Date: 18 October 2022
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Saphnelo

International non-proprietary name: anifrolumab
Pharmaceutical form: concentrate for solution for infusion
Dosage strength(s): 300 mg/2 ml
Route(s) of administration: intravenous
Marketing Authorisation Holder: AstraZeneca AG
Marketing Authorisation No.: 68512
Decision and Decision date: approved on 31 August 2022

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADCC	Antibody-dependent cell-mediated cytotoxicity
AE	Adverse event
BICLA	British Isles Lupus Assessment Group 2004-based Combined Lupus Assessment
BILAG	British Isles Lupus Assessment Group
CDC	Complement-dependent cytotoxicity
CI	Confidence interval
CLASI	Cutaneous Lupus Erythematosus Disease Area and Severity Index
EMA	European Medicines Agency
FDA	Food and Drug Administration (USA)
IC_{50}	Half-maximal inhibitory concentration
ICH	International Council for Harmonisation
IFN	Interferon
IFNAR1	Subunit 1 of type I interferon receptor
Ig	Immunoglobulin
IV	Intravenous
LoQ	List of Questions
MAH	Marketing Authorisation Holder
NSAIDs	Non-steroidal anti-inflammatory drugs
OCS	Oral corticosteroids
PD	Pharmacodynamics
PGA	Patient global assessment
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
q4w	Once every four weeks
RMP	Risk Management Plan
SAE	Serious adverse event
SC	Subcutaneous
SLE	Systemic lupus erythematosus
SLEDAI-2K	Systemic Lupus Erythematosus Disease Activity Index 2000
SRI(4)	Systemic Lupus Erythematosus Responder Index of ≥ 4
SwissPAR	Swiss Public Assessment Report
VAS	Visual analogue scale

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

New Active Substance status
The applicant requested the status of a new active entity for the active substance anifrolumab of the medicinal product mentioned above.

2.2 Indication and Dosage

2.2.1 Requested Indication

Saphnelo is indicated for the treatment of adult patients with moderate to severe systemic lupus erythematosus (SLE), in addition to standard therapy (see "Properties/Effects").

2.2.2 Approved Indication

Saphnelo is indicated for the treatment of adult patients with moderate to severe systemic lupus erythematosus (SLE), in addition to standard therapy (see "Properties/Effects").
Restrictions of use
The efficacy of Saphnelo has not been evaluated in patients with severe active lupus nephritis or severe active lupus of the central nervous system. The use of Saphnelo is not recommended in these situations.

2.2.3 Requested Dosage

Summary of the requested standard dosage:
The proposed dose of Saphnelo is 300 mg, administered as an intravenous infusion every 4 weeks.

2.2.4 Approved Dosage

(see appendix)

2.3 Regulatory History (Milestones)

Application	11 May 2021
Formal control completed	9 June 2021
List of Questions (LoQ)	5 October 2021
Answers to LoQ	25 January 2022
Preliminary Decision	25 April 2022
Answers to Preliminary Decision	3 June 2022
Final Decision	31 August 2022
Decision	approval

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3 Medical Context

Systemic lupus erythematosus (SLE) is a chronic, occasionally life-threatening, multisystem immune-mediated disorder. The precise aetiology and pathophysiology are unknown; however, women are more commonly affected than men (women:men = 9:1). Patients may present with a wide array of symptoms, signs and laboratory findings, and have a variable prognosis that depends upon the disease severity and type of organ involvement.
The goals of therapy for patients with SLE are to ensure long-term survival, achieve the lowest possible disease activity, prevent organ damage, minimise drug toxicity, improve quality of life and educate patients about their role in disease management.
Treatment of SLE is individualised based upon patient preferences, clinical manifestations, disease activity and severity, and comorbidities. In general, all patients with SLE with any degree and type of disease activity should be treated with hydroxychloroquine or chloroquine, unless these agents are contraindicated. Eighty percent of patients with non-organ-threatening SLE achieve disease remission with use of antimalarial drugs. Additional therapy is based on disease severity and the combination of manifestations:

- Patients with mild lupus manifestations may be treated with hydroxychloroquine or chloroquine, with and without non-steroidal anti-inflammatory drugs (NSAIDs), and/or short-term use of low-dose glucocorticoids (e.g. ≤ 7.5 mg prednisone equivalent per day).
- Patients with moderate lupus involvement often require a steroid-sparing immunosuppressive agent (e.g. azathioprine or methotrexate).
- Patients with severe or life-threatening manifestations secondary to major organ involvement generally require an initial period of intensive immunosuppressive therapy (induction therapy) to control the disease and halt tissue injury. Patients are usually treated for a short period of time with high doses of systemic glucocorticoids (e.g. intravenous "pulses" of methylprednisolone, 0.5 to 1 g/day for three days in acutely ill patients, or 1 to 2 mg/kg/day in more stable patients) used alone or in combination with other immunosuppressive agents. Examples of other immunosuppressive agents that may be used include mycophenolate, azathioprine, cyclophosphamide and rituximab. This initial therapy is subsequently followed by a longer period of less intensive, and ideally less toxic, maintenance therapy to consolidate remission and prevent flares. During this phase of treatment, the dose of prednisone or equivalent is reduced while monitoring clinical and laboratory measures of disease activity.

