1. NAME OF THE MEDICINAL PRODUCT

Saphnelo 120 mg solution for injection in pre-filled syringe
Saphnelo 120 mg solution for injection in pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe contains 120 mg of anifrolumab* in 0.8 ml.

Each pre-filled pen contains 120 mg of anifrolumab* in 0.8 ml.

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

Excipient with known effect

Each pre-filled syringe/pre-filled pen contains 0.4 mg polysorbate 80.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection)

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Saphnelo is indicated as an add-on therapy for the treatment of adult patients with moderate to severe, active autoantibody-positive systemic lupus erythematosus (SLE), despite standard therapy.

4.2 Posology and method of administration

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

A patient may self-inject or the patient caregiver may administer Saphnelo subcutaneously after the healthcare professional determines that it is appropriate. The healthcare professional should provide proper training in the subcutaneous injection technique according to the 'Instructions for Use' and education about signs and symptoms of hypersensitivity reactions (see section 4.4).

Posology

The recommended dose is 120 mg administered as a subcutaneous injection every week.

Missed dose
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.

Special populations

Elderly
No dose adjustment is required. There is limited information in subjects aged ≥65 years (n=33); no data are available in patients over 75 years of age (see section 5.2).

Renal impairment
No dose adjustment is required. 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 (see section 5.2).

Paediatric population
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

For subcutaneous use.

Saphnelo is administered as a subcutaneous injection into the thigh or abdomen, except for the 5 cm around the navel. If a healthcare professional 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 that is at least 3 cm away from the last injection site.

Comprehensive instructions for subcutaneous administration of Saphnelo in a pre-filled syringe or pre-filled pen are provided in the 'Instructions for Use'.

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.

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

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Patient groups excluded from clinical studies

Anifrolumab has not been studied in combination with other biologic therapies, including B-cell-targeted therapies. Therefore, treatment with anifrolumab is not recommended in combination with biologic therapies.

Anifrolumab has not been studied in patients with severe active central nervous system lupus or severe active lupus nephritis (see section 5.1).

Hypersensitivity

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

In the intravenous and subcutaneous clinical trials of 52-week treatment duration, serious hypersensitivity reactions (including angioedema) were reported for 0.5% of patients receiving anifrolumab.

If a serious hypersensitivity reaction (e.g., anaphylaxis) occurs, administration of anifrolumab should be interrupted immediately, and appropriate therapy initiated.

Infections

Anifrolumab increases the risk of respiratory infections and herpes zoster; disseminated herpes zoster events have been observed (see section 4.8). SLE patients also taking immunosuppressants may be at higher risk of herpes zoster infections.

In controlled-clinical trials serious and sometimes fatal infections (including pneumonia) occurred, including in patients receiving anifrolumab.

Due to the mechanism of action, anifrolumab should be used with caution in patients with a chronic infection, a history of recurrent infections, or known risk factors for infection. Treatment with anifrolumab should not be initiated in patients with any clinically significant active infection until the infection resolves or is adequately treated. Patients should be instructed 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, they should be closely monitored and careful consideration given to interrupting anifrolumab 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 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

Prior to initiating therapy, completion of all appropriate immunisations should be considered according to current immunisation guidelines. Concurrent use of live or live attenuated vaccines should be avoided in patients treated with anifrolumab.

Immune responses to non-live vaccines have been assessed in a small number of patients (see section 4.5).

Malignancy

The impact of treatment with anifrolumab 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 the intravenous and subcutaneous clinical trials of 52-week treatment duration, malignant neoplasm (including non-melanoma skin cancers) was reported for 0.9% of patients receiving anifrolumab compared to 0.6% patients receiving placebo (exposure-adjusted incidence rate [EAIR]: 0.95 and 0.64 events per 100 patient years [PY], respectively). Malignancies excluding non-melanoma skin cancers

were observed in 0.5% and 0.6% of patients receiving anifrolumab and placebo, respectively. In patients receiving anifrolumab, breast and squamous cell carcinoma were the malignancies observed in more than one patient.

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 therapy for patients who develop malignancy.

