16 October 2025
EMA/348230/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Saphnelo

International non-proprietary name: anifrolumab

Procedure No. EMEA/H/C/004975/X/0023

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

1. Background information on the procedure 8
1.1. Submission of the dossier 8
1.2. Legal basis and dossier content 8
1.3. Information on Paediatric requirements 8
1.4. Information relating to orphan market exclusivity 8
1.4.1. Similarity 8
1.5. Scientific advice 8
1.6. Steps taken for the assessment of the product 9

2. Scientific discussion 10
2.1. Problem statement 10
2.1.1. Disease or condition 11
2.1.2. Epidemiology 11
2.1.3. Clinical presentation, diagnosis prognosis 11
2.1.4. Management 12
2.2. About the product 12
2.3. Type of Application and aspects on development 12
2.4. Quality aspects 12
2.4.1. Introduction 12
2.4.2. Active Substance 13
2.4.3. Finished Medicinal Product 13
2.4.4. Discussion on chemical, pharmaceutical and biological aspects 18
2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects 19
2.5. Non-clinical aspects 19
2.5.1. Introduction 19
2.5.2. Pharmacology 19
2.5.3. Pharmacokinetics 19
2.5.4. Toxicology 20
2.5.5. Ecotoxicity/environmental risk assessment 21
2.5.6. Discussion on non-clinical aspects 21
2.5.7. Conclusion on the non-clinical aspects 21
2.6. Clinical aspects 22
2.6.1. Introduction 22
2.6.2. Clinical pharmacology 23
2.6.3. Discussion on clinical pharmacology 36
2.6.4. Conclusions on clinical pharmacology 39
2.6.5. Clinical efficacy 39
2.6.6. Discussion on clinical efficacy 72
2.6.7. Conclusions on the clinical efficacy 77
2.6.8. Clinical safety 77
2.6.9. Discussion on clinical safety 102
2.6.10. Conclusions on the clinical safety 107
2.7. Risk Management Plan 107
2.7.1. Safety concerns 107

2.7.2. Pharmacovigilance plan 107
2.7.3. Risk minimisation measures 110
2.7.4. Conclusion 110
2.8. Pharmacovigilance 110
2.8.1. Pharmacovigilance system 110
2.8.2. Periodic Safety Update Reports submission requirements 111
2.9. Product information 111
2.9.1. User consultation 111

3. Benefit-Risk Balance 111
3.1. Therapeutic Context 111
3.1.1. Disease or condition 111
3.1.2. Available therapies and unmet medical need 111
3.1.3. Main clinical studies 112
3.2. Favourable effects 112
3.3. Uncertainties and limitations about favourable effects 112
3.4. Unfavourable effects 112
3.5. Uncertainties and limitations about unfavourable effects 113
3.6. Effects Table 113
3.7. Benefit-risk assessment and discussion 115
3.7.1. Importance of favourable and unfavourable effects 115
3.7.2. Balance of benefits and risks 115
3.7.3. Additional considerations on the benefit-risk balance 115
3.8. Conclusions 116

4. Recommendations 116

List of abbreviations

CR	American College of Rheumatology
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
AI	autoinjector
ALB	Serum albumin
ANA	antinuclear antibody
APFS	Accessorised pre-filled syringe
APS	antiphospholipid syndrome
AUC	Area under the concentration-time curve
AUC_{sd}	AUC during the first dosing interval
AUC_{inf}	area under concentration-time curve from time zero extrapolated to infinity
AUC_{last}	area under concentration time curve from time zero to last quantifiable concentration
AUC_{ss}	AUC at steady state
BICLA	British Isles Lupus Assessment Group-2004-based Combined Lupus Assessment
BILAG	British Isles Lupus Assessment Group
BMI	body-mass index
B4SIGENE	4-gene signature status
$C_{ave,sd}$	Average concentration after first administration
$C_{ave,ss}$	Average concentration at steady state
CDL	clinical data lock
CI	Confidence interval
CL	Clearance
CL/F	apparent total body clearance of drug after extravascular administration
C_{ave}	average concentration
CHMP	Committee for Medicinal Products for Human Use
CLASI	Cutaneous Lupus Erythematosus Disease Area and Severity Index
C_{max}	maximum concentration
$C_{max,sd}$	Maximum concentration after first administration
$C_{max,ss}$	Maximum concentration at steady state
CHM	Cochran–Mantel–Haenszel
C_{min}	minimum concentration
$C_{min,sd}$	Minimum concentration after first administration

$C_{min,ss}$	Minimum concentration at steady state
COVID-19	Coronavirus disease 2019
CrCL	Creatinine clearance
CSP	clinical study protocol
CSR	clinical study report
C_{trough}	trough concentration
CV	Coefficient of variation /Cardiovascular
CV-EAC	Cardiovascular Event Adjudication Committee
CWRES	Conditional weighted residuals
EAIR	exposure-adjusted incidence rate
eGFR	estimated glomerular filtration rate
D	Day
DB	double-blind
DCO	Data cut-off
DMC	Data Monitoring Committee
dsDNA	double-stranded deoxyribonucleic acid
EMA	European Medicines Agency
E-R	Exposure-response (model)
EULAR	European Alliance of Associations for Rheumatology
F	bioavailability
FAS	full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GOF	Goodness-of-fit
HCP	Health Care Professionals
HCV	hepatitis C virus
HR	hazard ratio
IA	Interim analysis
ICE	intercurrent event
ICF	informed consent form
IFN	interferon
IFNAR1	subunit 1 of the type I interferon receptor
IMP	Investigational medicinal product
IP	investigational product
IPRED	Individual prediction
IV	Intravenous
K_a	first-order absorption rate constant
K_m	The concentration at which elimination of 50% of the maximum is achieved in Michaelis Menten equation

L	Liter
LS	least squares
LLOQ	lower limit of quantification
ULOQ	upper limit of quantification
mAb	monoclonal antibody
MACE	major acute cardiovascular events
MI (MAR)	multiple imputation (missing at random)
MRT	mean residence time of the unchanged drug in the systemic circulation from zero to infinity
NA	not applicable
nAb	neutralizing antibody
NC	noncompliance
NR	non-responder
NSAID	non-steroidal anti-inflammatory drug
OCS	oral corticosteroids
OLE	open-label extension
ORR	Objective response rate
OS	Overall survival
pAb	polyclonal antibody
pcVPC	Prediction corrected visual predictive check
PD	pharmacodynamic(s)
PEOT	premature end of treatment
PGA	Physician’s Global Assessment
PK	Pharmacokinetic(s)
PPK	Population pharmacokinetic(s)
PT	Preferred term
PY	Patient years
Q	Intercompartmental clearance
Q2W	Once every 2 weeks
Q3W	Once every 3 weeks
Q4W	Once every 4 weeks
QW	Once per week
RM	restricted medication
RSE	Relative standard error
SAP	statistical analysis plan
SC	subcutaneous
SD	standard deviation
SLE	Systemic Lupus Erythematosus
SLEDAI-2K	Systemic Lupus Erythematosus Disease Activity Index 2000

SoC	Standard of care
SOC	System organ class
SRI(4)	Systemic Lupus Erythematosus Responder Index of ≥ 4
$t_{1/2}$	half-life
$t_{1/2\lambda z}$	half-life associated with terminal slope (λz) of a semi-logarithmic concentration time curve
TE-ADA	treatment-emergent anti-drug antibody
t_{last}	time of last quantifiable concentration
USA	United States of America
V_c or V_2	Volume of distribution of the central compartment
V_{max}	The maximal elimination rate constant of Michaelis Menten equation
V_p or V_3	Volume of distribution of the peripheral compartment
VPC	Visual predictive check
VAS	visual analog scale
V_z/F	apparent volume of distribution following extravascular administration (based on terminal phase)

1. Background information on the procedure

1.1. Submission of the dossier

AstraZeneca AB submitted on 18 December 2024 an extension of the marketing authorisation to introduce a new pharmaceutical form (solution for injection) associated with a new route of administration (subcutaneous use) and a new strength (120 mg).

Furthermore, the PI is brought in line with the latest QRD template version 10.4.

1.2. Legal basis and dossier content

The legal basis for this application refers to:

Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I of Regulation (EC) No 1234/2008, (2) point(s) (c) (d) (e) - Extensions of marketing authorisations

1.3. Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0149/2023 covering the application on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0149/2023 was not yet completed as some measures were deferred.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Scientific advice

Table 1: Scientific advice and protocol assistance

Date	Topic (quality/ non-clinical/ clinical)	Reference number / Coordinator(s)	Brief summary of the advice
2016-05-26	Clinical	EMEA/H/SA/2903/2/2016/II	The Scientific advice pertained to the following non-clinical, and clinical aspects: Clinical development, Phase II, Study drug, Dose, Pharmacokinetics, Primary endpoints, Composite / Co-primary, Secondary endpoints, Methodology, Statistical Analysis, Sample size, Population, Inclusion, Exclusion, Special population
2018-07-26	Non-Clinical, Clinical	EMEA/H/SA/2903/3/2018/III	The Scientific advice pertained to the following non-clinical, and clinical aspects: Pre-clinical development, Clinical development, Phase III, Comparability, Study drug, Dose, Pharmacokinetics, Methodology, Statistical Analysis,
2023-02-23	Clinical	EMA/SA/0000121096	The Scientific advice pertained to the following clinical aspects: clinical and statistical alignment with the Agency on the acceptability of a Bayesian borrowing methodology
2022-08-29	Clinical	EMA/SA/0000095558	The Scientific advice pertained to the following and clinical aspects: design of the proposed global, single, Phase III study of anifrolumab to obtain an indication for the treatment of systemic sclerosis. Details of the study design, including intended target population, primary and key secondary efficacy endpoints, as well as the proposed statistical approach

1.6. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Outi Mäki-Ikola

The application was received by the EMA on	18 December 2024
The procedure started on	23 January 2025
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	14 April 2025
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	28 April 2025
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	22 May 2025
The MAH submitted the responses to the CHMP consolidated List of Questions on	16 July 2025
The CHMP Rapporteur circulated the CHMP Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	25 August 2025
The CHMP Rapporteur circulated the updated CHMP Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	11 September 2025
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the MAH on	18 September 2025
The MAH submitted the responses to the CHMP List of Outstanding Issues on	23 September 2025
The CHMP Rapporteur circulated the CHMP Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	01 October 2025
The CHMP Rapporteur circulated the updated CHMP Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	n/a
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Saphnelo on	16 October 2025

2. Scientific discussion

2.1. Problem statement

This application is a line extension concerning the development of a subcutaneous (SC) formulation of anifrolumab administered once weekly (QW).

2.1.1. Disease or condition

Systemic lupus erythematosus is a complex, chronic, and heterogeneous autoimmune disease of unknown etiology that affects multiple organ systems.

The sought indication is: "*Saphnelo is indicated as an add on therapy for the treatment of adult patients with moderate to severe, active autoantibody positive systemic lupus erythematosus (SLE), despite standard therapy*", which is identical to the approved wording for IV anifrolumab.

2.1.2. Epidemiology

The incidence and prevalence rates of SLE across the world are generally estimated at 0.3 to 23.7 cases per 100.000 person-years and 6.5 to 178.0 cases per 100.000 persons, respectively, although these types of estimates can be considered conservative as they do not capture cases of mild, undiagnosed, or misdiagnosed disease. There are wide geographical variations in the incidence and prevalence of SLE based on sex, age, and ethnicity. Systemic lupus erythematosus disproportionally affects females over males (~9:1) and primarily affects women of childbearing potential. Incidence and prevalence rates in people of African or Asian descent are 2 to 3 times higher than in Caucasian populations. In addition, non-Caucasians often have more severe clinical manifestations, such as increased haematological, serosal, neurological, and renal manifestations, and accrue more damage over time and at a faster pace. In about 15%-20% of cases, disease onset occurs during childhood and tends to be more severe with faster and more severe damage accrual.

Compared to the general population, the overall mortality in SLE is elevated, with a standardised mortality ratio (defined as the ratio of the number of deaths observed to deaths expected) of 2.4 reported in a large international cohort of 9.457 subjects followed for over 70.000 subject-years.

2.1.3. Clinical presentation, diagnosis prognosis

SLE is a chronic, multisystemic, disabling autoimmune rheumatic disease of unknown aetiology. Clinical manifestations of SLE can include constitutional symptoms, alopecia and rashes, serositis, inflammatory arthritis, renal disease, systemic vasculitis, lymphadenopathy, splenomegaly, haemolytic anaemia, cognitive dysfunction, and other central nervous system involvement. Arthritis and photosensitive skin rash are common presenting features. Patients may present with a single or a variety of clinical manifestations and the most frequent serologic finding (an abnormal anti-nuclear antibody (ANA) test) is sensitive but not specific for the diagnosis. This can make diagnosis and management of the disease challenging.

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'). Due to the variable nature of the disease and its treatment, patients experience reduced physical function, loss of employment, and significantly worse health-related quality of life. According to a recent survey of over 2000 SLE patients, severe fatigue was ranked as one of their most burdensome symptoms. Increased hospitalisations and side effects of medications add to the disease burden.

Uncontrolled, ongoing disease activity over time has been associated with poorer outcomes, such as organ damage and coronary artery disease in SLE. Higher doses of medications to control disease activity are associated with cumulative and irreversible organ damage (such as premature cataracts, retinopathy, osteoporotic fractures, cardiovascular damage, avascular necrosis, and infections and early mortality from causes such as infection and cardiovascular disease), shortening lifespan by about 10 years.

2.1.4. Management

Until the approval of the 2 available targeted therapies for SLE (belimumab, IV or SC) and IV anifrolumab, treatments were based on non-targeted therapies such as OCS and other immunosuppressive drugs. These remain a major component of SLE therapy. However, chronic steroid use, nonsteroidal anti-inflammatory drugs, and immunosuppressive agents have known safety concerns that contribute to long-term morbidity and mortality in SLE patients.

There continues to be a need for improvement in SLE treatment through enhanced convenience for patients.

2.2. About the product

Anifrolumab is a human IgG1κ mAb that inhibits binding of type I IFNs to IFNAR1. By blocking type 1 IFN signaling, anifrolumab reduces multiple innate and adaptive downstream inflammatory pathways.

The currently approved wording for IV anifrolumab is as follows: "*Saphnelo is indicated as an add on therapy for the treatment of adult patients with moderate to severe, active autoantibody positive systemic lupus erythematosus (SLE), despite standard therapy.*"

The same SLE population as for IV use is targeted for SC use; therefore, there is no proposed change to the approved indication. The recommended dose is 120 mg by SC administration QW.

The extension application concerns SC route of administration with new delivery devices, accessorised prefilled syringe (APFS) or prefilled pen/autoinjector (AI), with the options of administration by healthcare professionals and for at-home use (self-administration or by caregiver).

2.3. Type of Application and aspects on development

This submission refers to a type of application which is an extension of marketing authorisation of a complete and independent application.

The anifrolumab SC clinical programme included a pivotal global, multicenter, randomized, double-blind (DB), placebo-controlled, Phase III study (D3465C00001; TULIP SC). TULIP SC was an ongoing study during the procedure evaluating the safety and efficacy of anifrolumab SC administered by accessorised pre-filled syringe (APFS) in adults with moderate to severe SLE despite receiving standard of care.

The independent Data Monitoring Committee (DMC) made a recommendation that the interim analysis (IA) met the pre-specified efficacy criteria with no new safety findings. The MAH considered the data to provide substantial evidence that anifrolumab SC showed a positive benefit-risk profile that was consistent with the established profile of the approved IV treatment.

2.4. Quality aspects

2.4.1. Introduction

The finished product (FP) is presented as a solution for injection containing 150 mg/ml of anifrolumab as active substance.

Other ingredients are: histidine/ histidine hydrochloride monohydrate, lysine hydrochloride, trehalose dihydrate, polysorbate 80 (E 433), water for injections.

The product is available in pre-filled pen [also referred to as autoinjector (AI)] and in pre-filled syringe [also referred to as accessorised pre-filled syringe (APFS)].

The objective of this extension application is to add subcutaneous (SC) route of administration to be administered with new delivery devices, accessorised prefilled syringe or prefilled pen/autoinjector. The recommended dose and dosing regimen will be different than the currently approved intravenous (IV) administration, however the formulation and concentration of 150 mg/ml remain the same.

2.4.2. Active Substance

The active substance (AS), anifrolumab, a human, immunoglobulin G1 kappa (IgG1κ) monoclonal antibody produced in mouse myeloma cells (NS0) by recombinant DNA technology.

There are no changes to the active substance.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

Description of the product

The finished product is a sterile, preservative-free, liquid dosage form intended for subcutaneous injection.

The finished product is supplied:

- as a single-dose pre-filled pen: 120 mg of anifrolumab per AI with a 0.8 mL label-claim volume
- as a single-dose accessorised pre-filled syringe (APFS): 120 mg of anifrolumab per APFS with a 0.8 mL label-claim volume.

The finished product contains 150 mg/mL anifrolumab in L-histidine/L-histidine hydrochloride monohydrate, L-lysine hydrochloride, α,α-trehalose dihydrate, polysorbate 80, pH 5.9. The finished product is aseptically filled into a 1 mL long-staked needle glass syringe and stoppered with an elastomeric plunger stopper.

The active substance is provided ready to fill into syringes for manufacture of the finished product. The AS composition is the same as the finished product composition. All excipients present in the anifrolumab finished product are of compendial grade and are commonly used in the manufacturing of parenteral pharmaceutical preparations.

Formulation development

A summary of the finished product history from clinical to commercial development is provided. The 120 mg/syringe sterile finished product was developed to ensure anifrolumab quality over the intended finished product shelf life and to enable and provide convenience for a subcutaneous route of administration. The development of the formulation is described, and characterization of the intended commercial formulation is evaluated.

Overall, sufficient formulation development studies were conducted and in general the conclusions drawn by the applicant can be agreed. The results indicate that the formulation possessed appropriate robustness.

No formula overages are included. Overfill to ensure the deliverable volume of the finished finished product is included and is considered acceptable.

Manufacturing process development

Overview of the development history of the manufacturing processes including a summary description of the processes used to manufacture materials for all anifrolumab clinical studies has been provided.

The Applicant has conducted comparability assessments to evaluate the impact of the changes between the finished product manufacturing processes.

In conclusion, release test data, and for some comparability exercises also stability data, has been provided. As the Applicant has compared commercial PFS-SA material to all relevant materials: PFS-SA (clinical), vial (authorised), and vial, (clinical) and all provided test results demonstrate comparability, the comparability of the commercial PFS-SA to clinical FPS-SA and previously approved presentations, can be considered sufficiently demonstrated.

Process characterisation

Manufacturing process characterisation studies for finished product manufacturing process have been performed to assess the effects of manufacturing process parameters and environmental factors (product-contact materials and light exposure) on product quality to identify critical process parameters (CPPs). Results of the studies are presented in acceptable detail. Based on risk assessment and the cumulative potential leachables level calculated based on the total organic carbon results of the medium or high-risk materials, the materials used in the finished product manufacturing process were found to pose a low risk to patient safety.

Analytical equivalency characterization studies and device equivalency characterization studies were performed between prefilled syringe sub-assembly and accessorised prefilled syringe (PFS-SA/APFS) as well as between prefilled syringe sub-assembly and autoinjector (PFS-SA/AI). The purpose of analytical equivalency characterization studies is to assess potential impact of APFS or AI assembly process on anifrolumab product quality profile, and to support using PFS-SA as an equivalent material to APFS or AI for product quality lot release. The studies demonstrated that the assembly process does not impact anifrolumab product quality. Based on the studies, the testing of PFS-SA is supported.

Device equivalency characterization studies between the PFS-SA and APFS demonstrate that the device performance attributes could be tested at the PFS-SA intermediate stage as representative of the final APFS product. Also, device equivalency characterization studies between the PFS-SA and AI demonstrated that the device performance attributes could be tested at the PFS-SA intermediate stage as representative of the final AI product. Thus, assembly, labelling, and packaging processes do not meaningfully impact these device performance attributes. The functionality of the assembled APFS delivery devices over the claimed shelf life is adequately demonstrated.

Microbiological attributes

Sterility and endotoxin of the FP are tested as part of batch release, and sterility and container closure integrity are tested as part of the FP stability program. This is considered adequate. No failures of sterility, endotoxin, or container closure integrity tests have been observed to date in the FP container closure system. The container closure integrity of the intended commercial FP manufactured at the FP fill facility was qualified as part of the fill-finish validation program to demonstrate proper stoppering of the syringes.

Compatibility

Saphnelo FP is ready to use solution for injection in PFS (APFS) or solution for injection in pre-filled pen (AI) for subcutaneous administration. No reconstitution diluent(s) is used. Compatibility is adequately presented.

2.4.3.2. Manufacture of the product and process controls

Manufacture

The site responsible batch release in EEA of both PFS and AI finished product presentations is AstraZeneca AB, Gärtunavägen, Sweden. Valid proof of GMP compliance has been provided.

The standard manufacturing process is comprised of active substance thawing, pooling and mixing, bioburden reduction filtration and in-process hold, sterile filtration, aseptic filling into ready-to-use syringes and aseptic stoppering with ready-to-use plungers, visual inspection, and assembly, labeling and packaging. The assembly of PFS-SA is done either in autoinjector and accessorised pre-filled syringes. A narrative description of the full manufacturing process was provided, accompanied by a flow chart describing each step of the process including material inputs, critical/non-critical process parameters and in-process controls. Acceptable ranges for critical/non-critical process parameters and in-process controls were presented in tabulated form. The description of the manufacturing process and process controls is considered sufficient and meets relevant guideline. There are no reprocessing or reworking steps indicated in the finished product manufacturing process and the batch numbering system was explained.

Process controls

Control of critical finished product manufacturing process steps is described through critical process parameters, in-process controls and in-process hold time. Summaries of critical process parameters and in-process controls with acceptance criteria are provided and are considered appropriate. The limits for bioburden are in accordance with the relevant '*Guideline of Sterilisation of the Medicinal Drug Products (EMA/CHMP/QWP/850374/2015)*'. Filter integrity limits were defined during filter validation studies.

The finished product manufacturing process was validated with consecutive commercial scale process validation (PV) lots for PFS-SA finished product at the proposed commercial manufacturing site.

Manufacturing process validation covered all manufacturing steps and the data included critical and non-critical process parameters, in-process controls and additional in-process testing. Overall, all PV batches were successfully validated and the acceptance criteria were met thus demonstrating the consistency and reliability of the finished product manufacturing process.

The proposed hold time for thawed and mixed AS process intermediate after bioburden filtration is supported by the process validation data.

The aseptic process validation (media fills) was carried out with commercial filling line to demonstrate that the aseptic condition is maintained during the filling process. Media fill data was provided but was not assessed since it is considered to be covered by GMP.

Filters are used in sterile filtration and were validated using worst case conditions The validation results demonstrated that the formulation does not compromise the integrity of the filters. Furthermore, filters are compatible with the AS and according to the applicant the extractables are below the Threshold of Toxicological Concern for genotoxic impurities described in ICH M7. Overall, adequate and acceptable data of filter validation was presented.

The process validation of label, assembly and packing manufacturing for AI/APFS was executed on consecutive batches in accordance with the process validation protocol. No major or critical deviations were encountered during the process validation execution. All process validation acceptance criteria were met. Therefore, the assembly, labelling, and packaging process is capable of consistently producing packaged AI/APFS with acceptable attributes and has been successfully validated.

Shipping qualification of anifrolumab autoinjector device when packaged as a unitized load included simulated transportation in air and road modes that are representative of the commercial supply chain. Shipping validation data demonstrated that quality of finished product and functionality of AI were not affected when exposed to the supply chain routes from the filling site, to the label and pack site, and to the distribution centres. The shipping qualification included thermal and container integrity operational qualification and performance qualification studies. The provided data is considered acceptable.

2.4.3.3. Product specification

Specifications

Comprehensive panel of specification in accordance with ICH Q6B principles are set for PFS-SA including tests for general properties, identity, purity and impurities, safety, potency and quantity. Additionally, functionality tests are performed on PFS-SA and AI.

Overall, specifications cover all relevant characteristics of the finished product. Additionally, the acceptance criteria for all specification tests are considered acceptable and appropriately justified.