Anifrolumab is a human monoclonal antibody that binds to the type I interferon (IFN) receptor subunit 1, thereby blocking the activity of all type I interferons. Most adult patients with SLE (approximately 60-80%) express elevated levels of type I IFN-inducible genes associated with increased disease activity and severity.

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4 Quality Aspects

4.1 Drug Substance

Anifrolumab is a recombinant human IgG1 monoclonal antibody directed against the human interferon alpha receptor. By binding, anifrolumab blocks IFN-α-induced cellular signalling. Antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) activities are not part of anifrolumab's functionalities.
Anifrolumab consists of two heavy and two kappa light chains connected by inter-chain disulfide bonds. The heavy chain has a carbohydrate moiety. Anifrolumab is expressed in a host cell line and is manufactured using a fed-batch production process in a production bioreactor. The cell broth is harvested and anifrolumab is subsequently purified by several chromatographic steps. The purification manufacturing process also includes dedicated viral clearance steps.
The fermentation and purification process was validated, demonstrating a consistent manufacturing process that effectively reduces process-related impurities. The impurity clearance validation studies are supported by the impurity levels measured in the drug substance. Characterisation of the physicochemical and biological properties of the drug substance and its impurities was performed using state-of-the-art methods.
The specifications for release include relevant tests and limits, e.g. for appearance, identity, pH, several purity/impurity tests, protein concentration and biological activity. Batch analysis data of development, clinical and process validation batches were provided. All batch release data comply with the drug substance specifications valid at the time of batch release. All the analytical methods are described, and non-compendial methods were validated in accordance with ICH guidelines.
The drug substance is stored under appropriate storage conditions. No significant changes have been observed within the proposed shelf life.

4.2 Drug Product

The finished product is a sterile, preservative-free, liquid dosage form intended for intravenous infusion after dilution into 0.9% saline. The finished product is supplied as a single-dose vial containing 300 mg of anifrolumab in 2 ml. The drug product is formulated in an aqueous buffered solution at pH 5.9, containing L-histidine/L-histidine hydrochloride monohydrate, L-lysine hydrochloride, α,α-trehalose dihydrate and polysorbate 80. All excipients comply with the European Pharmacopoeia.
The selected manufacturing process consists mainly of drug substance thawing, pooling and mixing of the drug substance, sterile filtration, aseptic filling into vials and stoppering followed by capping. Process validation studies were executed at commercial scale using several validation batches.
The specifications include relevant tests and limits, e.g. for appearance, colour, clarity, identity, potency assay, pH, osmolality, purity and impurities tests, protein concentration, particles, sterility and bacterial endotoxins. All non-compendial methods were validated in accordance with ICH guidelines.
Batch analysis data for several batches from the commercial site were provided. The container closure systems in contact with the finished product consist of a glass vial with elastomeric stopper. The vial is capped with an aluminium seal. All components coming into contact with the finished product comply with the requirements of the European Pharmacopoeia.
The drug product is stored at 2 - 8°C. No meaningful changes have been observed within the proposed storage conditions. A shelf life of 36 months has been accepted.

4.3 Quality Conclusions

The manufacturing processes (drug substance and drug product) are well described and demonstrate a consistent quality of drug substance and drug product. The shelf lives of the drug substance and drug product are supported by data from recommended storage conditions, as well as accelerated and stress studies. Safety concerns with regard to viral and non-viral contaminants were satisfactorily addressed. The risk of adventitious agents is minimised.

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5 Nonclinical Aspects

5.1 Pharmacology

Anifrolumab bound subunit 1 of the type I interferon receptor (IFNAR1) on human and monkey peripheral blood mononuclear cells (PBMCs) *in vitro*, with equilibrium dissociation constants (K_D) of 0.29 nM and 0.65 nM. It competitively inhibited ^{125}I-IFN-α2a binding to IFNAR with an IC_{50} of 0.14 nM and dose-dependently inhibited downstream signalling of INFs *in vitro*, including CD38 and CD123 upregulation (IC_{50} 0.05 nM and 0.06 nM). Anifrolumab completely inhibited the activation of human interferon stimulated response element (ISRE) by type I IFNs, typically present in the sera of patients with systemic lupus erythematosus (IC_{50} 0.5 nM). It showed similar activity with cynomolgus monkey recombinant IFN receptor subtypes. Anifrolumab induced no antibody-dependent cellular cytotoxicity (ADCC) of IFNAR1-expressing cells and did not exhibit complement-dependent cytotoxicity (CDC) activity at clinically relevant concentrations.
Anifrolumab did not bind murine IFNAR nor inhibited murine type I IFN-induced ISRE activity. Therefore, the anti-murine IFNAR1 monoclonal IgG1 surrogate antibody 5A3 was used to examine the impact of IFNAR blockade in mouse models of lupus. Antibody treatment significantly reduced the induction of IFNAR1-dependent signalling *in vivo*. In addition, in a murine model of scleroderma, blocking IFN signalling with 5A3 inhibited cutaneous inflammation, vascular injury and dermal fibrosis. Secondary pharmacodynamics studies were not conducted, which is considered acceptable.
Consistent with ICH S6(R1), no formal safety pharmacology studies were conducted, but these evaluations were included in the single and repeat-dose subcutaneous (SC) and intravenous (IV) toxicity studies and did not indicate any safety concerns.

