Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Saphnelo

Active ingredient: Anifrolumab

Sponsor: AstraZeneca Pty Ltd

December 2022

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating therapeutic goods, including medicines, medical devices, and biologicals.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety, and efficacy.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to the Australian public outweigh any risks associated with the use of therapeutic goods.
- The TGA relies on the public, healthcare professionals and industry to report problems with therapeutic goods. The TGA investigates reports received to determine any necessary regulatory action.
- To report a problem with a therapeutic good, please see the information on the TGA website.

About AusPARs

- The Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission. Further information can be found in Australian Public Assessment Report (AusPAR) guidance.
- AusPARs are prepared and published by the TGA.
- AusPARs are static documents that provide information that relates to a submission at a particular point in time. The publication of an AusPAR is an important part of the transparency of the TGA's decision-making process.
- A new AusPAR may be provided to reflect changes to indications or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
ACR	American College of Rheumatology
ADA	Antidrug antibody
AE	Adverse event
ANA	Anti-nuclear antibody
ARTG	Australian Register of Therapeutic Goods
ASA	Australian specific annex
AUC	Area under the concentration time curve
BICLA	British Isles Lupus Assessment Group-based Combined Lupus Assessment
BILAG	British Isles Lupus Assessment Group (United Kingdom/Republic of Ireland)
BMI	Body mass index
CMI	Consumer Medicines Information
CPD	Certified Product Details
DLP	Data lock point
dsDNA	Double stranded deoxyribonucleic acid
EU	European Union
FDA	Food and Drug Administration (United States of America)
GVP	Good Pharmacovigilance Practices
HbA1c	Glycated haemoglobin
IFNAR1	Interferon alpha receptor 1
IP	Investigational product
PD	Pharmacodynamic(s)
PGA	Physician's Global Assessment
PI	Product Information

Abbreviation	Meaning
PK	Pharmacokinetic(s)
PopPK	Population pharmacokinetic(s)
PSUR	Periodic safety update reports
RMP	Risk management plan
SAE	Serious adverse event
SDI	Systemic Lupus International Collaborating Clinics / American College of Rheumatology Damage Index
SF-36-v2	36-Item Short Form Health Survey version 2
SLE	Systemic lupus erythematosus
SLEDAI-2K	Systemic Lupus Erythematosus Disease Activity Index 2000
SRI	Systemic Lupus Erythematosus Responder Index
TGA	Therapeutic Goods Administration
ULN	Upper limit of normal
US(A)	United States (of America)
VAS	Visual analog scale

Product submission

Submission details

Type of submission:	New biological entity
Product name:	Saphnelo
Active ingredient:	Anifrolumab
Decision:	Approved
Date of decision:	24 March 2022
Date of entry onto ARTG:	29 March 2022
ARTG number:	350930
▼ *Black Triangle Scheme:*	Yes. This product will remain in the scheme for 5 years, starting on the date the product is first supplied in Australia.
Sponsor's name and address:	AstraZeneca Pty Ltd 66 Talavera Road Macquarie Park NSW 2113
Dose form:	Concentrate for solution for infusion
Strength:	300 mg/2 mL
Container:	Vial
Pack size:	One
Approved therapeutic use:	*Saphnelo (anifrolumab) is indicated as add on treatment of adult patients with moderate to severe, active systemic lupus erythematosus (SLE), despite standard therapy.* *The safety and efficacy of Saphnelo have not been evaluated in patients with severe active lupus nephritis or severe active central nervous system lupus.*
Route of administration:	Intravenous
Dosage:	The recommended dose of Saphnelo is 300 mg every 4 weeks via intravenous infusion. Treatment should be initiated and supervised by a physician experienced in the treatment of systemic lupus erythematosus. Saphnelo is administered as an intravenous infusion over a 30-minute period. Following dilution with sodium chloride (0.9%) solution for injection. 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. See Section 4.4 Special warnings and precautions of the Product Information for specific information regarding hypersensitivity reaction, infection, immunisations and use with other biologic therapies, including B-cell-targeted therapies. For further information regarding dosage, refer to the Product Information.
Pregnancy category:	C Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details. The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. This must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your State or Territory.

Product background

This AusPAR describes the submission by AstraZeneca Pty Ltd (the sponsor) to register Saphnelo (anifrolumab) 300 mg/2 mL, concentrate for solution for infusion for the following proposed indication:

> *Saphnelo (anifrolumab) is indicated as add on for the treatment of adult patients with moderate to severe systemic lupus erythematosus (SLE) despite standard therapy.*

Systemic lupus erythematosus (SLE) is a complex, chronic, multi-system, disabling autoimmune rheumatic disease that can affect any organ system. Because every organ can be a target of attack by the immune system, patients present with a variety of clinical manifestations, including constitutional symptoms, alopecia and rashes, serositis, inflammatory arthritis, renal disease, systemic vasculitis, lymphadenopathy, splenomegaly, haemolytic anaemia, cognitive dysfunction, and other central nervous system involvement. These clinical manifestations are devastating for patients and can lead to reduced physical function, loss of employment, a major impact on health-related quality of life, frequent hospitalisations, and cumulative and irreversible organ damage.

The manifestations and progression of SLE are unpredictable and include periods of chronic activity, clinically inactive periods, and phases with heightened disease activity (disease flares). As well as the impact caused by their unpredictable nature, flares have

been directly associated with an increased risk of damage accrual,[1] and studies have shown a direct association between disease damage and survival in patients with SLE.[2,3]

In addition to the clinical manifestations of the disease itself, patients with SLE are at increased risk of developing serious comorbidities, including cardiovascular disease, stroke, osteoporosis, infection and malignancies.

In the Australian context, the prevalence of SLE ranges from 19 per 100,000 in Australians of European ancestry to 92 per 100,000 in Indigenous Australians.[4] SLE is nine times more common in females than males and the onset of disease usually occurs between 15 and 45 years of age.[5]

Compared to the general population, the overall mortality in SLE remains high, with a standardised mortality ratio (defined as the ratio of the number of deaths observed to deaths expected) of 2.4, in a large international cohort of 9,457 subjects followed for over 70,000 subject years.[6]

Most of the current therapies for SLE are nonspecific and inhibit broad inflammatory pathways leading to significant toxicity and organ damage.[7] For mild disease, first line treatments include antimalarials (hydroxychloroquine) and oral corticosteroids such as prednisone. Long-term use of hydroxychloroquine can cause retinopathy and poor adherence to treatment remains an issue with this drug.[8] Non-steroidal anti-inflammatory drugs are used for temporary symptom control, but in contrast to glucocorticoids and immunosuppressants, have no impact in disease progression.

Steroids remain a mainstay of treatment for mild to severe disease and although they provide benefits in SLE, over time, organ damage from steroid use increases. Chronic steroid use is a contributing factor in long-term morbidity and early cardiovascular mortality in patients with SLE.[2,3,9]

Additional treatment options for moderate to severe disease include immunosuppressants, such as methotrexate, azathioprine, and mycophenolate mofetil. The use of immunosuppressants is associated with an increased risk of infection, malignancy, cardiovascular disease, and bone marrow suppression, and are not effective in all patients for all manifestations of SLE.

Only one targeted therapy has been approved for SLE in the last 60 years. Belimumab;[10] is a neutralising anti-B-lymphocyte stimulator monoclonal antibody. It targets only one pathway, while patients are likely to have different underlying immunopathological

[1] Ugarte-Gil, M.F. et al. The Number of Flares Patients Experience Impacts on Damage Accrual in Systemic Lupus Erythematosus: Data from a Multiethnic Latin American Cohort, *Ann Rheum Dis*, 2015;7 4(6): 1019-1023.
[2] Petri, M. Long-Term Outcomes in Lupus, *Am J Manag Care*, 2001; 7(16 Suppl): S480-S485.
[3] Ruiz-Arruza, L. et al Glucocorticoids and Irreversible Damage in Patients with Systemic Lupus Erythematosus, *Rheumatology (Oxford)*, 2014; 53(8): 1470-1476.
[4] Nikpour M, Bridge JA, Richter S. A systematic review of prevalence, disease characteristics and management of systemic lupus erythematosus in Australia: identifying areas of unmet need. *Intern Med J* 2014; 44: 1170-1179.
[5] Apostolopoulos, D. Systemic Lupus Erythematosus. Australian Family Physician. Volume 42, No.10, October 2013 Pages 696-700.
[6] Bernatsky, S. et al. Mortality in Systemic Lupus Erythematosus, *Arthritis Rheum*, 2006; 54(8): 2550-2557.
[7] Lichtman, E.I. et al. Emerging Therapies for Systemic Lupus Erythematosus-Focus on Targeting Interferon-Alpha, *Clin Immunol*, 2012; 143(3): 210-221.
[8] Fanouriakis, A. et al. 2019 Update of the EULAR Recommendations for the Management of Systemic Lupus Erythematosus, *Ann Rheum Dis*, 2019; 78(6): 736-745.
[9] Apostolopoulos, D. and Morand, E.F. It Hasn't Gone Away: the Problem of Glucocorticoid use in Lupus Remains, *Rheumatology (Oxford)*, 2017; 56(suppl_1): i114-i122.
[10] Benlysta (belimumab) was first registered on the ARTG on 18 October 2012 (ARTG numbers: 173077 and 173078).

pathways driving their SLE disease manifestations.[11] As such, it is only effective in some patients.

Current therapies for SLE are either nonspecific and inhibit broad inflammatory pathways, leading to significant toxicity and organ damage, or target one pathway in a disease with multiple contributing pathways in its pathogenesis. There remains an urgent, unmet medical need for novel treatments with disease specific mechanisms of action that reduce overall disease activity and the concomitant use of steroids, while also reducing flares, comorbidities, and the risk of long-term organ damage.

The sponsor has given the following information regarding the mechanism of action and scientific rationale for the use of anifrolumab in the treatment of SLE:

> Anifrolumab is an anti-interferon alpha receptor 1 (IFNAR1) human IgG1κ monoclonal antibody that binds to subunit 1 of the IFNAR1 with high specificity and affinity. This binding inhibits type I interferon signalling by blocking the biologic activity of type I interferons. 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 interferon signalling inhibits interferon-responsive gene expression, as well as downstream inflammatory and immunological processes. To date, there is no approved treatment with this pharmacological mechanism of action.
>
> Anifrolumab is a new targeted therapy with a novel mechanism of action that has the potential to provide a clinically significant improvement to currently available therapies used in the treatment of SLE.

Given the central role of the interferon pathway in the pathogenesis of SLE, targeting Type I interferon signalling is expected to provide a therapeutic benefit for SLE patients. Anifrolumab is a monoclonal antibody that inhibits subunit 1 of the Type I interferon receptor and has the potential to provide a clinically significant improvement to currently available therapies in the target population for the treatment of SLE. To date, there is no approved treatment with this pharmacological mechanism of action.

Regulatory status

This product is considered a new biological entity for Australian regulatory purposes.

At the time the TGA considered this submission, similar submissions had been approved in Canada on 30 November 2021 and the United States of America (USA) on 30 July 2021. Similar submissions were under consideration in the European Union (EU) (submitted on 8 October 2020) and Switzerland (submitted on 8 May 2021).

The following table summarises these submissions and provides the indications where approved.

Table 1: International regulatory status

Region	Submission date	Status	Approved indications
Canada	9 November 2020	Approved on 30 November 2021	*Saphnelo (anifrolumab for injection) is indicated in addition to standard*

[11] Dörner, T. and Furie, R. Novel Paradigms in Systemic Lupus Erythematosus, *Lancet*, 2019; 393(10188): 2344-2358.

Region	Submission date	Status	Approved indications
			therapy for the treatment of adult patients with active, autoantibody positive, systemic lupus erythematosus (SLE).
European Union	8 October 2020	Under consideration	Under consideration
Switzerland	8 May 2021	Under consideration	Under consideration
United States of America	31 July 2020	30 July 2021	*Saphnelo (anifrolumab-fnia) is indicated for the treatment of adult patients with moderate to severe systemic lupus erythematosus (SLE), who are receiving standard therapy.*

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA PI/CMI search facility.

Registration timeline

The following table captures the key steps and dates for this submission.

Table 2: Timeline for Submission PM-2020-06383-1-2

Standard pathway

Description	Date
Submission dossier accepted and first round evaluation commenced	1 February 2021
First round evaluation completed	1 July 2021
Sponsor provides responses on questions raised in first round evaluation	30 August 2021
Second round evaluation completed	18 October 2021
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	4 January 2022

Description	Date
Sponsor's pre-Advisory Committee response	19 January 2022
Advisory Committee meeting	3 and 4 February 2022
Registration decision (Outcome)	24 March 2022
Completion of administrative activities and registration on the ARTG	29 March 2022
Number of working days from submission dossier acceptance to registration decision*	235

*Statutory timeframe for standard submissions is 255 working days

Submission overview and risk/benefit assessment

A summary of the TGA's assessment for this submission is provided below.

Relevant guidelines or guidance documents referred to by the Delegate are listed below:

- European Medicines Agency (EMA), Committee for Medicinal Products for Human Use (CHMP), ICH guideline S6 (R1) - Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals, EMA/CHMP/ICH/731268/1998, June 2011.
- European Medicines Evaluation Agency (EMEA), Committee for Medicinal Products for Human Use (CPMP), ICH Topic E1 Population Exposure: the Extent of Population Exposure to Assess Clinical Safety, Note for Guidance on Population Exposure: the Extent of Population Exposure to Assess Clinical Safety, CPMP/ICH/375/95, June 1995.

Quality

Anifrolumab is a human immunoglobulin G1 kappa monoclonal antibody directed against subunit 1 of the interferon alpha receptor 1 (IFNAR1). It is composed of two identical light chains and two identical heavy chains, with an overall molecular weight of approximately 148 kDa.

The sponsor has presented the drug product Saphnelo for registration. Saphnelo is a sterile, concentrated solution of anifrolumab presented in a vial for intravenous infusion following dilution with sodium chloride 0.9% (solution for injection.

The drug product contains anifrolumab 300 mg per 2 mL vial as the active ingredient. The drug product is aseptically filled into Type I glass vials and closed with an elastomeric stopper. The vial is capped with an aluminium seal.

Saphnelo should be stored at 2 to 8°C. The recommended shelf life for the drug product long-term storage condition is 2 to 8°C for 24 months.

There should be no more than 9 days of cumulative exposure at temperatures between -20 to 2°C. The product should be not be exposed to temperatures of 8 to 25°C for longer than 21 days between 8 to 25°C, and the product should not be exposed to temperatures between 25 to 40°C for any longer than 4 hours.

Conclusions

There are no objections on quality grounds to the approval of Saphnelo anifrolumab 300 mg concentrated injection vial.

Lot release, characterisation and stability test results from the drug substance comparability testing demonstrate that anifrolumab Process 3 material is comparable to Process 1 and 2 materials. Development of the manufacturing processes (Processes 1 to 3) have been well compared to each other and changes have been clearly identified and explained. The comparability of the commercial Process 3 to Processes 1 and 2 are acceptable and supported by characterisation and stability studies.

Quality-related proposed conditions of registration

- It is a condition of registration that all batches of Saphnelo anifrolumab imported into/manufactured in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).