Analytical procedures

Analytical procedures utilized in the specification tests of the finished product included both compendial and non-compendial methods. The validation data of in-house tests was provided in the dossier and are considered acceptable. Summaries of the analytical method transfer test results of in-house methods have been provided and are considered acceptable.

Batch analysis

Batch analytical data was provided for clinical batches and commercial scale batches. Overall, all batches met the acceptance criteria of release specification in place at the time indicating adequate batch-to-batch consistency and controlled manufacturing process.

Characterization of impurities:

Based on the risk assessment it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed (as requested) considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "*Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products*" (EMA/369136/2020). Based on the information provided it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary.

Container closure

Finished product in the primary packaging is referred to as the pre-filled syringe sub-assembly (PFS-SA). Device components are attached to the PFS-SA and do not contact the finished product solution. For the accessorised pre-filled syringe (APFS), the needle guard, finger flange and plunger rod are added to the PFS-SA to produce the APFS. For the autoinjector (AI), the PFS-SA is assembled with device components (drive unit and syringe) unit to produce the fully assembled AI.

The primary container closure system components and device components (accessories) have been adequately described. Material compliances to pharmacopoeias, specifications for incoming inspection schematic drawings and suppliers are stated. Certificates of analysis have been provided for syringes, stoppers and needle and considered adequate. The rationale for choosing the container closure system was provided and is considered acceptable. The safety and compatibility of the finished product PFS-SA were adequately evaluated.

The finished product contacting primary container components come pre-sterilized. Secondary packaging components include an opaque paperboard carton to protect the finished product from light exposure and an internal paperboard partition to secure the labelled device during transportation. Carton components are constructed from coated, bleached paper stock, with pre-printed artwork. This information is sufficient.

Devices have been further described in Section 3.2.R. This covers: Rationale for Regulatory Classification of the Product, Regulatory Compliance and Quality Systems, Device Description, Principles of Operation and Mode of Action, Device Components and Raw Materials, Design Changes from Clinical to Commercial, Design Verifications and Human Factors Engineering (HFE).

Notified body opinions on the conformity of the device part of a pharmaceutical product, with the relevant general safety and performance requirements (GSPR) for APFS and AI have been provided according to Annex I of Regulation (EU) 2017/745.

Overall, the provided data (P.7) as well as data from other CTD sections covering suitability of the CCS (P.2.4), confirmation of container closure integrity (P.2.5 and P.3.5.) and stability tests (P.8.1) indicate that the selected container closure systems are in general appropriate and enable adequate protection from microbial contamination.

2.4.3.4. Stability of the product

The proposed shelf life for the finished product is 48 months and is based on real time stability data from the PFS-SA batches at the long-term storage condition of 2-8°C.

Stability is monitored at three conditions: 2-8°C (recommended long-term storage condition), 23-27°C/55-65% RH (accelerated condition) and 38-42°C/70-80% RH (stress condition). The testing intervals are in line with ICH Q5C.

Overall, the finished product stability program designed by the Applicant follows ICH Q1A and ICH Q5C guidelines and the stability study protocols have been provided for all presentations and conditions. The presented stability data supports the shelf-life of 48 months (4 years) for PFS-SA.

As there is no contact between the solution and the components of the delivery device, it is considered sufficient to test APFS and AI stability from PFS-SA. However, functionality of the assembled delivery device over the whole claimed shelf life should be demonstrated. 48 months device functionality data is provided for APFS and AI and the functionality of the assembled APFS as well as the AI delivery devices over the claimed shelf life is adequately demonstrated.

Furthermore, design verification testing, presented in section R.2, includes performance testing after accelerated aging preconditioning to assure adequate performance of the APFS/AI device throughout the shelf life of the product.

The photostability study results for APFS and for AI demonstrate that the finished product commercial marketing packs are effective in protecting the finished product material from light exposure.

In-use stability studies to determine the suitability of a 7 days in-use duration at room temperature have been presented and support the statement in section 6.3 of the SmPC.

2.4.3.5. Adventitious agents

Adventitious agents evaluation of Saphnelo vial (iv) has been approved in previous submissions. Microbial control of the proposed finished product presentations have been adequately demonstrated and ensured throughout the finished product manufacturing process. No adventitious agents section has been provided in this extension application submission, which is considered acceptable.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

The objective of this extension application is to add subcutaneous (SC) route of administration to be administered with new delivery devices, accessorised prefilled syringe (APFS) or prefilled pen/autoinjector (AI). The currently approved Saphnelo IV product is not affected by this extension application. The recommended dose and dosing regimen will be different than the currently approved IV administration, however the formulation and concentration of 150 mg/ml remain the same. There are no changes to the active substance.

Overall, the provided quality dossier is of good quality, and all the relevant sections has been satisfactorily covered. The Applicant has compared Commercial PFS-SA material to all relevant materials: PFS-SA (clinical), vial (authorised), and vial (clinical), and all provided test result demonstrate comparability. The comparability of the commercial PFS-SA to clinical FPS-SA and previously approved presentations, can be considered sufficiently demonstrated. The manufacturing process and control strategy have been adequately presented. Manufacturing process validation data demonstrated the consistency and reliability of the finished product manufacturing process. Release and shelf-life specifications cover all relevant characteristics of the finished product and the acceptance criteria for all specification tests are considered acceptable and appropriately justified.

Finished product in the primary packaging is referred to as the pre-filled syringe sub-assembly (PFS-SA). Device components are attached to the PFS-SA and do not contact the finished product solution. For the accessorised pre-filled syringe (APFS), the needle guard, finger flange and plunger rod are added to the PFS-SA to produce the APFS. For the autoinjector (AI), the PFS-SA is assembled with device components (drive unit and syringe) unit to produce the fully assembled AI. The primary container closure system components and device components (accessories) have been adequately described. The safety and compatibility of the finished product PFS-SA were adequately evaluated.

Medical devices have been further described in Section 3.2.R.2. Notified body opinions have been provided for the accessorised prefilled syringe (APFS) and for the autoinjector (AI) according to Annex I of Regulation (EU) 2017/745, with the relevant general safety and performance requirements (GSPR).

Long-term storage shelf-life at 2-8°C has been proposed for both APFS and AI. The presented stability data supports the proposed shelf-life of 48 months for PFS-SA. The functionality of the assembled APFS and AI delivery devices over the claimed shelf life are adequately demonstrated.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.5. Non-clinical aspects

2.5.1. Introduction

No new nonclinical data was submitted in this extension application to support the proposal to add the new route of administration (subcutaneous (SC)). To support anifrolumab SC administration, summaries of the previous studies in cynomolgus monkey submitted for the original MAA were provided and are shortly summarised below. The non-clinical data for anifrolumab has been reviewed in previous procedures.

The information in sections 4.6 and 5.3 of the SmPC remain unchanged, except substituting the information of safety margins via IV and SC routes of administration under the *fertility*.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

N/A

2.5.2.2. Secondary pharmacodynamic studies

N/A

2.5.2.3. Safety pharmacology programme

N/A

2.5.2.4. Pharmacodynamic drug interactions

N/A

2.5.3. Pharmacokinetics

Following SC injection, absorption of anifrolumab from the dosing site was slow, with the peak serum concentration occurring approximately 2 days after administration in cynomolgus monkeys. The slopes of the terminal phases for IV infusion and SC injection were similar.

The maximum observed serum concentration (C_{max}) after SC and IV dosing was dose proportional. The nonlinear drug exposure (AUC) was likely the result of the receptor mediated clearance of anifrolumab at lower doses. The elimination half-life ($t_{1/2}$) of anifrolumab increased with dose and was at lower doses < 1 week and at higher doses > 2 weeks.

2.5.4. Toxicology

2.5.4.1. Single dose toxicity

N/A

2.5.4.2. Repeat dose toxicity

A GLP 9-month (39-week) repeat IV infusion or SC injection dose toxicity study in cynomolgus monkeys was conducted using anifrolumab 15 and 60 mg/kg/week SC dose levels (and 5 and 50 mg/kg/week IV dose) in cynomolgus monkeys (Study 7140-129). The findings noted were similar in the IV and SC route of administration groups. The NOAEL for female cynomolgus monkeys was 60 mg/kg SC (resulting a mean C_{max} of 3,230 ± 1,120 µg/mL and mean AUC_{0-7d} 19,500 ± 5,620 µg·d/mL), the highest doses tested in comparison, the NOAEL after IV dosing was 50 mg/kg IV (resulting in a mean C_{max} of 4,510 ± 1,200 µg/mL and mean AUC_{0-7d} 21,600 ± 5,780 µg·d/mL). Based on the arterial inflammation observed, the NOAEL for males was < 15 mg/kg SC (and <5 mg/kg IV). Of note, non-SLE vasculitis has not been a clinical safety finding attributed to anifrolumab in the clinical studies. The estimated safety margins for SC administrated anifrolumab (at NOAEL 15 mg/kg) and the MRHD of 120 mg SC every week were approximately 52 for AUC and 51 for C_{max} for the 39-week study.

2.5.4.3. Genotoxicity

N/A

2.5.4.4. Carcinogenicity

N/A

2.5.4.5. Reproductive and developmental toxicity

N/A

2.5.4.6. Toxicokinetic data

See section 2.5.4.2. on repeat dose toxicity.

2.5.4.7. Local tolerance

No anifrolumab-related adverse changes were observed at the infusion/injection sites as assessed by dermal Draize scoring, macroscopic, and histopathology examinations in cynomolgus monkeys in the repeated-dose toxicity studies.

2.5.4.8. Other toxicity studies

N/A

2.5.5. Ecotoxicity/environmental risk assessment

Anifrolumab is a monoclonal antibody, naturally occurring protein which non-hazardous and biodegradable. The environmental risk is negligible. As stated in the EMEA/CHMP/SWP/4447/00 Rev. 1-Corr. 2024 guideline, in the case of medicinal products comprised of naturally occurring substances as active substance, the ERA may consist of a justification for not submitting ERA studies. Such a justification was provided in the current variation submission and is acceptable.

2.5.6. Discussion on non-clinical aspects

No new non-clinical data was submitted in this extension application intended to add SC route of administration in addition to IV. This was acceptable to the CHMP. The toxicological and toxicokinetic studies included in the original MAA were considered adequate to support the SC administration anifrolumab of the current application.

The studies with SC route of administration were:

- Non-GLP single IV or SC dose toxicity, pharmacokinetics, pharmacodynamics, and immunogenicity Study of anifrolumab (MEDI-546) in male cynomolgus monkeys (Study 7140-142).
- GLP 9-month (39-week) repeat SC injection and IV infusion toxicity, toxicokinetic, and immunogenicity study of anifrolumab (MEDI-546) in cynomolgus monkeys with a 12-week recovery period monkeys (Study 7140-129).

Following SC injection, absorption of anifrolumab from the dosing site was slow, with the peak serum concentration occurring approximately 2 days after administration in cynomolgus monkeys. The C_{max} after SC and IV dosing was generally dose proportional.

The toxicology findings were similar after SC and IV route of administration in GLP 9-month (39-week) repeated dose study in cynomolgus monkeys with anifrolumab 15 and 60 mg/kg/week SC (and 5 and 50 mg/kg/week IV). The NOAEL for female cynomolgus monkeys was 60 mg/kg SC (C_{max} of 3,230 µg/mL and $AUC_{0\text{-}7d}$ 19,500 µg·d/mL). Based on the arterial inflammation observed, the NOAEL for males was < 15 mg/kg SC. The estimated safety margins were approximately 52 for AUC and 51 for C_{max}. No anifrolumab-related adverse changes were observed at the infusion/injection sites in cynomolgus monkeys. The safety margin following SC use has been included in the SmPC section 5.3.

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, anifrolumab is not expected to pose a risk to the environment.

2.5.7. Conclusion on the non-clinical aspects

No new non-clinical data was submitted. The nonclinical data including the repeated dose toxicology and toxicokinetic studies in cynomolgus monkeys using the SC (and IV) route of administration of anifrolumab, was acceptable for the proposed addition of the of the SC route of administration.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical studies were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical studies conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

A summary of the clinical studies relevant for the current application is shown in Table 2.

Table 2: Summary of clinical studies in the application

Study number (name)	Study design Primary objective Primary endpoint	Patient population and No. of randomized participants	Dose and route of administration	Study status
Pivotal Phase III study				
D3465C00001 (TULIP SC)	Phase III study of the safety and efficacy of SC anifrolumab in patients with moderate to severe SLE despite standard of care Primary objective To compare efficacy of anifrolumab with placebo on overall disease activity in patients with SLE. Primary endpoint BICLA response at Week 52	Adult patients 18 to 70 years of age with moderate to severe SLE N = 360 planned 1:1; IA based on first 220/360 planned randomized patients to complete 52-week treatment period or withdraw early from the study	Anifrolumab 120 mg or placebo SC QW administered via APFS	Ongoing Recruitment of 220 patients for IA was completed July 2023; recruitment of the full study (N = 367) was completed 21 Aug 2024 Interim CSR dated 15 Nov 2024 (Module 5.3.5.1)
Device comparability and bridging study				
D3465C00002 Device PK Bridging Study	A multicenter, randomized, open-label, parallel Phase 1 comparability study of anifrolumab administered using APFS or AI in Healthy Volunteers Primary objective To demonstrate that the PK exposure following single SC administration of anifrolumab by AI is comparable to the PK exposure following single SC administration of anifrolumab using APFS Primary endpoint AUC_{inf}, AUC_{last}, and C_{max}	Adult healthy volunteers 18 to 55 years of age N = 180	Anifrolumab 120 mg SC single dose administered via APFS or AI	Completed Final CSR, dated 15 Nov 2023 (Module 5.3.3.1)

Abbreviations: AI=Autoinjector; APFS=Accessorised pre-filled syringe; AUC=Area under the concentration-time curve; C_{max}=Maximum concentration; CSR=Clinical study report; IA=Interim analysis; QW=Once per week; SC=Subcutaneous

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Pharmacokinetics of anifrolumab administered by subcutaneous (SC) route has been studied in four clinical studies. Two clinical studies have been conducted to support the SC administration of the applied dose 120 mg of anifrolumab (Table *2*). An ongoing pivotal Phase III study (D3465C00001, hereafter referred to as "TULIP SC study") was conducted to support approval of an SC route of administration with a prefilled syringe (APFS) and a completed Phase I device PK bridging study (D3465C00002, hereafter referred to as "device PK bridging study") to support approval in an autoinjector (AI). Two additional completed clinical studies including SC administration of anifrolumab were submitted in the initial application for marketing authorisation. Phase I study D3461C00006 (study 06) was a randomized, placebo-controlled, double-blind, single-dose study to evaluate the safety, tolerability and pharmacokinetics of SC 300 mg and 600 mg SC anifrolumab doses, and 300 mg IV dose in healthy volunteers. Phase II study D3461C00008 (study 08) was a multicenter, randomized, placebo-controlled study characterizing the PK and PD, safety, and tolerability of SC anifrolumab in 36 SLE patients at doses of SC 150 mg or SC 300 mg or placebo, once every two weeks (Q2W) for 52 weeks (26 doses). The PK and PD data from this study was used to inform dose selection for Phase III clinical study with SLE patients. The PK data from these studies was included in the population PK analyses.

The final SC dose of 120 mg has been administered in 289 subjects including 180 healthy volunteers and 109 SLE patients.

Formulations of drug product used in the clinical development

The drug product is an APFS or AI is a sterile 150 mg/1 mL solution for injection. Each APFS or AI contains a nominal label claim of 120 mg anifrolumab in a 0.8 mL volume. The formulation is similar to the originally approved for IV infusion. The drug product batches used in pivotal TULIP SC study and device PK bridging study were manufactured using Clinical Process 3. The earlier SC clinical studies (study 06 and study 08) were conducted with drug product manufactured by Process 2. The excipient composition has not changed since the initial development. The drug product originating from Process 2 and from the earlier Process 3 were confirmed comparable in the initial marketing authorisation for IV presentation. The comparability of the drug product originating from the different manufacturing processes is based on comparison of the quality and physicochemical properties.

Bioanalytical methods

The validated MSD-ECL assay for the quantitation of anifrolumab was the same assay as approved in the initial MAA. An additional validation report including additional stability data was provided. The stability of the analyte was demonstrated for nine freeze/thaw cycles and for 2183 days at -80 °C. All other bioanalytical methods were also the same assay as approved in the initial MAA. Bioanalytical reports for both clinical studies were provided including in-run validation results. The results of the incurred sample repeats met the acceptance criteria.

Pharmacokinetic data analysis

Pharmacokinetic parameters were derived from dense PK data using non-compartmental methods with Phoenix WinNonlin Version 6.2 or 8.1 or higher depending on the study. All descriptive and inferential statistical computations were performed using SAS Version 9.2 or 9.4, or higher. The serum anifrolumab trough concentrations (C_{trough}) were reported with descriptive statistics at each visit and time point in those studies where sparse PK data was collected. The statistical analyses were conducted with appropriate models.

A population PK (PPK) model was developed to describe the PK anifrolumab following intravenous (IV) and subcutaneous (SC) administration. A total of 14,176 serum PK samples from 1,194 subjects in ten clinical studies were included in the dataset.

Absorption

In the Phase I PK study 06 in healthy volunteers, bioavailability of single doses of 300 mg SC anifrolumab given as two 1 ml SC injections, 300 mg IV anifrolumab given as 30 min infusion and 600 mg SC anifrolumab given as 4 ml SC using an infusion pump were compared following serum concentrations for up to 57 days. The median time to peak concentration T_{max} was 4.13 days (range 4.02 to 7.00 days) with mean C_{max} of 36.22 µg/ml (SD 11.63) after SC injection of 300 mg dose. The bioavailability in terms of AUC_{inf} after SC administration was approximately 16% lower compared to IV administration. Brief description of PK results and the concentration vs. time profiles were reported in the Saphnelo EPAR of the initial submission. The PK data was included in the population PK analyses.

Based on the population PK modelling, the estimated bioavailability of anifrolumab was 75% 72% after SC administration with a Ka of 0.189 day^{-1}.

Relative bioavailability /Device PK-bridging study

Phase I study (D3465C00002) was conducted to compare anifrolumab exposure after a single SC administration of 120 mg dose of anifrolumab using AI to administration of 120 mg dose using APFS in healthy male and female subjects, aged 18 to 55 years. In total 180 healthy volunteers were randomized 1:1:1:1:1:1 to one of the injection sites (upper arm, abdomen, or thigh) within a device group (APFS or AI) capped at 60 participants in each body weight category (50 to < 70 kg, 70 to < 90 kg, and 90 to 110 kg).
The geometric mean serum concentration vs. time profiles per device group are presented in Figure *1*. The serum concentration of anifrolumab reached maximum concentrations the median t_{max} being 5.00 days after administration by both AI (range 2.00 to 14.00 days) and APFS (range 2.00 to 11.00 days). Systemic exposure of anifrolumab following SC administration with AI device was comparable to APFS device as the 90% CIs for the geometric mean ratios of C_{max}, AUC_{inf}, and AUC_{last} were contained within the interval of 0.8 and 1.25 for the bioequivalence margins (Table *3*).

In the abdomen, the AI device group showed 15% and 21% larger geometric mean AUC_{inf} and AUC_{last} values than APFS device group. Following SC injection in the thigh and upper arm, the AI device showed 14% and 13% lower AUC_{last} than injections by APFS, respectively. Similarly, C_{max} was 21% larger for the AI device in the abdomen compared to the APFS device whereas it was 12% lower in both the thigh and upper arm. All PK parameters were deemed comparable between both device groups for each injection site.

The MAH has not compared exposures between the injection sites within a device (AI or APFS). Summary statistics of the main PK parameters are presented in Table *4*.

Figure 1: Geometric mean (± gSD) serum concentration (ng/mL) of Anifrolumab versus time by treatment (AI vs. APSF) (linear scale) (PK analysis set)

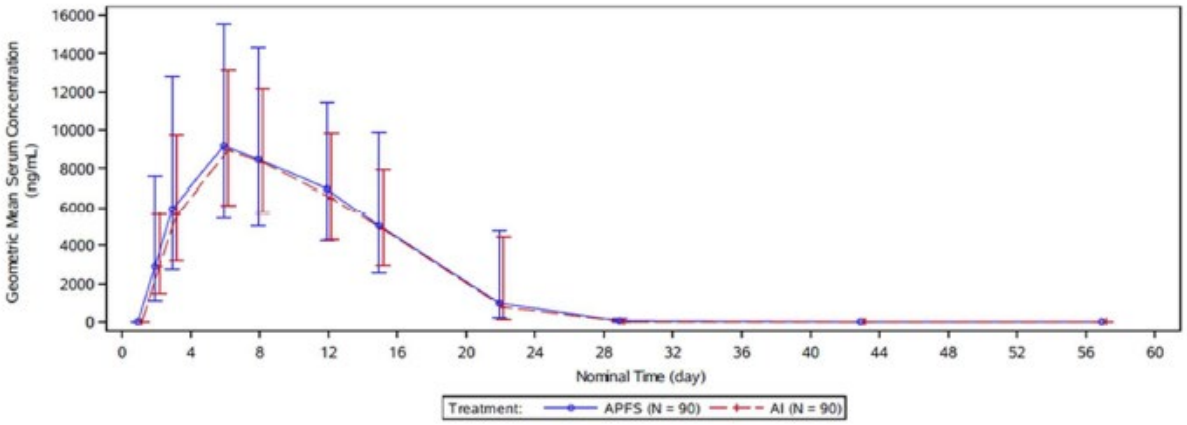


Table 3: Statistical comparison of primary PK parameters (PK analysis set).

Parameter (Unit)	Comparison	n	Geometric LS Mean	Comparison of Device Groups	
				Ratio	90% CI
C_{max} (ng/mL)	AI vs APFS	90 vs 90	9402 vs 9617	0.9777	(0.8880, 1.0764)
AUC_{inf} (day*ng/mL)	AI vs APFS	88 vs 89	121500 vs 125800	0.9658	(0.8727, 1.0689)
AUC_{last} (day*ng/mL)	AI vs APFS	90 vs 90	115700 vs 120000	0.9644	(0.8669, 1.0730)
AI=Autoinjector; APFS=Accessorised pre-filled syringe					

Table 4: Summary statistics (geometric mean and CV%) of anifrolumab PK parameters by injection site and device group.

Parameter (Unit)	Summary	Abdomen (N = 60)		Thigh (N = 60)		Upper Arm (N = 60)	
		AI (N = 30)	APFS (N = 31)	AI (N = 31)	APFS (N = 30)	AI (N = 29)	APFS (N = 29)
AUCinf (day*ng/mL)	gMean	134800	117200 [a]	131100 [a]	145600	101500 [b]	116700
	gCV%	44.48	59.28	35.05	46.28	39.34	58.27
	Median	140900	119100	134600	151600	100600	130600
	Min - Max	39600 - 239000	34700 - 281000	64400 – 254000	57600 - 362000	55100 - 223000	9350 - 180000
AUClast (day*ng/mL)	gMean	129800	107600	122500	142100	98160	112600
	gCV%	46.67	73.70	39.19	46.08	39.63	58.31
	Median	136000	115600	128700	149000	106700	127300
	Min - Max	34000 - 239000	14500 - 279000	64200 - 247000	57500 - 334000	48700 - 189000	9270 - 180000
Cmax (ng/mL)	gMean	10570	8768	10110	11450	7816	8865
	gCV%	38.56	61.87	29.71	37.89	27.45	52.02
	Median	10800	10000	10300	11950	7990	10000
	Min - Max	3990 - 19100	1730 - 18800	4820 - 17500	5900 - 24100	4630 - 13200	981 - 15400
tmax (day)	Median	5.00	5.00	5.00	5.00	6.00	5.00
	Min – Max	(2.00 – 11.00)	(2.00 – 11.00)	(5.00 – 11.00)	(2.00 – 7.00)	(2.00 – 14.00)	(2.00 – 7.00)
	gCV%	58.33	65.29	54.37	53.05	49.07	74.88

a Parameter was calculated with n = 30 participants. b Parameter was calculated with n = 28 participants.

Distribution

The estimated central volume of distribution (Vc) for anifrolumab was 3.48 L, based on the final PPK-model including exposures after SC administration, indicating typical distribution for IgG. The value is similar to the Vc of 2.93 L estimated in the population PK analyses following IV administration only.