5.2 Pharmacokinetics

The pharmacokinetics, immunogenicity and toxicokinetics of anifrolumab were investigated in cynomolgus monkeys following IV and SC administration.
After repeated weekly administration of up to 60 mg/kg SC and 50 mg/kg IV, exposure increased in proportion to dose. No gender effect was observed. The elimination half-life ($t_{1/2}$) of anifrolumab increased with dose. At low doses, $t_{1/2}$ was less than 1 week. At higher doses and with chronic administration, $t_{1/2}$ was >2 weeks, indicative of a probable target-mediated internalisation at low doses. Anti-drug antibodies (ADA) were detected in animals of both genders, and in a few male monkeys ADA were associated with the induction of mild arteritis. No other ADA-related effects were reported.
Tissue distribution, metabolism and excretion studies were not conducted in accordance with ICH S6(R1). Anifrolumab was detected in the monkeys' milk. The toxicokinetic data from the enhanced pre- and postnatal development study showed that anifrolumab crossed the placenta. The recommendations for pregnancy and lactation given in the information for healthcare professionals are adequate.

5.3 Toxicology

The toxicological evaluation of anifrolumab was conducted in cynomolgus monkeys based on the pharmacology data. Anifrolumab was given once weekly via SC and IV routes, in line with the clinical application (IV injection), and was formulated in the same buffer as the clinical drug product. The duration of the toxicological studies (up to 39 weeks) supports chronic treatment in humans.
No adverse effects were observed following a single dose up to 100 mg/kg. At 1 mg/kg, IFNAR1 remained occupied through to study day 8. No mortality was observed in the repeat-dose toxicity studies with doses up to 50 mg/kg/week IV or 60 mg/kg/dose SC. Following 39 weeks of anifrolumab administration and at the end of the 12-week recovery phase, treatment-related inflammation of arteries (mild arteritis) was observed in several male monkeys (at 2.3-fold human exposure). Several pathways may be involved in this arteritis, including Fc-mediated effects, cross-linking events or anifrolumab aggregation. Corresponding experiments excluded a direct effect of anifrolumab in the mentioned pathways. Besides ADA-induced minimal arteritis in multiple organs in a few male

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monkeys, no additional drug-related adverse effects were noted. The observed arteritis was considered the result of an immune-mediated reaction in the animals against a foreign human protein. This explanation is accepted as immune histochemistry experiments localised the complement component 3b to the affected arteries. The relevance of this immune reaction to human safety is unknown and no signals have been identified in the clinical studies so far.
A treatment-related hypersensitivity reaction occurred in one male after a single-dose IV injection of 5 mg/kg anifrolumab, but was not observed in the subsequent repeat-dose studies. In humans, hypersensitivity was observed in very few anifrolumab-treated patients and is adequately mentioned in the information for healthcare professionals.
In accordance with ICH S6(R1), no genotoxicity or carcinogenicity studies were performed. However, based on anifrolumab's mode of action (inhibition of IFNAR1), an immune-suppressing effect and therefore an increased risk of tumour formation cannot be excluded. Malignancy is considered an important potential risk in the RMP. This is adequately addressed in the information for healthcare professionals.
In compliance with ICH S6(R1), fertility was evaluated in the repeat-dose toxicity studies in sexually mature monkeys. There were no significant drug effects on male sperm evaluations or on the female menstrual cycle at any dose during the 39-week study. There were no anifrolumab-related adverse maternal, foetal or infant effects in the enhanced pre- and postnatal development study at exposure levels corresponding to up to 28-fold human exposure.
Juvenile animal studies were not performed. This is accepted as anifrolumab is not indicated for children. The PIP for anifrolumab does not require any nonclinical measures.
No adverse effects on the immune system, on the T-cell-dependent antigen response or local tolerance were found in cynomolgus monkeys up to exposures corresponding to 18-fold human exposure.
There are no concerns with regard to impurities or excipients. The RMP adequately describes the safety concerns identified in nonclinical studies and their relevance to human usage.
The risk to the environment is low as anifrolumab is a protein.

5.4 Nonclinical Conclusions

The pharmaco-toxicological profile of anifrolumab has been sufficiently characterised. The nonclinical documentation submitted is considered appropriate to support the approval of Saphnelo in the proposed indication. The nonclinical data that are relevant for safety are adequately mentioned in the information for healthcare professionals.

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6 Clinical and Clinical Pharmacology Aspects

6.1 Clinical Pharmacology

The evaluation of the clinical pharmacology data of this application has been carried out in reliance on previous regulatory decisions by the FDA. The available assessment reports and respective product information from the FDA were used as a basis for the clinical pharmacology evaluation. For further details concerning clinical pharmacology, see section 8.1 of this report.

6.2 Dose Finding and Dose Recommendation

Dose finding was based on PK-PD modelling of study D3461C00008, which compared the CLASI (Cutaneous Lupus Erythematosus Disease Area and Severity Index) activity score of 36 patients treated every two weeks (q2w) with placebo, 150 mg or 300 mg of anifrolumab. The results suggested 300 mg of anifrolumab to be sufficient to achieve pharmacodynamically adequate blood levels. Nevertheless, considering the possibility that 1000 mg of anifrolumab could improve tissue exposure, this dose was also examined in the phase 2 trial MUSE/1013 but did not show superior efficacy to the 300 mg dose.