Nonclinical

The submitted nonclinical dossier was in accordance with the relevant ICH guideline for the nonclinical assessment of biological medicines (ICH S6(R1)).[12] The overall quality of the nonclinical dossier was adequate. All pivotal safety-related studies were Good Laboratory Practice;[13] compliant.

In vitro anifrolumab binds to the interferon alpha receptor 1 (IFNAR1) receptor with nanomolar affinity and inhibits Type I interferon signalling, downstream immune responses, suppresses inflammatory responses, as well as activation of adaptive immune responses. Anifrolumab similarly binds cynomolgus monkey (but not rodent) IFNAR1 and inhibits Type I interferon induced cell signalling supporting the use of monkeys in toxicity studies.

An *in vivo* study using a murine model of lupus nephritis with a surrogate anti-IFNAR antibody, 5A3, showed significant inhibition of Type I interferon signalling, evident as suppressed induction of Type I interferon induced genes and reduced the onset or severity of kidney damage, supporting the proposed clinical indication and dose.

Anifrolumab did not induce complement dependent cytotoxicity or antibody dependent cellular cytotoxicity, but it is noted the tested concentrations were low.

Immunohistochemistry staining with anifrolumab of normal tissues of monkey and human origin was consistent with known IFNAR1 expression and a similar pattern was seen in both species.

No adverse effects on the function of central nervous, cardiovascular, or respiratory systems during clinical use are predicted from animal studies.

The pharmacokinetics (PK) of anifrolumab in monkeys and human subjects was generally consistent with the protein nature of the drug: long half-lives and limited distribution and considered acceptably similar in cynomolgus monkeys and human subjects.

Anifrolumab had a low order of acute intravenous toxicity in monkeys.

[12] European Medicines Agency (EMA), Committee for Medicinal Products for Human Use (CHMP), ICH guideline S6 (R1) - Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals, EMA/CHMP/ICH/731268/1998, June 2011.
[13] **Good Laboratory Practice** is a code of standards following the International Council on Harmonisation (ICH) relevant to testing of medicines in laboratories during drug development.

Repeat dose toxicity studies by the intravenous route were conducted in cynomolgus monkeys (up to 39 weeks). Anifrolumab was generally well tolerated. However, effects potentially secondary to anti-anifrolumab antibody formation were observed (arteritis in various organs potentially associated with deposition of drug-antidrug antibody (ADA) complexes and hypersensitivity reactions). However, there were no investigative studies of drug-ADA complex deposition and attribution of arteritis to immune complex deposition therefore remains speculative.

No genotoxicity or carcinogenicity studies were submitted, which is considered acceptable. A carcinogenicity risk assessment based on published literature with relevant knockout mice models, concluded there is evidence of a potential increased carcinogenic risk to patients. The relevance for malignancy risk in humans is unknown.

In an enhanced pre- or post-natal study in cynomolgus monkeys, treatment starting from the period of organogenesis (gestation Day 20) until early lactation (4 weeks after delivery) was not associated with maternal toxicity, effects on embryofetal development, pregnancy outcomes or postnatal development at high exposure levels of up to 28 times the clinical area under the concentration time curve. However, based on the pharmacological activity of the drug and the presence of circulating drug in infants following maternal exposure during gestation, a risk of a higher incidence of viral infections may be seen in infants exposed to anifrolumab during the last stages of pregnancy.

Anifrolumab was well tolerated locally in monkeys. Whilst no injection site reactions were seen when anifrolumab was administered as an intravenous infusion to monkeys, the vehicle used was different from the final clinical formulation, so the predictive value of the absence of findings is limited.

Under the nonclinical test conditions, anifrolumab did not demonstrate significant immunotoxic activity or perturb immunological responses. However, published literature indicated an increased susceptibility to viral infections in IFNAR1 knockout mice. A higher incidence and/or severity of viral infections may be seen in patients treated with anifrolumab.

Conclusions and recommendations

The proposed mechanism of action of inhibition of IFNAR1 receptor or Type I interferon signalling was demonstrated in primary pharmacology studies which lend support for the proposed treatment of patients with severe systemic lupus erythematosus (SLE).

The only notable findings in toxicity studies were associated with ADA formation (arteritis and hypersensitivity). While immunogenicity in animals is not always predictive of the human response, the findings do indicate the potential secondary effects that may be seen in patients who develop ADAs.

Local tolerance (by intravenous infusion) will need to be addressed by clinical data.

Materials used in nonclinical studies were development batches manufactured by 'Process 1'. Anifrolumab drug substance proposed for marketing in Australia is now manufactured by 'Process 3'. No bridging PK/pharmacodynamic (PD) studies were conducted to confirm there was no difference in the pharmacology and PK of the drug substance manufactured using the two different processes. Advice on comparability should be sought from the TGA quality evaluation indicating that the Process 1 and Process 3 drug substance or product are comparable. The applicability of the nonclinical findings is dependent on acceptable similarities between the two drug substances.

Provided that the drug manufactured by Process 1 is considered to be identical or highly comparable to the drug manufactured by Process 3 by the quality evaluation, there are no

nonclinical objections to the registration of Saphnelo for the proposed indication (see Section: Quality conclusions for further details).

Clinical

Summary of clinical studies

The clinical dossier consisted of:

- two Phase I pharmacology studies: Study D3461C00006 and Study MI-CP180;
- four Phase II pharmacology, efficacy and safety studies: Study CD-IA-MEDI-546-1013, Study D3461C00002, Study CD-IA-MEDI-546-1013 and Study CD-IA-MEDI-546-1145;
- three Phase III pharmacology, efficacy and safety studies: Study D3461C00004 (pivotal study). Study D3461C00005 (pivotal study) and Study D346100009 (long-term 3-year extension study).

The submission did not include paediatric data.

The sponsor advised that they have an agreed Paediatric Investigation Plan in Europe. The date on which the company is required to submit a report of a study conducted as part of the Paediatric Investigation Plan is March 2023.

Pharmacology

Pharmacokinetics

The summary of clinical pharmacology consists of pharmacokinetic (PK) data derived from eight studies that evaluated anifrolumab administered as an intravenous infusion: one study (Study D3461C00006) in healthy volunteers, one study (Study MI-CP180) in patients with scleroderma, and six studies (Studies D3461C00002, D3461C00004, D3461C00005, CD-IA-MEDI-546-1013, CD-IA-MEDi-546-1145 and D3461C00009) in patients with systemic lupus erythematosus (SLE).

Table 3: Overview of clinical pharmacology studies

PK topic	Subtopic	Study ID	Primary aim
PK in healthy adults	General PK - single dose	D3461C00006	PK, BA
PK in special populations	Target population;§ - multi-dose	D3461C00004 D3461C00005 CD-IA-MEDI-546-1013 CD-IA-MEDI-546-1145 D3461C00002	Efficacy and safety
	Other special population - scleroderma	MI-CP180	PK
Population PK analyses	Target population	PopPK Report	PopPK

Abbreviations: BA = bioavailability; ID = identification; PK = pharmacokinetics; PopPK = population pharmacokinetics.

§ Subjects who would be eligible to receive the drug if approved for the proposed indication.

Anifrolumab exhibits non-linear PK in the dose range of 100 to 1000 mg with area under the concentration versus time curve (AUC) increased more than dose proportionally. Following every 4 weeks intravenous administrations of anifrolumab, steady state was reached by Day 85. The steady state exposure (AUC) for 1000 mg every 4 weeks is approximately 4-fold higher compared to the steady state exposure of 300 mg every 4 weeks. The steady state exposure (AUC) for 300 mg every 4 weeks is approximately 3-fold higher compared to the steady state exposure of 150 mg every 4 weeks.

The dosing regimen of anifrolumab has been adequately explored. Results from the Phase II dose ranging study (Study CD-IA-MEDI-546-1013) showed that while both 300 mg and 1000 mg every 4 weeks dosing regimens were efficacious in SLE patients, 1000 mg dosing did not provide additional treatment benefit. Therefore, intravenous anifrolumab 300 mg every 4 weeks dosing regimen was selected for Phase III studies (Studies D3461C00004 and D3461C00005). A 150 mg dose group was included in the Phase III program to further elucidate dose response. The responder rate was numerically lower at 150 mg every 4 weeks. An exposure-response analysis for efficacy and safety indicated that the proposed intravenous 300 mg every 4 weeks dosing regimen provides the optimal benefit-risk balance in patients with SLE.

No dose adjustment of anifrolumab is recommended for any intrinsic or extrinsic factors.

In the Phase III Studies D3461C00004 and D3461C00005, 6 out of 352 subjects (1.7%) with anifrolumab intravenous 300 mg every 4 weeks treatment were detected antidrug antibody (ADA) positive post-Baseline. Due to the limited number of subjects, no conclusion could be drawn regarding the impact of positive ADA on anifrolumab PK, PD, efficacy and safety.

In patients with SLE, following the administration of anifrolumab at 300 mg given via intravenous infusion every 4 weeks for 52 weeks, neutralisation (80% or higher) of Type I interferon gene signature was observed from week 4 to Week 52 in blood samples of patients with elevated levels of Type I interferon inducible genes. This PD marker returned to baseline levels within 8 to 12 weeks following withdrawal of anifrolumab at the end of the 52-week treatment period. However, the clinical relevance of the Type I interferon gene signature neutralisation is unclear.

In SLE patients with positive anti-double stranded deoxyribonucleic acid (dsDNA) antibodies at Baseline (Studies D3461C00004 and D3461C00005), treatment with anifrolumab 300 mg led to numerical reductions in anti-dsDNA antibodies over time through Week 52.

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

Population pharmacokinetic data

Pharmacokinetic data from healthy volunteers (Study D3461C00006) and in patients with SLE (Studies CD-IA-MEDI-546-1013, D3461C00002, D3461C00004 and D3461C00005) were pooled to develop a population pharmacokinetic (PopPK) model to characterise the PK of anifrolumab and to evaluate the impacts of covariates, such as demographics and renal or liver function tests on PK exposure.

Based on the PopPK analysis, there was a modest decrease in median clearance (8.4%) after one year of treatment that resulted in a minor increase in exposure; however, the decrease in clearance was not considered clinically relevant.

Population pharmacokinetic analysis also showed that standard of care therapy such as oral corticosteroids, anti-malarial, and immunosuppressants (azathioprine, methotrexate, mycophenolate mofetil, mycophenolic acid, and mizoribine) along with commonly used

medications in SLE patients (non-steroidal anti-inflammatory drugs, angiotensin converting enzyme (ACE) inhibitors, and hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors) had no impact on the clearance of anifrolumab.

Pharmacodynamics

In the summaries, the sponsor has presented PD results only for the Type I interferon test high patients, suggesting that this is the subgroup of SLE patients who should be receiving treatment with anifrolumab. No results for the Type I interferon low patients are presented for comparison and no explanation for this omission is provided.

Anifrolumab doses of 300 mg or higher given intravenously resulted in a rapid, substantial and sustained neutralisation of Type I interferon inducible genes by Week 4. There was a lack of neutralisation in the 150 mg group.

In Study CD-IA-MEDI-546-1013 the median neutralisation of Type I interferon PD signature was similar in the 300 mg and 1000 mg dose groups, where an efficacy plateau was observed but no other doses were tested and no other dose regimen other than every 4 weeks was tested. The median neutralisation of the Type I interferon PD signature for the 150 mg dose was lower than that of the 300 mg dose.

Anifrolumab 300 mg also demonstrated a positive exposure to response relationship for the primary composite endpoints of changes to scores on the British Isles Lupus Assessment Group (BILAG)-based Composite Lupus Assessment (BICLA) and the Systemic Lupus Erythematosus Responder Index (SRI) and across the key secondary endpoints (maintained oral corticosteroids reduction and Cutaneous Lupus Erythematous Disease Activity and Severity Index;[14] response at Week 12 and reduction in flare rates).

Dose selection

The recommended dose regimen was stated to be based on PK/PD modelling which provided justification for the dose levels of 300 mg and 1000 mg used in Study CD-IA-MEDI-546-1013 and refined to a recommended dose of 300 mg in Studies D3461C00005 and D3461C00004.

No dose interval other than every 4 weeks appears to have been studied.

The dosing interval of every 4 weeks was questioned by the clinical evaluation during the review as this was not discussed in the studies or the summaries.

The sponsor's response with the simulation data supported the dosing interval of every 4 weeks and the results support the efficacy of the dose of 300 mg but there did not appear to be data for a higher dose between 300 mg and 1000 mg.

[14] The **Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI)** is a clinical instrument that quantifies disease activity and damage in cutaneous lupus erythematosus. The scoring system is based on the degree of erythema, scale, mucous membrane lesions, and nonscarring alopecia.
The **CLASI-A** score represents cuteanous lupus erythematosus (CLE) disease activity, that is the overall severity of CLE dermatologic involvement as observed during patient examination at a clinic visit.
The **CLASI-D** score represents observable CLE damage, that is, the overall extent of scaring, pigmentary change, and alopecia, observed by the clinician.
Note, the CLASI does not measure the impact of CLE activity and damage on other aspects of life, such as psychological stress, occupational disability, or lowered health-related quality of life even though it is well documented that CLE may have a major impact in these areas.

Efficacy

Pivotal studies

- Study D3461C00004 is a multicentre, randomised, double blind, placebo controlled, Phase III study evaluating the efficacy and safety of anifrolumab in adult subjects with active systemic lupus erythematosus (SLE).
- Study D3461C00005 is a multicentre, randomised, double blind, placebo controlled, Phase III study evaluating the efficacy and safety of two doses of anifrolumab in adult subjects with active SLE.

Other studies

- Study CD-IA-MEDI-546-1013 is a Phase II, randomised study to evaluate the efficacy and safety of anifrolumab in subjects with SLE.
- Study CD-IA-MEDI-546-1145 is a Phase II, open label extension study to evaluate long-term safety of anifrolumab in adults with SLE.
- Study D3461C00002 is a Phase II, multicentre, open label, dose escalation study to evaluate the safety and tolerability of intravenous dose of anifrolumab, a human monoclonal antibody directed against interferon alpha receptor 1 (IFNAR1), in Japanese subjects with active SLE.

Study D3461C00004

Study D3461C00004 (also known as the TULIP-2 trial);[15] is a Phase III, multicentre, randomised, double blind, placebo controlled study was conducted at 98 sites in 15 countries (Japan (17), South Korea (4), Belgium (2); Bulgaria (3), France (7), Germany (4), Lithuania (2), Russian Federation (5), Spain (7), Argentina (3), Brazil (5), Mexico (6), Canada (2), USA (27) and South Africa (4)) from July 2015 to December 2018.

The study consisted of a screening period of up to 30 days and a 52-week double blind treatment period after which the patients either continued the study for another 8 weeks to complete a 12-week safety follow up after the last dose of study drug or, if eligible enrolled into a long-term 3-year extension study (Study D346100009) which is still ongoing.

Following changes were made by protocol amendments (and statistical analysis plan were agreed with the US Food and Drug Administration (FDA) Division) just before the data base lock and unblinding of Study D3461C00004:

- Change from initial primary endpoint of Systemic Lupus Erythematosus Responder Index of at least 4 (SRI(4))[16] response at Week 52 to BICLA response at Week 52.