Elimination

Based on population PK analysis, the estimated typical (linear) CL was 0.146 L/day ([0.141 to 0.151] 95% CI) which is close to what was reported previously 0.193 L/day for IV anifrolumab only.

Anifrolumab has non-linear elimination caused by antigen sink effect resulting in more rapid elimination at lower concentrations. Therefore, elimination half-life decreases as concentration decreases.

Dose proportionality and time dependencies

Following IV administration, anifrolumab exposure increased more than dose-proportionally because of increase of elimination at low serum concentrations by target-mediated elimination of anifrolumab. Dose proportionality has not been evaluated after SC administration. Subcutaneous doses of 150 mg, 300 mg and 600 mg in addition to the applied 120 mg dose have been used in the clinical studies.

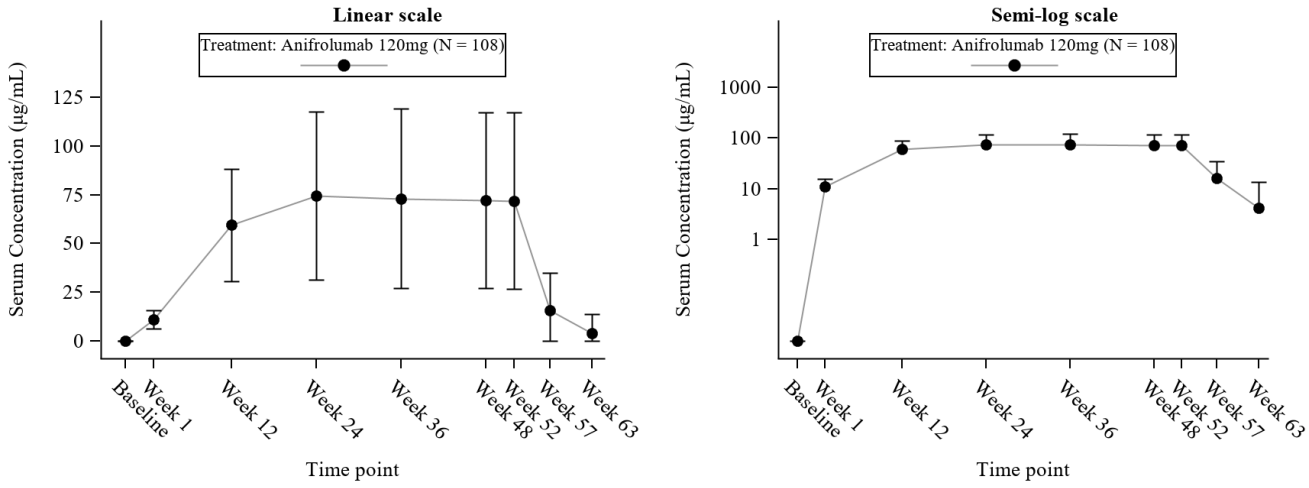
In the PK study 006 in healthy volunteers, exposure to anifrolumab increased approximately dose-proportionally following single SC dose administration of anifrolumab when the dose was increased from 300 mg to 600 mg with the arithmetic mean C_{max} increasing from 36.22 to 63.86 µg/mL and AUC_{inf} increasing from 784.6 to 1828 day*µg/mL (6 subjects per treatment group).

Pharmacokinetics in target population

Pharmacokinetics of 120 mg dose of SC anifrolumab in the patients with SLE was investigated in the Phase III pivotal TULIP SC Study. Anifrolumab was administered SC via an APFS into abdomen, thigh or upper arm either by the patient or his/her caregiver at home following training by investigator or study personnel. The SC doses were to be administered at least 5 days apart. The three injection sites were to be rotated. By the cut-of date, 108 patients of 175 randomised patients were included in the PK analysis set.

Following SC administration of 120 mg dose once a week, at 12 week time point the geometric mean serum anifrolumab C_{trough} value was 47.873 µg/ml (CV% 143.0%) with median (min, max) 57.711 µg/ml (0.010, 139.254). The steady state was reached between 12 and 24 weeks with geometric mean C_{trough} of 57.126 µg/ml (CV% 156.7%) corresponding median (min, max) 70.558 µg/ml (0.010 µg/ml, 208.458 µg/ml) at 24 week time point (n=96). For the Week 57 and 63 time points, the anifrolumab C_{trough} were reported for those patients who did not enter the OLE treatment period. Therefore, anifrolumab concentrations started decline from week 52 onwards as the last SC dose was given on Week 51. The serum C_{trough} vs. time profiles for SLE patients up to 63 weeks are presented in Figure *2*.

Figure 2: Serum anifrolumab trough concentrations (C_{trough}) (mean ± SD) on linear and semi-logarithmic scale following 120 mg once weekly SC injection by APFS in SLE patients.



Population PK modelling and simulations

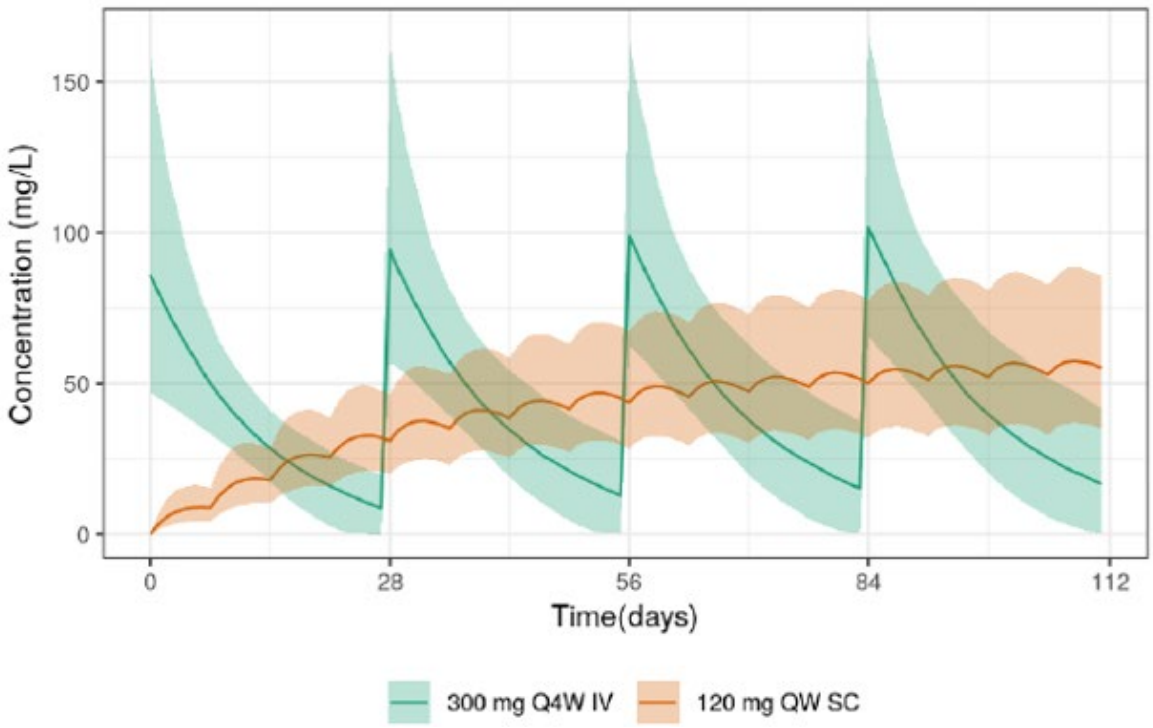
The final PPK model was a two-compartment model with parallel first-order and Michaelis-Menten kinetics clearances from the central compartment. Absorption from SC administration site was characterized with estimated bioavailability (F1) and absorption rate constant (Ka). Interindividual variability was characterized on first-order clearance (CL), central volume (Vc), peripheral volume (Vp), the maximum velocity of saturated clearance process (Vmax), and Ka. The covariates were as follows: on CL, baseline body weight, albumin level, creatinine clearance, IFN 4-gene signature status (B4SIGENE), and sex; on Vc, baseline body weight; on Vmax, race. Parameter estimates are shown in Table *5*.

Table 5: Parameter estimates for final anifrolumab PPK model

Parameter	Estimate	RSE (%)	95% CI	Shrinkage (%)	Unit
1. CL	0.146	1.70	[0.141 ; 0.151]	-	L/d
2. V2	3.48	2.06	[3.33 ; 3.62]	-	L
3. Q	0.0700	1.97	[0.0673 ; 0.0727]	-	L/d
4. V3	1.72	4.68	[1.56 ; 1.88]	-	L
5. KA	0.189	4.16	[0.174 ; 0.205]	-	1/d
6. F1	0.746	1.83	[0.719 ; 0.772]	-	-
7. VMAX	3.22	2.23	[3.08 ; 3.36]	-	mg/d
8. KM	0.252	3.39	[0.235 ; 0.268]	-	mg/L
CrCL on CL	0.287	16.1	[0.197 ; 0.378]	-	-
B4SIGENE Low on CL	-0.194	13.1	[-0.243 ; - 0.144]	-	-
Albumin on CL	-1.14	11.3	[-1.39 ; - 0.887]	-	-
Body weight on CL	0.602	9.91	[0.485 ; 0.718]	-	-
Body weight on V2	0.475	12.0	[0.364 ; 0.586]	-	-
Black race on Vmax	0.000686	5590	[-0.0744 ; 0.0758]	-	-
Asian race on Vmax	-0.115	47.5	[-0.223 ; - 0.00793]	-	-
'Other' race on Vmax	0.0934	44.7	[0.0116 ; 0.175]	-	-
Male sex on CL	0.178	29.8	[0.0744 ; 0.282]	-	-
ETA CL	30.6	2.67	[30.5 ; 30.6]	27.7	% CV
ETA V2	35.8	1.42	[35.8 ; 35.8]	24.9	% CV
ETA VMAX	30.5	3.21	[30.5 ; 30.5]	33.3	% CV
ETA V3	73.2	3.52	[73.1 ; 73.2]	43.4	% CV
ETA KA	32.6	9.10	[32.5 ; 32.6]	73.3	% CV
Proportional Error	54.9	0.141	[54.9 ; 54.9]	8.54	% CV

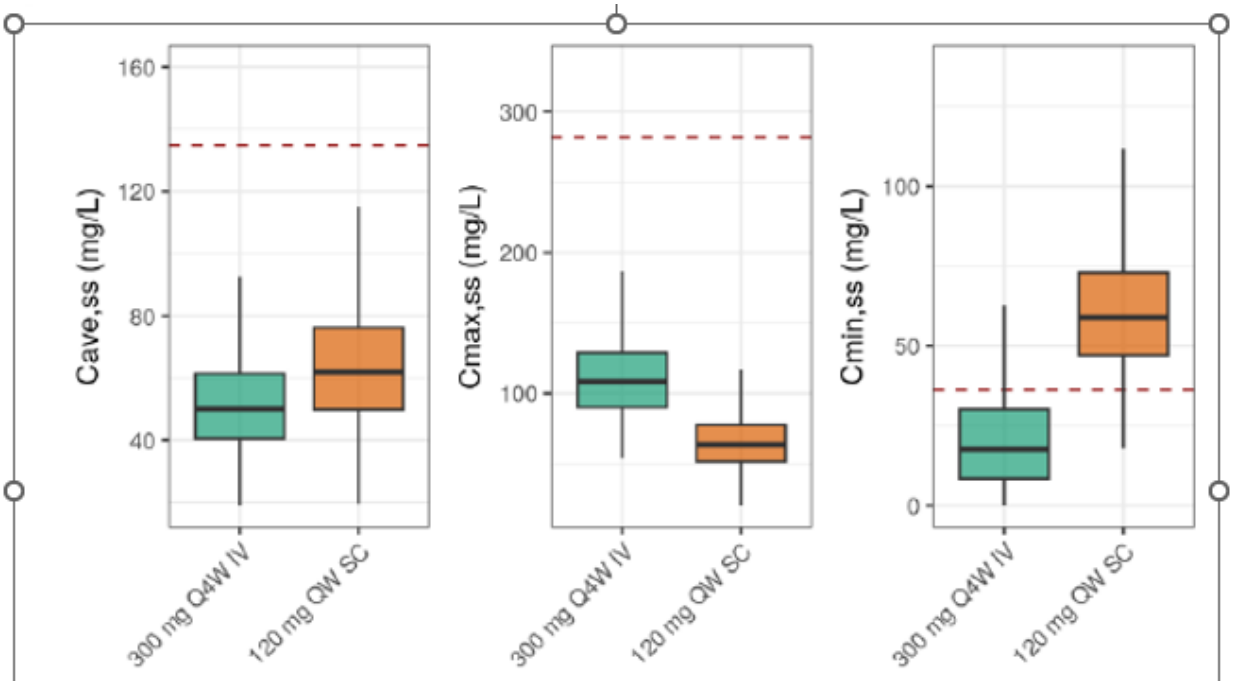
Anifrolumab concentration-time curves for the first 112 days after 120 mg QW SC and 300 mg Q4W IV dosing regimens are shown in Figure *3* The estimated time to reach steady state was approximately 112 days for both regimens. Simulations indicate that distribution of average concentration at steady state ($C_{ave,ss}$) is overlapping for the two regimens, whereas maximum concentrations ($C_{max,ss}$) are lower and minimum concentrations ($C_{min,ss}$) are higher for the 120 mg QW SC regimen compared with 300 mg Q4W IV (Figure *4*). Importantly, $C_{min,ss}$ of 120 mg QW SC is less than that of 1000 mg Q4W IV regimen, which was evaluated in phase 2 study CD-IA-MEDI-546-1013 (refer to the initial MAA). The simulated median $C_{min,ss}$ are 53.93 and 110.6 mg/L for 120 mg QW SC and 1000 mg Q4W IV, respectively.

Figure 3: Simulated anifrolumab concentration-time curves of 300 mg Q4W IV and 120 mg QW SC regimens.



Solid lines represent the median and shaded areas represent the 95% prediction interval of 1000 simulations

Figure 4: Simulated anifrolumab concentrations at steady state for 120 mg QW SC and 300 mg Q4W IV.

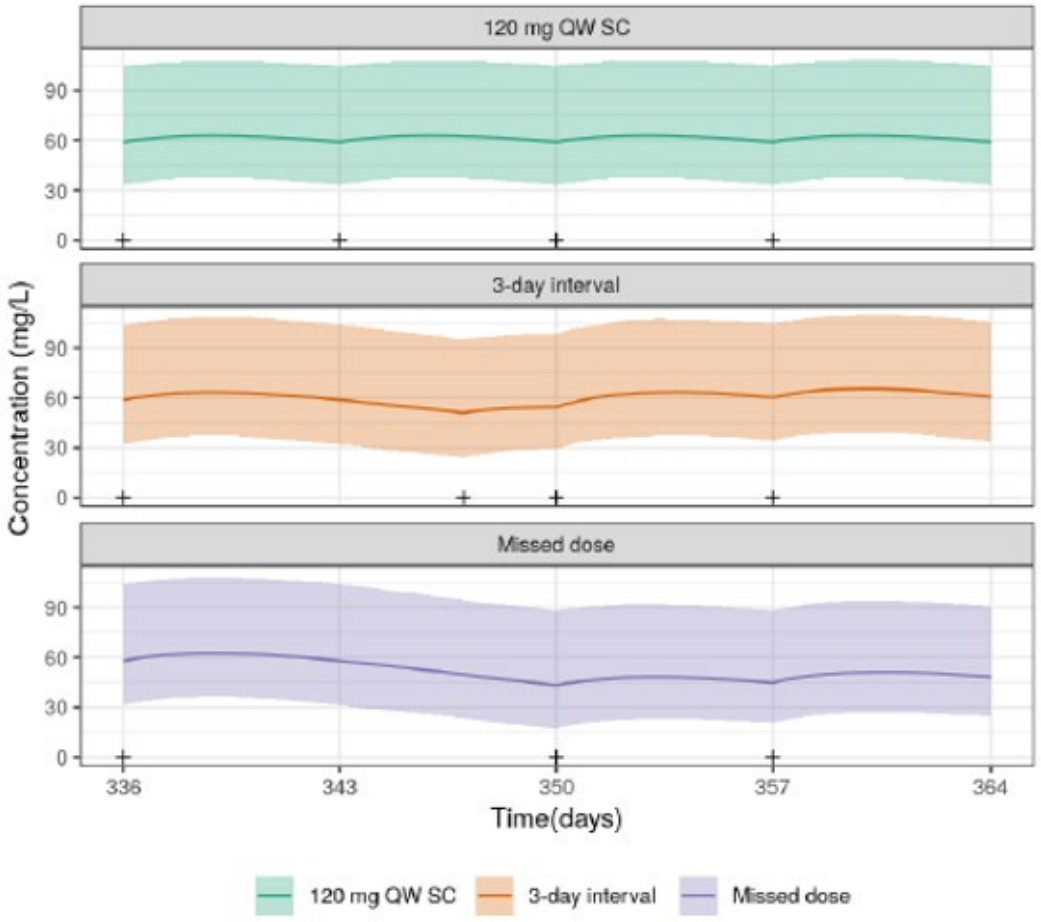


Dashed red line represents the lower 5th percentile of simulations of 1000mg Q4W IV for $C_{ave,ss}$, $C_{max,ss}$, $C_{min\ ss}$, respectively

Simulations were performed to assess missed doses during weekly SC dosing (Figure *5* and Table *6*). A missed dose would obviously result in reduced exposure, however the C_{min} would still be higher than

after IV monthly dosing. Total monthly dose would be reduced from 349 mg (120 mg x 4 doses x 0.728 bioavailability) to 262 mg (120 mg x 3 doses x 0.728 bioavailability), i.e., missing one dose in one month is still 87% of the dose received in one 300 mg IV dose.

Figure 5: Simulation of non-adherence scenarios after subcutaneous administration.



Symbol (+) indicates a dosing event

Table 6: Exposure metrics of non-adherence scenarios after subcutaneous administration.

Treatment	$AUC_{ss,d0-d28}$ (mg.d/L) Median [90% CI]	$C_{ave,ss}$ (mg/L) Median [90% CI]	$C_{min,ss}$ (mg/L) Median [90% CI]	$C_{max,ss}$ (mg/L) Median [90% CI]
120 mg QW SC	1773 [1048-3077]	63.32 [37.43-109.9]	60.48 [34.52-107.3]	64.94 [38.82-110.8]
120 mg QW SC - Missed dose	1505 [779.6-2783]	53.74 [27.84-99.40]	44.67 [17.79-89.91]	64.20 [37.61-111.1]
120 mg QW SC - 3-day interval	1735 [991.4-3023]	61.95 [35.41-108.0]	52.78 [25.06-97.78]	67.27 [40.35-112.7]

$AUC_{ss,d0-d28}$=AUC over 28 days at steady state; $C_{ave,ss}$=Average concentration at steady state; $C_{max,ss}$ Maximum concentration at steady state; $C_{min,ss}$=Minimum concentration at steady state; QW=Once per week; SC=Subcutaneous

Simulations were also performed to assess transition from one route of administration to the other (Figure *6* and Table *7*).

Figure 6: Simulation of transition from intravenous (300 mg Q4W IV) to subcutaneous (120 mg QW SC) dosing and vice versa.

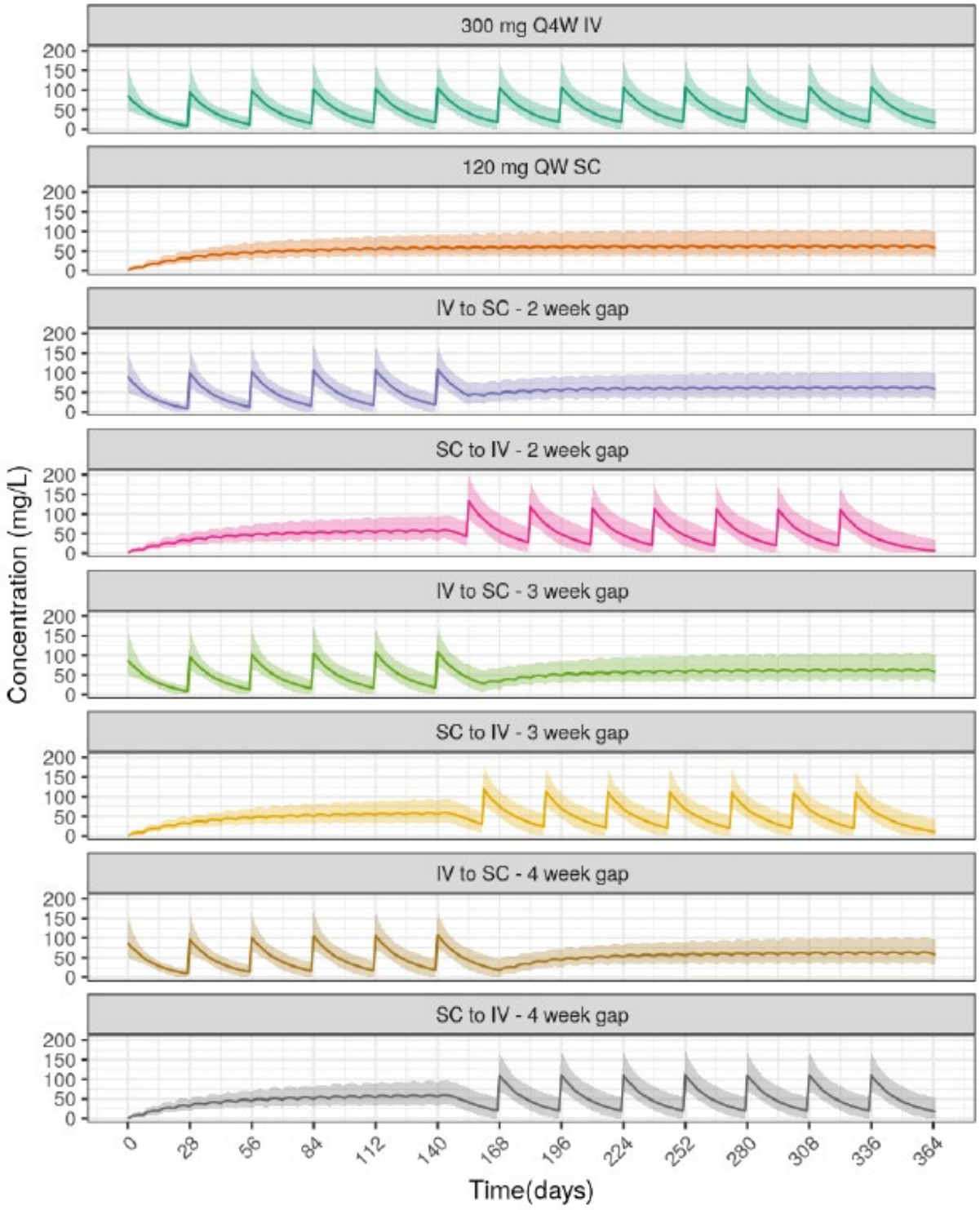


Table 7: Simulated exposure metrics: Transition from intravenous (300 mg Q4W IV) to subcutaneous (120 mg QW SC) dosing and vice versa.