6.3 Efficacy

The applicant provided two randomised, placebo-controlled, double-blind, pivotal, phase 3 studies (study 05/TULIP1 with n=457 patients randomised, and study 04/TULIP2 with n=365 patients randomised) and one supportive randomised, placebo-controlled, double-blind phase 2 study (MUSE/1013, n=307) in adult patients with moderate to severe systemic lupus erythematosus (SLE), who were receiving standard therapy. Oral corticosteroids (OCS) anti-malarials and/or immunosuppressants were standard treatment in all studies. OCS tapering was encouraged, but doses needed to be stable in the 12 weeks before primary endpoint assessment at week 52 in studies 04 and 05 and during the 8 weeks preceding week 24 and week 52 of study MUSE/1013.
All studies had a 52-week treatment period, similar eligibility criteria and investigated the proposed dose of 300 mg administered every 4 weeks (q4w). The Systemic Lupus Erythematosus Responder Index of ≥ 4 (SRI(4)) was chosen as the primary endpoint based on the results of study MUSE/1013. However, the first phase 3 study 05/TULIP1 did not reach statistical significance. Study 05/TULIP1 did show an improvement in the secondary endpoint of the British Isles Lupus Assessment Group-2004-based Combined Lupus Assessment (BICLA) at 52 weeks. This led to a change in the primary endpoint of the second phase 3 study 04/TULIP2 from SRI(4) to BICLA response. Blinding of study 04/TULIP2 was maintained when the amendment was performed and data integrity was adequately protected.
Both BICLA and SRI(4) are recommended as primary endpoints in the “Guideline on clinical investigation of medicinal products for the treatment of systemic lupus erythematosus and lupus nephritis (EMA/CHMP/51230/2013)”.

SRI(4) response was defined as follows:

- Reduction from baseline of ≥4 points in the SLEDAI-2K (Systemic Lupus Erythematosus Disease Activity Index 2000);
- No new organ system affected as defined by 1 or more BILAG A (British Isles Lupus Assessment Group) or 2 or more BILAG B items compared to baseline;
- No worsening from baseline in the patients’ lupus disease activity defined by an increase ≥0.30 points on a 3-point PGA (patient global assessment) visual analogue scale (VAS);
- No discontinuation of treatment;
- No use of restricted medication beyond the protocol-allowed threshold.

BICLA response was defined as follows:

- Reduction of all baseline BILAG-2004 A to B/C/D and baseline BILAG-2004 B to C/D, and no BILAG-2004 worsening in other organ systems (worsening defined as ≥1 new BILAG-2004 A or ≥2 new BILAG-2004 B); and

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- No worsening from baseline in SLEDAI-2K (worsening defined as an increase of >0 points); and
- No worsening from baseline in the patients' lupus disease activity (worsening defined as an increase ≥0.30 points on a 3-point PGA VAS); and
- No discontinuation of investigational product; and
- No use of restricted medications beyond the protocol-allowed threshold before assessment.

Study 05/TULIP1 compared anifrolumab 150 mg q4w vs. anifrolumab 300 mg q4w vs placebo, randomised 1:2:2. The primary endpoint was SRI(4). At week 52, 36.2% of the patients (n=180) treated with anifrolumab 300 mg reached the primary endpoint compared to 40.4% of the patients (n=184) treated with placebo.
During the review of the unblinded data after the week 52 database lock, it became apparent that some of the restrictions on concomitant medication prescribed in the protocol were not implemented as intended in the protocol and were not in accordance with clinical practice. As a result, a number of patients who would be considered responders in clinical practice were scored as non-responders. These rules included the restricted use of non-steroidal anti-inflammatory drugs (NSAIDs).

For comparison reasons, the efficacy endpoints of studies 04 and 05, which included categorisation of patients as non-responders based on the use of restricted medications, were re-determined for study 05 using the rules for restricted medication of study 04.
SRI(4) at week 52 using the restricted medication rules of study 04 showed a numerically improved result in the anifrolumab arm (49.0%) compared to the placebo arm (43.0%).

Regarding BICLA response (primary endpoint study 04/TULIP2), a numerical benefit was described in patients treated with anifrolumab compared to placebo (47.1% vs. 30.2%) in study 05/TULIP1.

In study 04/TULIP2, patients were randomised 1:1 to anifrolumab 300 mg q4w vs. placebo. The primary endpoint BICLA response at 52 weeks was statistically significantly improved in patients treated with anifrolumab compared to placebo (47.8% vs. 31.5%, difference 16.3% [95% CI 6.3, 26.3]; p=0.0013). In the small subgroup of men, there was only a small numerical benefit in terms of BICLA response compared to placebo (44.6% vs. 39.7%).
Key secondary endpoints included in the multiplicity-controlled testing strategy, such as BICLA at week 52 in IFN test-high subjects, maintained OCS reduction at week 52 and CLASI response at week 12, were statistically significantly improved in the anifrolumab arm. BICLA at week 52 in IFN test-high subjects was 48.0% vs. 30.7% (difference 17.3% [95% CI 6.5, 28.2]; p=0.0018), maintained OCS reduction at week 52 was 51.5% vs. 30.2% (difference 21.2% [95% CI 6.8, 35.7]; p=0.0040) and CLASI response at week 12 was 49.0% vs. 25.0% (difference 24.0% [95% CI 4.3, 43.6]; p=0.0168) for anifrolumab vs. placebo, respectively.
SRI(4) response at week 12 was numerically higher in the anifrolumab arm compared to placebo (55.5% vs. 37.3%, difference 18.2% [95%CI 8.1, 28.3]).