Excipient with known effect

This medicinal product contains 0.4 mg of polysorbate 80 (E 433) in each pre-filled syringe/pre-filled pen, which is equivalent to 0.5 mg/ml. Polysorbates may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Anifrolumab is not expected to undergo metabolism by hepatic enzymes or renal elimination.

The formation of some CYP450 enzymes is suppressed by increased levels of certain cytokines during chronic inflammation. Anifrolumab modestly suppresses the levels of some cytokines; the impact on CYP450 activity is unknown. In patients who are being treated with other medicines that are CYP substrates with a narrow therapeutic index, where the dose is individually adjusted (e.g., warfarin), therapeutic monitoring is recommended.

Immune response

Non-live vaccines
Immune response to non-live seasonal influenza vaccine was assessed in a small number of adult patients with moderate to severe SLE in an exploratory study. Humoral antibody responses induced by seasonal influenza virus vaccination were numerically comparable between patients receiving anifrolumab in addition to standard of care and those receiving standard of care alone.

Live vaccines
The concurrent use of anifrolumab with live and live attenuated vaccines has not been studied (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are limited data (less than 300 pregnancy outcomes) from the use of Saphnelo in pregnant women.

Animal studies are inconclusive with respect to reproductive toxicity (see section 5.3).

Saphnelo is not recommended during pregnancy and in women of childbearing potential not using contraception, unless the possible benefit justifies the potential risk.

Breast-feeding

It is not known whether anifrolumab is excreted in human milk. Anifrolumab was detected in the milk of female cynomolgus monkeys (see section 5.3).

A risk to the suckling child cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue from Saphnelo therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

There are no fertility data in humans.

Animal studies show no adverse effects of anifrolumab 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

Summary of the safety profile

The most commonly reported adverse reactions during anifrolumab treatment were upper respiratory tract infection (32%), bronchitis (9.8%), infusion-related reaction (9.4%) and herpes zoster (5.4%). The most common serious adverse reactions were herpes zoster (0.3%) and bronchitis (0.3%).

Tabulated list of adverse reactions

Adverse reactions reported from controlled clinical trials and post-marketing data are classified by MedDRA System Organ Class (SOC), see Table 1. 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 <1/1 000); very rare (<1/10 000) and not known (cannot be estimated from available data).

Table 1 Adverse reactions

MedDRA SOC	MedDRA Preferred Term	Frequency
Infections and infestations	Upper respiratory tract infection*	Very common
	Bronchitis*	Common
	Herpes zoster	Common
	Respiratory tract infection*	Common
Immune system disorders	Hypersensitivity	Common
	Anaphylactic reaction	Uncommon§
Musculoskeletal and connective tissue disorders	Arthralgia	Not known
Injury, poisoning and procedural complications	Infusion-related reaction‡	Common

* Grouped terms: Upper respiratory tract infection (including Upper respiratory tract infection, Nasopharyngitis, Pharyngitis); Bronchitis (including Bronchitis, Bronchitis viral, Tracheobronchitis); Respiratory tract infection (including Respiratory tract infection, Respiratory tract infection viral, Respiratory tract infection bacterial).

§ See 'Description of selected adverse reactions' below and section 4.4.

‡ Applies to intravenous infusion route of administration only.

Long-term safety:

Patients who completed Trials 1 and 2, the Phase III intravenous trials through Week 52 were eligible to continue on treatment in a randomised, double-blind, placebo-controlled long-term extension (LTE) for an additional 3 years (see section 5.1). The overall long-term safety profile of intravenous anifrolumab was consistent with the 52-week trials.

Description of selected adverse reactions

Hypersensitivity
In controlled intravenous and subcutaneous clinical trials of 52-week treatment duration, the incidence of hypersensitivity reactions was 2.2% in the anifrolumab group and 0.5% in the placebo group. Hypersensitivity reactions were predominantly mild to moderate in intensity. One event of hypersensitivity in the subcutaneous trial led to discontinuation of anifrolumab.

In the intravenous clinical trials of 52-week treatment duration, all hypersensitivity reactions were reported within the first 6 infusions. One serious adverse reaction of hypersensitivity was reported during the patient's first infusion; the patient continued to receive anifrolumab with premedication given for subsequent infusions.