Treatment	$AUC_{,d0-d365}$ (mg.d/L) Median [90% CI]	$C_{ave,d0-d365}$ (mg/L) Median [90% CI]	$C_{min,ss}$ (mg/L) Median [90% CI]	$C_{max,ss}$ (mg/L) Median [90% CI]	$C_{ave,d140-d168}$ (mg/L) Median [90% CI]	$C_{max,d140-d168}$ (mg/L) Median [90% CI]	$C_{min,d140-d168}$ (mg/L) Median [90% CI]
1000 mg Q4W IV	75010 [47410-115200]	205.5 [129.9-315.6]	111.1 [35.69-223.4]	418.8 [281.2-633.3]	-	-	-
120 mg QW SC	20510 [12920-32450]	56.19 [35.40-88.90]	55.55 [34.30-87.57]	65.50 [39.93-107.9]	-	-	-
300 mg Q4W IV	17000 [10580-26890]	46.57 [28.99-73.68]	16.89 [0.2157-44.71]	107.9 [69.63-173.7]	-	-	-
IV to SC – 2 week gap	19690 [12010-30600]	53.95 [32.90-83.83]	18.12 [0.1714-44.70]	108.1 [69.08-171.5]	58.00 [36.24-88.04]	100.7 [65.50-155.3]	41.29 [18.20-71.75]
IV to SC – 3 week gap	19060 [11520-30810]	52.22 [31.55-84.40]	17.68 [0.1730-46.71]	107.7 [70.56-171.5]	51.30 [31.35-84.34]	100.9 [67.18-154.9]	27.17 [5.313-60.30]
IV to SC – 4 week gap	18460 [11240-28600]	50.59 [30.78-78.35]	18.02 [0.1651-44.78]	106.7 [70.41-166.9]	49.02 [29.20-77.43]	99.96 [66.58-150.6]	18.02 [0.1655-45.85]
SC to IV – 2 week gap	17730 [10960-29520]	48.58 [30.02-80.88]	18.27 [0.1467-54.30]	134.4 [86.84-204.1]	72.68 [46.89-113.6]	134.4 [86.84-204.1]	44.98 [19.52-82.79]
SC to IV – 3 week gap	17580 [10400-27930]	48.18 [28.50-76.52]	18.45 [0.1578-51.61]	119.9 [77.62-182.7]	60.66 [35.87-95.70]	119.9 [77.62-182.7]	31.68 [7.320-64.44]
SC to IV – 4 week gap	17520 [10480-28960]	48.00 [28.71-79.33]	18.09 [0.1879-52.55]	111.0 [70.27-170.9]	43.17 [20.28-78.56]	110.6 [70.02-170.2]	21.08 [0.4826-54.76]

$AUC_{,d0-d365}$=AUC over 365 days; $C_{ave,d0-d365}$=Average concentration over 365 days; $C_{ave,d140-d168}$=Average concentration from day 140 to day 168; $C_{max,d140-d168}$=Maximum concentration from day 140 to day 168; $C_{max,ss}$=Maximum concentration at steady state; $C_{min,d140-d168}$=Minimum concentration from day 140 to day 168; $C_{min,ss}$=Minimum concentration at steady state; IV=Intravenous; QW=Once per week; Q4W=Once every 4 weeks; SC=Subcutaneous

Special populations

The MAH has not conducted specific studies in special populations like patients with renal impairment or hepatic impairment. The covariate effects were evaluated by PPK modelling and simulations.

The impact of the selected covariates in the final PPK model on area under the concentration-time curve at steady state (AUC_{ss}) and maximum concentration at steady state ($C_{max,ss}$) based on a univariate assessment are presented as tornado plots in Figure *7* and Figure *8*, respectively. Overall, no covariate showed a substantial impact on AUC_{ss} and $C_{max,ss}$ with the covariate effect being no greater than 23%. Weight had the most pronounced impact with a decrease in AUC_{ss} of 22.9% and a decrease in $C_{max,ss}$ of 21.31% for the 95th percentile of the weight distribution (107 kg) compared with reference subject weighing 68 kg. The pivotal TULIP SC study was considered to include a presentive weight range of SLE patients (median 70.4 kg, min.-max. 43.9-144 kg).

Figure 7: Impact of covariates on anifrolumab AUC at steady state.

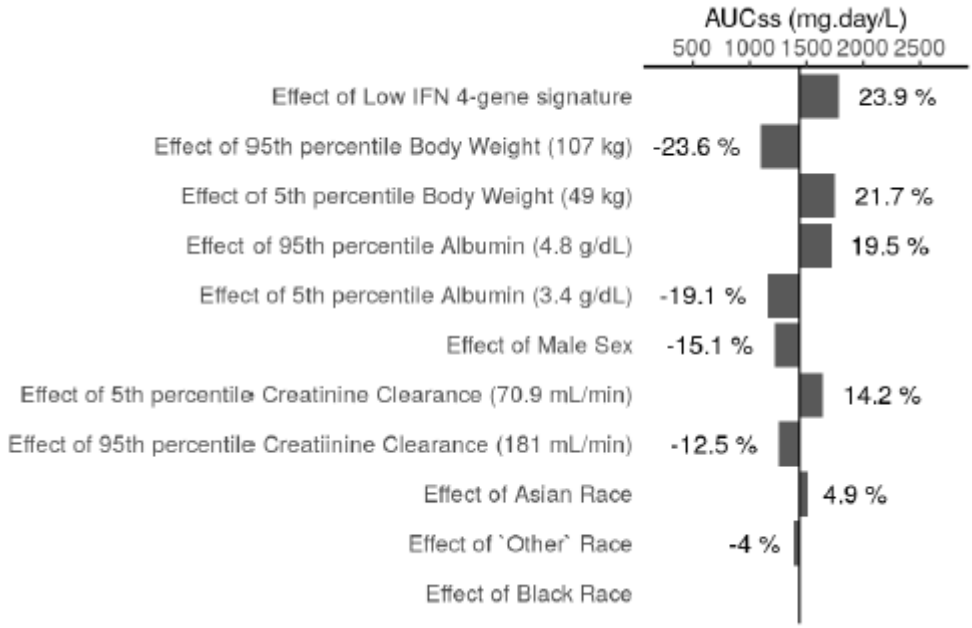
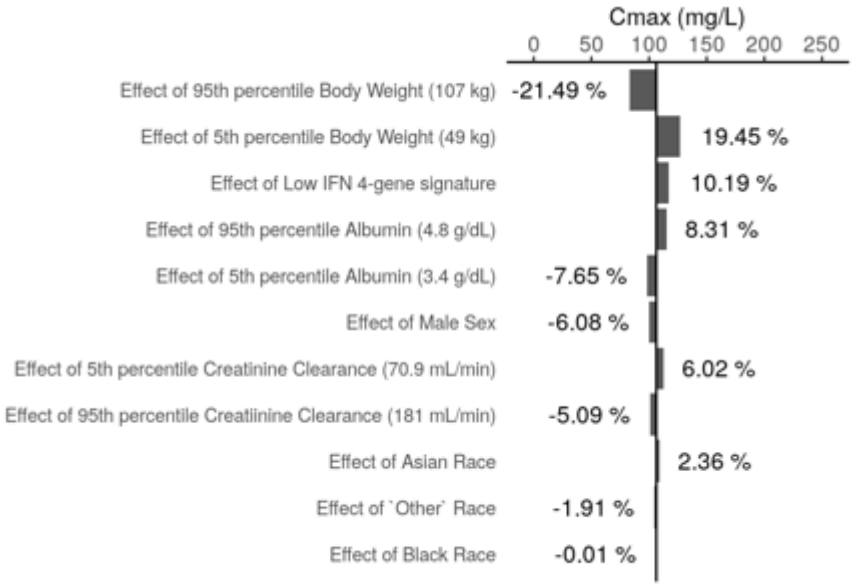


Figure 8: Impact of covariates on anifrolumab C_{max} at steady state.



Reference: 106.92 mg/L. Bars represent the relative change (%) from the reference. Reference is 68 kg female with presence of B4SIGENE, 4.1 g/dL albumin, 113 mL/min creatinine clearance, and white race. Dosing is 300 mg IV Q4W.

Effect of ADA on PK

In the TULIP SC study, geometric mean anifrolumab serum concentrations (C_{trough}) were lower in ADA-positive patients (N=11) compared to ADA-negative patients (N=97). Mean anifrolumab serum concentration time profiles of ADA-positive patients were generally below the median of those in ADA-negative patients, but the concentrations fell within the range of the concentrations seen in the ADA-negative group.

ADA status was not formally evaluated as a covariate in the PPK analysis because only 3.3% (N=39) of subjects in the dataset were ADA positive at any time.

Pharmacokinetic interaction studies

Clinical drug-drug interaction studies have not been conducted with anifrolumab due to low interaction potential own to its elimination pathway via proteolytic enzymes and target mediated degradation.

Concomitant medication were tested as covariate in the PPK analyses. The following medication reported to be in use at baseline in the TULIP SC study were tested: antimalarial drugs, azathioprine, methotrexate, mycophenolate, ACE inhibitors, HMG inhibitors and NSAIDs. The PPK modelling showed that this medication had no meaningful impact on steady state AUC and C_{max} of anifrolumab.

2.6.2.2. Pharmacodynamics

Mechanism of action

Anifrolumab is a human IgG1κ mAb that inhibits binding of type I IFNs to IFNAR1. By blocking type 1 IFN signaling, anifrolumab reduces multiple innate and adaptive downstream inflammatory pathways.

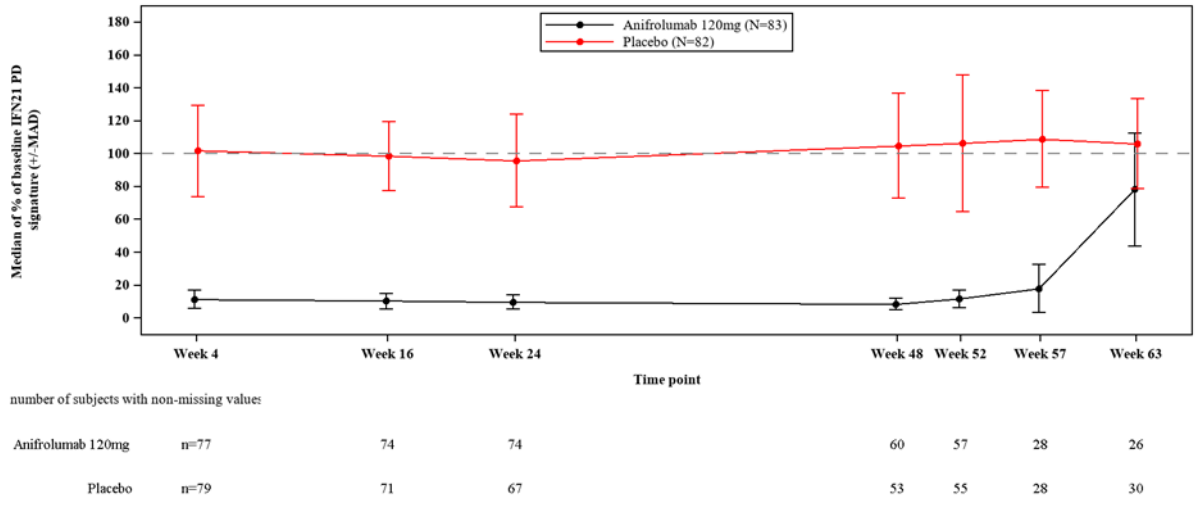
Primary and Secondary pharmacology

The PD effects of SC anifrolumab was investigated as part of the phase III study (TULIP SC). Type I IFN-inducible signature in whole blood was assessed by a 21-gene assay to measure the expression of type I IFN-inducible genes in the whole blood. The DCO for PD assessments was 28 May 2024. The analysis were performed using the FAS (n=220).

Anifrolumab 120 mg SC QW treatment resulted in rapid neutralization of the type I IFN gene signature by Week 4 and attained ≥ 88% median neutralization, which was sustained through double-blind treatment (Week 52), in patients with high type I IFN PD signature (Figure *9*).

No OLE data were included in Figure *9*, and thus, Weeks 57 and 63 reflected the post-treatment follow-up period for patients who did not enter the OLE. At these timepoints, type I IFN PD signature began to return to the baseline levels in the anifrolumab group.

Figure 9: Type I IFN PD Signature as Percent of Baseline Type I IFN PD Signature Among Patients with a High IFN Test Result Over Time, Line Plot (FAS)



Change in type I IFN PD signature expression over time is shown as percent of baseline signature levels, which are set to 100%.

Median levels of type I IFN PD signature for each treatment group are derived based on individual subjects 100 (((baseline-Week X)/baseline)*100) for the 21 genes.

2.6.3. Discussion on clinical pharmacology

Bioanalytical methods

All bioanalytical methods were the same as in the initial MAA.

Pharmacokinetics

The pharmacokinetics of anifrolumab following subcutaneous administration has been well characterised in healthy volunteers and in the target population, SLE patients. Two clinical studies were conducted with the applied dose of 120 mg. The pivotal phase 3 TULIP SC study in target population, SLE patients was conducted with SC anifrolumab administered using a prefilled syringe, and a relative bioavailability study in healthy volunteers was conducted to bridge exposures between an autoinjector and the prefilled syringe. Subcutaneous absorption of anifrolumab is slow with peak concentrations reached within approximately 5 days after SC injection by both devices.

Pharmacokinetics of anifrolumab following SC injection of 120 mg by an autoinjector (AI) was compared to SC injection by prefilled syringe (APFS) in healthy volunteers. The AI batch had lower total protein content compared to the APFS batch producing in average 6% difference in the total dose of anifrolumab (estimated doses 113.6 mg/0.8 ml vs. 120.8 mg/0.8 ml, respectively). However, although the point estimates for the AI vs. APFS GLSM ratios of the primary PK parameters were below unity, the 90% CIs for the GLSM ratios imply that bioequivalence is not compromised by the difference in total protein content, thus, this issue was not pursued further by the CHMP. Furthermore, based on the provided PK data, non-linear PK of anifrolumab seemed to compromise calculation of terminal elimination phase related PK parameters and accurate estimation of AUC_{inf}, nevertheless, AUC_{last} showed comparable results. Despite the observed deficiencies, the study was considered sufficiently robust for comparison of the two devices. The 90% CIs for the geometric mean ratios of AI vs. APSF for primary PK parameters showed bioequivalence of the two devices. The MAH has not provided comparison of exposures between the injection sites for each AI and APFS, separately. Among the three injection sites, SC injections with AI into thigh and abdomen produced comparable mean systemic exposures (AUC_{last}) of anifrolumab while SC injection into upper arm produced approximately 25 % to 32 % lower exposure compared to the other two injection sites. The mean exposures following SC injections by APFS into thigh were in average 32 % to 26 % higher than injection into abdomen and upper arm, respectively. Comparison of the range of the exposures between the injection sites indicates overall lower exposures for SC injections to upper arm for both devices compared to the other injection sites. In the SmPC section 4.2, self-administered subcutaneous injection of anifrolumab is advised to be injected into thigh or abdomen. Healthcare professional or caregiver could administer the injection also in the upper arm. Thus, although slightly lower range of exposures could be observed for SC injections in the upper arm compared to the other injection sites, the overall impact on drug exposures were not considered remarkable if an injection is occasionally administered into the upper arm by a healthcare professional or a caregiver. Overall, the range of exposures overlapped between the injection sites and the between-subject variabilities were high for both devices, 38-74% for APFS and 27-47% for AI. Therefore, all the three injection sites were considered acceptable to the CHMP. The provided clinical data was found adequate to support the instructions for administration of subcutaneous injection in the SmPC section 4.2.

Population PK modelling and simulations

PK of anifrolumab following SC and IV administration was evaluated using PPK analysis. The final pooled dataset model was a two-compartment model with two parallel clearances (first-order and Michaelis-Menten) from the central compartment. Absorption following SC administration was described with estimated bioavailability (F1) and absorption rate constant (Ka). Inter-subject variability (IIV) was characterised on linear clearance (CL), central volume (Vc), peripheral volume (Vp), the maximum velocity of Michaelis-Menten kinetics clearance process (Vmax), and absorption rate constant. Residual unexplained variability was described using proportional error model (additive on log scale). Statistically significant covariates that were retained in the final model were as follows: on CL: baseline body weight, albumin level, creatinine clearance, 4-gene type 1 IFN gene signature status, and sex; on Vc: baseline body weight; on Vmax: Race. The non-parametric distribution of the parameter estimates (bootstrap) showed a good agreement with the NONMEM estimates and diagnostic plots indicated no major problems with model performance. The estimates of CL (0.146 L/day), Vc (3.48 L), and Vp (1.72 L) were close to the values estimated previously using a dataset with only IV data. The final PPK model was considered adequate to evaluate clinical relevance of covariates on exposure to anifrolumab and to simulate PK profiles and exposure measures of untested clinical scenarios (e.g., effect of missed dose on exposure).

Simulations using the PPK model showed that at steady state the distribution of average concentration ($C_{ave,ss}$) is overlapping for the regimens 120 mg QW SC and 300 mg Q4W IV, whereas maximum concentrations ($C_{max,ss}$) are lower and minimum concentrations ($C_{min,ss}$) are higher for the 120 mg QW SC regimen compared with 300 mg Q4W IV. Importantly, $C_{min,ss}$ of 120 mg QW SC is less than that of 1000 mg Q4W IV regimen, which was previously evaluated in a phase 2 study (refer to the initial MAA of Saphnelo).

Simulations were performed to assess missed doses during weekly SC dosing (Figure *5* and **Table *7***). A patient may remember to take their dose some days after the expected dose day. Simulations indicate that in this case, the patient can take the dose as soon as they remember and resume dosing on the usual day of administration providing that a minimum interval of 3 days is maintained between SC injections.

Simulations were also performed to assess transition from one route of administration to the other (Figure *6* and Table *8*). Based on the simulated concentration-time profiles and exposure metrics, the following instructions were derived for transition from one route of administration to the other:

- Transition from IV to SC administration: The first SC injection should be administered approximately 2 weeks after the last IV dose.
- Transition from SC to IV administration: The first IV infusion should be administered approximately 3 to 4 weeks after the last SC dose.

Instructions regarding missed SC doses and transitioning between routes of administration are included in section 4.2 of the SmPC.

Special populations

Dedicated clinical studies in special populations like patients with renal impairment or hepatic impairment have not been conducted, but covariate effects were evaluated by PPK approach.

The PPK model indicated that SLE patients with mild to moderate decrease in estimated glomerular filtration rate (eGFR) had comparable CL for anifrolumab after SC administration to patients with normal eGFR values. Likewise, baseline hepatic function tests (liver enzymes, total bilirubin) had no statistically significant effect on CL of anifrolumab. These results were consistent with the observations for SLE patients with IV administration only. No dose adjustment is considered necessary for patients with renal

or hepatic impairment. The clinical studies did not include patients with severe renal impairment or with end-stage renal disease (eGFR <30 mL/min/1.73 m^2).

PPK modelling and simulations indicate that body weight is the most important covariate affecting exposure and causing interindividual variability. There was a statistically significant difference in weight-adjusted CL between females and males, with males expected to have 15.1% lower AUC than females. The observation is not clinically relevant (see Figure *7* and Figure *8*) and dose adjustment based on weight or other intrinsic and extrinsic factors is not required. Presence of baseline type I IFN 4-gene signature was observed to decrease AUC by less than 20% in PPK analyses. Disease status had no effect on exposure of anifrolumab with SLE patients showing similar PK compared to healthy volunteers. A slightly higher clearance in male subjects compared to females was observed in the PPK analyses with SC administration, but this not considered as clinically relevant.

Race was a statistically significant covariate for V_{max} but did not impact the CL of anifrolumab. Similar steady state AUC and C_{max} were observed across regions and ethnicity. The body weight adjusted CL in the Asian population was similar to the non-Asian population.

Age (median: 40.0 years, range: 18 to 70 years) did not impact the CL of anifrolumab in the PPK analyses. Of the patients with SLE exposed to anifrolumab in clinical studies, 33/952 (3.466%) participants were ≥ 65 years of age.

Overall, age, race, ethnicity, region, gender, and baseline type I IFN 4-gene signature status had no clinically relevant impact on exposure of anifrolumab. In the SmPC sections 4.2 and 5.2, the proposed information for renal impairment and hepatic impairment, and the information related covariates (age, race, ethnicity, region, gender, IFN status, body weight) is similar to the IV anifrolumab. This was acceptable to the CHMP.

The number of ADA positive patients was low in the clinical studies with SC administration, thus, no definitive conclusions on effect of ADA on PK of anifrolumab could be made. Exploratory graphical analyses indicated that ADA are not expected to have clinically relevant effect on exposure.

PK drug interactions

Commonly used concomitant medications at baseline were tested as covariates in the PPK analysis, none of them was included in the anifrolumab PPK model. The method was not considered robust: changes in concomitant medications after baseline and in their posology were not taken into account. The issue was not pursued because anifrolumab is a large protein and its kinetics is not expected to be affected by small molecule drugs.

The SmPC sections 4.5 and 5.2 concerning drug interactions is the same as for IV anifrolumab, which was acceptable to the CHMP. Particularly, as anifrolumab could suppress levels of some cytokines, the SmPC includes warning for concomitant use of narrow therapeutic medicines that are CYP-substrates.

Pharmacodynamics

The results using the Type I IFN PD signature demonstrated that SC anifrolumab at 120 mg dose QW suppressed the expression of Type I IFN-inducible genes. The effect was rapid and sustainable throughout the 52 weeks treatment. The level of suppression was comparable to that seen with 300 mg IV anifrolumab in pivotal 04 and 05 studies, as well as at 300 mg and 1000 mg doses in the 1013 study. Therefore, the proposal in section 5.1 Pharmacodynamic effects that is aligned with the approved text with IV anifrolumab is acceptable (see separate attachment for detailed SmPC comments).

No PK/PD and exposure-response models were provided to support the current application, this was acceptable to the CHMP.

2.6.4. Conclusions on clinical pharmacology

The pharmacokinetics of anifrolumab following subcutaneous administration has been sufficiently characterised in healthy volunteers and in the target population, SLE patients, in the two clinical studies and by the PPK analyses.

In terms of pharmacodynamics, the results using the Type I IFN signature demonstrated that SC anifrolumab at 120 mg dose QW suppressed the expression of Type I IFN-inducible genes. The effect was rapid and sustainable throughout the 52 weeks treatment. The level of suppression was comparable to that seen with 300 mg IV anifrolumab in pivotal 04 and 05 studies, as well as at 300 mg and 1000 mg doses in the 1013 study.

2.6.5. Clinical efficacy

The anifrolumab SC clinical programme included a pivotal global, multicenter, randomized, double-blind (DB), placebo-controlled, Phase III study (TULIP SC). TULIP SC was an ongoing study during the procedure evaluating the safety and efficacy of anifrolumab SC administered by APFS in adults with moderate to severe SLE despite receiving standard of care (Table *8*).

The efficacy assessments are based on an interim analysis (IA) of the first 220 randomized of 360 planned patients in TULIP SC who completed the 52-week DB treatment period or withdrew early from the study. The study has continued as planned as DB after the data-cut-off (DCO) for the IA (23 July 2024).

Table 8: Summary of TULIP SC clinical study

Study number (Acronym) Sponsor EudraCT number NCT Number	Study title	Primary objective	Primary endpoint	Treatments, doses, regimen, route of administration, and number of randomized patients	Patient population	Duration
D3465C00001 (TULIP SC) AstraZeneca EudraCT No: 2020-004529-22 NCT No: 2022-502396-28	A Multicentre, Randomised, Double-blind, Placebo-controlled, Phase 3 Study Evaluating the Efficacy and Safety of Subcutaneous Anifrolumab in Adult Patients with Systemic Lupus Erythematosus	To compare efficacy of anifrolumab with placebo on overall disease activity in patients with SLE.	BICLA response at Week 52	Anifrolumab 120 mg SC QW N = 109 Placebo SC QW N = 111 IA based on first 220 randomized/360 planned patients to complete 52-week DB treatment period or withdraw early from the study Total randomized patients at the time of the IA DCO (23 July 2024) (N = 346) Total randomized patients at the time of the IA CDL (13 Sep 2024) (N = 367)	Adult patients 18 to 70 years of age with moderate to severe SLE	52-week DB, placebo-controlled treatment period (ongoing) Additional 52-week OLE period, with anifrolumab 12-week follow-up period after last dose of IP

2.6.5.1. Dose response study(ies)

No dose-response studies were conducted. The dose of 120 mg QW for TULIP SC study was selected to provide comparable and noninferior (i.e., at least as high as) median Cave to 300 mg IV in a single injection and noninferior PD suppression to that of 300 mg IV. In addition, the Cave of 120 mg SC QW over 52 weeks had minimal overlap with that of 1000 mg IV, which was evaluated for up to a year in patients with SLE in the Phase IIb study 1013. Further, the simulated 120 mg SC QW steady-state Cmax remained below the steady-state Cmax observed for the approved anifrolumab IV dosing regimen.