[15] Study D3461C00004 (TULIP-2 trial): A multicentre, randomised, double-blind, placebo-controlled, Phase III study evaluating the efficacy and safety of anifrolumab in adult subjects with active systemic lupus erythematosus. ClinicalTrials.gov Identifier: NCT02446899.
Publication: Morand EF, Furie R, Tanaka Y, Bruce IN, Askanase AD, Richez C, Bae SC, Brohawn PZ, Pineda L, Berglind A, Tummala R; TULIP-2 Trial Investigators. Trial of Anifrolumab in Active Systemic Lupus Erythematosus. N Engl J Med. 2020 Jan 16;382(3):211-221.

[16] The **Systemic Lupus Erythematosus Responder Index (SRI)** is a disease activity assessment that quantify decrease and increase in disease activity in a broad spectrum of manifestations. It comprises criteria from three different internationally validated indices, SELENA-SLE Disease Activity Index, Physician Global Assessment (PGA) and the British Isles Lupus Assessment Group (BILAG) 2004.
Achieving an **SRI4 response** is defined as a SLEDAI improvement of 4 points or more, a PGA score not worsening by 0.3 points or more (10% or more), and BILAG as recording no new A's and not having 2 or more new B's. The SRI response is considered as being achieved (or not) compared with Baseline (or a specified timepoint).

- Change in key secondary endpoint from SRI(4) response at Week 52 in interferon test high subgroup to BICLA response at Week 52 in interferon test high subgroup.
- Added key secondary endpoint of proportion of subjects with 50% or more reduction in number of swollen and tender joints at Week 52 in subjects with at least 6 swollen and tender joints at Baseline.
- Systemic Lupus Erythematosus Responder Index of at least 4 response at Week 24 demoted from key to another secondary endpoint.
- No change in key secondary endpoints of proportion of subjects who achieve an oral corticosteroids dose 7.5 gm/day or less at Week 40 maintained through Week 52; proportion of subjects with 50% or more reduction in Cutaneous Lupus Erythematous Disease Activity and Severity Index (CLASI) activity score at Week 12 in subgroup with baseline CLASI at least 10; annualised flare rate defined by one or more new BILAG-2004 A or two or more new B items compared to the previous visit.

Inclusion and exclusion criteria

Inclusion criteria

- Healthy male and female (non-childbearing potential) aged from 18 to 70 years and weight at least 40.0 kg at screening.
- Diagnosis of paediatric or adult SLE according to the American College of Rheumatology (ACR) 1982 revised criteria at least 24 weeks prior to enrolment and fulfilled at least 4 or the 11 ACR modified 1982 classification criteria for SLE, at least one of which was:
  - Positive anti-nuclear antibody (ANA) test at screening by immunofluorescent assay at the central laboratory with titre at least 1:80; or
  - anti-double stranded deoxyribonucleic acid (dsDNA) antibodies at screening elevated to above normal (including indeterminate), as per the central laboratory; or
  - anti-Smith antibody at screening elevated to above normal as per the central laboratory.
- At screening, Disease Activity Adjudication Group confirmation of:
  - Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K)[17] criteria: SLEDAI-2K score at least 6 points and 'clinical' SLEDAI-2K score at least 4 points.
  - British Isles Lupus Assessment Group (BILAG)-2004 Level Criteria: at least one of the following:
    - BILAG-2004 level A disease in at least one organ system
    - BILAG-2004 level B disease in at least two organ systems
  - Physician's Global Assessment (PGA)[18] score at least 1 on a 0 to 3 visual analog scale (VAS) at screening; was currently receiving at least one of the protocol specified medication.

[17] The **Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K)** was developed to measure disease activity in systemic lupus erythematosus and is suitable for use in clinical trials and studies of prognosis in systemic lupus erythematosus. It is based on the presence of 24 descriptors in nine organ systems over the preceding 30 days. Descriptors of SLEDAI-2K are documented as present or absent. Each of the descriptors has a weighted score and the total score of SLEDAI-2K is the sum of all 24 descriptor scores.
[18] The **Physician's Global Assessment (PGA)** is a visual analogue score that reflects the clinician's judgement of overall systemic lupus erythematosus disease activity.

- No history, signs, or symptoms of active or latent tuberculosis or recent contact with person with active tuberculosis and negative screen for tuberculosis including chest X-ray.

Exclusion criteria

- At screening, any of the following:
  - aspartate aminotransferase higher than 2.0 x upper limit of normal (ULN)
  - alanine aminotransferase higher than 2.0 x ULN
  - total bilirubin higher than ULN (unless due to Gilbert's syndrome)
  - serum creatinine high than 181 µmol/L
  - urine protein to creatinine ratio higher than 226.30 mg/mmol
  - neutrophil count less than 1.0 x 10^9/L
  - platelet count less than 25 x 10^9/L
  - haemoglobin less than 80 g/L, or less than 70 g/L if related to patient's SLE such as in active haemolytic anaemia
  - glycosylated haemoglobin (HbA1c)[19] higher than 8% at screening (diabetic patients only).
- Receiving any of the following:
  - azathioprine more than 200 mg/day
  - mycophenolate mofetil more than 2 g/day or mycophenolic acid more than 1.44 g/day
  - oral, subcutaneous, or intramuscular methotrexate more than 25 mg/week
  - mizoribine more than150 mg/day
  - any change in route of administration of oral, subcutaneous, or intramuscular methotrexate anytime within the 8 weeks prior to signing of the informed consent form through Day 1.
- Active or unstable neuropsychiatric or renal SLE.
- History of a primary immunodeficiency, splenectomy or underlying condition that predisposes to infection.
- Confirmed hepatitis B or C, severe herpes infection or any herpes zoster, cytomegalovirus or Epstein Barr virus infection that had not completely resolved within 12 weeks prior to enrolment.

Patients were randomised in a 1:1 ratio to receive one of two treatments:300 mg anifrolumab intravenous infusion via an infusion pump over 30 minutes or placebo.

Both study drugs were given every 4 weeks for a total of 13 doses (Week 0 to 48).

[19] **Haemoglobin A1c or glycated haemoglobin (HbA1c)** is a minor component of haemoglobin chemically linked to glucose. Levels of HbA1c vary and are relative to the overall blood glucose concentration. Unlike a blood glucose concentration, levels of HbA1c are not influenced by daily fluctuations in the blood glucose concentration but reflect the average glucose levels over the prior 6 to 8 weeks. Measurement of HbA1c is used in the diagnosis of diabetes mellitus and is useful indicator of how well the blood glucose level has been controlled in the recent past and may be used to monitor the effects of diet, exercise, and drug therapy on blood glucose in patients with diabetes. In healthy people without diabetes, the HbA1c level is less than 7 percent of total haemoglobin.

Patients continued their SLE medication which consisted of one or any combination of the following: oral corticosteroids, antimalarials and/or immunosuppressants.

The primary efficacy outcome was the difference in proportion of subjects achieving a BICLA response at Week 52.

A response at Week 52 was defined as:

- reduction of all baseline BILAG-2004 A to B, C or D and baseline BILAG-2004 B to C or D, and no BILAG-2004 worsening in other organ systems (worsening defined as one or more new BILAG-2004 A or two or more new BILAG-2004 B); and
- no worsening from Baseline in SLEDAI-2K (worsening defined as an increase of more than zero point); and
- no worsening from Baseline in the patients' lupus disease activity (worsening defined as an increase of 0.30 points or more on a 3-point PGA VAS; and
- no discontinuation of the investigational product (IP); and
- no use of restricted medications beyond the protocol allowed threshold before assessment.

The secondary efficacy outcomes included the followings:

- The proportion of patients in the Type I interferon gene signature test high subgroup who achieved a BICLA response at Week 52
- The proportion of patients who maintained oral corticosteroids reduction, defined as:
  - achieved an oral corticosteroids dose no more than 7.5 mg/day prednisone or equivalent at Week 40; and
  - maintained an oral corticosteroids dose no more than 7.5 mg/day prednisone or equivalent from Week 40 to 52; and
  - no discontinuation of the IP; and
  - no use of restricted medications beyond the protocol allowed threshold before assessment.
- The proportion of patients with a 50% reduction in CLASI activity score compared to Baseline, defined as:
  - achieved at least 50% reduction in CLASI activity score at Week 12 compared to Baseline; and
  - no discontinuation of the IP; and
  - no use of restricted medications beyond the protocol-allowed threshold before assessment.
- The proportion of patients with at least 50% reduction from Baseline in number of swollen and tender joints, defined as:
  - achieved at least 50% reduction in number of both swollen and tender joints, separately; and
  - no discontinuation of the IP; and
  - no use of restricted medications beyond the protocol-allowed threshold before assessment.
- Annualised flare rate over 52 weeks with flare defined as either one or more new BILAG-2004 A or two or more new BILAG-2004 B items compared to previous visit.

Other efficacy outcomes included the followings:

- The proportion of patients who achieved SRI (4), SRI (5), SRI (6), SRI (7), or SRI (8) response, where SRI (X) (X = 4, 5, 6, 7, or 8), defined as:
  - reduction from Baseline of at least X points in SLEDAI-2K; and
  - no new organ systems affected defined as at least one new BILAG-2004 A or at least two 2 new BILAG-2004 B; and
  - no worsening from Baseline in the patients' lupus disease activity defined by an increase at least 0.30 points on a 3 point PGA VAS; and
  - no discontinuation of the IP; and
  - no use of restricted medications beyond the protocol allowed threshold before assessment.
- The proportion of patients with BILAG-2004 (A and B) by organ system.
- Change from Baseline in SLEDAI-2K total score and proportion of patients with an improvement in SLEDAI scores at Weeks 24 and 52.
- Change from Baseline in number of swollen and tender joints and proportion of responders (20% and 50% reduction from Baseline) at Week 52.
- Proportion of patients with major clinical response and/or partial clinical response.
- Change from Baseline in PGA (VAS 0 to 3).
- The proportion of patients who achieved Lupus Low Disease Activity State at Week 52, defined as:
  - Systemic Lupus Erythematosus Disease Activity Index 2000 score no greater than 4, with no activity in major organ systems and no haemolytic anaemia (as assessed by BILAG-2004); and
  - no new lupus disease activity compared with the previous assessment (SLEDAI-2K item score 0); and
  - Physician's Global Assessment VAS score (scale 0 to 3) no greater than 1; and
  - prednisone (or equivalent) dose no more than 7.5 mg/day; and
  - no discontinuation of the IP; and
  - No use of restricted medications beyond the protocol allowed threshold before assessment.
- Change from Baseline in systemic lupus international collaborating clinics/American College of Rheumatology Damage Index (SDI)[20] global score at Week 52.
- Changes from Baseline in 36-Item Short Form Health Survey version 2 (SF-36-v2)[21] (acute recall) domain and component scores, and proportion of SF-36-v2 responders at Week 52.
- Change from Baseline in pain numerical rating scale.
- Change from Baseline in Functional Assessment of Chronic Illness Therapy-fatigue item and total scores.

[20] **The systemic lupus international collaborating clinics / American College of Rheumatology Damage index (SDI)** was developed to quantify damage that has occurred since onset of lupus, which has been shown to be a valid measure for damage and correlates with mortality.
[21] The **36-Item Short Form Health Survey version 2 (SF-36-v2)** is a patient reported survey that measures patient's quality of life, functional health and well-being. The lower the score the more disability the patient is considered to carry.

- Change from Baseline in patient global assessment (VAS 1 to 100 mm).
- Change from Baseline in lupus quality of life domain scores.
- The proportion of patients in each Euro quality of life 5 dimensions (EQ-5D-5L)[22] health state by dimension, as well as change from Baseline in VAS score and summary utility index over time.
- Work Productivity and Activity Improvement-Lupus score levels (percentages) and changes from Baseline.

The estimand of primary interest was the difference in the proportions of response between anifrolumab and placebo at Week 52 in the full analysis set, where the response is captured with a composite binary endpoint and is defined by improvement from Baseline in disease activity as measured by BILAG-2004, no worsening in SLEDAI-2K and PGA, and ability to adhere to the planned course of treatment.

The null hypothesis was that the proportion of patients achieving a BICLA response on anifrolumab 300 mg was equal to that on placebo.

Table 4: Study D3461C00004: Subject disposition (all subjects)

	Number (%) of subjects		
	Anifrolumab 300mg	Placebo	Total
Subjects enrolled; [a]			**649**
Subjects randomised; [b]	**181**	**184**	**365 (56.2)**
Subjects randomised but not treated with investigational product; [c]	**1 (0.2)**	**2 (0.3)**	**3 (0.5)**
Adverse event	1 (0.2)	0	1 (0.2)
Failure to meet randomisation criteria	0	2 (0.3)	2 (0.3)
Subjects in the full analysis set	**180**	**182**	**362**
Subjects who completed the study	**156 (86.7)**	**136 (74.7)**	**292 (80.7)**
Subjects withdrawn from the study	**24 (13.3)**	**46 (25.3)**	**70 (19.3)**
Adverse event	3 (1.7)	7 (3.8)	10 (2.8)
Condition under investigation worsened	1 (0.6)	4 (2.2)	5 (1.4)
Development of study specific withdrawal criteria	1 (0.6)	0	1 (0.3)
Lack of efficacy	2 (1.1)	8 (4.4)	10 (2.8)
Lost to follow up	1 (0.6)	3 (1.6)	4 (1.1)

[22] Developed by **EuroQol, Euro quality of life 5 dimensions (EQ-5D)** is a standardised instrument f+B24or use as a measure of health outcome. Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status.

	Number (%) of subjects		
	Anifrolumab 300mg	Placebo	Total
Severe non-compliance to protocol	0	1 (0.5)	1 (0.3)
Withdrawal by subject	11 (6.1)	19 (10.4)	30 (8.3)
Other	5 (2.8)	4 (2.2)	9 (2.5)
Subjects who completed study treatment	**153 (85.0)**	**130 (71.4)**	**283 (78.2)**
Subjects discontinuing study treatment	**27 (15.0)**	**52 (28.6)**	**79 (21.8)**
Adverse event	5 (2.8)	14 (7.7)	19 (5.2)
Condition under investigation worsened	2 (1.1)	4 (2.2)	6 (1.7)
Lack of efficacy	2 (1.1)	12 (6.6)	14 (3.9)
Lost to follow-up	2 (1.1)	3 (1.6)	5 (1.4)
Severe non-compliance to protocol	0	1 (0.5)	1 (0.3)
Withdrawal by subject	7 (3.9)	16 (8.8)	23 (6.4)
Other	9 (5.0)	2 (1.1)	11 (3.0)
Subjects enrolled to the long-term extension study	**133 (73.9)**	**104 (57.1)**	**237 (65.5)**

a Informed consent received.

b Percentages are based upon all enrolled subjects.

c Withdrawn from study according to analysis visit window. If applicable, measurements of follow-up visits are re-mapped to the respective analysis visit window up to Week 52.

If not stated otherwise, percentages are based upon all subjects in the full analysis set.

The full analysis set comprises all subjects who received at least one dose of investigational products.

Completion of the study is based upon the number of subjects completing Week 52 (Visit 14) and either enrolled to long-term extension or completed Follow-up Visit 2.

Completion of Week 52 is based upon the number of subjects completing up to and including Week 52 (Visit 14 or early discontinuation visit).

Completion of study treatment is based upon the number of subjects completing treatment with the investigational product up to and including Week 48 (Visit 13).

