPHNELO pre-filled pen has reached room temperature, do not return to the refrigerator. Discard if not used within 7 days at room temperature storage.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

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

Diluted solution for infusion

For storage conditions after dilution of the medicinal product, see Section 6.3 Shelf life.

6.5 NATURE AND CONTENTS OF CONTAINER

Vial

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.

Saphnelo is available in pack size of 1 vial per pack.

Pre-filled pen

0.8 mL of solution in a type I glass syringe with a 27-gauge, 12.7 mm stainless steel needle, rigid needle shield and FluroTec coated plunger stopper. The pre-filled pen consists of the syringe and handheld, mechanical (spring-based) injection device.

Saphnelo is available in pack size of 1 or 4 pre-filled pens per pack**.

** Not all pack sizes may be available.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

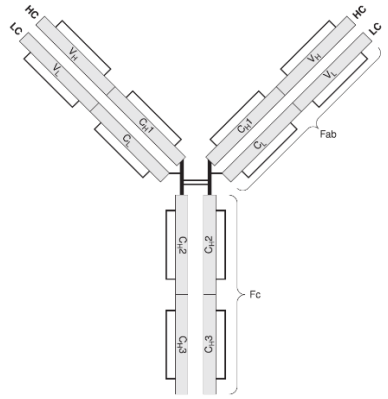
In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

Anifrolumab is a human, immunoglobulin G1 kappa (IgG1κ) monoclonal antibody produced in mouse myeloma cells (NS0) by recombinant DNA technology. Anifrolumab has a molecular weight of approximately 148 kDa.

Figure 3 General structure of anifrolumab



CAS number

1326232-46-5

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription only medicine (Schedule 4).

8 SPONSOR

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9 DATE OF FIRST APPROVAL

29 March 2022

10 DATE OF REVISION

30 September 2026

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.2	Revision of language to remove specificity that the product should remain in the carton to come to room temperature Editorial changes to the temperature storage out of refrigerator

Section changed	Summary of new information
6.3	Editorial changes to the time out of refrigeration details
6.5	Editorial changes to the description for the pre-filled pen container; Addition of a new pack size of 4 pre-filled pen; Addition of clarity for the availability of registered pack sizes

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