2.6.5.2. Main study

Title of study

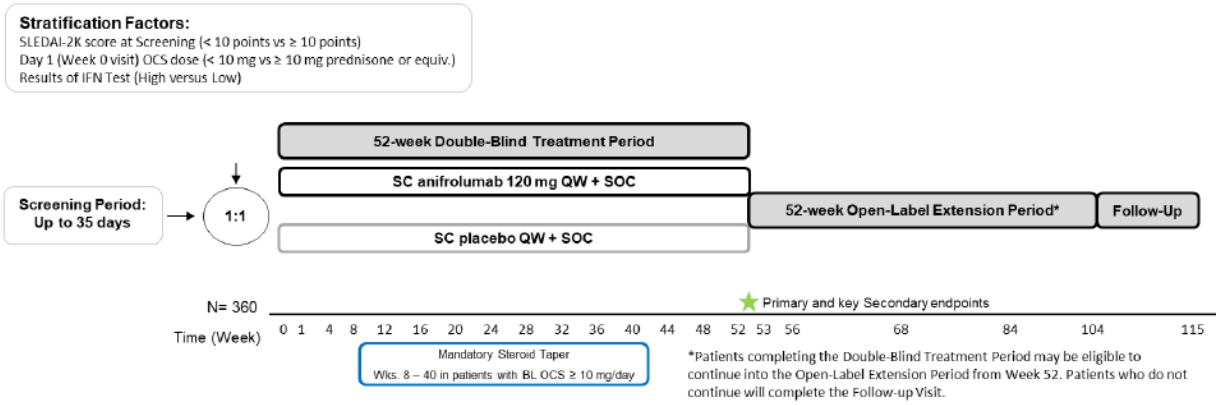
A Multicentre, Randomised, Double-blind, Placebo-controlled, Phase 3 Study Evaluating the Efficacy and Safety of Subcutaneous Anifrolumab in Adult Patients with Systemic Lupus Erythematosus.

Methods

The Phase III study TULIP SC comprises a 52-week DB treatment period, followed by a 52-week OLE period, and 12-week safety follow-up period (Figure *10*). The DB portion of the study was designed to evaluate the efficacy, safety, and tolerability of anifrolumab 120 mg SC QW added to standard of care compared with placebo SC QW added to standard to care in adult patients with moderate to severe SLE.

The OLE was primarily designed to collect data on longer-term safety and tolerability.

Figure 10: TULIP SC study



BL, baseline; SOC, standard of care

- **Study Participants**

The key eligibility criteria are described below. The patients were males or females aged 18 to 70 years of age.

Key inclusion criteria

- Diagnosis of paediatric or adult SLE according to the ACR 1997 revised criteria for ≥ 24 weeks prior to signing the ICF
- Autoantibody-positive at Screening for at least one of: ANA titer ≥ 1:80, anti-dsDNA, anti-Smith
- Receiving at least one of the following standard therapy regimens

- Oral prednisone (or equivalent) monotherapy minimum daily dose ≥ 7.5 mg/day for at least 6 weeks prior to signing ICF, stable for at least 2 weeks before randomization, maximum daily dose ≤ 40 mg/day
- Antimalarials and/or immunosuppressant(s) with or without OCS with start date ≥ 12 weeks and stable for ≥ 8 weeks prior to signing ICF
  - Permitted medications include: antimalarials, azathioprine, mycophenolate mofetil/mycophenolic acid, methotrexate, mizoribine, cyclosporine and tacrolimus (Note: For safety reasons, combinations of mycophenolate mofetil or mycophenolic acid or mycophenolate sodium, azathioprine, methotrexate, tacrolimus or cyclosporine are not permitted. Combination of mizoribine should be discussed with the medical monitor.)
  - Maximum allowed daily dose: Azathioprine: ≤ 200 mg/day; Mycophenolate mofetil ≤ 2 g/day or mycophenolic acid ≤ 1.44 g/day; Oral, SC, or intramuscular (IM) methotrexate ≤ 25 mg/week; Mizoribine ≤ 150 mg/day; Cyclosporine ≤ 3 mg/kg/day; Tacrolimus ≤ 0.2 mg/kg/day

- Total SLEDAI-2K ≥ 6 points, with ≥ 4 points coming from clinical components ("Clinical" SLEDAI-2K) at Screening AND clinical SLEDAI of ≥ 4 points at Day 1 (randomisation)
- BILAG-2004 score of severe disease activity in at least 1 organ system [BILAG level A] or moderate disease activity in at least 2 organ systems [BILAG level B])
- PGA score ≥ 1.0 on a 0 to 3 VAS at Screening

<u>Key exclusion criteria</u>

- History or current diagnosis of a clinically significant non-SLE related vasculitis syndrome
- History or evidence of suicidal ideation or behavior
- Active severe or unstable neuropsychiatric SLE
- Active severe SLE-driven renal disease where protocol-specified standard therapy is considered insufficient
- Diagnosis (within 1 year of signing the ICF) of mixed connective tissue disease or any history of overlap syndromes of SLE and systemic sclerosis
- History of, or current diagnosis of, catastrophic antiphospholipid syndrome (APS) within 1 year prior to signing the ICF. Patients with other degrees of APS adequately controlled by anticoagulants or aspirin for at least 12 weeks can be recruited to the study
- History of, or current, inflammatory joint or skin disease other than SLE that, in the opinion of the investigator, could interfere with the inflammatory arthritis or skin assessments and confound the disease activity assessments
- History of any non-SLE disease that has required treatment with oral or parenteral corticosteroids for more than a total of 2 weeks within the last 24 weeks prior to signing the ICF
- History of recurrent infection requiring hospitalization and IV antibiotics
- Known history of a primary immunodeficiency, splenectomy, or any underlying condition that predisposes the patient to infection

- Active hepatitis B infection, as confirmed by central laboratory, for: Hepatitis B surface antigen (HBsAg); or Hepatitis B core antibody (HBcAb) and hepatitis B virus (HBV) DNA detected above the lower limit of quantitation (LLOQ)
- Active hepatitis C infection (defined as positive hepatitis C virus [HCV] antibody and detectable HCV ribonucleotide (RNA)
- Any severe case of herpes zoster at any time prior to Day 1 or any herpes zoster infection that has not completely resolved within 12 weeks prior to signing the ICF
- Any clinical cytomegalovirus (CMV) or Epstein-Barr virus infection that has not completely resolved within 12 weeks prior to signing the ICF
- Opportunistic infection requiring hospitalisation or IV antimicrobial treatment within 3 years of randomization
- Clinically significant chronic infection (ie, osteomyelitis, bronchiectasis, etc) within 8 weeks prior to signing the ICF (chronic nail infections are allowed); any infection requiring hospitalisation or treatment with IV anti-infectives not completed at least 4 weeks prior to signing the ICF
- History of cancer, apart from squamous or basal cell carcinoma with documented success of curative therapy or cervical cancer in situ treated with apparent success with curative therapy
- Receipt of any commercially available biologic agent within 5 half-lives prior to signing of the ICF
- Regular use of > 1 NSAID within 2 weeks prior to Week 0 (Day 1); OR receipt of fluctuating doses of a NSAID within 2 weeks prior to Week 0 (Day 1)
- Receipt of any commercially available Janus kinase (JAK) inhibitor (e.g., tofacitinib or baricitinib) ≤ 12 weeks or Bruton's tyrosine kinase (BTK) inhibitor (e.g., ibrutinib, acalabrutinib, zanubrutinib) ≤ 24 weeks prior to signing the ICF

- **Treatments**

During the 52-week DB period, patients received anifrolumab 120 mg SC QW added to SoC or placebo SC QW added to SoC in a 1 ml APFS with 0.8 ml volume. During Weeks 8-40, patients with a baseline OCS ≥10 mg/day were required to taper their OCS dose to ≤7.5 mg/day, unless there was worsening of disease activity. Non-protocol permitted changes to SoC medications for SLE were only allowed if necessary to treat an AE or increased disease activity. Further, patients were instructed not to start any new medications/regimens or make changes to any existing medications/regimens, including over-the-counter products, without first consulting the Investigator.

During the 52-week OLE treatment period in the study, the patients received anifrolumab 120 mg QW. Permitted SoC medications included OCS, antimalarials, and immunosuppressants, but the maximally permitted doses were not to be exceeded.

- **Objectives**

The primary objective of the study was to compare efficacy of anifrolumab with placebo on overall disease activity in patients with moderate-to severe SLE despite receiving standard therapy.

Key secondary objectives were:

- To compare the efficacy of anifrolumab with placebo on improvement in overall disease activity and low (or reduced) OCS use.
- To compare the efficacy of anifrolumab with placebo on the onset of a sustained reduction in disease activity.

- To compare the efficacy of anifrolumab with placebo on the onset of first flare.

Other secondary objectives were:

- To compare the efficacy of anifrolumab with placebo on maintained reduction in OCS use among patients with moderate or high OCS use at baseline.
- To compare the efficacy of anifrolumab with placebo on the reduction in moderate to severe flares.
- To compare the efficacy of anifrolumab with placebo on an additional measure of overall disease activity.

The statistical analyses were based on demonstrating superiority of anifrolumab against placebo.

- **Outcomes/endpoints**

The primary endpoint was the proportion of patients who are BICLA responders at Week 52.

The key instruments used for the assessment of disease activity including the BICLA response were BILAG-2004, SLEDAI-2K and PGA.

The **BILAG-2004** is a translational index with 9 organ systems (General, Mucocutaneous, Neuropsychiatric, Musculoskeletal, Cardiorespiratory, Gastrointestinal, Ophthalmic, Renal and Haematology) that is able to capture changing severity of clinical manifestations. It has ordinal scales by design, where it records disease activity across the different organ systems at a glance by comparing the immediate past 4 weeks to the 4 weeks preceding them. BILAG scoring is based on the principle of physicians' Intention-to-Treat and categorises disease activity into 5 different levels from A to E:

- Grade A represents very active disease requiring immunosuppressive drugs and/or a prednisone dose of > 20 mg/day or equivalent;
- Grade B represents moderate disease activity requiring a lower dose of corticosteroids (≤ 20 mg prednisone/day), topical steroids, topical immunosuppressives, antimalarials, or NSAID;
- Grade C indicates mild stable disease;
- Grade D implies no disease activity but the system has previously been affected;
- Grade E indicates no current or previous disease activity.

The **SLEDAI-2K** disease activity index consists of a list of organ manifestations, each with a definition. A certified investigator or designated physician will complete the SLEDAI-2K assessment and decide whether each manifestation is "present" or "absent" in the last 4 weeks. The assessment also includes the collection of blood and urine for assessment of the laboratory categories of the SLEDAI-2K.

The SLEDAI-2K assessment consists of 24 lupus-related items in which signs, symptoms, and laboratory tests for each of 9 organ systems are given a weighted score. Items present in the last 28 days are scored and summed to create a total score. For example, items in the renal organ system are given a weight of 4 points each. The SLEDAI-2K score range is 0 to 105 points with 0 indicating inactive disease.

The "Clinical" SLEDAI-2K score is the SLEDAI-2K assessment score without the inclusion of points attributable to any urine or laboratory results including immunologic measures. Its use may permit earlier clinical decisions to be made (such as OCS reduction or treating increased disease activity) without waiting for immunologic measures (including anti-dsDNA antibodies and C3, C4, and CH50 complement levels). However, in any circumstance where the "Clinical" SLEDAI-2K score is used, sites must subsequently update the SLEDAI-2K assessment when laboratory data become available.

For any joint to count as an "active joint", both tenderness and swelling present in that joint was a requirement.

The **PGA** represents the physician's overall assessment of average SLE disease severity on a visual analog scale (VAS) scale with 0 (no disease) to 3 (severe) disease activity over the last 4 weeks.

A BICLA responder was defined as a patient meeting all of the following criteria:

- Reduction of all baseline BILAG-2004 A to B/C/D and baseline BILAG-2004 B to C/D, and no BILAG-2004 worsening in other organ systems, as defined by ≥ 1 new BILAG-2004 A or ≥ 2 new BILAG-2004 B.
- No worsening from baseline in SLEDAI-2K, where worsening is defined as an increase from baseline of > 0 points in SLEDAI-2K.
- No worsening from baseline in patients' lupus disease activity, where worsening is defined by an increase ≥ 0.30 points on a 3-point PGA VAS.

Key secondary endpoints:

BICLA response at Week 52 with maintained low (or reduced) use of OCS

The proportion of patients with BICLA response at Week 52 who also have maintained low (or reduced) use of OCS in the anifrolumab treatment group was compared to that in the placebo group. To be a responder, a patient was to be a BICLA responder and had maintained low (reduced) OCS use defined as follows:

- If baseline OCS ≥ 10 mg/day an OCS dose of ≤ 7.5 mg/day prednisone or equivalent must be achieved by Week 40 and an OCS dose ≤ 7.5 mg/day prednisone or equivalent must be maintained from Week 40 to Week 52.
- If baseline OCS < 10 mg/day, OCS dose at Week 40 must be less than or equal to OCS dose at baseline, with no increase from Week 40 OCS dose between Week 40 and Week 52.

Time to BICLA response sustained through Week 52.

Time to BICLA response sustained through Week 52 was defined as the date of first BICLA response in which all subsequent BICLA assessments result in a BICLA response sustained up to, and including, Week 52.

Time to flare through Week 52

Time to flare was defined as the time from the first dose of study intervention during the DB treatment period to the first flare over the 52-week treatment period. A flare was defined as either 1 or more new BILAG-2004 A or 2 or more new BILAG-2004 B items compared to the previous visit.

Other secondary endpoints:

Proportion of patients who achieve an OCS dose ≤ 7.5 mg/day at Week 40, which is maintained through Week 52 in the subgroup of patients with baseline OCS ≥ 10 mg/day

Maintained OCS reduction was defined by meeting all of the following criteria:

- Achieve an OCS dose ≤ 7.5 mg/day prednisone or equivalent by Week 40
- Maintain an OCS dose ≤ 7.5 mg/day prednisone or equivalent from Week 40 to Week 52

Annualised flare rate through Week 52

The flare rate in the anifrolumab treatment group was compared with the flare rate in the placebo group. A flare was defined as either 1 or more new BILAG 2004 A or 2 or more new BILAG-2004 B items compared to the previous visit.

Proportion of patients achieving an SRI(4) response at Week 52

The difference in response between anifrolumab and placebo in SRI(4) at Week 52 was analysed using the same method as for the primary analysis. To be an SRI(4) responder, the patient had to meet all of the following criteria:

- Reduction from baseline of ≥ 4 points in the SLEDAI-2K
- SLEDAI-2K will be derived as the sum of the scores for all items. A ≥ 4 points reduction is reached if the change from baseline is ≤ 4
- No new organ systems affected as defined by 1 or more BILAG-2004 A or 2 or more BILAG-2004 B items compared to baseline using BILAG-2004
- No worsening from baseline in the patients' lupus disease activity, where worsening is defined by an increase ≥ 0.30 points on a 3-point PGA VAS

- **Sample size**

The application is based on a pre-specified IA, performed once the first 220 randomised patients of the total planned 360 patients completed the 52-week DB treatment period or withdrew early from the study. The study was planned to continue regardless of the IA results and is ongoing, with a CDL planned after all 367 randomised patients complete the 52-week placebo-controlled DB treatment period or withdraw early from the study.

The sample size of approximately 360 patients for the final analyses was determined based on a fixed study design, powered to detect a clinically meaningful difference of at least 10% in the proportion of BICLA responders at Week 52 comparing anifrolumab to placebo (primary endpoint). For the primary endpoint, the α level for the IA was determined based on the Pocock spending function. Based on 220 patients eligible for the IA and 367 patients confirmed randomized at completion of recruitment, the information fraction is 0.60 (220/367), resulting in α_IA of 3.54% and α_Final Analysis of 2.57%.

- **Randomisation and Blinding (masking)**

All patients were centrally assigned to randomized study intervention using an Interactive Response Technology/Randomisation and Trial Supply Management (IRT/RTSM) system. Randomization was stratified by SLEDAI-2K score at screening (< 10 vs ≥ 10 points), OCS use on Day 1 (< 10 mg vs ≥ 10 mg prednisone or equivalent per day), and type I IFN gene signature test result (high vs low).

This study design included assessor, investigator, and patient blinding. In the event of a medical emergency where unblinding was considered necessary for the safety of the patient due to possible impact on-treatment decisions, the investigator could unblind an individual patient's study intervention allocation after consulting with the study medical monitor.

- **Statistical methods**

The primary endpoint estimand was designed to answer a clinically relevant question, comparing the proportion of patients able to both complete the study treatment and achieve a clinically meaningful treatment response without further medication being required.

For patients who had intercurrent event (ICE) due to restricted medication (RM) use, premature end of treatment (PEOT), and/or death, the BICLA response after the ICE was set to non-response as per the

composite strategy. For patients who had ICE due to noncompliance (NC), response after NC was imputed using the hypothetical strategy.

The same estimand strategy was implemented for BICLA response at Week 52 with maintained low (or reduced) use of OCS.

Time to BICLA response sustained through Week 52 was defined as the date of first BICLA response in which all subsequent BICLA assessments result in a BICLA response sustained up to, and including, Week 52. The definition of BICLA response was the same as for the primary endpoint. A composite handling strategy was used for intercurrent events of study intervention discontinuation, restricted medication use, and death, resulting in non-response from the time of the event. Missing data due to study withdrawal or lost to follow up was handled by censoring the patient. Patients who did not achieve BICLA response by Week 52 or whose response was not sustained up to Week 52 was censored at Week 52.

Time to flare was defined as the time from the first dose of study intervention during the DB treatment period to the first flare over the 52-week treatment period. A flare was defined as either 1 or more new BILAG-2004 A or 2 or more new BILAG-2004 B items compared to the previous visit. A composite handling strategy was used for the intercurrent events of restricted medication use, study intervention discontinuation, and death, resulting in a flare on the date of the event. Missing data due to study withdrawal or lost to follow up was handled by censoring the patient on the date of the last assessment. Patients who did not experience an intercurrent event or a flare by Week 52 were censored at Week 52; unless the Week 52 BILAG assessment was not performed, then the date of last available BILAG assessment prior to Week 52 was used as the censoring date.

All efficacy analyses were conducted using the FAS. Patients who withdrew consent to participate in the study are included up to the date of their study termination. For the IA, the FAS consisted of the first 220 randomized patients who completed the Week 52 DB treatment period or withdrew early from the study.

The summary measure for the primary endpoint was the difference in the proportion of subjects achieving BICLA response at Week 52 using the FAS, comparing the anifrolumab to the placebo groups. Multiple imputation method was used for missing value.

The null hypothesis was that the proportion of subjects achieving BICLA response on anifrolumab is equal to that on placebo. The alternative hypothesis is that the proportion of subjects achieving BICLA response on anifrolumab is not equal to that on placebo, i.e.,

H0: difference in proportion achieving BICLA response (anifrolumab vs placebo) = 0

Ha: difference in proportion achieving BICLA response (anifrolumab vs placebo) ≠ 0.

The primary endpoint, BICLA response at Week 52, was analysed using a stratified CMH method.

The application was based on a pre-specified IA of TULIP SC, performed once the first 220 randomised patients of the total planned 360 patients completed the 52-week DB treatment period or withdrew early from the study. The study was planned to continue regardless of the IA results and was ongoing during the procedure, with a CDL planned after all 367 randomized patients complete the 52-week placebo-controlled DB treatment period or withdraw early from the study.

For the IA, only the primary endpoint, BICLA response at Week 52, was hypothesis tested (i.e., multiplicity protected).

The key secondary endpoints were not hypothesis tested for the IA in the multiple testing procedure, but point estimates, CIs, and nominal p-values are provided.

Results

- **Participant flow**

First patient was enrolled on 8-June-2021 and last patient was enrolled on 18-July-2024. The analyses are based on a clinical data lock date of 13-September-2024 and data cut-off date of 23-July-2024 for the IA.

Overall, 695 patients were screened and of the 220 patients included in the FAS for the IA, 78.6% completed the DB treatment and 21.8% withdrew from study without entering OLE (Table 9).

Table 9: Study disposition (Full Analysis Set)

	Anifrolumab 120mg n (%)	Placebo n (%)	Total n (%)
Subjects randomized	109	111	220
Subjects randomized, not treated	0	0	0
Subjects started double-blind treatment [a]	109	111	220
Subjects completed or discontinued double-blind treatment	109 (100)	111 (100)	220 (100)
Subjects completed double-blind treatment	86 (78.9)	87 (78.4)	173 (78.6)
Subjects discontinued double-blind treatment	23 (21.1)	24 (21.6)	47 (21.4)
SUBJECT DECISION	9 (8.3)	7 (6.3)	16 (7.3)
ADVERSE EVENT	9 (8.3)	3 (2.7)	12 (5.5)
LACK OF THERAPEUTIC RESPONSE	1 (0.9)	4 (3.6)	5 (2.3)
DEVELOPMENT OF STUDY SPECIFIC DISCONTINUATION CRITERIA	1 (0.9)	1 (0.9)	2 (0.9)
SUBJECT LOST TO FOLLOW-UP	0	1 (0.9)	1 (0.5)
PREGNANCY	0	1 (0.9)	1 (0.5)
OTHER	3 (2.8)	7 (6.3)	10 (4.5)
Subjects ongoing study follow-up without entering open-label extension	9 (8.3)	3 (2.7)	12 (5.5)
Subjects completed study without entering open-label extension	44 (40.4)	45 (40.5)	89 (40.5)
Subjects withdrawn from study without entering open-label extension	22 (20.2)	26 (23.4)	48 (21.8)
DEVELOPMENT OF STUDY-SPECIFIC WITHDRAWAL CRITERIA	1 (0.9)	2 (1.8)	3 (1.4)
OTHER	2 (1.8)	3 (2.7)	5 (2.3)
ADVERSE EVENT	3 (2.8)	2 (1.8)	5 (2.3)
LOST TO FOLLOW-UP	1 (0.9)	2 (1.8)	3 (1.4)
WITHDRAWAL BY SUBJECT	11 (10.1)	11 (9.9)	22 (10.0)
PHYSICIAN DECISION	4 (3.7)	6 (5.4)	10 (4.5)
Subjects enter open-label extension treatment [b]	34 (100)	37 (100)	71 (100)
Subjects ongoing open-label extension treatment	33 (97.1)	37 (100)	70 (98.6)
Subjects completed or discontinued open-label extension treatment	1 (2.9)	0	1 (1.4)
Subjects completed open-label extension treatment	0	0	0
Subjects discontinued open-label extension treatment	1 (2.9)	0	1 (1.4)
OTHER	1 (2.9)	0	1 (1.4)
Subjects ongoing study follow-up	1 (2.9)	0	1 (1.4)
Subjects completed study	0	0	0
Subjects withdrawn from study	0	0	0

Screened subjects are those who signed informed consent. Discontinued treatment subjects are those who prematurely and permanently discontinued study intervention. Completed study subjects are those completed and exit study according study protocol.
[a] Percentages are based on the number of subjects who started double-blind treatment.
[b] Percentages are based on the number of subjects who started open-label extension treatment.

The most commonly reported important protocol deviation was randomisation (incorrect randomisation or stratification) in the anifrolumab group and study intervention administration in the placebo group (Table *10*).

Table 10: Important protocol deviations (Full analysis set)

	Anifrolumab 120mg N = 109 n (%)	Placebo N = 111 n (%)	Total N = 220 n (%)
Subjects with at least one important protocol deviation	6 (5.5)	1 (0.9)	7 (3.2)
Randomization	3 (2.8)	0	3 (1.4)
Study Intervention Administration	2 (1.8)	1 (0.9)	3 (1.4)
Subject Discontinuation	1 (0.9)	0	1 (0.5)
Subjects with at least one important protocol deviation related to global/country/area situation	0	0	0

	Anifrolumab 120mg N = 109 n (%)	Placebo N = 111 n (%)	Total N = 220 n (%)
Subjects with at least one important protocol deviation	6 (5.5)	1 (0.9)	7 (3.2)
Randomization	3 (2.8)	0	3 (1.4)
Study Intervention Administration	2 (1.8)	1 (0.9)	3 (1.4)
Subject Discontinuation	1 (0.9)	0	1 (0.5)
Subjects with at least one important protocol deviation related to global/country/area situation	0	0	0

The same subject may have more than one important protocol deviation.