Enrolled to the long-term extension is based on the Week 52 status of the electronic case report form.

No concerns regarding protocol deviations in terms of study conduct or the safety of the patients and they were not judged to influence the study outcome.

Overall, the demographic characteristics of the patients were generally balanced between the treatment groups. The population had a median age of 43.0 years, and was predominantly female (93.4%) and White (59.9%). The proportion of patients 65 years of age and older was 1.7% (2.8% in the anifrolumab 300 mg group and 0.5% in the placebo group). There were fewer African Americans in the anifrolumab 300 mg group compared

to the placebo group (9.4% versus 13.7%), all of whom, with the exception of one patient from Brazil, were from the USA.

The largest proportions of patients were enrolled in the USA or Canada (36.5%), Europe (26.8%), and Latin America (18.5%). Within each geographic region, the proportions of patients were generally balanced across treatment group. Most patients in the Asia Pacific region were enrolled in Japan (43 of 53, 81.1%)

The baseline characteristics of the patients (height, weight and body mass index (BMI)) were generally balanced between the treatment groups. The median BMI was 25.6 kg/m^2 and 39.0% of patients had a BMI of higher than 28 kg/m^2.

The SLE disease characteristics of the patients were generally balanced between the treatment groups. Overall, this patient population had moderate to severe disease activity at Baseline, with a mean SLEDAI-2K score of 11.5 and a SLEDAI-2K score at Baseline of at least 10 in 71.8% of patients, a mean BILAG score of 18.8, and a median PGA score of 1.70. Overall, 48.6% of patients had severe disease in at least one organ system (BILAG-2004 level A) and 46.7% of patients had moderate disease in at least two organ systems (BILAG-2004 level B). The most common organ manifestations were of the mucocutaneous and musculoskeletal systems. A total of 24.6% of patients had moderate to severe skin disease (CLASI activity score at least 10 points) at Baseline, with a mean CLASI activity score of 7.9. Joint characteristics at Baseline were generally balanced across treatment groups, with the mean numbers of active, swollen, and tender joints per patient being 6.4, 6.8, and 10.0, respectively.

Some organ damage at Baseline (SDI score at least 1) was observed in 31.5% of patients, with a mean overall SDI score of 0.5. Patients had a median time from initial SLE diagnosis to randomisation of 85 months (approximately 7 years). Cushingoid features were generally similar across treatment groups with 25.7% of patients with at least one Cushingoid feature at Baseline. The most commonly reported Cushingoid features were moon face (15.7%), central obesity (11.9%), and easy bruising (8.8%).

Overall, 83.1% of patients were classified as Type I interferon gene signature test high at screening. A total of 89.8% of patients had elevated or abnormal ANA titres and 43.9% tested positive for anti-dsDNA antibodies. The proportions of patients with abnormal serological marker expression at Baseline were generally balanced between the anifrolumab 300 mg and placebo groups. In the overall patient population, 39.8% of patients had low or abnormal C3 complement levels, 26.2% had low or abnormal C4 complement levels, and 8.6% had low or abnormal total haemolytic complement complement levels.

Study results

The primary outcome was the difference in the proportion of patients who achieved a BICLA response at Week 52.

Patients treated with anifrolumab 300 mg intravenously every 4 weeks had a statistically significant and clinically meaningful benefit in overall disease activity, as measured by BICLA response rates at Week 52, compared with patients in the placebo group (47.8% versus 31.5%; difference 16.3%, 95% CI: 6.3, 26.3; p = 0.0013).

Table 5: Study D3461C00004 British Isles Lupus Assessment Group-based Composite Lupus Assessment response rate, treatment comparison at Week 52, stratified Cochran-Mantel-Haenszel approach (full analysis set)

			Number (%) of subjects;[a]			Comparison with placebo;[a]		
Time point	Treatment group	n	Responder	Non-responder	95% CI Response Rate	Difference in Response Rates	95% CI Difference	p-value;[b]
Week 52	Anifrolumab 300mg	180	86 (47.8)	94 (52.2)	40.6, 55.1	16.3	6.3, 26.3	0.0013
	Placebo	182	57 (31.5)	125 (68.5)	24.7, 38.3			

Abbreviations: CI = confidence interval; n = number of subjects in analysis group.

a The responder/non-responder rates (percentages), the difference in estimates, and associated 95% CIs are weighted and are calculated using a stratified Cochran-Mantel-Haenszel approach, with stratification factors (Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) score at screening (less than 10 points versus at least 10 points), Week 0 oral corticosteroids dose (less than 10 mg/day versus at least 10 mg/day prednisone or equivalent) and Type I interferon test result at screening (high versus low)).

b Unadjusted p-value for Week 52.

Percentages are based upon all subjects in the full analysis set.

Baseline is defined as the last measurement prior to randomisation and dose administration on Day 1.

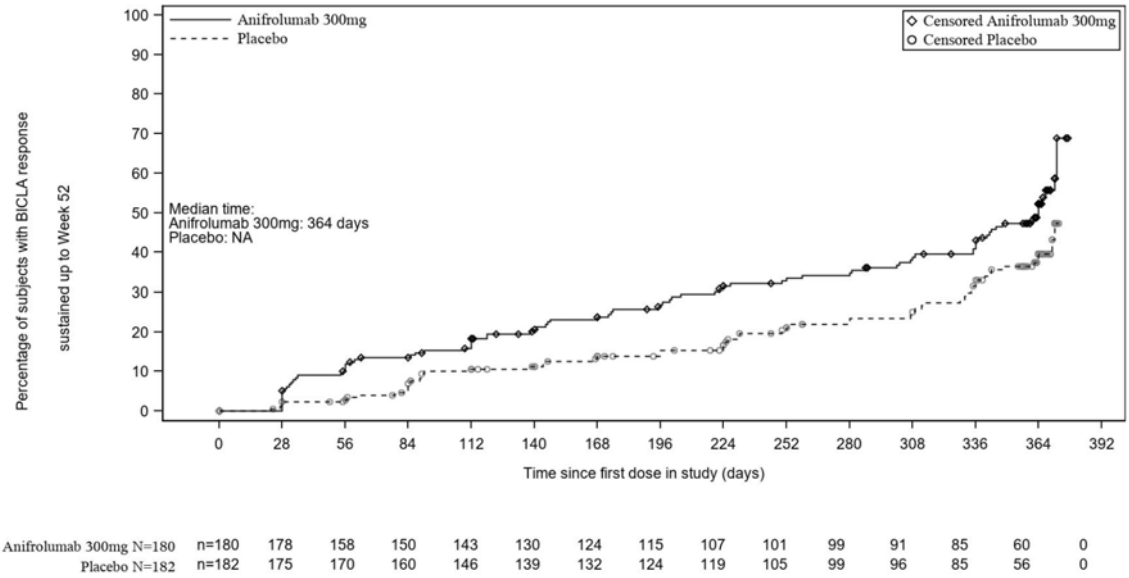
British Isles Lupus Assessment Group-based Composite Lupus Assessment response is defined as a reduction of all baseline British Isles Lupus Assessment Group 2004 A and B scores and no worsening in other organ systems, no worsening from Baseline in SLEDAI-2K, and no increase of 0.30 points of more on a 3-point Physician's Global Assessment visual analog scale from Baseline. Subjects treated with restricted medication beyond protocol allowed threshold, and those discontinued investigational product, are regarded as non-responders.

A numerical difference for the anifrolumab 300 mg group compared with the placebo group began at Week 8 and was maintained throughout the treatment period.

At Week 52, a numerically larger proportion of patients in the anifrolumab 300 mg group met each of the individual components of BICLA compared with patients in the placebo group (BILAG improvement (48.9% versus 32.4%), no worsening of SLEDAI-2K (67.8% versus 51.6%), no worsening of PGA (67.8% versus 52.2%), no discontinuation of the IP (85.0% versus 71.4%), and no use of medication beyond protocol allowed threshold (80.0% versus 67.6%)).

The proportion of patients who achieved a BICLA response sustained up to Week 52 was numerically higher in the anifrolumab 300 mg group compared with the placebo group (47.8% versus 31.3%), with patients in the anifrolumab 300 mg 55% more likely to achieve a sustained BICLA response at any time in the study (hazard ratio = 1.55; 95% CI: 1.11, 2.18).

Figure 1: Study D3461C00004: Time to British Isles Lupus Assessment Group-based Composite Lupus Assessment response sustained up to Week 52 (days), Kaplan-Meier plot (full analysis set)



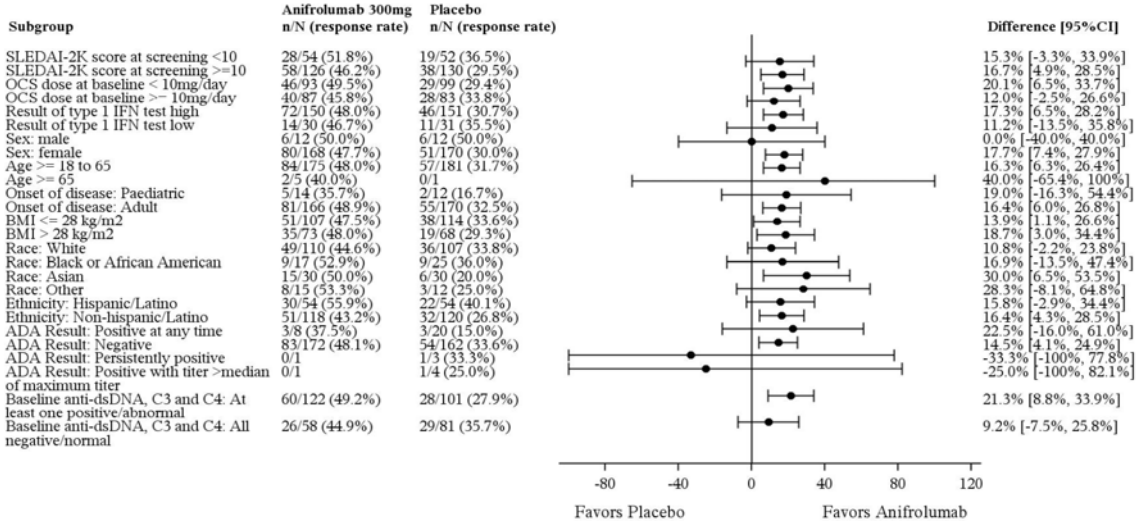
Abbreviations: BICLA = British Isles Lupus Assessment Group-based Composite Lupus Assessment; N = number of subjects in treatment group. n = number of subjects in analysis group; NA = not applicable.

British Isles Lupus Assessment Group-based Composite Lupus Assessment (BICLA) response is defined as reduction of all baseline BILAG-2004 A and B scores and no worsening in other organ systems, no worsening from Baseline in Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K), and no increase of 0.30 points or more on a 3-point Physician's Global Assessment visual analog scale from Baseline. Subjects treated with restricted medication beyond protocol allowed threshold, and those who discontinued investigational product, are regarded as non-responders.

Time to BICLA response sustained up to Week 52 is defined as the visit of first BICLA response which is sustained up to, and including, Week 52. A subject is considered to have achieved BICLA response sustained up to Week 52 if response is achieved at Week 52 with 'time to' defined as the first time point where BICLA response is achieved when maintained through week 52. Subjects without a BICLA response sustained up to Week 52 will be censored at the date of premature discontinuation of investigational product, or Week 52, whichever occurs earlier.

A wide range of subgroup analyses were performed, and the results were generally consistent with the overall population, with no particular patterns or trends observed.

Figure 2: Study D3461C00004: British Isles Lupus Assessment Group-based Composite Lupus Assessment response rate at Week 52, by subgroup, estimated difference (%) and confidence intervals comparing anifrolumab with placebo, forest plot (full analysis set)



Abbreviations: ADA = antidrug antibody; CI = confidence interval; dsDNA = double stranded deoxyribonucleic acid; IFN = interferon; N = number of subjects in treatment group; n = number of subjects in analysis group; OCS = oral corticosteroid; SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index 2000.

Percentages are based upon all subjects in the full analysis set.

Baseline is defined as the last measurement prior to randomisation and dose administration on Day 1.

Races 'Native Hawaiian or other Pacific Islander' and 'American Indian or Alaska Native' are included in the 'Other' subgroup.

British Isles Lupus Assessment Group-based Composite Lupus Assessment response is defined as a reduction of all baseline British Isles Lupus Assessment Group 2004 A and B scores and no worsening in other organ systems, no worsening from Baseline in SLEDAI-2K, and no increase of 0.30 points or more on a 3-point Physician's Global Assessment visual analog scale from Baseline. Subjects treated with restricted medication beyond protocol allowed thresholds, and those who discontinued investigational product, are regarded as non-responders.

The model used is stratified, as far as applicable, by SLEDAI-2K score at screening (less than 10 points versus at least 10 points), Week 0 oral corticosteroids dose (less than10 mg/day versus at least 10 mg/day prednisone or equivalent) and Type I interferon test result at screening (high versus low).

In the analyses of key secondary efficacy endpoints, anifrolumab also demonstrated statistically significant and clinically meaningful benefits in its steroid sparing effect and in improving SLE skin manifestations. In patients with oral corticosteroids at least 10 mg/day at Baseline, 21.2% more patients in the anifrolumab 300 mg group were able to taper their oral corticosteroids dose to target compared with the placebo group (95% CI: 6.8, 35.7; p = 0.0135). In patients with baseline CLASI activity score at least 10, 24% more were able to achieve a 50% or more reduction from Baseline in CLASI activity score at Week 12 (95% CI: 4.3, 43.6; p = 0.0392). The treatment effect was generally maintained over time with a difference in response rates of 18.3% at Week 52. A numerically higher reduction in annual rate of flares was observed for anifrolumab compared with placebo (difference of 0.67; 95% CI: 0.48, 0.94). The time to first flare was numerically longer in the anifrolumab 300 mg compared with the placebo group (hazard ratio = 0.65; 95% CI: 0.46, 0.91).

However, there was no notable difference observed between treatments in the proportion of patients with at least a 50% reduction in swollen and tender joint counts at Week 52 (difference of 4.7; 95% CI: -10.6, 20.0; p = 0.5469).

Table 6: Study D3461C00004 Results for key secondary outcomes

			Number (%) of subjects [a]			Comparison with Placebo [a]			
Time point	Treatment group	n	Responder	Non-responder	95% CI Response Rate	Difference in Response Rates	95% CI Difference	Unadjusted p value	Adjusted p value
BICLA response rate in patients with high interferon test result									
Week 52	Anifrolumab 300mg	150	72 (48.0)	78 (52.0)	40.1, 56.0	17.3	6.5, 28.2	0.0018	0.0022
	Placebo	151	46 (30.7)	105 (69.3)	23.3, 38.1				
Maintained oral corticosteroids reduction in patients with oral corticosteroids≥10 mg/day									
Week 52	Anifrolumab 300mg	87	45 (51.5)	42 (48.5)	41.1, 61.8	21.2	6.8, 35.7	0.0040	0.0135
	Placebo	83	25 (30.2)	58 (69.8)	20.1, 40.3				
Reduction in CLASI activity score in patients with baseline CLASI activity score ≥10									
Week 12	Anifrolumab 300mg	49	24 (49.0)	25 (51.0)	35.0, 63.0	24.0	4.3. 43.6	0.0168	0.0392
	Placebo	40	10 (25.0)	30 (75.0)	11.2, 38.8				
Joint response rate (50% reduction) in patients with at least 6 swollen and 6 tender joints at Baseline									
Week 52	Anifrolumab 300mg	71	30 (42.2)	41 (57.8)	30.7, 53.7	4.7	-10.6, 20.0	0.5469	0.5469
	Placebo	90	34 (37.5)	56 (62.5)	27.4, 47.5				

Abbreviations: BICLA = British Isles Lupus Assessment Group-based Composite Lupus Assessment; CI = confidence interval; CLASI = Cutaneous Lupus Erythematosus Disease Area and Severity Index.

a The responder/non-responder rates (percentages), the difference in estimates, and associated 95% CIs are weighted and are calculated using a stratified Cochran-Mantel Haenszel approach, with stratification factors (Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) score at screening (less than 10 points versus at least 10 points), Week 0 oral corticosteroids dose (less than 10 mg/day versus at least 10 mg/day prednisone or equivalent) and Type I interferon test result at screening (high versus low)).