The primary endpoint of study 1013/MUSE was SRI(4) + OCS tapering at week 24, which was statistically significantly improved in patients treated with anifrolumab compared to placebo (34.3% vs. 17.6%). The secondary endpoint SRI(4) at week 52 was not multiplicity controlled and was in favour of anifrolumab (62.8% vs. 38.8%, difference 24.0% [95%CI 10.9, 37.2]). BICLA response at week 52 was 53.3% for anifrolumab vs. 25.1% for placebo (difference 28.4% [95%CI 15.3, 21.5]).

The required duration of treatment has not been established and the applicant will investigate the optimal criteria at which anifrolumab therapy needs to be continued or discontinued. Given this unresolved issue and in light of responses observed up to 52 weeks, limitation of the treatment duration to 52 weeks in case of no response is recommended.

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6.4 Safety

The supportive safety pool included study 04, study 05 and the dose-finding study 1013. A total of 925 patients were included: 459 patients in the anifrolumab 300 mg q4w group and 466 patients in the placebo group.
In this patient pool, mild adverse events (AEs) were numerically more frequent with anifrolumab compared to placebo, whereas more severe AEs were less frequent. Compared to placebo, respiratory tract infections, herpes zoster and arthralgia were reported more frequently. During the treatment phase, 6 malignancies were recorded out of 459 patients treated with anifrolumab and 3 out of 466 patients treated with placebo.
In the overall “all anifrolumab safety pool” (n=837 patients exposed to at least one dose of anifrolumab of 150 mg, 300 mg or 1000 mg from studies 05, 04, 09, 1013 and 1145), the incidence of grade 5 adverse events was 0.7% (n=6; exposure-adjusted incidence rate (EAIR) per 100 patient-years (PY): 0.3) in the anifrolumab group compared with 1.0% (n=3; EAIR/100 PY: 0.6) in the placebo group (n=286). In the “all anifrolumab safety pool”, malignancies were reported in 13 patients (1.6%; EAIR: 0.6/100 PY) in the all anifrolumab group and 5 patients (1.7%; EAIR: 1.0/100 PY) in the placebo group.

In the long-term phase 3 safety update, which included patients from study 09 (a 3-year extension study of studies 04 and 05), the rate of any AEs was increased in patients exposed to anifrolumab compared to placebo (93.3% vs. 86.6%). Moderate and severe AEs were reported more frequently in the anifrolumab group compared to placebo (47.8% vs. 40.8% and 15.3% vs. 9.3%, respectively). Rates of serious AEs (SAEs) were similar in both treatment groups (21.7% vs. 22.2%). Grade 5 AEs occurred in n=3 (0.8%) in the anifrolumab group and n=0 in the placebo group.
Rates of herpes zoster, tuberculosis (including latent tuberculosis) and influenza were increased in the anifrolumab group compared to placebo (11.7% vs. 3.0%, 5.0% vs. 0.8%, 5.6% vs. 3.0%, respectively).

6.5 Final Clinical and Clinical Pharmacology Benefit Risk Assessment

Systemic lupus erythematosus is a chronic, life-threatening autoimmune disease that can potentially affect all organs. Women are more commonly affected than men (9:1). SLE is not curable and the goal of therapy is to minimise symptoms and prevent potential organ damage. Treatment is individualised and based on the patient's symptoms and findings. Antimalarials (hydroxychloroquine or chloroquine) are recommended standard treatment for all patients. Other therapeutic agents include non-steroidal anti-inflammatory drugs, glucocorticoids and immunosuppressants (e.g. azathioprine or methotrexate). Belimumab (IgG1λ monoclonal antibody) is the only biological approved for the treatment of SLE.
Overall, there is a high medical need for new, specific therapeutic options.

Two phase 3 studies (05/TULIP1 and 04/TULIP2) and one large phase 2 study (1013/MUSE) were submitted to assess efficacy and safety, all involving a 52-week, double-blind comparison of anifrolumab at the requested 300 mg q4w dose versus placebo.

The selected primary and secondary endpoints were consistent with the EMA’s "Guideline on clinical investigation of medicinal products for the treatment of systemic lupus erythematosus and lupus nephritis (EMA/CHMP/51230/2013)". Both BICLA and SRI(4) are recommended endpoints and, to date, no defined gold standard exists for the measurement of disease activity in SLE.

Due to a lack of statistical significance in the primary endpoint SRI(4) of formal negative study 05/TULIP1), the primary endpoint of the second phase 3 study (04/TULIP2) was changed while the study was ongoing. This data-driven change in statistical design is a clear weakness. However, the amendment process has been described in detail and there are no significant data integrity concerns.

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The pivotal, positive study 04 (TULIP2) described a statistically significant benefit in the primary endpoint BICLA response at week 52 of anifrolumab versus placebo and was statistically significant in three key secondary endpoints controlled for multiple testing: BICLA response in the IFN gene signature high subgroup, proportion of patients who maintained OCS dose reduction and proportion of patients with a ≥50% reduction in CLASI activity score. The subgroup analyses presented describe overall consistent benefits for anifrolumab over placebo.