In terms of first ICE of RM/PEOT/Death at or before week 52, RM use was reported in 11 (10.1%) and 13 (11.7%) patients and PEOT in 17 (15.6%) and 16 (14.4%) of patients in anifrolumab and placebo groups, respectively. No deaths occurred.

Table 11: Intercurrent event of restricted medication use during double-blind treatment period (Full analysis set)

ATC Classification Generic Drug Name (WHODrug Global 202403 B3)	Anifrolumab 120mg N=109 n (%)	Placebo N=111 n (%)	Total N=220 n (%)
AMINOQUINOLINES	1 (0.9)	3 (2.7)	4 (1.8)
HYDROXYCHLOROQUINE	1 (0.9)	3 (2.7)	4 (1.8)
DIPHENYLMETHANE DERIVATIVES	1 (0.9)	0	1 (0.5)
HYDROXYZINE	1 (0.9)	0	1 (0.5)
GLUCOCORTICOIDS	9 (8.3)	12 (10.8)	21 (9.5)
DEFLAZACORT	0	2 (1.8)	2 (0.9)
HYDROCORTISONE	2 (1.8)	2 (1.8)	4 (1.8)
MEPREDNISONE	0	1 (0.9)	1 (0.5)
METHYLPREDNISOLONE	1 (0.9)	1 (0.9)	2 (0.9)
METHYLPREDNISOLONE ACETATE	1 (0.9)	0	1 (0.5)
METHYLPREDNISOLONE SODIUM SUCCINATE	1 (0.9)	0	1 (0.5)
PREDNISOLONE	1 (0.9)	0	1 (0.5)
PREDNISONE	5 (4.6)	6 (5.4)	11 (5.0)
OTHER BLOOD PRODUCTS	0	1 (0.9)	1 (0.5)
RED BLOOD CELLS	0	1 (0.9)	1 (0.5)
OTHER IMMUNOSUPPRESSANTS	1 (0.9)	0	1 (0.5)
METHOTREXATE	1 (0.9)	0	1 (0.5)

Concomitant medications that were reviewed and determined to affect either the interpretation or the existence of the measurements associated with the clinical question of interest.
Medications initiated within 28 days of the last double-blind treatment is considered.
Subjects are counted once per ATC Classification and Generic Drug Name regardless of the frequency of medication usage.
A subject may have more than one medication that meets the criteria of first intercurrent event of restricted medication, in which case, the subject is counted in multiple medications in the table.
Table is sorted in alphabetical order for ATC Classification and Generic Drug Name.
ATC Classification Anatomical Therapeutic Chemical Classification; IP Investigational product; n number of subjects per category; N Number of subjects per treatment group; WHODrug Global World Health Organization Global Drug Dictionary.

- **Conduct of the study**

Two amendments were made after the patient recruitment began that included substantial changes to the protocol impacting the study conduct and initial planned analyses.

Amendment 2 (14 July 2022): Changes included e.g. additions of Patient Global Impression of Change (PGIC) and Patient Global Impression of Severity (PGIS) as new patient reported outcome instruments, updated inclusion criterion 9 for screening SLEDAI-2K (with the rationale to clarify that to count as "active" a joint must be both tender and swollen, and to strengthen requirement for rash), deletion of exclusion criterion 9 concerning subjects with concurrent diagnosis of fibromyalgia to remove redundancy with inclusion criterion 12, addition of the section on capturing major acute cardiovascular events (MACE) and adjudication by Cardiovascular Event Adjudication Committee (CV-EAC) and updated list of prohibited medications.

Amendment 3 (14 June 2023): The study design was updated and the possibility for all eligible patients completing the DB treatment period to continue in an OLE period was added. Additionally, the screening period was extended from 30 days to 35 days. Overall, the update included several substantial changes that also affected the DB period. For example, the following modifications impacting the eligibility criteria and/or use of allowed or prohibited concomitant medications were made (with MAH's rationale):

- Tacrolimus and cyclosporine were added to the list of standard therapy regimen allowed before study entry (to reflect the standard clinical use of tacrolimus and cyclosporine as SoC).
- Clarification that combinations of mycophenolate mofetil or mycophenolic acid or mycophenolate sodium azathioprine, methotrexate, or tacrolimus are not permitted, and that such combination would be a reason for study intervention termination (combination of 2 immunosuppressants is not allowed for safety reasons).
- Wording regarding additional corticosteroid usage during the Double-Blind Period added (clarification of allowable additional corticosteroid use).

The changes to the planned analyses are summarised in Table *12*.

Table 12: Changes to the planned analyses

Key details of change	Reason for change	SAP amendment?
Changes made before unblinding of study data		
In the primary endpoint, the ICE of withdrawal from study was updated to categorize non-death related events categorized as missing data while death remained as ICE. Missing data to be handled via multiple imputation methods.	To align with Health Authorities guidance and expectations	Yes
In the primary endpoint, ICE of NC was added for reasons related to global/country situation, including handling strategy for all relevant endpoints and analyses.	To address the impact of pandemic and war related NC.	Yes
Multiple testing procedure was updated with details for the IA, removal of BICLA response assessment at Week 16, and reordered key secondary endpoints for sequential testing.	To align with CSP version 4.0, including that BICLA response at Week 16 no longer reflects an early response	Yes
For key secondary endpoints, updates specified composite strategy to handle certain ICEs and described methods to use for missing data.	To align main analyses with the composite strategy for handling of ICEs and to meet Health Authority guidance.	Yes

Key details of change	Reason for change	SAP amendment?
Certain other secondary endpoints were recategorized as exploratory analyses.	To align with CSP version 4.0	Yes
Analyses for the open label extension period were added, and exploratory endpoints not included in the CSP moved to a separate exploratory analysis plan.	To align with CSP version 4.0 and to simplify and focus the SAP to analyses that will be written into the CSR	Yes
For the primary endpoint, the multiple imputation regression model was modified to include only the immediate previous visit's evaluation as a covariate rather than all previous visits' evaluations.	To simplify the multiple imputation model	Yes
For the primary endpoint, method for tipping point analysis was updated to vary underlying assumed response probability for patients with NC ICE or missing assessment at Week 52.	To meet guidance from the United States Food and Drug Administration	Yes
An additional sensitivity analysis was added for the time to the first sustained BICLA response (secondary endpoint). The sensitivity analysis assesses the impact of dropping the requirement for at least 3 consecutive visits for BICLA responders.	To align with initial CSP-specified analysis that did not include the requirement of 3 consecutive visits	Yes
Analyses for DORIS and LLDAS endpoints were added as exploratory endpoints to be performed at the final analysis.	To characterize SLE-related remission endpoints at the final DB analysis (these endpoints have not been assessed at the IA)	Yes
Clarifications were added regarding: the IA sample size for PK, PD, and immunogenicity analyses; the inclusion of by-visit evaluation on the same day as the open-label treatment first dose date into the by-visit summary; and the change to require 20 patients instead of 25 patients with available data in the combined treatment groups for the subgroup analyses.	To clarify and update data presentation in final outputs	Yes
Changes made after unblinding of study data		
No changes	Not applicable	Not applicable

- **Baseline data**

The demographics at baseline are shown in Table *13*.

Table 13: Demographics (Full Analysis Set)

Demographic characteristic	Statistic	Anifrolumab 120mg N = 109	Placebo N = 111	Total N = 220
Age (years)	n	109	111	220
	Mean	43.0	42.3	42.7
	SD	12.43	11.39	11.89
	Median	44.0	43.0	43.0
	Min	21	19	19
	Max	70	68	70
Age group (years)				
> = 18 to < 65	n (%)	102 (93.6)	110 (99.1)	212 (96.4)
> = 65	n (%)	7 (6.4)	1 (0.9)	8 (3.6)
Sex				
Female	n (%)	94 (86.2)	102 (91.9)	196 (89.1)
Male	n (%)	15 (13.8)	9 (8.1)	24 (10.9)
Race				
White	n (%)	81 (74.3)	91 (82.0)	172 (78.2)
Black or African American	n (%)	2 (1.8)	6 (5.4)	8 (3.6)
Asian	n (%)	10 (9.2)	6 (5.4)	16 (7.3)
Native Hawaiian or Other Pacific Islander	n (%)	0	0	0
American Indian or Alaska Native	n (%)	8 (7.3)	7 (6.3)	15 (6.8)
Other	n (%)	8 (7.3)	1 (0.9)	9 (4.1)
Not Reported	n (%)	0	0	0
Ethnicity				
Hispanic or Latino	n (%)	47 (43.1)	53 (47.7)	100 (45.5)
Not Hispanic or Latino	n (%)	62 (56.9)	58 (52.3)	120 (54.5)
BMI (kg/m2)	n	109	111	220
	Mean	27.82	27.27	27.54
	SD	6.430	6.600	6.507
	Median	26.50	25.81	26.34
	Min	17.9	16.6	16.6
	Max	47.1	48.8	48.8
BMI group (kg/m2)				
< = 28	n (%)	65 (59.6)	67 (60.4)	132 (60.0)
> 28	n (%)	44 (40.4)	44 (39.6)	88 (40.0)
Region				
United States of America	n (%)	11 (10.1)	11 (9.9)	22 (10.0)
Europe	n (%)	45 (41.3)	47 (42.3)	92 (41.8)
Asia	n (%)	8 (7.3)	6 (5.4)	14 (6.4)
Latin America	n (%)	45 (41.3)	47 (42.3)	92 (41.8)
Rest of World	n (%)	0	0	0

The SLE disease characteristics at baseline are shown in Table *14*.

The most commonly affected organ systems (BILAG A or B at baseline) were the musculoskeletal (94.6%) and mucocutaneous (92.3%) systems; 2.3% renal and 1.9% cardiorespiratory domain involvement. At baseline, 95.5% were seropositive for ANA antibodies and 40.5% for anti dsDNA antibodies; 33.2% of patients had low C3, and 24.1% low C4.

Table 14: SLE Disease Characteristics (Full Analysis Set)

Demographic characteristic	Statistic	Anifrolumab 120mg N = 109	Placebo N = 111	Total N = 220
Time from initial SLE diagnosis to randomization (months)	n	109	111	220
	Mean	121.980	108.202	115.028
	SD	113.011	92.184	103.026
	Median	88.082	80.230	83.844
	Min	0.986	0.854	0.854
	Max	461.339	466.431	466.431
SLEDAI-2K score at screening				
< 10 points	n (%)	36 (33.0)	36 (32.4)	72 (32.7)
>= 10 points	n (%)	73 (67.0)	75 (67.6)	148 (67.3)
	n	109	111	220
	Mean	11.2	10.4	10.8
	SD	3.73	2.61	3.24
	Median	10.0	10.0	10.0
	Min	6	6	6
	Max	22	18	22
SLEDAI-2K score at baseline				
< 10 points	n (%)	33 (30.3)	39 (35.1)	72 (32.7)
>= 10 points	n (%)	76 (69.7)	72 (64.9)	148 (67.3)
	n	109	111	220
	Mean	11.3	10.5	10.9
	SD	3.83	2.88	3.40
	Median	10.0	10.0	10.0
	Min	6	6	6
	Max	26	18	26
Clinical SLEDAI-2K score at baseline	n	109	111	220
	Mean	8.9	8.4	8.6
	SD	2.66	2.14	2.42
	Median	8.0	8.0	8.0
	Min	4	6	4
	Max	18	18	18
Overall BILAG at screening				
At least one A	n (%)	50 (45.9)	45 (40.5)	95 (43.2)

No A and at least 2 Bs	n (%)	57 (52.3)	65 (58.6)	122 (55.5)
No A and < 2 Bs	n (%)	2 (1.8)	0	2 (0.9)
Not Available	n (%)	0	1 (0.9)	1 (0.5)
Overall BILAG at baseline				
At least one A	n (%)	51 (46.8)	47 (42.3)	98 (44.5)
No A and at least 2 Bs	n (%)	52 (47.7)	59 (53.2)	111 (50.5)
No A and < 2 Bs	n (%)	6 (5.5)	5 (4.5)	11 (5.0)
Not Available	n (%)	0	0	0
BILAG-2004 global score at baseline	n	109	111	220
	Mean	18.5	18.1	18.3
	SD	4.01	3.61	3.81
	Median	17.0	17.0	17.0
	Min	4	9	4
	Max	32	28	32
PGA score at baseline	n	109	111	220
	Mean	1.92	1.88	1.90
	SD	0.411	0.389	0.400
	Median	2.00	1.90	2.00
	Min	1.0	1.0	1.0
	Max	2.8	2.8	2.8
CLASI activity score at baseline				
< 10	n (%)	72 (66.1)	80 (72.1)	152 (69.1)
> = 10	n (%)	37 (33.9)	31 (27.9)	68 (30.9)
0	n (%)	1 (0.9)	0	1 (0.5)
> 0	n (%)	108 (99.1)	111 (100)	219 (99.5)
	n	109	111	220
	Mean	8.7	7.8	8.2
	SD	6.79	5.62	6.23
	Median	7.0	6.0	6.0
	Min	0	1	0
	Max	36	25	36
SDI global score at baseline				
0	n (%)	71 (65.1)	82 (73.9)	153 (69.5)

>= 1	n (%)	38 (34.9)	29 (26.1)	67 (30.5)
	n	109	111	220
	Mean	0.5	0.4	0.4
	SD	0.81	0.76	0.79
	Median	0.0	0.0	0.0
	Min	0	0	0
	Max	3	5	5
Joint count at baseline				
Swollen joints	> 0 n (%)	108 (99.1)	109 (98.2)	217 (98.6)
	Mean	7.5	7.3	7.4
	SD	4.26	4.30	4.27
	Median	7.0	6.0	6.0
	Min	0	0	0
	Max	28	24	28
Tender joints	> 0 n (%)	107 (98.2)	110 (99.1)	217 (98.6)
	Mean	11.5	10.7	11.1
	SD	6.38	5.56	5.98
	Median	12.0	10.0	10.0
	Min	0	0	0
	Max	28	28	28
Active joints	> 0 n (%)	105 (96.3)	109 (98.2)	214 (97.3)
	Mean	7.1	6.8	7.0
	SD	4.35	4.09	4.21
	Median	6.0	6.0	6.0
	Min	0	0	0
	Max	28	24	28

The clinical SLEDAI-2K score is the SLEDAI-2K score excluding items attributable to any urine or laboratory results including immunologic measures, which includes: vasculitis, arthritis, myositis, rash, alopecia, mucosal ulcers, pleurisy, and pericarditis.
Active joints are defined for the joints where both swollen and tender are in the same joint.
Only subjects with baseline positive anti-dsDNA and abnormal complement level, respectively, are included in the summary statistics for the respective variables.

Medical and surgical history was generally similar between patients in the anifrolumab and placebo groups. The most commonly reported risk factors, excluding common characteristics of SLE, were hypertension (25.7% and 27.9%), obesity (16.5% and 19.8%), hypothyroidism (14.7% and 10.8%), and COVID-19 (13.8% and 11.7%, respectively).

CV risk factors were generally similar between the anifrolumab and placebo groups. The most common risk factors were hypertension (25.0% and 25.9%), cigarette smoking (14.8% and 12.9%), and hyperlipidemia (10.8% and 7.1%, respectively). Surgical history was reported by 28.4% and 36.0% of patients in the anifrolumab and placebo groups, respectively.

The most frequently used prior medications in the anifrolumab and placebo groups were glucocorticoids (85.3% and 84.7%), aminoquinolines (78.0% and 88.3%), and other immunosuppressants (45.0% and 40.5%). The most frequently used prior SLE-related treatments were methotrexate (22.0% and 23.4%), azathioprine (22.9% and 18.0%), and hydroxychloroquine (13.8% and 18.0%, respectively). Prior belimumab use was reported in 9.2% and 9.9%, and prior rituximab use in 0.9% and 1.8% of patients in the anifrolumab and placebo groups, respectively.

At baseline, 82.3% of patients included in the FAS were on OCS, i.e. 85.3% and 79.3% of patients in the anifrolumab and placebo groups, respectively. 55.9% of patients were on immunosuppressants

(61.5% and 50.5%) and 80.5% were on antimalarials (78.0% and 82.9%). Commonly used immunosuppressant included azathioprine (23.9% and 18.0%), methotrexate (19.3% and 21.6%), and mycophenolate (18.3 and 11.7%, respectively). NSAIDs were used in 12.8% and 23.4%, and other SLE medications by 30.3% and 30.6% of patients in the anifrolumab and placebo groups, respectively (Table Table *15*).

Table 15: SLE-related treatment at baseline (Full analysis set)

Medication Categories	Statistic	Anifrolumab 120mg N = 109	Placebo N = 111	Total N = 220
Any SLE-related medication	n (%)	109 (100)	107 (96.4)	216 (98.2)
OCS				
Yes	n (%)	93 (85.3)	88 (79.3)	181 (82.3)
No	n (%)	16 (14.7)	23 (20.7)	39 (17.7)
OCS dose (mg/day)				
< 10 mg/day	n (%)	52 (47.7)	65 (58.6)	117 (53.2)
> = 10 mg/day	n (%)	57 (52.3)	46 (41.4)	103 (46.8)
	n	109	111	220
	Mean	8.638	7.450	8.039
	SD	5.972	6.401	6.207
	Median	10.000	5.000	7.500
	Min	0.000	0.000	0.000
	Max	25.000	30.000	30.000
OCS dose (mg/day) excluding patients not taking OCS				
< 10 mg/day	n (%)	36 (33.0)	42 (37.8)	78 (35.5)
> = 10 mg/day	n (%)	57 (52.3)	46 (41.4)	103 (46.8)
	n	93	88	181
	Mean	10.124	9.398	9.771
	SD	5.164	5.770	5.464
	Median	10.000	10.000	10.000
	Min	1.250	2.000	1.250
	Max	25.000	30.000	30.000
OCS only				
Yes	n (%)	3 (2.8)	1 (0.9)	4 (1.8)

Medication Categories	Statistic	Anifrolumab 120mg N = 109	Placebo N = 111	Total N = 220
No	n (%)	106 (97.2)	110 (99.1)	216 (98.2)
OCS dose (mg/day)	n	3	1	4
	Mean	9.17	10.00	9.38
	SD	1.443		1.250
	Median	10.00	10.00	10.00
	Min	7.5	10.0	7.5
	Max	10.0	10.0	10.0
OCS in combination with immunosuppressants				
Yes	n (%)	57 (52.3)	49 (44.1)	106 (48.2)
No	n (%)	52 (47.7)	62 (55.9)	114 (51.8)
OCS dose (mg/day)	n	57	49	106
	Mean	10.627	10.469	10.554
	SD	5.277	6.498	5.844
	Median	10.000	10.000	10.000
	Min	5.000	2.500	2.500
	Max	25.000	30.000	30.000
OCS in combination with anti-malarials				
Yes	n (%)	71 (65.1)	77 (69.4)	148 (67.3)
No	n (%)	38 (34.9)	34 (30.6)	72 (32.7)
OCS dose (mg/day)	n	71	77	148
	Mean	10.204	9.312	9.740
	SD	5.473	5.826	5.658
	Median	10.000	10.000	10.000
	Min	1.250	2.000	1.250
	Max	25.000	30.000	30.000
OCS in combination with anti-malarials and immunosuppressants				
Yes	n (%)	38 (34.9)	39 (35.1)	77 (35.0)
No	n (%)	71 (65.1)	72 (64.9)	143 (65.0)
OCS dose (mg/day)	n	38	39	77
	Mean	10.954	10.590	10.769
	SD	5.691	6.711	6.190
	Median	10.000	10.000	10.000

Medication Categories	Statistic	Anifrolumab 120mg N = 109	Placebo N = 111	Total N = 220
	Min	5.000	2.500	2.500
	Max	25.000	30.000	30.000
Anti-malarials	n (%)	85 (78.0)	92 (82.9)	177 (80.5)
Anti-malarials only	n (%)	6 (5.5)	9 (8.1)	15 (6.8)
Anti-malarials in combination with OCS and/or immunosuppressants	n (%)	79 (72.5)	83 (74.8)	162 (73.6)
Immunosuppressants	n (%)	67 (61.5)	56 (50.5)	123 (55.9)
Azathioprine (mg/day)	n (%)	26 (23.9)	20 (18.0)	46 (20.9)
	Mean	95.2	96.3	95.7
	SD	36.76	35.61	35.86
	Median	100.0	100.0	100.0
	Min	50	50	50
	Max	150	150	150
Methotrexate (mg/week)	n (%)	21 (19.3)	24 (21.6)	45 (20.5)
	Mean	15.952	14.387	15.118
	SD	5.091	4.817	4.953
	Median	15.000	15.000	15.000
	Min	7.500	2.800	2.800
	Max	25.000	25.000	25.000
Mycophenolate (g/day)[a]	n (%)	20 (18.3)	13 (11.7)	33 (15.0)
	Mean	1.519	1.224	1.403
	SD	0.526	0.573	0.555
	Median	1.720	1.000	1.440
	Min	0.50	0.25	0.25
	Max	2.00	2.00	2.00
Cyclosporine (mg/kg/day)	n (%)	0	0	0
	Mean			
	SD			
	Median			
	Min			
	Max			
Tacrolimus (mg/kg/day)	n (%)	0	0	0
	Mean			

Medication Categories	Statistic	Anifrolumab 120mg N = 109	Placebo N = 111	Total N = 220
	SD			
	Median			
	Min			
	Max			
Mizoribine (mg/day)	n (%)	0	0	0
	Mean			
	SD			
	Median			
	Min			
	Max			
More than 1 immunosuppressant	n (%)	1 (0.9)	1 (0.9)	2 (0.9)
NSAIDs	n (%)	14 (12.8)	26 (23.4)	40 (18.2)
Other SLE medications	n (%)	33 (30.3)	34 (30.6)	67 (30.5)

Medication selection is based on collected medications in the Prior and Concomitant medication pages.
Medications are coded according to WHODrug Global World Health Organization Global Drug Dictionary.
SLE-related medications at baseline are defined as all medications with therapy reason of "disease under study" or "disease under study, clinical failure of study" with an intake at the date of first dose of investigational product.
Immunosuppressant: azathioprine, mycophenolate mofetil/mycophenolic acid, methotrexate, cyclosporine, tacrolimus, or mizoribine.
[a] Mycophenolate or mycophenolic acid.

During the DB treatment period, the most commonly used concomitant medications were glucocorticoids in 88.1% and 88.3% of patients, aminoquinolines in 78.0% and 88.3% of patients, and other immunosuppressants in 41.4% and 45.9% of patients in anifrolumab and placebo groups, respectively.

- **Numbers analysed**

Altogether 220 patients were included in the FAS for the IA, 109 patients in the anifrolumab group and 111 patients in the placebo group.

- **Outcomes and estimation**

Primary endpoint

The primary endpoint BICLA response rate at week 52 was 59.4% for anifrolumab and 43.9% for placebo, resulting in a 15.5% treatment difference (95% CI 2.3, 28.6).

The efficacy results for the primary and key secondary endpoints are shown in Table *16*.

Table 16: Overview of key efficacy results (FAS)

						Comparison with Placebo			
Endpoint	**Type of estimate Type of comparison**	**Group**	**n**	**Estimate**	**95% CI**	**Estimate**	**95% CI**	**p-value**	**Reject H0**
Primary									
BICLA response at Week 52	Response rate Rate difference	Anifrolumab 120mg N = 109	65	59.4	(50.1, 68.7)	15.5	(2.3, 28.6)	0.0211	Yes
		Placebo N = 111	49	43.9	(34.6, 53.3)				
Key Secondary									
BICLA response at Week 52 with Maintained Low (or reduced) OCS use	Response rate Rate difference	Anifrolumab 120mg N = 109	65	59.4	(50.1, 68.7)	19.9	(6.9, 32.9)	0.0027	NA
		Placebo N = 111	44	39.5	(30.4, 48.7)				
Time to BICLA response sustained through Week 52	Percentage of response Hazard ratio	Anifrolumab 120mg N = 109	43	39.8	(31.3, 49.7)	2.038	(1.248, 3.408)	0.0052	NA
		Placebo N = 111	24	22.8	(15.9, 32.1)				
Time to First Flare through Week 52	Percentage of flare Hazard ratio	Anifrolumab 120mg N = 109	42	39.3	(30.7, 49.2)	0.757	(0.499, 1.141)	0.1841	NA
		Placebo N = 111	50	46.6	(37.6, 56.5)				

Only subjects with non-missing covariates/stratification factors are included in the analysis. At the interim analysis, only the primary endpoint will be tested at 0.0354 level. The 0.0354 is determined based on the information fraction at the time of the interim analysis using Pocock spending function. All other p-values are nominal. The responder/non-responder rates (percentages), are performed using stratified CMH adjusting for the stratification factors. Missing data are imputed using multiple imputation as specified in the SAP, and all results are combined to obtain a single estimated treatment effect as per the Rubins rule. For Time to BICLA sustained response and time to Flare through Week 52, Kaplan-Meier estimate with its 95% CI is presented for each treatment group. Hazard ratios, and 95% CIs for Hazard ratios are estimated using a Cox regression model with treatment groups and the stratification factors. Stratification factors levels are: type I IFN gene signature test result = high and SLEDAI < 10 points, IFN = high and SLEDAI > = 10 points, and IFN = low.