Percentages are based upon all subjects in the full analysis set.

Baseline is defined as the last measurement prior to randomisation and dose administration on Day 1.

British Isles Lupus Assessment Group-based Composite Lupus Assessment response is defined as a reduction of all baseline British Isles Lupus Assessment Group 2004 A and B scores and no worsening in other organ systems, no worsening from Baseline in SLEDAI-2K, and no increase of 0.30 points or more on a 3-point Physician's Global Assessment visual analog scale from Baseline. Subjects treated with

restricted medication beyond protocol allowed thresholds, and those who discontinued investigational product, are regarded as non-responders.

Table 7: Study D3461C00004 Results for key secondary outcomes - flare rate

				Annual rate		Rate ratio, comparison with placebo			
Timepoint	Treatment group	n	Number of flares	Estimate	95% CI	Estimate	95% CI	Unadjusted p value	Adjusted p value
Week 52	Anifrolumab 300mg	86	170.2	0.43	0.31, 0.59	0.67	0.48, 0.94	0.0202	0.0809
	Placebo	122	164.6	0.64	0.47, 0.86				

Abbreviation: CI = confidence interval.

a The responder/non-responder rates (percentages), the difference in estimates, and associated 95% CIs are weighted and are calculated using a stratified Cochran-Mantel Haenszel approach, with stratification factors (Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) score at screening (less than 10 points versus at least 10 points), Week 0 oral corticosteroids dose (less than 10 mg/day versus at least 10 mg/day prednisone or equivalent) and Type I interferon test result at screening (high versus low)).

Percentages are based upon all subjects in the full analysis set.

Baseline is defined as the last measurement prior to randomisation and dose administration on Day 1.

British Isles Lupus Assessment Group-based Composite Lupus Assessment response is defined as a reduction of all baseline British Isles Lupus Assessment Group 2004 A and B scores and no worsening in other organ systems, no worsening from Baseline in SLEDAI-2K, and no increase of 0.30 points or more on a 3-point Physician's Global Assessment visual analog scale from Baseline. Subjects treated with restricted medication beyond protocol allowed thresholds, and those who discontinued investigational product, are regarded as non-responders.

Anifrolumab 300 mg resulted in numerically greater rates of improvement compared with placebo across a range of composite and organ-specific disease activity other efficacy outcomes:

- A numerically higher SRI(4) response rate was observed in the anifrolumab 300 mg group compared with the placebo group over time, with a difference of 18.2% at Week 52 (95% CI: 8.1, 28.3).
- At higher SLEDAI thresholds (SRI(5), SRI(6), SRI(7), and SRI(8)), numerically higher SRI response rates were consistently observed in the anifrolumab 300 mg group compared with the placebo group over time, with differences ranging from 10.7% to 17.6% at Week 52.
- Anifrolumab 300 mg resulted in a numerical reduction in fatigue and improvement in quality of life.

Study D3461C00005

Study D3461C00005 (also known as the TULIP-1 trial);[23] is a Phase III, multicentre, randomised, double blind, placebo controlled study conducted at 123 sites in 18 countries (Australia (2), New Zealand (1), South Korea (4), Taiwan (3), Germany (4), Hungary (4),

[23] Study D3461C00005 (TULIP-1 trial): A multicentre, randomised, double-blind, placebo-controlled, Phase III study evaluating the efficacy and safety of two doses of anifrolumab in adult subjects with active systemic lupus erythematosus. ClinicalTrials.gov Identifier: NCT02446912.
Published as: Furie, R et al. Type I interferon inhibitor anifrolumab in active systemic lupus erythematosus (TULIP-1): a randomised, controlled, Phase III trial. The Lancet Rheumatology, Volume 1, Issue 4, 2019, Pages e208-e219.

Italy (2), Poland (12), Romania (8), Ukraine, United Kingdom (4), Argentina (2), Brazil (3), Chile (3), Columbia (5), Peru (6), USA (47), Israel (5)) from June 2015 to July 2018.

The study comprised a screening period of up to 30 days and a 52-week double blind treatment period. At Week 52, patients either continued the study for another 8 weeks to complete a 12 week follow up period or, if eligible, enrolled into a separate long-term extension study (Study D3461C00009) which is ongoing.

Primary objective

To evaluate the effect of anifrolumab 300 mg compared with placebo on disease activity as measured by the difference in the proportion of patients who achieve an (SRI(4)) at Week 52.

Secondary objectives

To evaluate the effect of anifrolumab 300 mg with placebo on:

- the proportion of patients with SRI(4) at Week 52 in the Type I interferon gene signature test high subgroup;
- the proportion of patients who achieved an oral corticosteroids dose no more than 7.5 mg/day at Week 40, which was maintained through Week 52 in the subgroup of patients with baseline oral corticosteroids at least 10 mg/day;
- the proportion of patients with a 50% or more reduction CLASI activity score at Week 12 in the subgroup of patients with baseline CLASI activity score at least 10;
- the proportion of patients with SRI(4) at Week 24;
- the annualised flare rate through 52 weeks.

Inclusion and exclusion were similar to Study D3461C00004.

All patients were randomised 1:2:2 to one of three treatments:

- 150 mg anifrolumab administered by intravenous infusion every 4 weeks for 13 doses.
- 300 mg anifrolumab administered by intravenous infusion every 4 weeks for 13 doses.
- Placebo (0.9% saline) administered by intravenous infusion every 4 weeks for 13 doses.

All infusions were delivered via an infusion pump over a minimum of 30 minutes every 4 weeks.

During the study all patients were taking either one or any combination of the following oral corticosteroids, antimalarial and/or immunosuppressants.

The primary efficacy outcome was the proportion of patients achieving a reduction from Baseline in overall disease activity as measured by SRI(4) at Week 52 defined as:

- reduction from Baseline of at least 4 points in the SLEDAI-2K; and
- no new organ system affected as defined by one or more BILAG-2004 A or 2 or more BILAG-2004 B items compared to Baseline using BILAG-2004; and
- no worsening from Baseline in the patients' lupus disease activity defined by an increase of 0.30 points or more on a 3-point PGA VAS; and
- no discontinuation of the IP or use of restricted medications beyond the protocol allowed threshold before assessment.

The secondary and other efficacy outcomes were similar as for Study D3461C00004.

Table 8: Study D3461C00005 Subject disposition (all subjects)

	Number (%) of subjects			
	Anifrolumab 150 mg	Anifrolumab 300 mg	Placebo	Total
Subjects enrolled; [a]				847
Subjects randomised; [b]	93	180	184	457 (54.0)
Subjects in the full analysis set	93	180	184	457
Subjects who completed the study	74 (79.6)	145 (80.6)	144 (78.3)	363 (79.4)
Subjects withdrawn from the study	17 (18.3)	34 (18.9)	35 (19.0)	86 (18.8)
Adverse event	3 (3.2)	12 (6.7)	5 (2.7)	20 (4.4)
Condition under investigation worsened	0	1 (0.6)	1 (0.5)	2 (0.4)
Development of study specific withdrawal criteria	1 (1.1)	0	0	1 (0.2)
Lack of efficacy	1 (1.1)	4 (2.2)	7 (3.8)	12 (2.6)
Lost to follow-up	0	0	2 (1.1)	2 (0.4)
Severe non-compliance to protocol	1 (1.1)	0	1 (0.5)	2 (0.4)
Withdrawal by subject	9 (9.7)	15 (8.3)	15 (8.2)	39 (8.5)
Other	2 (2.2)	2 (1.1)	4 (2.2)	8 (1.8)
Subjects who completed study treatment	75 (80.6)	144 (80.0)	146 (79.3)	365 (79.9)
Subjects discontinuing study treatment	18 (19.4)	36 (20.0)	38 (20.7)	92 (20.1)
Adverse event	7 (7.5)	15 (8.3)	8 (4.3)	30 (6.6)
Condition under investigation worsened	1 (1.1)	1 (0.6)	4 (2.2)	6 (1.3)
Lack of efficacy	3 (3.2)	3 (1.7)	9 (4.9)	15 (3.3)
Lost to follow-up	0	0	2 (1.1)	2 (0.4)
Severe non-compliance to protocol	2 (2.2)	0	2 (1.1)	4 (0.9)
Withdrawal by subject	4 (4.3)	14 (7.8)	13 (7.1)	31 (6.8)
Other	1 (1.1)	3 (1.7)	0	4 (0.9)
Subjects enrolled to the long-term extension study	69 (74.2)	126 (70.0)	129 (70.1)	324 (70.9)

a Informed consent received.

b Percentages are based upon all enrolled subjects.

If not stated otherwise, percentages are based upon all subjects in the full analysis set.

The full analysis set comprises all subjects who received at least one dose of investigational product.

Completion of the study is based upon the number of subjects completing Week 52 (Visit 14) and either enrolled to long-term extension or completed 12 weeks of follow-up after their last dose of investigational product (Follow-up Visit 2, or Week 52 for patients who prematurely discontinued investigational product more than 12 weeks prior).

Completion of Week 52 is based upon the number of subjects completing up to and including Week 52 (Visit 14 or early discontinuation visit).

Completion of study treatment is based upon the number of subjects completing treatment with investigational product up to and including Week 48 (Visit 13).

Enrolled to the long-term extension is based on the Week 52 status of the electronic case report form.

No concerns regarding protocol deviations in terms of study conduct or the safety of the patients and they were judged to not influence the study outcome.

The demographic characteristics of the patients were generally balanced across the treatment groups. The population had a median age of 41.0 years and was predominantly female (92.3%) and White (71.3%). The proportion of patients at least 65 years of age was 4.4% (3.2% in the anifrolumab 150 mg group, 6.1% in the anifrolumab 300 mg group, and 3.3% in the placebo group). The largest proportions of patients were enrolled in the USA (40.7%) (Canada did not participate) and Europe (37.9%). Within each geographic region, the proportions of patients were generally balanced across treatment groups with some minor differences.

The baseline characteristics of the patients (height, weight and BMI) were generally balanced across the treatment groups. The median BMI was 26.2 kg/m^2 and 41.8% of patients had a BMI of higher than 28 kg/m^2.

Overall, this patient population had moderate to severe disease activity at Baseline, with a mean SLEDAI-2K score of 11.3 and a SLEDAI-2K score at Baseline of at least 10 in 71.8% of patients, a mean BILAG score of 19.2, and a median PGA score of 1.90. Overall, 47.5% of patients had severe disease in at least one organ system (BILAG-2004 level A) and 46.2% of patients had moderate disease in at least two organ systems (BILAG-2004 level B). The most common organ manifestations were of the mucocutaneous and musculoskeletal systems. A total of 31.1% of patients had moderate to severe skin disease (CLASI activity score at least 10 points) at Baseline, with a mean CLASI activity score of 8.2. Joint characteristics at Baseline were generally balanced across treatment groups, with the mean numbers of active, swollen, and tender joints per patient being 6.8, 7.2, and 11.1, respectively. Some organ damage at Baseline (SDI score of at least 1) was observed in 35.0% of patients, with a mean overall SDI score of 0.6. Patients had a median time from initial SLE diagnosis to randomisation of 84 months (7 years). Cushingoid features were generally similar across treatment groups with 38.9% of patients with at least one Cushingoid feature at Baseline. The most commonly reported Cushingoid features were easy bruising (19.5%), moon face (18.8%), and central obesity (16.2%).

Overall, 82.1% of patients were classified as Type I interferon gene signature test high at Baseline. A total of 90.2% of patients had elevated or abnormal ANA titres and 45.3% tested positive for anti-dsDNA antibodies.

Study results

The primary objective was to evaluate the effect of anifrolumab compared with placebo on disease activity as measured by the proportion of patients achieving a reduction in overall SLE disease activity (SRI(4) response rate) at Week 52.

The primary objective of the study was not met. At Week 52 the results were generally similar between patients in the anifrolumab 300 mg group compared with patients in the placebo group. The difference of -4.2% did not meet statistical significance (p = 0.412).

When the revised restricted medication rules were applied in the *post-hoc* analysis, the SRI(4) response rate at Week 52 was still generally similar between patients in the anifrolumab 300 mg group compared with patients in the placebo group (difference of 3.9%, p = 0.455)

Table 9: Study D3461C00005 Systemic Lupus Erythematosus Responder Index of at least 4 response rate, treatment comparison at Week 52, stratified Cochran-Mantel-Haenszel approach (full analysis set)

			Number (%) of subjects;[a]			Comparison with placebo;[a]		
Timepoint	Treatment group	n	Responder	Non-responder	95% CI Response Rate	Difference in Response Rates	95% CI Difference	p-value;[b]
Original prespecified restricted medication rules								
Week 52	Anifrolumab 150 mg (N=93)	93	35 (37.6)	58 (62.4)	27.7, 47.5	-2.6	-14.7, 9.6	
	Anifrolumab 300 mg (N=180)	180	65 (36.2)	115 (63.8)	29.1, 43.3	-4.2	-14.2, 5.8	0.412
	Placebo (N=184)	184	74 (40.4)	110 (59.6)	33.3, 47.5			
***Post-hoc* revised restricted medication rules**								
Week 52	Anifrolumab 150 mg (N=93)	93	45 (48.4)	48 (51.6)	38.5, 58.4	5.5	-6.7, 17.8	
	Anifrolumab 300 mg (N=180)	180	84 (46.9)	96 (53.1)	39.6, 54.1	3.9	-6.3, 14.1	0.455
	Placebo (N=184)	184	79 (43.0)	105 (57.0)	35.9, 50.1			

Abbreviations: CI=confidence interval; n = number of subjects in analysis group.

a The responder/non-responder rates (percentages), the difference in estimates, and associated 95% CIs are weighted and are calculated using a stratified Cochran-Mantel-Haenszel approach, with stratification factors (Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) score at screening (less than 10 points versus at least 10 points), Week 0 oral corticosteroids dose (less than 10 mg/day versus at least 10 mg/day prednisone or equivalent) and Type I interferon gene signature test result at screening (high versus low)).

b Unadjusted p-value for Week 52

Percentages are based upon all subjects in the full analysis set.

Baseline is defined as the last measurement prior to randomisation and dose administration on Day 1.