The other phase 3 study (05/TULIP1) did not reach statistical significance in the primary endpoint SRI(4) response at week 52. Due to the hierarchical testing strategy, the secondary endpoints were not formally tested and the overall results could only be considered exploratory. However, the secondary endpoint BICLA response at week 52 showed a numerical advantage for the anifrolumab arm compared to placebo (47.1% vs. 30.2%). Due to presumed misapplication of medication rules included in the response assessment, a post-hoc analysis of SRI(4) response at week 52 with revised medication rules was performed, showing a numeric benefit in the anifrolumab arm.
A definitive reason for not meeting the predefined primary endpoint in study 05 could not be determined.

The phase 2 study (1013/MUSE) achieved statistical significance in the primary endpoint (SRI(4) at day 169. A numerical advantage in BICLA response at week 52 was observed for the anifrolumab arm compared to placebo (53.3% vs. 25.1%).

Safety:
Mild AEs were slightly more common with anifrolumab than with placebo. The differences were mainly due to respiratory tract infections, bronchitis, herpes zoster and arthralgia. In the actual treatment phases, slight imbalances to the disadvantage of anifrolumab regarding malignancies and deaths were also described. However, these trends did not continue in the long-term extensions, and in some cases even regressed. The data submitted to date on long-term extension are incomplete and leave open, among other things, the possibility of anifrolumab becoming increasingly favourable with increasing treatment duration as a result of patient selection. Overall, however, the submitted safety data did not show any signals that would be classified as prohibitive.
However, the experience to date is too small to draw reliable conclusions about rare but potentially prohibitive adverse drug reactions. Longer follow-up is needed for a valid assessment of the risk of secondary malignancies and the vaccine efficacy of inactivated vaccines under treatment with anifrolumab.
Submission of the clinical study report of study 09, scheduled for Q3 2022, was formulated as a requirement. In addition, the results of the ongoing study D3461C00023 on anifrolumab and inactivated vaccines need to be submitted as soon as available.

Benefit-risk assessment:
Given the challenging disease profile with insufficiently standardised efficacy parameters and the high unmet medical need, a positive benefit-risk ratio is concluded despite the existing limitations of the submitted data. From a clinical point of view, the observed level of BICLA response in all three randomised trials is considered relevant. The increased risk of infections is adequately reflected in the product information and must be taken into account in clinical practice. There is no clear evidence regarding increased deaths or malignancies at the present time. Overall, however, the long-term safety profile must continue to be monitored, which is ensured by currently ongoing studies.

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7 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order to further investigate and monitor the risks as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisations.

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8 Appendix

Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to Saphnelo was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the reference document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

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▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

Saphnelo®

Composition

Active substances

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

Excipients

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

Pharmaceutical form and active substance quantity per unit

Concentrate for solution for infusion (sterile concentrate); 150 mg/mL in single-dose vial for intravenous administration.
One vial of 2.0 mL of concentrate contains 300 mg of anifrolumab.
Clear to opalescent, colourless to slightly yellow, pH 5.9 solution.

Indications/Uses

Saphnelo is indicated for the treatment of adult patients with moderate to severe systemic lupus erythematosus (SLE), in addition to standard therapy (see “Properties/Effects”).

Restrictions of use

The efficacy of Saphnelo has not been evaluated in patients with severe active lupus nephritis or severe active lupus of the central nervous system. The use of Saphnelo is not recommended in these situations.

Dosage/Administration

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

Usual dosage

The recommended dose of Saphnelo is 300 mg, administered as an intravenous infusion over a 30-minute period, every 4 weeks.
If no improvement in disease control is seen after twelve months of treatment with Saphnelo, discontinuation of treatment should be considered.

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To ensure traceability of biotechnological medicinal products, it is recommended that the trade name and batch number should be documented for each treatment.

Patients with hepatic disorders

No dose adjustment is required. No specific studies have been conducted in patients with hepatic impairment (see “Pharmacokinetics”).

Patients with renal disorders

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 “Pharmacokinetics”).

Elderly patients (≥65 years old)

No dose adjustment is required. There is limited information in subjects aged ≥65 years (see “Pharmacokinetics”).

Children and adolescents

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

Delayed administration

If a planned infusion is missed, administer Saphnelo as soon as possible. A minimum interval of 14 days should be maintained between doses.

Mode of administration

TRADENAME 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.
For instructions on the dilution and storage of the medicinal product before administration, see “Instructions for handling”.

Contraindications

Hypersensitivity to the active substance or to any of the excipients according to composition.

Warnings and precautions

Hypersensitivity

Serious hypersensitivity reactions including anaphylaxis have been reported following Saphnelo administration (see “Undesirable effects”).

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In the placebo-controlled-clinical trials, serious hypersensitivity events (including angioedema) were reported for 0.6% of patients receiving anifrolumab. There was one event of anaphylactic reaction in the SLE development program following the administration of anifrolumab.
In patients with a history of infusion-related reactions and/or of hypersensitivity reactions, pre-medication (e.g. an antihistamine) prior to the infusion of anifrolumab should be considered.
If a serious infusion-related or hypersensitivity reaction (e.g., anaphylaxis) occurs, administration of Saphnelo should be interrupted immediately, and appropriate therapy initiated.