At Week 52, a larger proportion of patients with BICLA response in the anifrolumab 120 mg SC group displayed BILAG improvement compared with patients in the placebo group, while similar proportions of patients in the anifrolumab and placebo groups had no worsening of SLEDAI-2K and no worsening of PGA (Table *17*).

Table 17: BICLA Response Rate at Week 52 by BICLA Components (FAS)

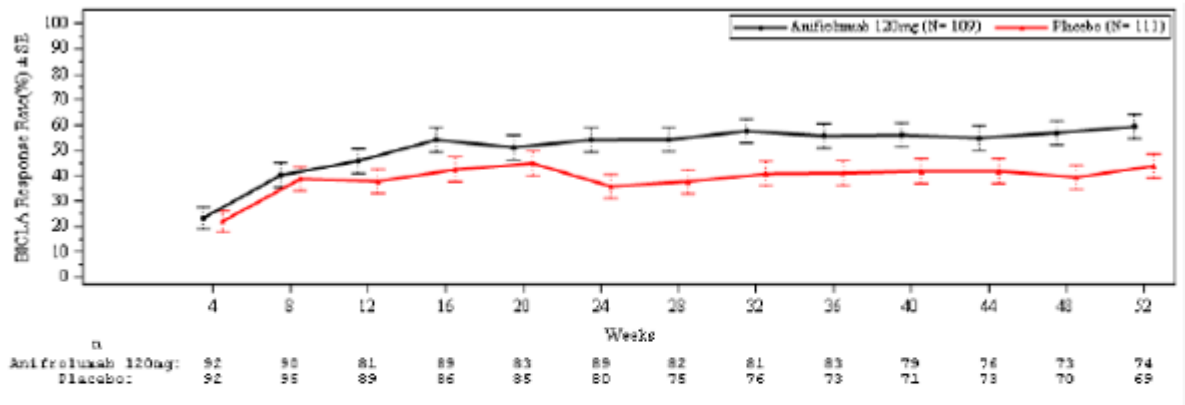
BICLA Response at Week 52	Anifrolumab 120 mg (N = 109)	Placebo (N = 111)
Number (%) responders [a]	65 (59.4)	49 (43.9)
Comparison with placebo		
Difference in response rate	15.5	
95% CI of difference in response rate	(2.3, 28.6)	
P-value [b]	0.0211	
Components of BICLA response		
BILAG improvement, n (%)	65 (59.5)	49 (44.1)
No worsening of SLEDAI-2K, n (%)	81 (74.3)	80 (71.6)
No worsening of PGA, n (%)	81 (74.4)	82 (73.7)

[a] Patients with the ICEs of RM, PEOT, or death were considered BICLA non-responders. See Table 14.2.1.1 for analytical details.

[b] At the interim analysis, the primary endpoint will be tested at 0.0354 level.

The BICLA response rates by visit is shown in Figure *11*. The results demonstrated a nominal significance for treatment differences at all timepoints from Week 24 and onwards, except for Week 44.

Figure 11: BICLA Response Rate by Visit (Primary Analysis): RM, PEOT and Deaths Result in NR, NC is Handled with MI (MAR) - Line Plot (FAS)



The analyses are performed using stratified CMH adjusting for the stratification factors. Missing data are imputed using multiple imputation as specified in the SAP, and all results are combined to obtain a single estimated treatment effect as per the Rubins rule.

Stratification factors levels are: type I IFN gene signature test result = high and SLEDAI<10 points, IFN=high and SLEDAI>=10 points, and IFN=low.

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 SLEDAI-2K, and no increase >=0.30 points on a 3-point PGA VAS from baseline.

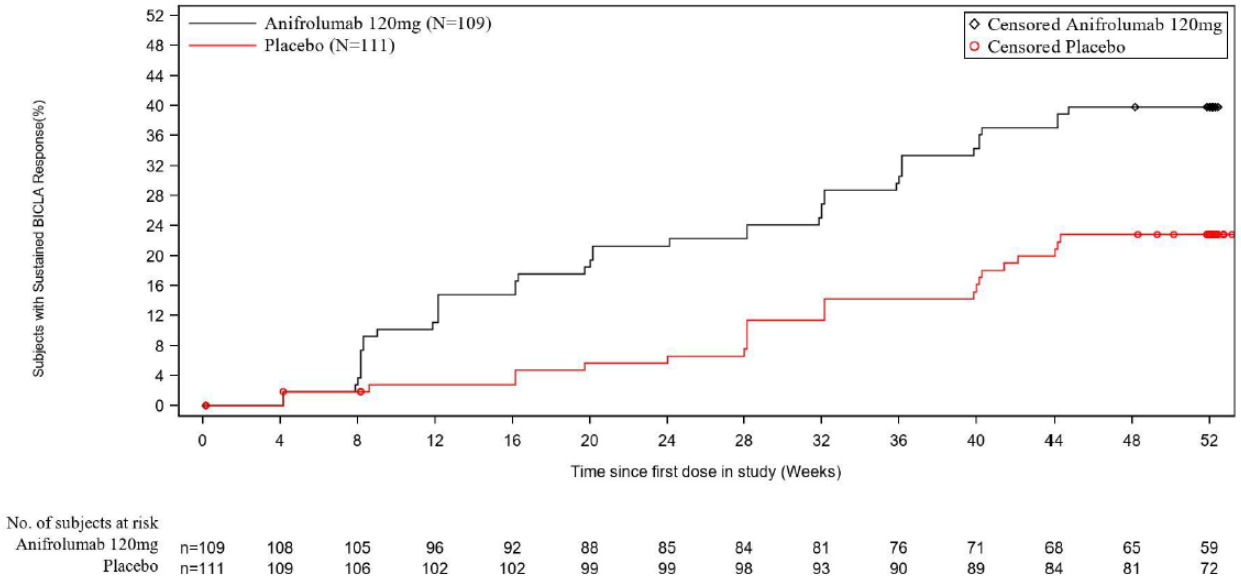
The results of a sensitivity analysis of the primary endpoint, excluding patients with no BILAG A or B or baseline PGA VAS score > 2.7, were consistent with the primary analysis with nominal significance for treatment differences at all timepoints from Week 24 and onwards, except for Weeks 40 and 44. At week 52, the BICLA response rate was 58.6% for anifrolumab and 43.9% for placebo, resulting in a treatment difference of 14.6% (95% CI 1.3, 27.9).

The results of supplementary analyses of the primary endpoint were consistent with and supported the findings of the main analysis.

Key secondary endpoints

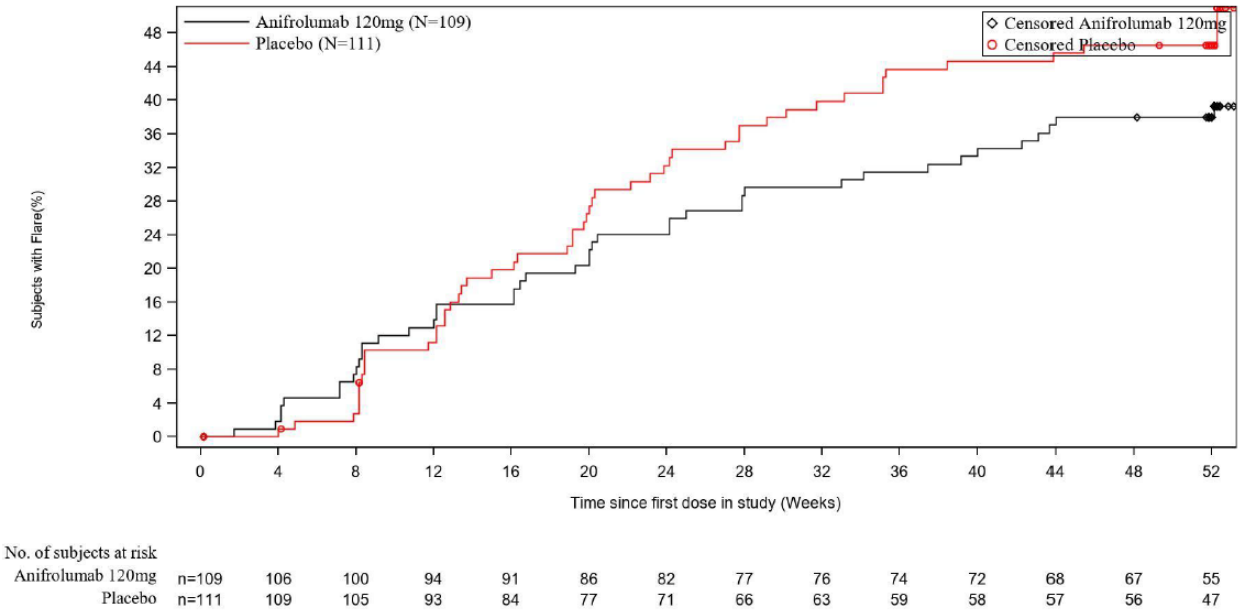
A greater proportion of patients treated with anifrolumab achieved a BICLA response at Week 52 while achieving or maintaining low OCS use, compared with placebo (Table *17*). Treatment with anifrolumab also reduced the time to the first BICLA response and numerically delayed the time to the first flare (Table *17* and Figure *12* and Figure *13*).

Figure 12: Time to BICLA Response Sustained Through Week 52 (Primary Analysis): RM, PEOT and Death Result in NR and NC is Censored - Kaplan-Meier Plot (FAS)



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 SLEDAI-2K, and no increase >= 0.30 points on a 3 point PGA VAS from baseline. Subjects had first intercurrent event of RM/PEOT/Death are regarded as no observed event.
BICLA British Isles Lupus Assessment Group-based Composite Lupus Assessment; SLEDAI-2K Systemic Lupus Erythematosus Disease Activity Index 2000; PGA: Physician's Global Assessment VAS: Visual Analogue Scale; n Number of subjects in analysis; N Number of subjects per treatment group.
NR Non-responder; RM Restricted Medication use; PEOT Premature End of Treatment; NC Non compliance for reasons related to civil crisis, natural disaster, or public health crisis.

Figure 13: Time to First Flare (Primary Analysis): RM, PEOT, Deaths are Flare and NC is Censored - Kaplan-Meier Plot (FAS)



Flare is defined as either 1 or more new BILAG-2004 A or 2 or more new BILAG-2004 B items compared to the previous visit.
If an ICE of RM/PEOT/Death occurred, it is considered as a flare in the event that ICE is not in the same visit window of the previous observed flare.
n Number of subjects in analysis; N Number of subjects per treatment group; PEOT Premature End of Treatment; RM Restricted Medication use; NC Non compliance for reasons related to civil crisis, natural disaster, or public health crisis.

Other secondary endpoints

A higher proportion of patients with baseline OCS ≥ 10 mg/day receiving anifrolumab achieved an OCS dose of ≤ 7.5 mg/day by Week 40, which was maintained through Week 52, compared with patients receiving placebo (74.2% vs 48.6%; difference 25.6% [95% CI 7.6, 43.5]; nominal p = 0.0053).

There was a slight numerical reduction of the annual flare rate for the anifrolumab group compared with the placebo group (0.80 rate ratio anifrolumab:placebo [95% CI 0.52, 1.23]; nominal p = 0.3018).

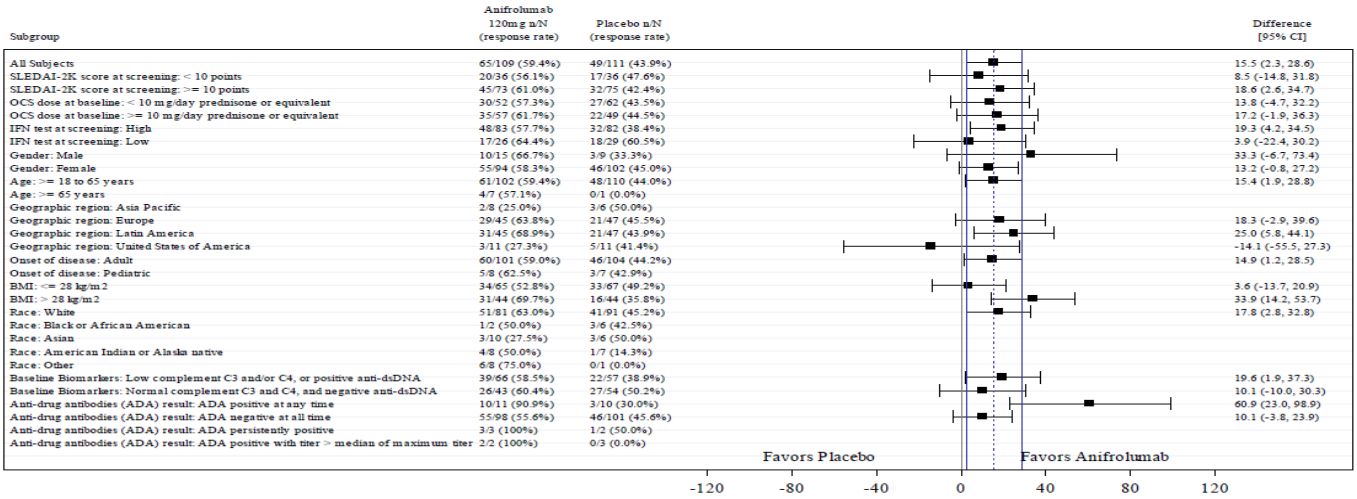
A numerically higher proportion of patients treated with anifrolumab achieved an SRI(4) response at Week 52 compared with patients receiving placebo (67.8% vs 59.4%; difference 8.4% [95% CI -4.5, 21.1]; nominal p = 0.2012).

- **Ancillary analyses**

Subgroup analysis

The BICLA response rates across the pre-defined subgroups, including ADA-positive and ADA-negative subgroups, are shown in Figure *14*.

Figure 14: BICLA Response Rate at Week 52 (Subgroup Analysis): RM, PEOT and Deaths Result in NR, NC is Handled with MI (MAR) – forest plot (FAS)



The analyses are performed using stratified CMH adjusting for the stratification factors. Missing data are imputed using multiple imputation as specified in the SAP, and all results are combined to obtain a single estimated treatment effect as per the Rubins rule.
Stratification factors used for each subgroup may vary depending on the number of participants within each stratum for the subgroup of interest. Factors used in the stratified CMH for each subgroup can be found in the corresponding subgroup summary table
A positive rate difference favours Anifrolumab.
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 SLEDAI-2K, and no increase >=0.30 points on a 3 point PGA VAS from baseline.
BICLA British Isles Lupus Assessment Group-based Composite Lupus Assessment; SLEDAI-2K Systemic Lupus Erythematosus Disease
Activity Index 2000; PGA: Physician's Global Assessment; VAS: Visual Analogue Scale; OCS Oral corticosteroids; IFN Interferon.
n Number of subjects in analysis; N Number of subjects per treatment group.
CMH Cochran–Mantel–Haenszel; CI Confidence interval; NR Non-responder; RM Restricted Medication use; PEOT Premature End of Treatment; NC Non compliance for reasons related to civil crisis, natural disaster, or public health crisis; MAR Missing at Random; MI Multiple Imputation.

- **Summary of main efficacy results**

The following table summarises the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 18: Summary of efficacy for study D3465C00001 (TULIP SC)

Title	A Multicentre, Randomised, Double-blind, Placebo-controlled, Phase 3 Study Evaluating the Efficacy and Safety of Subcutaneous Anifrolumab in Adult Patients with Systemic Lupus Erythematosus		
Study identifier	D3465C00001 EudraCT/EU CT Number: 2020-004529-22/2022-502396-28 NCT Number: NCT04877691		
Design	Phase III, multicenter, multinational, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of an SC treatment regimen of anifrolumab versus placebo in adult patients with moderate to severe SLE despite receiving standard therapy. The primary objective of the study was to compare efficacy of anifrolumab with placebo on overall disease activity in patients with SLE. The efficacy assessments in this application are based on an IA of the first 220 randomized of 360 planned patients in TULIP SC who completed the 52-week DB treatment period or withdrew early from the study. Randomization was stratified using SLEDAI-2K score at screening (< 10 points vs ≥ 10 points), Week 0 (Day 1) OCS dose (< 10 mg/day vs ≥ 10 mg/day prednisone or equivalent), and results of the type I interferon gene signature test at screening (high vs low).		
	Duration of Main phase:		52 weeks
Hypothesis	Superiority		
Treatments groups	Anifrolumab 120 mg		Anifrolumab 120 mg administered SC QW for 52 weeks N = 109 included in IA for efficacy
	Placebo		Placebo administered SC QW for 52 weeks N = 111 included in the IA for efficacy
Endpoints and definitions	Primary endpoint	BICLA response at Week 52	BICLA response at Week 52 is a composite binary endpoint whereby responders are defined by meeting all of the following criteria: • Improvement from baseline in disease activity as measured by BILAG-2004 (adjudicated). Improvement is defined as a reduction of all baseline BILAG-2004 A to B/C/D and baseline BILAG-2004 B to C/D, and no BILAG-2004 worsening in other organ systems, where worsening is defined as ≥ 1 new BILAG-2004 A or ≥ 2 new BILAG 2004 B. • No worsening from baseline in SLEDAI-2K, where worsening is as defined as an increase from baseline of > 0 points in SLEDAI-2K total score. Increase from baseline corresponds to the change from baseline. SLEDAI-2K is derived as the sum of the scores for all items. • No worsening from baseline in subjects' lupus disease activity, where worsening is defined by an increase ≥ 0.30 points on a 3-point PGA VAS.

			For the IA, only the primary endpoint, BICLA response at Week 52, was hypothesis tested (ie, multiplicity protected).
	Key Secondary	Proportion of patients who are BICLA responders at Week 52 and have maintained low (or reduced) OCS use through Week 52	Maintained low (or reduced) OCS, assessed in conjunction with BICLA response, is defined as: • If baseline OCS ≥ 10 mg/day, an OCS dose of ≤ 7.5 mg/day prednisone or equivalent must be achieved by Week 40 and an OCS dose ≤ 7.5 mg/day prednisone or equivalent must be maintained from Week 40 to Week 52. • If baseline OCS < 10 mg/day, OCS dose at Week 40 must be less than or equal to OCS dose at baseline, with no increase from Week 40 OCS dose between Week 40 and Week 52. Not hypothesis tested for the IA in the MTP, but point estimates, CIs, and nominal p-values are provided.
	Key Secondary	Time to first BICLA response sustained through Week 52	Defined for patients who are BICLA responders, and who responded for a minimum 3 consecutive visits including Week 52 (ie, at least responded since Week 44). Not hypothesis tested for the IA in the MTP, but point estimates, CIs, and nominal p-values are provided.
	Key Secondary	Time to first flare through Week 52	Flares were defined as either one or more new BILAG-2004 A or 2 or more new BILAG 2004 B items compared to the previous visit. Not hypothesis tested for the IA in the MTP, but point estimates, CIs, and nominal p-values are provided.
	Other Secondary	OCS response	Proportion of patients with baseline OCS ≥ 10 mg/day who have maintained OCS reduction through Week 52 defined by meeting all of the following criteria: • Achieve an OCS dose of ≤ 7.5 mg/day prednisone or equivalent by Week 40. • Maintain an OCS dose ≤ 7.5 mg/day prednisone or equivalent from Week 40 to Week 52.
	Other Secondary	Annualized flare	Annualized flare rate through Week 52 with flare defined as either one or more new BILAG-2004 A or 2 or more new BILAG-2004 B items compared to the previous visit.
	Other Secondary	SRI(4) response	Proportion of patients achieving SRI(4) response at Week 52, defined by meeting all of the following criteria: • Reduction from baseline of ≥ 4 points in the SLEDAI-2K. • No new organ systems affected as defined by one or more BILAG-2004 A or 2 or more BILAG-2004 B items compared to baseline using BILAG-2004. • No worsening from baseline in the patients' lupus disease activity, where worsening is

			defined by an increase ≥ 0.30 points on a 3-point PGA VAS.
Clinical Data Lock	13 September 2024		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Full Analysis Set: All randomized patients who received at least one dose of IP and were analyzed according to their randomized treatment irrespective of whether or not they have received treatment as randomized or prematurely discontinued. For the IA, the FAS consisted of the first 220 randomized patients who completed Week 52 or withdrew early from the study. Week 52 For efficacy analyses in the DB phase of this study, ICEs accounted for in the estimands included: • RM use • PEOT • Death • NC for reasons related to civil crisis, natural disaster, or public health crisis For the primary efficacy analysis, for patients who had ICE due to RM use, PEOT, and/or death, the BICLA response after the ICE was set to non-response as per the composite strategy. For patients who had ICE due to NC, response after NC was imputed using the hypothetical strategy. For the primary endpoint, the α level for the IA was determined based on the Pocock spending function. Based on 220 patients eligible for the IA and 367 patients confirmed randomized at completion of recruitment, the information fraction is 0.60 (220/367), resulting α_IA of 3.54% and α_Final Analysis of 2.57%.		
Descriptive statistics and estimate variability	Treatment group	Anifrolumab 120 mg	Placebo
	Number of patients	109	111
	Primary endpoint: BICLA response at Week 52 Response rate	59.4%	43.9%
	95% CI	(50.1, 68.7)	(34.6, 53.3)
	Key Secondary endpoint: Proportion of patients who are BICLA responders at Week 52 and have maintained low (or reduced) OCS use through Week 52 Response rate	59.4%	39.5%
	95% CI	(50.1, 68.7)	(30.4, 48.7)
	Key secondary: Time to first BICLA response sustained through Week 52 Percentage of response	39.8%	22.8%
	95% CI	(31.3, 49.7)	(15.9, 32.1)
	Key secondary: Time to first flare through Week 52 Percentage of flare	39.3%	46.6%
	95% CI	(30.7, 49.2)	(37.6, 56.5)

	Other secondary: OCS response Response rate	74.2%	48.6%
	95% CI	(62.4, 85.9)	(35.0, 62.2)
	Other secondary: Annualized flare rate Rate	0.59	0.75
	95% CI	(0.42, 0.83)	(0.55, 1.00)
	Other secondary: SRI(4) response Response rate	67.8%	59.4%
	95% CI	(58.9, 76.7)	(50.2, 68.7)
Effect estimate per comparison	Primary endpoint: BICLA response at Week 52	Comparison groups	Anifrolumab 120 mg vs Placebo
		Rate difference	15.5%
		95% CI	(2.3, 28.6)
		P-value (stratified CMH method)	0.0211
	Key secondary: Proportion of subjects who are BICLA responders at Week 52 and have maintained low (or reduced) OCS use through Week 52	Comparison groups	Anifrolumab 120 mg vs Placebo
		Rate difference	19.9%
		95% CI	(6.9, 32.9)
		Nominal P-value (stratified CMH method)	0.0027
	Key secondary: Time to first BICLA response sustained through Week 52	Comparison groups	Anifrolumab 120 mg vs Placebo
		Hazard ratio	2.038
		95% CI	(1.248, 3.408)
		Nominal P-value (Cox proportional hazards)	0.0052
	Key secondary: Time to first flare through Week 52	Comparison groups	Anifrolumab 120 mg vs Placebo
		Hazard ratio	0.757
		95% CI	(0.499, 1.141)
		Nominal P-value (Cox proportional hazards)	0.1841
	Other secondary: OCS response	Comparison groups	Anifrolumab 120 mg vs Placebo
		Rate difference	25.6%
		95% CI	(7.6, 43.5)
		Nominal P-value (stratified CMH method)	0.0053
	Other secondary: Annualized flare rate	Comparison groups	Anifrolumab 120 mg vs Placebo
		Rate ratio	0.80
		95% CI	(0.52, 1.23)
		Nominal P-value	0.3018

		(negative binomial regression model)	
	Other secondary: SRI(4) response	Comparison groups	Anifrolumab 120 mg vs Placebo
		Rate difference	8.4
		95% CI	(-4.5, 21.2)
		Nominal P-value (stratified CMH method)	0.2012
Notes	**Disposition:** The proportions of patients who discontinued DB treatment were similar between groups (21.1% and 21.6% in the anifrolumab and placebo groups, respectively). The proportions of patients who withdrew from study without entering OLE were similar between the groups (20.2% and 23.4% in the anifrolumab and placebo groups, respectively). The most common reasons for discontinuation of IP were AE and subject decision. The most common reasons for withdrawal from the study were withdrawal by subject and physician decision. **BICLA components for the primary endpoint of BICLA response:** A larger proportion of patients with BICLA response in the anifrolumab 120 mg SC group displayed BILAG improvement (59.5%) compared with patients in the placebo group (44.1%), while consistent proportions of patients in the anifrolumab and placebo groups had no worsening of SLEDAI-2K (74.3% and 71.6%, respectively) and no worsening of PGA (74.4% and 73.7%, respectively). While there were no differences between the treatment groups with regard to no worsening of SLEDAI-2K or PGA, improvement in both measures was seen with anifrolumab compared with placebo. • LS Mean difference for SLEDAI-2K was -1.52; 95% CI, -2.55 to -0.49; p = 0.0042. • LS Mean difference for PGA was -0.19; 95% CI, -0.35 to -0.03; p = 0.0204. **Disposition of ICEs:** The proportions of patients with first ICEs of RM (10.1% and 11.7%) and PEOT use (15.6% and 14.4%) were consistent between the anifrolumab and placebo groups. **Time course of BICLA response:** A separation in BICLA response rate favoring anifrolumab over placebo was apparent from Week 12 and was maintained throughout the DB treatment period with nominal significance for treatment differences at all timepoints from Week 24 and onwards, except for Week 44.		