Systemic Lupus Erythematosus Responder Index of at least 4 response is defined as a reduction from Baseline of at least 4 points in the SLEDAI-2K, no new British Isles Lupus Assessment Group 2004 organ systems affected (defined as at least one new A item or at least two new B items compared to Baseline)

and no increase of 0.30 points or more on a 3-point Physician's Global Assessment visual analog scale. Subjects treated with restricted medication beyond protocol-allowed threshold, and those who discontinued investigational product, are regarded as non-responders.

As statistical significance was not met for the primary endpoint, none of the key secondary endpoints were formally tested, according to the prespecified statistical plan. The observed findings for the anifrolumab 300 mg group versus placebo were:

- similar SRI(4) response rates were observed at Week 24 in the overall population and at Week 52 in Type I interferon gene signature test high patients;
- numerically more patients (with oral corticosteroids at least 10 mg/day at Baseline) were able to taper their oral corticosteroids dose to target (no more than 7.5 mg/day at Week 40 maintained through Week 52);
- numerically more patients (with baseline CLASI activity score of at least 10) achieved a 50% or more reduction from Baseline in skin activity at 12 weeks;
- the annualised rate of flares was numerically lower (improved).

The major problem with the sponsor's assessment of the study is the major *post-hoc* analysis of the study and the change in emphasis of the study from the SRI(4) response to the BICLA response.

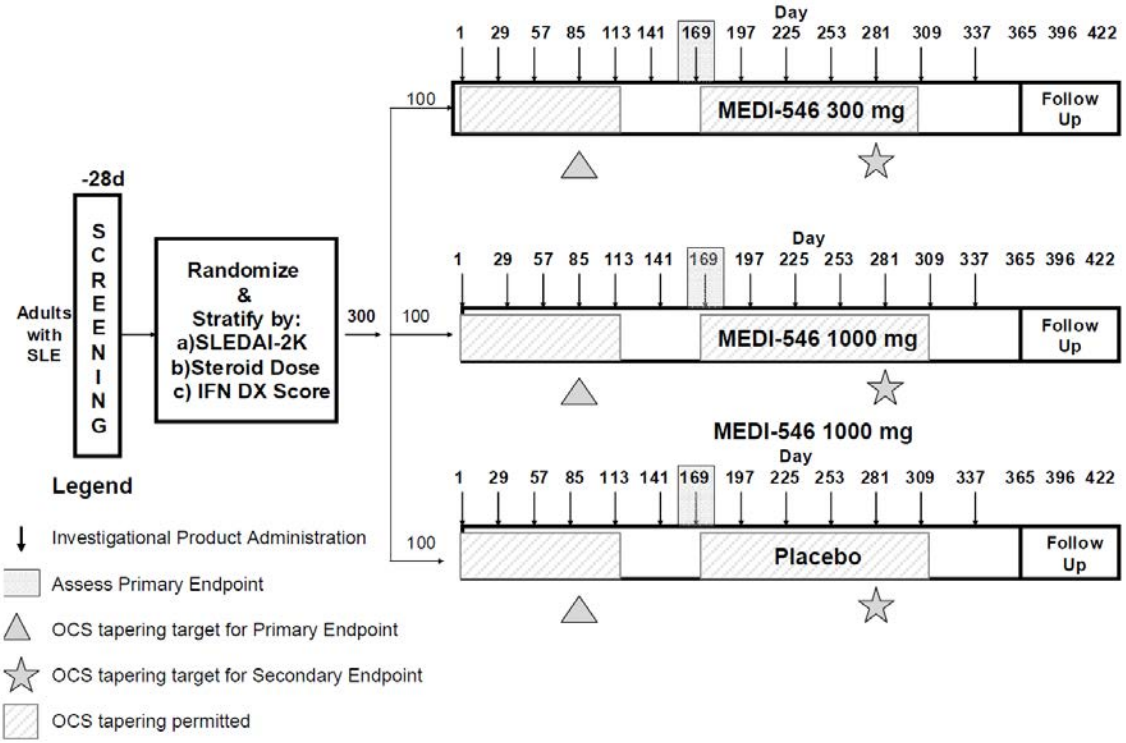
The Delegate agrees with the clinical evaluation's observation that as BICLA response at Week 52 was not part of the multiplicity procedure in Studies D3461C00005 and CD-IA-MEDI-546-1013, and hence cannot be interpreted in terms of statistical significance and can only be considered exploratory.

Study CD-IA-MEDI-546-1013

Study CD-IA-MEDI-546-1013 was a 52-week, multicentre, randomised, double blind, placebo controlled, parallel group study. Patients were randomised in a 1:1:1 fashion to anifrolumab 1000 mg, anifrolumab 300 mg, or placebo (see Figure 3 below).

A total of 305 patients were randomised to anifrolumab 300 mg, 1000 mg or placebo for a total of 13 doses (52 weeks). The primary outcome as the SRI(4) response rate at Week 24. Secondary outcomes were SRI(4) response rate at Week 52 and reducing background oral corticosteroids dosage. The BICLA response rate was an exploratory efficacy outcome.

Figure 3: Study CD IA-MEDI-546-1013 Study design



Abbreviations: d = days; IFN DX = 4-gene Type I interferon test; MEDI-546 = anifrolumab; OCS = oral corticosteroids; SLE = systemic lupus erythematosus; SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index 2000.

The primary outcome was met. The SRI(4) response rate for 300 mg anifrolumab was 34 of 99 (34%) compared with 18 of 102 (17.6%), p = 0.014.

The response in patients with interferon gene signature high patients was similar to the general population, 300 mg anifrolumab 27 of 75 (36%) compared with 10 of 76 (13.2%), p = 0.004.

The results for the secondary outcome of maintained oral corticosteroids tapering at Week 52 were 31 of 55 (56%) compared with 17 of 64 (27%), p = 0.001.

The BICLA response with oral corticosteroids tapering for the 300 mg anifrolumab group were 28% at Week 24 and 43% at Week 52 compared with placebo, 11% at Week 24 and 17% at Week 52.

Overall, while there was a statistically significant difference between anifrolumab 300 mg and placebo, the response rate was low.

Study CD-IA-MEDI-546-1145

Study CD-IA-MEDI-546-1145 was primarily an extension study to Study CD-IA-MEDI-546-1013 whose primary aim was to evaluate the long-term safety in patients who had completed the previous patients. The patients enrolled consisted of 70% of the population who had received anifrolumab at different doses for 12 months in Study CD-IA-MEDI-546-1013 as well as 30% of patients who had received placebo. Further all patients were commenced on anifrolumab 1000 mg and changed to 300 mg during the course of the study. The results are presented for the overall population and the heterogeneous nature of the population is not discussed or the results for the different populations presented.

Efficacy as measured by the SLEDAI-2K responses was an exploratory objective in this study.

The results found that patients receiving long-term treatment with anifrolumab showed a numerical trend towards a decrease from Baseline in SLEDAI-2K Global Score that continued throughout 156 weeks of treatment, reversing following cessation of treatment.

Study D3461C00002

Study D3461C00002 was a small Phase II study conducted in Japanese patients in Japan. The primary objective of the study was safety. Efficacy as measured by SRI(4) responder rate was an exploratory outcome.

Stage I of the study evaluated single doses of 6 patients treated with 100 mg, 5 treated with 300 mg and 6 treated with 1000 mg.

Stage II consisted of repeated doses of anifrolumab, initially at the dose received in Stage I but was changed during the study to all patients receiving 300 mg for 156 weeks.

The study was not placebo controlled for efficacy and the number of patients in each dose group make it impossible to draw any conclusions on efficacy.

Analyses performed across trials: pooled and meta-analyses

The sponsor-based efficacy on the data from three clinical studies: Studies D3461C00004 (pivotal), D3461C00005 (supportive) and CD-IA-MEDI-546-1103 (supportive).

Studies D3461C00004 and D3461C00005 had similar design, duration (52 weeks) and outcome measures. Studies D3461C00004 and D3461C00005 were pooled but excluded the anifrolumab 150 mg group from Study D3461C00005. Study CD-IA-MEDI-546-1103 was not always included in the pooling due to the different steroid tapering rules and as the study primary outcome was at 24 weeks.

Table 10: Studies D3461C00004, D3461C00005, and CD-IA-MEDI-546-1013 Primary efficacy endpoint, British Isles Lupus Assessment Group-based Composite Lupus Assessment response rate at Week 52 (full analysis sets)

BICLA response at Week 52	Study 04		Study 05			Study 1013	
	Anifrolumab 300 mg (N=180)	Placebo (N=182)	Anifrolumab 150 mg (N=93)	Anifrolumab 300 mg (N=180)	Placebo (N=184)	Anifrolumab 300 mg (N=99)	Placebo (N=102)
N	180	182	93	180	184	99	101
Number (%) responders	86 (47.8)	57 (31.5)	35 (37.7)	85 (47.1)	55 (30.2)	53 (53.3)	26 (25.1)
Comparison with placebo							
Difference in response rate	16.3			17.0		28.4	
95% CI of difference in response rate	6.3, 26.3			7.2, 26.8		15.3, 41.5	
Nominal p-value;[a]	0.001			<0.001		<0.001	

Abbreviations: BICLA = British Isles Lupus Assessment Group-based Composite Lupus Assessment; CI = Confidence interval; n = number of patients in analysis group; NA = not available; N = number of patients

in treatment group; Study 04 = Study D3461C00004; Study 05 = Study D3461C00005; Study 1013 = Study CS-IA-MEDI-546-1013.

a British Isles Lupus Assessment Group (BILAG)-based Composite Lupus Assessment (BICLA) response at Week 52 is not part of the multiplicity procedure in Studies 05 and 1013, and cannot be interpreted in terms of statistical significance.

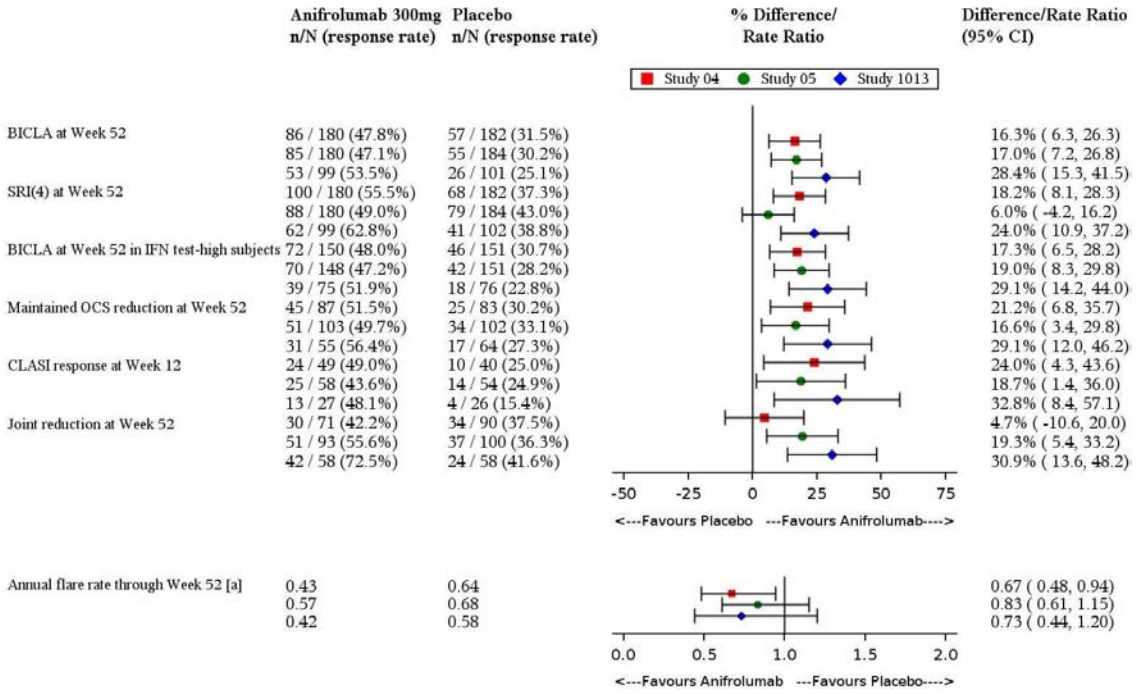
The p-value for Study 1013 is based on the pre-specified logistic regression model for comparison of anifrolumab 300 mg versus placebo, adjusted for randomisation stratification factors.

Studies 04 and 05 results are based on the Study 04 restricted medications rules. Study 1013 results are based on the Study 1013 rules for restricted medications.

One patient in the placebo group is excluded from the analysis of BICLA response in Study 1013 due to not having an 'A' or 'B' BILAG-2004 item at Baseline.

The responder rates and the difference in estimates and associated 95% CI, are calculated using a stratified Cochran-Mantel-Haenszel approach, with stratification factors Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) score at screening, Day 1 oral corticosteroids dose, and Type I interferon gene signature test result at screening.

Figure 4: Studies D3461C00004, D3461C00005, and CD-IA-MEDI-546-1013 Efficacy of anifrolumab in the proposed indication (full analysis sets)



Abbreviations: BICLA = British Isles Lupus Assessment Group-based Composite Lupus Assessment; CI = Confidence interval; CLASI = Cutaneous Lupus Erythematosus Disease Area and Severity Index; IFN = Interferon; N = number of patients in treatment group; n = number of patients with response; OCS = oral corticosteroids; SRI = Systemic lupus erythematosus Responder Index; SRI(4) = at least 4-point reduction in Systemic Lupus Erythematosus Disease Activity Index 2000 score in the SRI; Study 04 = Study D3461C00004; Study 05 = Study D3461C00005; Study 1013 = Study CS-IA-MEDI-546-1013.

a Note that this is a rate ratio rather than a rate difference as with all other endpoints. This is calculated as annualised rate of anifrolumab over placebo.

The upper scale is related to the difference in response rates; the lower scale is related to the rate ratio of flares.

Key efficacy endpoints are the primary and key secondary endpoints from Study 04 plus SRI(4) at Week 52 (the primary endpoint in Study 05 and a secondary endpoint in Study 04).

Full analysis set includes all patients randomised who received at least one dose of investigational product, analysed according to randomised treatment.

One patient in the placebo group is excluded from the analysis of BICLA response in Study 1013 due to not having an 'A' or 'B' British Isles Lupus Assessment Group 2004 item at Baseline.

Study 04 restricted medication rules are applied to Studies 04 and 05.

Responder rates were analysed using the Cochran-Mantel-Haenszel approach and flare rates were analysed using a negative binomial regression model.

Safety

Exposure

Overall, the safety profile of anifrolumab is based on a total of 1029 patients who received anifrolumab at any dose for any indication. Of these, 837 were patients with SLE who received intravenous anifrolumab at doses of 150, 300 or 1000 mg.

A total of 360 patients received anifrolumab at the proposed dose regimen (300 mg every 4 weeks) with 326 exposed for greater than 6 months, 238 exposed for greater than one year, 161 exposed for greater than 3 years (156 weeks) and 32 for greater than 4 years (208 weeks).

The EU guideline;[24] for the assessment of safety in a new chemical entity requires:

- usually 300 to 600 patients treated for 6 months;
- usually 100 patients exposed for minimum of 12 months;
- total number of patients treated is 1500.

While there have been a total of 1029 patients treated with any dose of anifrolumab, this includes patients from the ongoing studies not included in the submission (Studies D3461C00009 and D3461C00007);[25,26] which made it difficult to interpret for the clinical evaluation. The Delegate agrees with the clinical evaluation that the 326 exposed for greater than 6 months is barely meeting the 300 to 600 required in the EU guideline.