In the SLE development program, anaphylactic reaction was reported in one patient, which occurred following the intravenous administration of 150 mg anifrolumab, the patient was treated and recovered (see section 4.4).

Infusion-related reactions
In the controlled intravenous clinical trials of 52-week treatment duration, the incidence of infusion-related reactions was 9.4% in the anifrolumab group and 7.1% in the placebo group. Infusion-related reactions were mild or moderate in intensity (the most common symptoms were headache, nausea, vomiting, fatigue, and dizziness); none were serious, and none led to discontinuation of anifrolumab. Infusion-related reactions were most commonly reported at the start of treatment, on the first and second infusions, with fewer reports on subsequent infusions.

Respiratory infections
In the controlled intravenous and subcutaneous clinical trials of 52-week treatment duration, the incidence rates for anifrolumab compared to placebo were: upper respiratory tract infection (32% vs 21%), bronchitis (9.8% vs 5.2%) and respiratory tract infection (2.8% vs 1.2%). Infections were predominantly non-serious, mild or moderate in intensity and resolved without discontinuation of anifrolumab therapy (see section 4.4).

Herpes zoster
In the controlled intravenous and subcutaneous clinical trials of 52-week treatment duration, the incidence of herpes zoster infections was 5.4% in the anifrolumab group and 1.2% in the placebo group (see section 4.4). The mean time to onset in patients receiving anifrolumab was 132 days (range 2-351 days).

In the LTE (intravenous administration), incidence rates decreased over time.

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

Immunogenicity

In the intravenous Phase III trials, treatment-emergent anti-drug antibodies were detected in 6 out of 352 patients (1.7%) treated with anifrolumab at the recommended dosing regimen during the 60-week study period.

In the LTE (years 2 through 4 on treatment), treatment-emergent anti-drug antibodies were detected in an additional 5 patients treated with anifrolumab.

Due to methodological limitations, the clinical relevance of these findings is not known.

In the subcutaneous Phase III trial, treatment-emergent anti-drug antibodies were detected in 9 out of 178 patients (5.1%) treated with anifrolumab during the 52-week treatment period, no neutralising antibodies were detected.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via:

Ireland
HPRA Pharmacovigilance
Website: www.hpra.ie

Malta
ADR Reporting Website: https://medicinesauthority.gov.mt/adrportal

4.9 Overdose

In clinical trials, doses of up to 1 000 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.

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 SLE.

Pharmacodynamic effects

In adult patients with SLE, administration of anifrolumab ≥300 mg intravenous every 4 weeks and 120 mg subcutaneous once weekly, 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. 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.

Anifrolumab 150 mg (intravenous) showed <20% suppression of the gene signature at early timepoints, that reached a maximum of <60% by the end of the treatment period.

In SLE patients with positive anti-dsDNA antibodies at baseline, treatment with anifrolumab 300 mg intravenously every 4 weeks and 120 mg subcutaneously once weekly led to numerical reductions in anti-dsDNA antibodies over time through Week 52.

In patients with low complement levels (C3 and C4), increases in complement levels were observed in patients receiving anifrolumab 300 mg intravenously through Week 52.

Clinical efficacy

Intravenous administration
The safety and efficacy of anifrolumab were evaluated in two 52-week treatment period, multicentre, randomised, double-blind, placebo-controlled, Phase III studies (Trial 1 [TULIP 1] and Trial 2 [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 British Isles Lupus Assessment Group (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. With the exception of OCS (prednisone or equivalent) where tapering was a component of the protocol, patients continued to receive their existing SLE therapy at stable doses during the clinical trials. 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. Both studies were conducted in North America, Europe, South America and Asia. Patients received anifrolumab or placebo, administered by intravenous infusion, every 4 weeks.

Trial 1 (N=457) and Trial 2 (N=362) were similar in design.

In Trial 1 the primary endpoint was SLE Responder Index (SRI-4) response, 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 lupus disease activity defined by an increase ≥0.30 points on a 3-point PGA visual analogue scale (VAS);
- No use of restricted medicinal products beyond the protocol-allowed thresholds;
- No discontinuation of treatment.