Infections

Immunosuppressants, including Saphnelo, may be associated with severe and even fatal infections. Saphnelo increases the risk of respiratory infections and herpes zoster (disseminated herpes zoster events have been observed) see “Undesirable effects”.
In the placebo-controlled-clinical trials, the overall rate of serious infections for patients receiving anifrolumab was 4.8% compared to 5.6% for placebo (corresponding to exposure-adjusted incidence rates [EAIR] of 5.4 and 6.6 per 100 patient years, respectively).
Studies in patients with a history of primary immunodeficiency have not been conducted.
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.
The placebo-controlled clinical studies excluded patients with a history of active, or latent tuberculosis in whom an adequate course of treatment could not be confirmed. Anti-tuberculosis (Anti-TB) therapy should be considered prior to initiating treatment with anifrolumab in patients with untreated latent TB. Anifrolumab should not be given to patients with active TB.

Immunisations/vaccinations

No data are available on the response to live or attenuated vaccines. Based on the currently available evidence, it cannot be assessed to what extent Saphnelo inhibits the immune response to neo- and/or booster antigens. The time interval between live vaccination and treatment with Saphnelo must be in compliance with current immunisation guidelines for immunomodulatory agents.
Prior to initiating therapy with Saphnelo, consider completion of all appropriate immunisations according to current immunisation guidelines (including varicella and prophylactic herpes zoster vaccinations). 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 the placebo-controlled-clinical trials, at any dose, malignancies (excluding non-melanoma skin cancers) were observed in 0.7% and 0.6% of patients receiving Saphnelo and placebo, respectively. Malignant neoplasm (including non-melanoma skin cancers) was reported for 1.2% patients receiving anifrolumab, compared to 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.
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.

Not recommended for concomitant use with other biologic agents

Saphnelo has not been studied in combination with other biologic therapies, including B-cell targeted therapies.
The use of Saphnelo is therefore not recommended in combination with biologic therapies.

Interactions

No drug-drug interaction studies have been performed with Saphnelo.
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.

Pregnancy, lactation

Pregnancy

There are no or limited amount of data (less than 300 pregnancy outcomes) from the use of anifrolumab in pregnant women. Animal studies do not indicate harmful effects with respect to reproductive toxicity (see “Preclinical data”).
Saphnelo should not be used during pregnancy unless the potential benefit to the woman justifies the potential risk to the fetus.

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Lactation

It is not known whether anifrolumab is excreted in human milk. Anifrolumab was detected in the milk of female cynomolgus monkeys (see “Preclinical data”).
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 woman.

Fertility

There are no fertility data in humans.
Animal studies show no adverse effects of anifrolumab on indirect measures of fertility (see “Preclinical data”).

Effects on ability to drive and use machines

The effect of Saphnelo on the ability to drive and use machines has not been studied specifically.

Undesirable effects

Summary of the safety profile

The safety of anifrolumab has been evaluated in a total of 1029 adult subjects, of which 837 patients had SLE and received IV anifrolumab (150 mg, 300 mg, or 1000 mg) during clinical trials. Of these, 688 patients with SLE received anifrolumab for at least one year and 263 patients received anifrolumab for at least 3 years.
The data described in Table 1 reflect the exposure to Saphnelo 300 mg administered by IV infusion every 4 weeks 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 were nasopharyngitis, upper respiratory tract infection, bronchitis, infusion-related reaction, and herpes zoster.
The proportion of patients who discontinued treatment due to adverse events was 4.1% for anifrolumab and 5.2% for placebo.

List of adverse reactions

The adverse reactions should be arranged according to MedDRA system organ classes and the conventional frequencies as follows:
"very common" (≥1/10)
"common" (≥1/100, <1/10),
"uncommon" (≥1/1,000, <1/100)
"rare" (≥1/10,000, <1/ 1,000)

"very rare" (<1/10,000)

"not known" (frequency cannot be estimated from the available data)

Table 1

Adverse drug reactions

MedDRA SOC	MedDRA Preferred Term	Saphnelo (N=459)
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).

§ Frequency 'uncommon': based on one event of anaphylactic reaction reported in SLE patients who received IV anifrolumab at any dose (N=837), see "Description of specific adverse reactions" below and section "Warnings and precautions".

Description of specific adverse reactions

Hypersensitivity and infusion-related reactions

Hypersensitivity reactions were predominantly mild to moderate in intensity and did not lead to discontinuation of anifrolumab therapy. 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 "Warnings and precautions").
Infusion-related reactions were mild or moderate in intensity, the most common symptoms were headache, nausea, vomiting, fatigue, and dizziness.

Respiratory infections

Infections were predominantly non-serious, mild or moderate in intensity and resolved without discontinuation of anifrolumab therapy (see "Warnings and precautions").

Herpes zoster

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 disseminated presentation have been reported (see "Warnings and precautions").

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Immunogenicity/anti-anifrolumab antibodies

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% of patients treated with Saphnelo developed *in-vitro* detected neutralising antibodies. The clinical relevance of anti-anifrolumab antibodies is unknown.

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

Signs and symptoms

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

Treatment

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

Properties/Effects

ATC code

L04AA51

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.
Type I IFNs may 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. The clinical relevance of neutralisation of the type I IFN gene signature is, however, unclear.
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 with 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% of patients treated with anifrolumab and 5.8% of patients receiving placebo had converted to anti-dsDNA negative.
In patients with low complement (C3 and C4) levels at baseline, treatment with anifrolumab 300 mg led to greater numerical increases in complement over the 52-week treatment period.

Clinical efficacy

The safety and efficacy of Saphnelo were evaluated in two 52-week treatment period, multicentre, randomised, double-blind, placebo-controlled phase 3 studies (Trial 2 [TULIP 1] and Trial 3 [TULIP 2]) and a multicentre, randomized, double-blind, placebo-controlled phase 2 study (Trial 1 [MUSE]). 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. 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 studies were conducted in North America, Europe, South America and Asia. Patients received anifrolumab or placebo, administered by IV infusion, every 4 weeks.