Adverse events

In the clinical studies adverse events (AEs) were common with 88% of patients who received the proposed dose reporting at least one AE. Most were mild to moderate in intensity but 11% reported serious adverse events (SAEs) (compared with 16% on placebo). AEs leading to discontinuation were low (5%) and comparable to placebo, with no specific AEs predominating.

The most commonly reported AEs were nasopharyngitis, upper respiratory tract infection, urinary tract infection, infusion-related reaction, bronchitis, headache, herpes zoster, back pain, cough, arthralgia, sinusitis, and vomiting.

[24] European Medicines Evaluation Agency (EMEA), Committee for Medicinal Products for Human Use (CPMP), ICH Topic E1 Population Exposure: the Extent of Population Exposure to Assess Clinical Safety, Note for Guidance on Population Exposure: the Extent of Population Exposure to Assess Clinical Safety, CPMP/ICH/375/95, June 1995.

[25] Study D3461C00009 (also known as the TULIP SLE LTE trial; ClinicalTrials.gov Identifier: NCT02794285) is a multicentre, randomised, double-blind, placebo-controlled Phase III extension study to characterise the long-term safety and tolerability of anifrolumab in adult subjects with active systemic lupus erythematosus.
Published as: Kalunian KC, Furie R, Morand EF, et al. A Randomized, Placebo-Controlled Phase III Extension Trial of the Long-Term Safety and Tolerability of Anifrolumab in Active Systemic Lupus Erythematosus *Arthritis Rheumatol.* 2022;10.1002/art.42392.

[26] Study D3461C00007 (also known as the TULIP-LN1 trial; ClinicalTrials.gov Identifier: NCT02547922) is a multicentre, randomised, double-blind, placebo-controlled, Phase II study evaluating the efficacy and safety of anifrolumab in adult subjects with active proliferative lupus nephritis.
Published as: Jayne D, Rovin B, Mysler EF, et al. Phase II randomised trial of type I interferon inhibitor anifrolumab in patients with active lupus nephritis. *Ann Rheum Dis*. 2022;81(4):496-506.

Infections were more common in the patients who received anifrolumab than in those receiving placebo. The difference between the overall rates of infection appeared to be driven by differences in the incidence rates of mild and moderate infections involving the respiratory tract, excluding pneumonia (comparable in both treatment groups), and separately, herpes zoster.

Herpes zoster infection was more common in patients receiving anifrolumab (6.4%) compared with those receiving placebo (1.4%).

Serious adverse events

While most cases were mild or moderate in intensity, one patient reported an SAE and two patients discontinued therapy due to the AE.

There were no cases of active tuberculosis. An increased rate of latent tuberculosis occurred in the anifrolumab arms, in particular during the long-term extension study. The relationship between tuberculosis and systemic lupus erythematosus (SLE) is unclear, although a high suspicion of tuberculosis and planned monitoring for active and latent tuberculosis should be considered, in particular in SLE patients from endemic countries and with high cumulative steroid exposure.

Major adverse cardiovascular events were rare and balanced between anifrolumab and placebo arms. There were no cases of suicide or self-injury.

Hypersensitivity including one case of anaphylaxis, and infusion-related reactions were more common in patients receiving anifrolumab. The commonly reported infusion-related AEs were headache, nausea, vomiting and fatigue.

There were 2 deaths in the anifrolumab 300 mg intravenous group during the 52-week study period. No patients randomised to the placebo plus standard of care group died during the 52-week study period. Overall, there were 14 deaths (11 deaths in the anifrolumab intravenous group and 3 deaths in the placebo group) during the anifrolumab clinical studies in the anifrolumab development program for SLE including all doses for 52-weeks (Studies CD-IA-MEDI-546-1013, D3461C00005 and D3461C00004) and placebo controlled long-term extension Study D3461C00009 (participants in Studies D3461C00005 and D3461C00004 continuing on either anifrolumab or placebo for greater than 52 weeks).

Key patient data for patients with fatal AEs are summarised in Table 11, based on the FDA's review.[27]

[27] United States Food and Drug Administration (FDA) NDA/BLA Multi-Disciplinary Review and Evaluation on Saphnelo (anifrolumab-fnia) for adults with SLE. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/761123Orig1s000MultidisciplineR.pdf.

Table 11: United States Food and Drug Administration review Summary of adverse events with outcome of death (safety analysis set)

Demographics	STUDY	ARM	# DOSES	SAE/DAYS From last Dose To SAE	CAUSE OF DEATH/DAYS LD TO DEATH	RELATED/ UNRELATED
42/F/A	05 LTE 09	150 300	37	Influenza-Like Illness/29 [Neg Flu A/B tests] Myocarditis/34	Cardiogenic Shock related to Myocarditis/43	Both SAE and Death considered Unrelated
64/F/W	04 LTE 09	300 300	35	Pneumonia/6 Thrombocytopenia/21	Pneumonia/57	Both SAEs and Death considered Unrelated
54/F/H	05 LTE 09	300 300	35	Pneumonia/24	Pneumonia/29	Unrelated
28/F/H	04 LTE 9	300 300	50	COVID Pneumonia/6	COVID-19 Pneumonia/52	Unrelated
51/F/H	05 LTE 09	150 300	33	SLE exacerbation/54	SLE exacerbation/60	Unrelated
47/F/W	05 LTE 09	PBO 300	50	COVID-19/21	COVID-19/48	Unrelated
37/F/O	04 LTE 9	PBO 300	44	COVID-19/2 COVID-19 Pneumonia/6	COVID-19 Pneumonia/25	Unrelated
60/F/W	1013	1000	1	Colitis/27	Colitis complicated by MAS/34	Unrelated
54/F/O	1013 OLE 1145	PBO 1000 (16) 300 (16)	32	Pneumonia/20	Pneumonia complicated by Septic Shock/20	Related
53/F/W	04	300	8	Pneumonia/24	Pneumonia complicated by Septic Shock/26	Related
65/F/O	05	300	2	Possible Partial Bowel Obstruction/4 Nosocomial Pneumonia/22	Nosocomial Pneumonia/36	Unrelated
25/F/B	05	PBO	9	Encephalitis/36	Acute meningo-encephalitis/36	Unrelated
55/F/B	05 LTE 09	PBO PBO	22	Pulmonary HTN/128	Severe Pulm HTN/190	Unrelated
50/F/W	04 LTE 09	PBO PBO	35	MI/37	Possible Heart Attack/37	Unrelated

Abbreviations: # = number; COVID = coronavirus disease; HTN = hypertension; LTE = long-term extension; MAS = macrophage activation syndrome; MI = myocardial infarction; Neg = negative; OLE = open label extension; PBO = placebo; SAE = serious adverse event; SLE = systemic lupus erythematosus.

*Reference: extracted from Table 48 of NDA/BLA Multi-Disciplinary Review and Evaluation on Saphnelo (anifrolumab-fnia) for adults with SLE by the United States Food and Drug Administration.

There were 6 malignancies in the anifrolumab 300 mg intravenous group during the 52-week study period and 3 malignancies in the placebo group. There were 2 additional

malignancies in the placebo group for a total of 5, as compared to 6 in the anifrolumab 300 mg intravenous group from the ongoing Phase III long-term extension study of 300 mg.

Anti-drug antibodies

Anti-drug antibody positive responses were observed in the anifrolumab 300 mg group with a prevalence of 7.0% and an incidence of 1.7%. In patients treated with placebo the prevalence was 9.6% and the incidence was 4.8%. Thus, there was little to no specific induction of an ADA response to anifrolumab. Median ADA titres in the anifrolumab 300 mg group were similar to placebo.

Only two patients in the anifrolumab 300 mg group were neutralising antibody positive at any time point (one at Baseline and one at Week 12) compared with seven patients in the placebo group. These results do not support specific induction of a neutralising ADA response.

Anti-drug antibody was not associated with increased clearance of anifrolumab or loss of pharmacodynamic activity compared with ADA negative patients. There was no apparent trend or pattern suggesting a correlation between the presence of anifrolumab ADA and occurrence of AEs, SAEs, discontinuations due to AEs, or AEs of special interest.

Limitations associated with the anifrolumab intravenous safety database include the lack of concomitant intravenous cyclophosphamide or other biologics including those that target B-cells (for example, rituximab;[28] or belimumab), and the lack of patients with severe renal lupus and central nervous system disease. The small numbers of patients available for subgroup analysis of gender (males), age (65 years of age and older as well as children 18 years of age and younger), and race precludes determination of the product's safety profile in these subgroups.

Risk management plan

The sponsor has submitted draft EU-risk management plan (RMP) version 1 succession 1 (dated 18 September 2020; data lock point (DLP) 19 March 2020) and Australian specific annex (ASA) version 1.0 succession 1 (dated 1 December 2020) in support of this application. At the second round of evaluation, the sponsor submitted EU-RMP version 1 succession 2 (dated 3 May 2021; DLP 19 March 2020) and ASA version 1.0 succession 2 (dated 18 August 2021). At the third round of evaluation, the sponsor submitted EU-RMP version 1 succession 3 (dated 30 August 2021; DLP 19 March 2020) and ASA version 1.0 succession 3 (dated 22 October 2021).

The summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 12. Further information regarding the TGA's risk management approach can be found in risk management plans for medicines and biologicals and the TGA's risk management approach.

[28] Mabthera (rituximab) was first registered on the ARTG on 6 October 1998 (ARTG numbers: 60318 and 60319).

Table 12: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Herpes zoster	✓	–	✓	–
Important potential risks	Malignancy	✓*	✓‡	✓	–
	Serious infection	✓	✓‡	✓	–
Missing information	Use in pregnant and breastfeeding women	✓	✓ †	✓	–
	Effects on responses to inactivated vaccines	✓	✓‡	✓	–

* Follow-up questionnaires

† Drug utilisation study

‡ Clinical trials

- The summary of safety concerns included the important potential risk 'malignancy' and the missing information 'Use in pregnant and breastfeeding women' at the first round of evaluation. The sponsor was requested but did not agree to add 'Safety in indigenous Australians', 'Use in patients 65 years and older' and 'Use in patients with lupus nephritis, severe renal impairment or end stage renal disease' as missing information, with adequate justification at the second round of evaluation. The important identified risk of 'herpes zoster', the important potential risk of 'serious infection' and the missing information 'effects on responses to inactivated viruses' were added at second round of evaluation to align with the EU-RMP. The summary of safety concerns is acceptable.
- Routine pharmacovigilance has been included for all safety concerns and this has been clarified in the ASA. Follow up questionnaires were proposed for malignancy and pregnancy at the first round of evaluation, however the pregnancy questionnaire was removed at the second round of evaluation. Additional pharmacovigilance was included for the important potential risk of malignancy and for missing information. At the third round of evaluation, the sponsor included additional pharmacovigilance for the important potential risk of serious infection and provided further details of the planned pregnancy study. The pharmacovigilance plan is acceptable.
- Routine risk minimisation activities have been proposed for all safety concerns, however at the second round of evaluation, the sponsor was requested to clarify which activities are being carried out for the missing information 'effects on responses to inactivated vaccines'. In response, the sponsor has amended the vaccination warning in Section 4.4 of the Product Information (PI) to include all vaccines and updated the ASA accordingly. The sponsor did not agree to additional risk minimisation for herpes zoster and serious infections at the third round of evaluation, however additional warnings have been added to the PI for herpes zoster, and an additional pharmacovigilance study has been included for serious infections. The sponsor also did not agree to add a warning on urinary tract infections to the Consumer Medicines Information (CMI) with adequate justification. The risk minimisation plan is acceptable from an RMP perspective.

Risk-benefit analysis

Delegate's considerations

Anifrolumab exhibits non-linear pharmacokinetics (PK) in the dose range of 100 mg to 1000 mg with area under the concentration time curve increased more than dose proportionally. Following every 4 weeks intravenous administrations of anifrolumab, steady state was reached by Day 85. Results from Phase II dose ranging study (Study CD-IA-MEDI-546-1013) showed that while both 300 mg and 1000 mg every 4 weeks dosing regimens were efficacious in systemic lupus erythematosus (SLE) patients, 1000 mg dosing did not provide additional treatment benefit. Therefore, intravenous 300 mg every 4 weeks dosing regimen was selected for Phase III studies. A 150 mg dose group was also included in the Phase III program to further elucidate dose response. The responder rate was numerically lower at 150 mg every 4 weeks.

As anifrolumab was not expected to have a narrow therapeutic window, fixed dosing regimen was considered. Fixed dosing regimen decreases dosing errors and improves operational ease during dosing. Based on exposure response analysis for efficacy and safety, the proposed dosing regimen of intravenous 300 mg every 4 weeks provides the optimal benefit-risk balance in patients with SLE.

To support the proposed indication in moderate to severe SLE, the sponsor provided the results from three trials, Studies CD-IA-MEDI-546-1013, D3461C00005 and D3461C00004 that evaluated intravenous anifrolumab 300 mg every 4 weeks as well as two additional doses (150 mg every 4 weeks and 1000 mg every 4 weeks) versus placebo in adults patients with active SLE on stable immunosuppressive background medications.

All the three trials were multicentric, randomised, double blind, placebo controlled, 52-week trials that evaluated the efficacy, safety, and immunogenicity of anifrolumab 300 mg intravenous every 4 weeks versus placebo in 925 adult subjects with active SLE receiving standard therapy.

In all three trials, Studies CD-IA-MEDI-546-1013, D3461C00005 and D3461C00004, the SRI(4) was originally selected as the primary endpoint, to establish efficacy. Systemic Lupus Erythematosus Responder Index of at least 4 (SRI(4)) was included as the primary endpoint at week 24 in Study CD-IA-MEDI-546-1013 and proposed as the primary endpoint at Week 52 in Studies D3461C00005 and D3461C00004. SRI(4) is a composite clinical endpoint to assess clinical response in SLE and has been successfully used to support the approval of belimumab. All three studies included the British Isles Lupus Assessment Group (BILAG)-based Composite Lupus Assessment (BICLA) endpoint. The Delegate notes that BICLA and SRI(4) are both considered clinically meaningful endpoints for evaluating a treatment effect on clinical response in SLE as per adopted EU guidelines.

In Study CD-IA-MEDI-546-1013, a higher proportion of anifrolumab 300 mg intravenous subjects (34%) achieved the primary endpoint, SRI(4) response with oral corticosteroid tapering at Week 24, as compared to the placebo group (18%) (odds ratio (90% CI): 2.4 (1.3, 4.3)). Study CD-IA-MEDI-546-1013 was designed as a proof-of-concept and dose ranging study and did not appropriately control for multiplicity; the primary endpoint of SRI(4) is viewed as only having achieved nominal significance for benefit of anifrolumab 300 mg intravenously compared to placebo. However, Study CD-IA-MEDI-546-1013 was randomised, placebo controlled, 52 weeks in duration, and assessed the proposed dosing regimen in an appropriate patient population and estimated effects were consistent with clinically meaningful benefit.