In Trial 2 the primary endpoint was British Isles Lupus Assessment Group based Composite Lupus Assessment (BICLA) response at Week 52, 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;
- No worsening from baseline in lupus disease activity, where worsening is defined by an increase ≥0.30 points on a 3-point PGA VAS;
- No use of restricted medicinal products beyond the protocol-allowed thresholds;
- No discontinuation of treatment.

The secondary efficacy endpoints included in both studies included maintenance of OCS reduction and annual flare rate. Both studies evaluated the efficacy of anifrolumab 300 mg versus placebo.

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 1 and 2 respectively. In both trials, 72% of patients had high disease activity (SLEDAI-2K score ≥10). In Trials 1 and 2 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 1: 87%, Trial 2: 85%) and musculoskeletal (Trial 1: 89%, Trial 2: 88%) systems.

In Trials 1 and 2, 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.

Baseline concomitant standard therapy included oral corticosteroids (Trial 1: 83%, Trial 2: 81%), antimalarials (Trial 1: 73%, Trial 2: 70%) and immunosuppressants (Trial 1: 47%, Trial 2: 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 1 and 10.7 mg in Trial 2. 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.

For BICLA and SRI-4 response, patients who withdrew from treatment prior to Week 52 were considered non-responders. In Trial 1 and 2 respectively, 35 (19%) and 27 (15%) patients receiving anifrolumab, and 38 (21%) and 52 (29%) patients receiving placebo withdrew from treatment prior to Week 52. The results are presented in Table 2.

Table 2 Efficacy results in adults with SLE in Trial 1 and Trial 2

	Trial 1		**Trial 2**	
	Anifrolumab 300 mg	**Placebo**	**Anifrolumab 300 mg**	**Placebo**
BICLA response at Week 52*				
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 medicinal products beyond protocol allowed threshold, n (%)	140 (77.8)	128 (69.6)	144 (80.0)	123 (67.6)
SRI-4 response at Week 52*				
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)	

	Trial 1		Trial 2	
	Anifrolumab 300 mg	**Placebo**	**Anifrolumab 300 mg**	**Placebo**
Sustained OCS reduction ‡				
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)	
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)	

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.
All patients received standard therapy.

* BICLA and SRI(4) are based on the composite estimand where treatment discontinuation or restricted medicinal product use are part of the response criteria.

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

‡ 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.

Long-term extension: Patients who completed Trials 1 and 2 (feeder trials) through Week 52 were eligible to continue on treatment in a randomised, double-blind, placebo-controlled, 3-year LTE. Patients who had received anifrolumab, either 150 mg or 300 mg, in Trials 1 and 2 received anifrolumab 300 mg in the LTE. Patients who had received placebo in Trials 1 and 2 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 the LTE.

Long-term efficacy was evaluated in patients who received anifrolumab 300 mg or placebo in a feeder trial and continued to receive the same treatment in the LTE (anifrolumab N=257; placebo N=112). Of these, 69% of patients who received anifrolumab (177/257) and 46% of patients who received placebo (52/112) completed a total of 4 years on treatment. At Week 208, the mean SLEDAI-2K score (SE) was 3.4 (0.25) and 4.0 (0.46) in patients who received anifrolumab (n=140) and placebo (n=44) respectively.

Subcutaneous administration
The safety and efficacy of anifrolumab administered subcutaneously were evaluated in a 52-week treatment period, multicentre, randomised, double-blind, placebo-controlled, Phase III 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% had severe disease (BILAG A) in at least 1 organ system and 50% had moderate disease (BILAG B) in at least 2 organ systems. The most commonly affected organ systems (BILAG A or B at baseline) were the musculoskeletal (95%) and

mucocutaneous (92%) systems; 2% cardiorespiratory and 2% renal organ domain involvement. At baseline, 95% were seropositive for ANA antibodies 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 antimalarials (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 3 BICLA response rate at Week 52

	Anifrolumab 120 mg	**Placebo**
BICLA response rate		
Responder rate, % (n/N)*	59.4 (65/109)	43.9 (49/111)
Difference, % (95% CI)	15.5 (2.3, 28.6)	
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)

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
All patients received standard therapy.
* Patients who discontinued treatment or used restricted medicinal products, beyond protocol allowed thresholds, or died are considered non-responders.
‡ Missing data were imputed using multiple imputation.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with anifrolumab in one or more subset of the paediatric population in treatment of systemic lupus erythematosus (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The pharmacokinetics (PK) of anifrolumab was studied in adult patients with SLE following intravenous doses ranging from 100 to 1 000 mg administered once every 4 weeks and 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 1 000 mg. PK exposure decreased more rapidly at doses lower than 300 mg every 4 weeks (the recommended intravenous dose).