The efficacy of Saphnelo was demonstrated based on clinical response based on the composite endpoints, the British Isles Lupus Assessment Group based Composite Lupus Assessment (BICLA) and the SLE Responder Index (SRI-4).

The primary endpoint in Trial 2, 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 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.

The primary endpoint of Trial 3, 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;
- 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 discontinuation of treatment;
- No use of restricted medication beyond the protocol-allowed thresholds.

In Trial 1 305 patients were randomised in a 1:1:1-ratio 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 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 British Isles Lupus Assessment Group based Composite Lupus Assessment (BICLA) was 53.5% for anifrolumab and 25.1% for placebo at Week 52.

Trial 2 and 3 were similar in design. In Trial 2, 457 patients were randomised in a 1:2:2-ratio and received anifrolumab 150 mg or 300 mg, or placebo. In Trial 3, 362 patients were randomised in a 1:1-ratio and received anifrolumab 300 mg or placebo. The primary endpoint was improvement in disease activity evaluated at 52 weeks, measured by SRI-4 (Trial 2) and BICLA (Trial 3), respectively (for definition see above). The relevant common secondary efficacy endpoint included in both studies

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was the maintenance of OCS reduction. Both studies evaluated the efficacy of anifrolumab 300 mg versus placebo.

Patient demographics were generally similar in both trials; 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, 47% 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.

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).

Efficacy is shown in Table 2.

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

	Trial 2[d]		Trial 3[d]	
	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) [a]		16.3 (6.3, 26.3) [b]	
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)

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	Trial 2[d]		Trial 3[d]	
	Anifrolumab 300 mg	**Placebo**	**Anifrolumab 300 mg**	**Placebo**
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 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) [c]		18.2 (8.1, 28.3)	
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) [e]		21.2 (6.8, 35.7)	

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; SRI-4: SLE Responder Index.
* BICLA and SRI(4) are based on the composite estimand where treatment discontinuation or restricted medication use are part of the response criteria.
† Patients who discontinued treatment or used restricted medications 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.
[a] BICLA Trial 2: Not formally tested in a pre-specified testing scheme and findings should be interpreted with caution and based on post-hoc analysis
[b] BICLA Trial 3: primary endpoint, statistically significant
[c] SRI(4) in Trial 2: primary endpoint, not statistically significant
[d] In both Trials 2 and 3, patients who discontinued investigational product or initiated restricted medications beyond the protocol-specified thresholds are considered non-responders. For consistency, the results presented for Trial 2 represent the post-hoc analysis using the restricted medication thresholds as defined in Trial 3.
[e] Regarding secondary endpoint OCS reduction in Trial 2: endpoint not formally tested

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). The results for male patients and patients aged over 65 years of age should be interpreted with caution due to the sample size within the subgroups.

Effect on Concomitant Steroid Treatment: In the 47% of patients of Trial 3 with a baseline OCS use ≥10 mg/day, anifrolumab demonstrated a statistically significant reduction in OCS use, of at least 25% to ≤7.5 mg/day at Weeks 40 maintained through to Week 52 (p-value=0.004); 51.5% of patients in the anifrolumab group versus 30.2% in the placebo achieved this level of steroid reduction (difference 21.2% [95% CI 6.8, 35.7]).

Pharmacokinetics

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. Following the 300 mg every 4 weeks intravenous administrations of anifrolumab, steady-state was reached by Day 85. The accumulation ratio was approximately 1.36 for C_{max} and 2.49 for C_{trough}.

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.

Metabolism

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.
Following the administration of anifrolumab at a dose of 300 mg via intravenous infusion every 4 weeks, 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% reduction after 1 year of 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.

Non-linearity

Anifrolumab exhibits nonlinear PK with overproportionally increased exposure 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).

Kinetics in specific patient groups

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.

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

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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.

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.

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.

Preclinical data

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

Genotoxicity 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.

Reproductive toxicity

In a pre- and postnatal development study, conducted in cynomolgus monkeys, there were no maternal, embryo-fetal, 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 28 times the exposure at the maximum recommended human dose (MRHD) on an AUC basis. Anifrolumab was detected in the milk of female cynomolgus monkeys administered Anifrolumab.

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).

Other information

Incompatibilities

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

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the pack.

Shelf life after opening

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).

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. Do not shake. Keep out of the reach of children.

Diluted solution for infusion

For storage conditions after dilution of the medicinal product, see “Shelf life after opening”.

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Instructions for 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 of sodium chloride 9 mg/mL (0.9%) solution for injection, from a 100 mL infusion bag.
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 should be administered immediately after preparation. If the solution for infusion has been stored in a refrigerator (see “Shelf life after opening”), 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 or 0.22 micron in-line filter.
3. Upon completion of the infusion, flush the infusion set with 25 mL sodium chloride 9 mg/mL (0.9%) solution for infusion to ensure that all of the solution for infusion has been administered.
4. Do not co-administer any other medicinal products through the same infusion line.

Disposal

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

Authorisation number

68512 (Swissmedic)

Packs

Saphnelo 300 mg/2 ml: 1 vial [A]

Marketing authorisation holder

AstraZeneca AG, 6340 Baar

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