The first Phase III study completed, Study D3461C00005, did not show a statistically significant difference in SRI(4) response rate between anifrolumab 300 mg intravenous and placebo groups at Week 52(anifrolumab 36% compared to placebo 40%; risk

difference (95% CI): -4.2 (-14.2, 5.8)). Further analyses, the sponsor observed that some of the protocol specified restrictions on medication were not implemented as intended per-protocol;[29] and were not appropriate based on clinical practice. Number of subjects who would be considered responders in clinical practice were deemed non-responders due to these overly restrictive medication rules. These rules included restricted use of non-steroidal anti-inflammatory drugs and limited oral corticosteroids used for mild SLE flares. While Study D3461C00005 did not show statistically significant improvement in the prespecified primary endpoint (SRI(4)), it did show nominally significant changes in the key secondary BICLA endpoint in favour of anifrolumab 300 mg intravenous dose. Specifically, under the revised restricted medication rules, at Week 52, a higher proportion of anifrolumab 300 mg intravenous subjects (47%) achieved BICLA response as compared to the placebo group (30%) (risk difference (95% CI): 17.0 (7.2, 26.8)). Also, disease activity measured by the SLE disease activity index updated in Year 2000 (Systemic Lupus Erythematosus Disease Activity Index 2000), showed a dose dependent separation in favour of anifrolumab in Study D3461C00005.

In agreement with the FDA, the sponsor changed the primary endpoint to BICLA response rate at Week 52 for the second Phase III study (Study D3461C00004) prior to database lock and unblinding. Study D3461C00004 achieved statistically significant and clinically meaningful results using primary endpoints incorporating either BICLA or SRI(4) composite endpoints at Week 52. A higher proportion of anifrolumab intravenous subjects (47.8%) achieved the 52-week BICLA primary endpoint as compared to the placebo group (31.3%) (risk difference (95% CI): 16.3 (6.3, 26.3)).

The sponsor also conducted further exploratory *post-hoc* analysis to understand the apparent discrepancy between SRI(4) and BICLA responses within Study D3461C00005 and between Studies D3461C00004 and D3461C00005 on the request of FDA. There was a clinically meaningful difference between the treatment groups in the proportion of patients who were both an SRI (4) responder and BICLA responder, in favour of anifrolumab in both studies. These dual responders, based on 2 validated endpoints, confirm the beneficial effect of anifrolumab on overall disease activity in patients with moderate to severe SLE.

One subset of patients in Study D3461C00005 appears to be driving the overall discrepant result on SRI(4) in Study D3461C00005. In this subset, more patients in the placebo group were able to achieve a SRI(4) response than patients in the anifrolumab group. This may be due to an imbalance between the treatment groups in baseline disease severity, and the degree of steroid use during the study, leading to more patients in the placebo group achieving complete resolution of arthritis, which alone meets the criteria for a SRI(4) response.

In summary, Study D3461C00004 represents an adequate and well controlled trial showing favourable and statistically significant changes on the pre-specified, clinically meaningful primary and secondary endpoints when comparing anifrolumab 300 mg intravenously versus placebo. As Study D3461C00005, the first Phase III trial, failed on its primary endpoint and Study CD-IA-MEDI-546-1013 was designed only as a proof of concept and dose ranging study with inadequate multiplicity control, both cannot be considered as successful adequate and well-controlled trials when considered independently. However, the clinical delegate feels that when these trials are considered in combination, the consistent results observed in Studies CD-IA-MEDI-546-1013 and D3461C00005 do provide confirmatory evidence that support the effectiveness of anifrolumab 300 mg intravenously.

[29] The **per-protocol (PP)** analysis is restricted to the participants who strictly adhered to the protocol. Also known as 'on-treatment' analysis.

The safety of anifrolumab in the SLE clinical program was consistent with expected increased risk of infection due to immunosuppression, in particularly for viral infections in which Type I interferon is a central part of the immune response.

While the 52-week incidence of serious infections between placebo and anifrolumab arms in all three trials submitted to support approval was balanced between anifrolumab and placebo arms (anifrolumab 4.8% (22 of 459) versus placebo 5.6% (26 of 466)). The proportion of subjects with any infections was higher in subjects treated with anifrolumab 300 mg (69.7%; 320 of 459) as compared to subjects in the placebo arms (55.4%; exposure adjusted incidence rate 99.9 of 100 patient years). Herpes zoster infections, in particularly, occurred at a higher rate in anifrolumab treated subjects compared to placebo (6.1% versus 1.3%). In the 52-week controlled study period, fatal infections occurred in 0.4% of patients receiving anifrolumab and 0.2% of patients receiving placebo. In long-term, placebo controlled assessment of subjects on anifrolumab 300 mg beyond 52 weeks, a total of seven deaths were attributed to infections in anifrolumab treated subjects (four pneumonia and three coronavirus disease 2019) as compared to none on placebo. Certain infections occurred more frequently in patients treated with anifrolumab, including nasopharyngitis (anifrolumab 300 16.3% versus placebo 9.4%); upper respiratory infection (15.5% versus 9.7%); bronchitis (9.8% versus 4.3%); herpes zoster (6.1% versus 1.3%); influenza (2.6% versus 1.9%); and latent tuberculosis (0.9% versus (0.2%).[27]

There was one case of anaphylaxis with the anifrolumab 150 mg intravenous dose and no cases of anaphylaxis with the anifrolumab 300 mg or 1000 mg intravenous doses. There were more infusion-related reactions (9.4% versus 7.1%) and hypersensitivity reactions (2.6% versus 0.6%), including 2 cases of angioedema, in the anifrolumab 300 mg intravenous group as compared to the placebo group.

Overall, increased risk of hypersensitivity and infusion-related reactions and the increased risk for infections, in particular respiratory infections and herpes zoster, the increased risk for potentially fatal outcome from serious infections for anifrolumab 300 mg is similar to the only other approved targeted therapy for SLE and represents an acceptable safety profile for this indication.

Post-marketing studies (as committed to the FDA) will be required to assess the safety and PK of anifrolumab when used with standard therapy in paediatric SLE patients ages 5 to 17 years, to assess adverse pregnancy outcomes and adverse effects on exposed infants, and to measure the presence of the drug in human breast milk.

A significant unmet medical need exists for safe and efficacious treatment for patients with SLE. Reducing the risk of severe SLE flares, lowering the SLE disease activity and decrease in daily steroid dose may result in less morbidity and mortality associated with this disease. Less long-term end organ damage from patients' underlying disease, less treatment with immunosuppressive agents commonly used to treat SLE with their own inherent toxicities, as well as fewer hospitalisations with less loss of absent workdays.

In summary, the efficacy and safety data generated from Studies CD-IA-MEDI-546-1013, D3461C00004, and D3461C00005, support a favourable benefit-risk assessment for approval of the 300 mg dosing regimen of anifrolumab intravenous as add on therapy for adult patients with active SLE, a disease with high unmet need.

Proposed action

The Delegate considers that sufficient data and justification have been provided to support the registration of anifrolumab on quality, safety and efficacy grounds as a add on treatment of moderate to severe systemic lupus erythematosus in adult patients despite standard therapy (subjected to the Advisory Committee on Medicines (ACM) deliberations and product information changes).

Questions for the sponsor

The sponsor provided the following response to questions from the Delegate.

1. Can the sponsor please provide the latest exposure data to address the concerns raised, relating to the safety database highlighted in the clinical study report?

The latest available exposure data (up to 19 March 2020) is summarised in Table 13 below.

Table 13: Studies Study D3461C00004, Study D3461C00005, Study D346100009, Study CS-IA-MEDI-546-1013 and Study CD-IA-MEDi-546-1145 Duration of exposure to intravenous anifrolumab every 4 weeks (safety analysis sets)

Studies included	Phase III Studies ONLY (studies 04, 05, and 09)	Phase II and Phase III SLE Studies (studies 04, 05, 09, 1013, and 1145)	
Doses included	Anifrolumab IV 300 mg ONLY Patients (n)	Anifrolumab IV 300 mg ONLY [a] Patients (n)	Anifrolumab IV 150, 300, and 1000 mg Patients (n)
Data cutoff date	Up to 19 March 2020	Up to 19 March 2020	Up to 19 March 2020
Exposure time			
≥ 1 day	360	563	837
≥ 24 weeks	326	516	766
≥ 52 weeks	294	472	694
≥ 104 weeks	237	363	548
≥ 156 weeks	161	212	375
≥ 208 weeks	32	41	147

Abbreviations: IV = intravenously; n = number of subjects in analysis group; Study 04 = Study D3461C00004; Study 05 = Study D3461C00005; Study 09 = Study D346100009; Study 1013 = Study CS-IA-MEDI-546-1013; Study 1145 = Study CD-IA-MEDi-546-1145

a Patients who received two different doses of anifrolumab are counted in the dose category of the highest dose received, and when calculating length of exposure, patients who received two different doses are counted as having received the highest dose for the entire course of their treatment.

The Phase III long-term data ('Phase III studies only' column) and all anifrolumab safety pool ('Phase II and Phase III systemic lupus erythematosus studies' column) include data from ongoing Study D3461C00009;[25] up to 19 March 2020.

2. Can the sponsor please provide the latest information on deaths if different from the United States Food and Drug Administration review.

Study D3461C00009;[25] is ongoing and remains blinded to all patients and investigators. Accordingly, the sponsor has not included treatment assignments for the deaths reported from Study D3461C00009 below. All dosing has completed for Study D3461C00009 and last subject last visit was in December 2021. Database lock is targeted for March 2022 and completion of the clinical study report is targeted for September 2022.

A total of 3 deaths have been reported during the interval period between the 18 January 2021 cut-off date for the information provided to the FDA and up to (and including) 3 January 2022.

Two cases were reported from the ongoing Study D3461C00009:[25]

- The first case was reported as 'unknown cause of death' in a 32-year-old female from the USA. The investigator assessed the event as not related to study therapy. Minimal information has been received to date, and efforts continue to obtain further information.

- The second case was reported as 'lung adenocarcinoma' in a 55-year-old male from Germany with multiple confounding factors. The investigator assessed the event as not related to study therapy.

The third case was received from post-marketing sources. The case was reported as 'passed away' in a 64-year-old male from USA with very limited information. The cause of death was not reported.

3. Can the sponsor please provide the final European Summaries of Product Characteristics (SmPC) if available.

The final EU SmPCs were provided.

Advisory Committee considerations

The Advisory Committee on Medicines (ACM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following.

Specific advice to the Delegate

1. What are ACM's views on the efficacy of anifrolumab and to what extent is there sufficient clinical trial evidence to support the proposed indication for the treatment of moderate to severe systemic lupus erythematosus in adult patients despite standard therapy?

The ACM agreed that there is sufficient clinical trial evidence to demonstrate that anifrolumab provides modest benefit for moderate to severe systemic lupus erythematosus (SLE) with a focus on skin and joint disease.

The ACM noted that while the TULIP-2 trial (Study D3461C00004) using the BICLA measurements met the primary efficacy endpoint, the TULIP-1 trial (Study D3461C00005) using the SRI measurement did not.

The ACM commented that the complexity of the outcome measures chosen (and changed) for the two pivotal studies and variations in the analysis of the TULIP-1 trial (Study D3461C00005) made the interpretation of efficacy difficult.

The ACM recognised the complexity of SLE and acknowledged the difficulties in finding large effect sizes in this heterogenous group of patients. The ACM noted that within the TULIP-2 trial (Study D3461C00004) at Baseline the disease activity and previous treatments applied to the enrolled patients would suggest a group with quite severe disease and although the differences between the anifrolumab and placebo treated patients were small the number needed to treat to achieve a BICLA response at 52 weeks was 6 which is likely to be of clinical utility.

The ACM commented that patients with active or unstable neuropsychiatric or renal SLE were excluded from the TULIP-2 trial (Study D3461C00004). As such the ACM was of the view that there is insufficient evidence for use of anifrolumab in renal and central nervous system disease sub-groups. The ACM acknowledged the TULIP-LN1 trial (Study D3461C00007);[26] which focuses on lupus nephritis, however noted that this study was not included within the data set provided to the TGA.

Given the complex and diverse presentations of SLE in addition to the insufficient evidence in support of the use of anifrolumab in some SLE sub-groups the ACM agreed that this treatment should be initiated and supervised by a physician experienced in the treatment of SLE.

Overall, the ACM was supportive of an indication for the treatment of moderate to severe SLE in adults that excluded use in patients within neuropsychiatric SLE and/or lupus

nephritis and was initiated and supervised by a physician experienced in the treatment of SLE.

2. Do we need to restrict the indication for Type I interferon signature test 'high' response patients only?

The ACM was of the view that based on current data it is not appropriate to restrict usage to patients with a Type I interferon signature test 'high' response.

The ACM advised that there is limited evidence to indicate that the gene signature is an effect modifier. In providing this advice, the ACM noted the small number of patients (approximately 16%) with normal Type I interferon gene signature that had a similar response to those with high levels.

The ACM also noted that the Type I interferon gene signature test is not readily available in Australia.

3. Does the ACM consider that the safety of Anifrolumab in the proposed indication is sufficiently well characterised and communicated in the Product Information?

The ACM was of the view that the known safety profile of anifrolumab was well characterised within the PI. However, the ACM acknowledged the reasonably limited number of patients exposed to anifrolumab.

The ACM agreed that based on limited data in pregnancy anifrolumab should not be used during pregnancy and this should be clearly stated within the PI.

4. The Committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

The ACM advised that the following points could be included within the PI, as appropriate:

- List of standard therapies and doses that are required to have been trialled for at least 3 months and deemed ineffective prior to commencing anifrolumab.
- Skin score and number of active joints reported in the clinical trials.
- Recommendation that patients are tested for hepatitis B, C, and tuberculosis, where relevant.
- That patients are reviewed every six months and anifrolumab is discontinued if ineffective.

Conclusion

The ACM considered this product to have an overall positive benefit-risk profile for the indication:

> *Saphnelo (anifrolumab) is indicated as add on for the treatment of adult patients with moderate to severe systemic lupus erythematosus (SLE) despite standard therapy, excluding patients with neuropsychiatric SLE and/or lupus nephritis.*
>
> *Treatment should be initiated and supervised by a physician experienced in the treatment of SLE.*

Outcome

Based on a review of quality, safety, and efficacy, the TGA approved the registration of Saphnelo (anifrolumab) 300 mg/2 mL, concentrate for solution for infusion, vial, indicated for:

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

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

Specific conditions of registration applying to these goods

- Saphnelo (anifrolumab) is to be included in the Black Triangle Scheme. The PI and CMI for Saphnelo must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.
- The Saphnelo EU-risk management plan (RMP) (version 1 succession 3, dated 30 August 2021, data lock point 19 March 2020), with Australian specific annex (version 1.0 succession 3, dated 22 October 2021), included with Submission PM-2020-06383-1-2, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

  An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

  Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of the approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of the approval letter. The annual submission may be made up of two PSURs each covering six months. If the sponsor wishes, the six monthly reports may be submitted separately as they become available.

  If the product is approved in the EU during the three years period, reports can be provided in line with the published list of EU reference dates no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of the approval letter.

  The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on Good Pharmacovigilance Practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.
- It is a condition of registration that all batches of Saphnelo anifrolumab imported into/manufactured in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).
- For all injectable products the Product Information must be included with the product as a package insert.

Attachment 1. Product Information

The PI for Saphnelo approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA PI/CMI search facility.

Therapeutic Goods Administration

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