Absorption

Based on population PK analysis, following subcutaneous administration, the estimated bioavailability of anifrolumab was approximately 75%. Steady-state exposure was reached after approximately 16 weeks of subcutaneous administration.

Distribution

Based on population PK analysis, the estimated central and peripheral volumes of distribution for anifrolumab were 3.48 L and 1.72 L, respectively for a 68 kg patient.

Biotransformation

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

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

Elimination

Due to saturation of IFNAR1-mediated clearance at higher doses, exposure increases are greater-than-dose-proportional.

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 the majority (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
Based on the population PK analysis, age (range 18 to 70 years) did not impact the clearance of anifrolumab; the population PK dataset included 33 (3%) patients ≥65 years of age.

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 urine protein/creatinine ratio (UPCR) >2 mg/mg were excluded from the clinical trials. Based on population PK analyses, increased 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 PK analyses, baseline hepatic function biomarkers (ALT and AST ≤2.0 × ULN, and total bilirubin) had no clinically relevant effect on anifrolumab clearance.

Interactions

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 hazard 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 postnatal development study, conducted in cynomolgus monkeys, there was an increased incidence of embryo-foetal loss; the incidence of these findings were within historical control values and were not statistically significant. The relevance of these findings to humans is not known. No maternal, or postnatal developmental effects were observed for exposures up to approximately 28-times the maximum recommended human dose (MRHD) on an AUC basis. Based on the available data, a potential effect of anifrolumab on conception and implantation cannot be excluded.

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 approximately 58-times the intravenous MRHD and 52-times the subcutaneous MRHD, on an AUC basis.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Histidine
Histidine hydrochloride monohydrate
Lysine hydrochloride
Trehalose dihydrate
Polysorbate 80 (E 433)
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

4 years.

If needed, Saphnelo pre-filled syringe/pre-filled pen may be stored at room temperature (20 °C – 25 °C) for a maximum of 7 days protected from light. Once Saphnelo pre-filled syringe/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 – 8 °C).
Store in the original package in order to protect from light.
Do not freeze, shake or expose to heat.

6.5 Nature and contents of container

Pre-filled syringe

0.8 ml of solution in a type I glass syringe with a 27-gauge, 12.7 mm stainless steel needle with a rigid needle shield and a bromobutyl plunger stopper. The pre-filled syringe is assembled with a needle guard, plunger rod and a finger flange.

Pack size of 1 pre-filled syringe.

Pre-filled pen

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

Pack size:
- 1 pre-filled pen
- 4 pre-filled pens
- Multipack containing 12 (3 packs of 4) pre-filled pens

Not all presentations and pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

This medicinal product is for single-use only.

1. Remove Saphnelo pre-filled syringe/pre-filled pen from the refrigerator and allow the solution for injection to come to room temperature for 60 minutes.

2. Visually inspect the solution for injection for particulate matter and discolouration prior to administration. Discard the pre-filled syringe or pre-filled pen if the solution is cloudy, discoloured or visible particles are observed.

3. Comprehensive instructions for the preparation and administration of Saphnelo using the pre-filled syringe or pre-filled pen are given in the ‘Instructions for Use’.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

AstraZeneca AB
SE-151 85
Södertälje
Sweden

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1623/002	1 pre-filled syringe
EU/1/21/1623/003	1 pre-filled pen
EU/1/21/1623/004	4 pre-filled pens
EU/1/21/1623/005	12 (3 x 4) pre-filled pens (multipack)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14 February 2022
Date of latest renewal: 27 August 2026

10. DATE OF REVISION OF THE TEXT

27 August 2026

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

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