AE, Adverse event; BICLA, British Isles Lupus Assessment Group-based Composite Lupus Assessment; BILAG, LBritish Isles Lupus Assessment Group; CI, Confidence interval; CMH, Cochran–Mantel–Haenszel; DB, Double-blind; LFAS, Full analysis set; IA, Interim analysis; ICE, Intercurrent event; IP, Investigational product; LS, Least squares; LMTP, Multiple testing procedure; NC, Non-compliance for reasons related to civil crisis, natural disaster, or public

health crisis; OCS, Oral corticosteroid steroid; OLE, Open-label extension; PEOT, Premature End of Treatment; PGA,

Physician's Global Assessment; QW, Once weekly; RM, Restricted Medication use; SC, Subcutaneous; SLE,

Systemic lupus erythematosus; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000; SRI(4),

Systemic Lupus Erythematosus Responder Index of $\geqslant$ 4; VAS, Visual analog scale.

2.6.5.3. Clinical studies in special populations

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
TULIP SC Full Analysis Set (N = 220)	8/220	-	-
TULIP SC Safety Analysis Set (N = 346)	10/346	-	-

2.6.5.4. In vitro biomarker test for patient selection for efficacy

N/A

2.6.5.5. Analysis performed across studies (pooled analyses and meta-analysis)

Comparison of the primary and key secondary endpoints in TULIP SC vs. IV Studies 04 and 05

To support the overall efficacy assessment of SC anifrolumab, the efficacy results observed with anifrolumab 120 mg SC QW was compared with that of anifrolumab 300 mg IV Q4W for the primary endpoint of BICLA response at Week 52 (a pre-specified endpoint in studies 04 and 05) and a post-hoc analysis of the 3 key secondary endpoints in TULIP SC for the IV studies (Table *19*).

Table 19: Summary of Efficacy Results in TULIP SC and IV studies 04 and 05

Endpoint	Type of estimate	Study	Treatment difference vs placebo (95% CI)	p-value
BICLA response at Week 52	Rate difference	TULIP SC	15.5% (2.3, 28.6)	0.0211
		IV study 04	16.3% (6.3, 26.3)	0.001
		IV study 05	17.0% (7.2, 26.8)	< 0.001
Proportion of patients who achieved a BICLA response while achieving or maintaining low OCS use	Rate difference	TULIP SC	19.9% (6.9, 32.9)	0.0027
		IV study 04	15.0% (5.0, 25.0)	0.0032
		IV study 05	19.0% (9.1, 28.9)	0.0002
Time to BICLA response sustained through Week 52	Hazard ratio	TULIP SC	2.038 (1.248, 3.408)	0.0052
		IV study 04	1.714 (1.070, 2.788)	0.0267
		IV study 05	2.015 (1.281, 3.236)	0.0029
Time to First Flare through Week 52	Hazard ratio	TULIP SC	0.757 (0.499, 1.141)	0.1841
		IV study 04	0.554 (0.413, 0.739)	< 0.0001
		IV study 05	0.721 (0.543, 0.953)	0.0222

BICLA British Isles Lupus Assessment Group-based Composite Lupus Assessment; CI confidence interval; IV intravenous; OCS oral corticosteroids; SC subcutaneous.

2.6.5.6. Supportive study(ies)

N/A

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

The anifrolumab SC clinical programme included one pivotal global, multicenter, randomised, DB, placebo-controlled, Phase III study (TULIP SC). Given the approval of the IV anifrolumab, a single phase III study was considered sufficient for the assessment of efficacy of SC anifrolumab in the same target population and same indication, i.e. as an add-on therapy for the treatment of adult patients with moderate to severe, active autoantibody-positive systemic lupus erythematosus (SLE), despite standard therapy.

The efficacy assessments of this line extension application were based on an IA of the first 220 patients in TULIP SC study who completed the 52-week DB treatment period or withdrew early from the study.

No dose-response studies were conducted for SC anifrolumab. Based on the PK/PD data of the Phase II SC study D3461C00008, as well as data from the anifrolumab IV studies, a dose of 120 mg QW

was selected for the TULIP SC study, as it was expected to provide at least similar efficacy to 300 mg IV Q4W used in the anifrolumab pivotal IV studies 04 and 05.

The eligibility criteria in TULIP SC study with the minimum SLEDAI-2K and BILAG criteria outlined a SLE population with active disease of at least moderate severity despite of standard of care. The criteria defining the SLE patients were essentially the same to the eligibility criteria used in the key studies that formed the basis for the approval of the IV anifrolumab.

The same stratification factors as in the pivotal 04 and 05 studies supporting the initial approval for the IV formulation were used, i.e. SLEDAI-2K score at screening (< 10 vs ≥ 10 points), OCS use on Day 1 (< 10 vs ≥ 10 mg prednisone or equivalent per day), and type I IFN gene signature test result (high vs low).

The key instruments used for the assessment of disease activity by the investigator were standard, including BILAG-2004, SLEDAI-2K and PGA.

Altogether, the target population and the used efficacy assessments in TULIP SC study were essentially the same as in the pivotal IV anifrolumab studies, supporting no change to the proposed indication approved for the IV formulation: "*Saphnelo is indicated as an add-on therapy for the treatment of adult patients with moderate to severe, active autoantibody-positive systemic lupus erythematosus (SLE), despite standard therapy*." This was endorsed by the CHMP.

The primary endpoint BICLA response is a validated composite index to assess SLE disease activity and acceptable from the regulatory point of view as it is in line with the Guideline on clinical investigation of medicinal products for the treatment of systemic lupus erythematosus and lupus nephritis (EMA/CHMP/51230/2013 corr 1). BICLA was also the primary endpoint in study 04, another pivotal study that contributed to the approval of the IV anifrolumab (for detailed discussion on endpoint selection, see section "2.5.6. Discussion on clinical efficacy" in EPAR of Saphnelo). Although SRI(4) was proposed as the primary endpoint during the initial EMA SA (EMEA/H/SA/2903/3/2018/III), the BICLA response was selected as the primary endpoint before the study commenced. Overall, BICLA response was considered appropriate primary endpoint for the TULIP SC study.

For the primary estimand, FAS population was used meaning that all patients who were randomised and received at least one dose were included. In principle, this is not acceptable, and all randomised patients should have been used. However, as in practice, there is no difference in these two populations, this did not impact the results. A composite strategy was used for the intercurrent events due to discontinuation (or death) and use of restricted medication, and these patients were counted as non-responders, whereas hypothetical strategy was applied for the intercurrent events due to non-compliance as a result of factors external to the study. The estimand was considered adequate and the clinical questions of interest relevant. The study was conducted during the COVID-19 pandemic and the war in Ukraine commenced during the study and there were sites in Ukraine. Therefore, it may have been that these external events have a major impact on the reliability of the results. This risk, however, did not materialise.

BICLA response at week 52 with maintained low (or reduced) use of OCS, time to BICLA response sustained through week 52 and time to flare through week 52 were selected as key secondary endpoints. It is notable that these endpoints differed from the proposed key secondary endpoints at the time of the EMA SA (EMEA/H/SA/2903/3/2018/III). Further, none of the key secondary endpoints

in the pivotal anifrolumab IV studies (i.e. maintained OCS tapering, CLASI response, joints and annualized flare rate) were included as key secondary endpoints in the TULIP SC study.

The estimand as defined for time to sustained BICLA response and the clinical question it is designed to answer is difficult to comprehend. In the analysis, all patients are included and patients who did not receive a BICLA response are censored at the last BICLA assessment during the double-blind treatment period if they had no ICEs prior to that. This means that these patients are still expected to have an equal chance to respond which is unlikely true. Furthermore, in the analysis data up to week 52 is included, though, per definition, no new responders can occur for the last 3 assessment time points (because sustained response needs to be at least over 3 weeks). It is very likely that with the analysis defined as it is a difference in time to sustained response is observed even when this actually only reflects the difference between the arms at week 52 as per the primary endpoint. A sustained response in the placebo arm in any case is a phenomena difficult to comprehend. The MAH was invited to comment and discuss which question the analysis is intended to answer and propose a more meaningful way to analyse the data. The Applicant provided additional analyses, which confirm that a higher number of sustained responses were achieved in the anifrolumab group. However, the results as pre-defined in the SAP and presented in the CSR with HRs, CIs and p-values (and corrected results as presented in the errata document) are not considered methodologically reliable. The issue is not pursued further because it does not impact results in the SmPC.

While time to flare is a recognised efficacy variable in the EMA guideline, the guideline states that an effect on the prevention of flares (decreased frequency/severity) should be measured either as a primary endpoint or as a key secondary endpoint. On the other hand, the other two endpoints are connected to the BICLA response and do not describe the treatment effect in the whole study population. As stated in the EMA guideline, supportive evidence derived from secondary endpoints is of particular interest to fully characterize the treatment effect, given the heterogeneity of SLE manifestations (see discussion on the IA below). With these considerations, the MAH was requested to justify the choice and clinical relevance of the key secondary endpoints and the chosen IA strategy. On request, the MAH provided some further justification for the clinical relevance of the endpoints. However, no discussion on the differences between choice of endpoints between the SC and IV indications was provided.

In terms of OCS tapering, the used target of ≤ 7.5 mg/day in the (key) secondary endpoints can be considered acceptable, although e.g. the most recent EULAR guideline (2024) recommends more stringent target of ≤ 5 mg/day.

The statistical methods outlined for the primary and secondary endpoints are overall standard and similar to those used in the IV studies.

An interim analysis with only 60% of the patients (i.e. 220/367 patients) was introduced late into the study. Enrolment continued after the 220 patients had been enrolled and the study was ongoing at the time of the assessment with further data to be collected. The MAH specified the interim analysis only for the primary endpoint and the secondary endpoints will be formally tested only when data on all 367 patients is available. This plan is not consistent with the regulatory strategy as the MAH submitted the dossier based on the interim analysis. Ideally, confirmatory results for all clinically relevant and important endpoints should have been available at the time of submission. Furthermore, the IA has been introduced late into the study as discussed below. These points are discussed under key Secondary Endpoint of Time to BICLA Response Sustained Through Week 52 above.

A comparison of the shared primary endpoint BICLA response at week 52 between TULIP SC and pivotal anifrolumab IV studies and post-hoc analysis of the key secondary endpoints across the studies (not originally included in the IV program) was also performed. While this comparison is helpful, it is considered only as supportive evidence in the current application.

Efficacy data and additional analyses

Changes in the planned conduct of the study

After the patient recruitment began, substantial changes were made to the study protocol with Amendment 2 and particularly Amendment 3 that added the 52-week OLE period to the study. Despite many of the substantial changes also concerned the DB period, including modifications to the eligibility criteria and allowed concomitant medications, the CHMP considered that a major impact on patient management and, as a consequence, safety and efficacy results was unlikely.

The analysis plan was changed in a profound manner. First, an efficacy interim analysis was added in an amendment and the timing and efficacy boundary of the interim analysis were again changed in a later amendment both occurring after first patient was enrolled. Furthermore, the list of secondary endpoints to be tested in a confirmatory manner (referred to as key secondary) was changed multiple times. The current interim analysis strategy was such that the interim was conducted only for the primary endpoint and secondary endpoints were to be tested only when week 52 data was available for all patients.

Importantly, there were no concerns at this stage that the changes would be data driven based on results of this double-blind study. From that point of view the study integrity was not considered compromised. Nevertheless, the CHMP reminded that such several, late, fundamental changes are not considered good practice.

Participant flow and numbers analysed

Out of the 220 randomised patients, 109 received anifrolumab and 111 placebo. Similar proportions of patients discontinued the treatment in anifrolumab and placebo groups (21.1% and 21.6%), most common reasons being subject decision (8.3% and 6.3%) and AEs (8.3% and 2.7%). Similar proportions also withdrew from the study without entering the OLE period (20.2% and 23.4% in the anifrolumab and placebo groups, respectively). Further, similar numbers completed the study without entering the OLE period (40.4% and 40.5% in the anifrolumab and placebo groups, respectively). In fact, only a small proportion of patients entered the OLE period (34/109 and 37/111). In a placebo-controlled study, it would have been a reasonable expectation that patients are interested to enter the OLE. The MAH clarified that the small number of patients entering the OLE period was due to the late protocol amendment to include the OLE period to the study. The number of important protocol violations were reported in 6 (5.5%) patients in the anifrolumab group and in 1 (0.9%) patient in the placebo group. The most commonly reported important protocol deviations were randomisation (incorrect randomisation or stratification) for 3 (2.8%) patients in the anifrolumab group and study intervention administration for 2 (1.8%) and 1 (0.9%) patients in the anifrolumab and placebo groups, respectively.

Overall, similar proportions of patients in the anifrolumab group and placebo groups had premature end of treatment and use of restricted medication, i.e. ICEs that were handled as per the composite strategy (patients were considered as non-responders in the primary analysis of efficacy). Thus, no bias was evident in this regard.

Baseline and demographics

The demographic characteristics between the treatment groups were well balanced, mean age was 42.7 and 89.1% were female.

The following SLE disease characteristics at baseline indicated slightly higher disease activity in the anifrolumab group vs. placebo group: proportion of patients with SLEDAI-2K score ≥10 (69.7% vs. 64.9%), mean clinical SLEDAI-2K (8.9 vs. 8.4), proportion of patients with at least one BILAG A

(46.8% vs. 42.3%), mean BILAG-global score (18.5 vs. 18.1) and mean PGA score (1.92 vs. 1.88, in the anifrolumab vs. placebo groups, respectively).

The medical and surgical history was generally well balanced between the group. However, the use of OCS and immunosuppressants at baseline was higher in the anifrolumab group vs. placebo group (85.3% vs. 79.3% and 61.5% vs. 50.5%, respectively). Upon CHMP's request, the MAH further clarified that despite the imbalance in the disease severity (i.e. SLEDAI-2K score < 10 points vs. ≥ 10 points) and in the use of SLE-related treatments (i.e. OCS dose <10 mg/day vs ≥10 mg/day and use vs. no use of immunosuppressants) between anifrolumab and placebo, the point estimates in all of these subgroups favoured anifrolumab over placebo in terms of BICLA response rate at week 52. Therefore, these imbalances were not thought to impact the overall interpretation of the study results. This was agreed by the CHMP.

Primary and secondary efficacy outcomes

Another concern was issued to clarify the primary analysis results because there was a discrepancy in the numbers and it was not evident how the number and type of ICEs was constructed and matched between tables, for example Study Disposition and Restricted Medication use. The MAH clarified that for both the primary endpoint of BICLA response as well as its components, the percentages presented are adjusted rates, calculated using stratified CMH and adjusting for stratification factors and used multiple imputation for some ICEs as defined in the SAP. Therefore, this issue was resolved, and a corresponding footnote was added to the SmPC. Regarding the question related to the ICEs, the MAH submitted an errata document, which included updated numbers for all efficacy results. On request, the MAH further clarified the numbers and confirmed that the results in the errata document are correct and supersede the results of the CSR. In conclusion, (IA as described in the errata document), the response rate of BICLA response at week 52 was 59.4% for anifrolumab and 43.9% for placebo, resulting in a 15.5% treatment difference (95% CI 2.3, 28.6). Therefore, the primary endpoint was met. The results of the sensitivity and supplementary analyses were consistent with those of the primary analysis.

The key secondary endpoints were all numerically in favour of anifrolumab, including BICLA response at week 52 with maintained low (or reduced) use of OCS, time to BICLA response sustained through week 52, and time to flare through week 52. The selection of the key secondary endpoints was different from the IV studies (see discussion above) and other than time to first flare do not measure clearly different manifestations of SLE compared to the primary endpoint. It was considered a major weakness that these endpoints were not hypothesis tested for the IA in the multiple testing procedure, which was planned only at the time of the final analysis.

There were only 42 and 50 events in the time to flare analysis, for anifrolumab and placebo respectively. Subjects treated with restricted medication, those with premature end of treatment, and those who died were regarded as flare in the time to first flare analysis. The MAH clarified, that 18.3% and 25.2% of patients in anifrolumab and placebo group, respectively, had clinical BILAG flares. The proportions of patients with first events due to an ICE of RM, PEOT (due to other reason), death were similar between the treatment arms, while fewer patients in the anifrolumab arm had a first ICE of PEOT (due to lack of efficacy), which is consistent with the overall efficacy results observed with SC anifrolumab vs. placebo.

As discussed in the methods section, the time to BICLA response sustained through week 52 does not appear to answer to any well-defined and clear question and is therefore of negligible value.

Nevertheless, the efficacy data as a whole, including the other secondary endpoints (i.e. reduced OCS dose to $\leqslant$ 7.5 mg/day in those with baseline OCS $\geqslant$ 10 mg/day, annual flare rate and SRI(4) response), suggest a modest, but clinically relevant efficacy for SC anifrolumab that is broadly similar to the efficacy seen with the approved IV anifrolumab (see also the post-hoc analysis of the TULIP

SC study vs. IV studies). The MAH has committed to submit the final CSR corresponding to the week 52 results for all patients, once available, and expected on 1Q2026.

Subgroup analysis

In the predefined subgroup analyses, point estimates showing favourable effect for anifrolumab over placebo was observed in all subgroups, except for geographical region United States of America and Asian race, which is likely random variability and related to the small number of patients in these subgroups.

Regarding the effect of immunogenicity on efficacy, the point estimates favouring anifrolumab over placebo was seen in both ADA negative and ADA positive subgroups. However, the number of ADA positive patients was too small to make any definite conclusions.

Post-hoc analysis

To support the SC anifrolumab efficacy assessment, the MAH also conducted a comparison of TULIP SC study and IV anifrolumab phase 3 studies 04 and 05 using the shared primary endpoint, i.e. BICLA response at week 52 and the key secondary endpoint of the TULIP SC study. Although the SLE disease characteristics of the study population in the studies were similar, the caveats in the non-randomized, post-hoc comparison across studies are recognised. Although there were apparent differences in the absolute BICLA response rates at week 52 between SC TULIP and IV anifrolumab studies, the estimated treatment effect between the studies was similar, i.e. 15.5% (95% CI 2.3, 28.6) in TULIP SC study, 16.3% (95% CI 6.3, 26.3) in the IV study 04 and 17.0% (95% CI 7.2, 26.8) in the IV study 05. Also, the key secondary endpoints selected for the TULIP SC study showed similar results to those in the IV anifrolumab studies, supporting broadly comparable efficacy between SC anifrolumab and IV anifrolumab.

2.6.7. Conclusions on the clinical efficacy

The efficacy data of TULIP SC study suggested a modest, but clinically relevant efficacy for SC anifrolumab that is broadly similar to the efficacy seen with the approved IV anifrolumab. Therefore, the clinical efficacy data supports the approval of the SC formulations as an add-on therapy for the treatment of adult patients with moderate to severe, active autoantibody-positive systemic lupus erythematosus (SLE), despite standard therapy.

2.6.8. Clinical safety

The safety data for the proposed new route of administration for Saphnelo (anifrolumab) 120 mg SC QW in the treatment of moderate to severe SLE, derive mainly from the single, pivotal, phase 3, randomized, double-blind (DB), multinational, multicenter, parallel-group, placebo-controlled study (TULIP SC; D3465C00001). Within this procedure, the MAH has provided safety results from an interim analysis (IA) of this pivotal study (N=346/367).

The analysis of safety data was based on the 52-week double-blind treatment period, including all available data up to the data cut off for the IA (23 July 2024), irrespective of whether they are ongoing in the study, have completed the 52-week double-blind treatment period, or have withdrawn from the study early (Safety Analysis Set, N = 346). All safety analyses for the 52-week double-blind treatment period were performed using the Safety Analysis Set, which included all patients who received at least one dose of the IMP.

To confirm that the safety of anifrolumab 120 mg SC QW was consistent with the established profile for anifrolumab 300 mg IV Q4W for up to 52 weeks of double-blind treatment, pooled safety data

from 2 Phase III studies D3461C00004 and D3461C00005, and one Phase II study CD-IA-MEDI-546-1013 (hereafter referred to as studies 04, 05, and 1013, respectively) are presented side-by-side with the TULIP SC data.

The SC Safety Analysis Set includes patients with a wider range of exposure times than those included in the IA FAS (the analysis set for assessment of efficacy; N = 220), as not all patients had completed the DB treatment period or withdrawn from the study early. Thus, a subset of AE analyses was also conducted for the population of 220 patients only (referred to as the SC 220 Safety Analysis Set). This was to confirm conclusions drawn from the comparison of SC and IV EAIR in a population where most patients had completed the 52 weeks DB treatment period.

Some data were also submitted for the open-label extension part of the study.

Demographic and baseline disease-related characteristics (Safety Analysis Set)

Demographic and baseline disease-related characteristics (Table *20*) were generally balanced between the anifrolumab 120 mg SC QW and placebo groups in TULIP SC. Patients in the study were representative of the intended target population for treatment with anifrolumab SC.

Baseline demographics and characteristics in TULIP SC were generally consistent with those of the patients included in IV studies 04 and 05. Differences were observed for race, ethnicity, and geographic region. A greater proportion of patients in TULIP SC were enrolled in Latin America and in Europe; a greater proportion of patients in the IV studies were enrolled in North America.

Table 20: Disease specific baseline characteristics (SC vs IV Safety analysis set)

		SC			**IV**		
	Statistic	**Anifrolumab 120 mg N = 176**	**Placebo N = 170**	**Total N = 346**	**Anifrolumab 300 mg N = 459**	**Placebo N = 466**	**Total N = 925**
SLEDAI-2K score at screening	N*	110	110	220	459	466	925
< 10	n (%)	37 (33.6)	35 (31.8)	72 (32.7)	148 (32.2)	146 (31.3)	294 (31.8)
> = 10	n (%)	73 (66.4)	75 (68.2)	148 (67.3)	311 (67.8)	320 (68.7)	631 (68.2)
	n	110	110	220	459	466	925
	Mean	11.2	10.4	10.8	11.3	11.2	11.2
	SD	3.72	2.62	3.24	3.82	3.81	3.81
	Median	10.0	10.0	10.0	10.0	10.0	10.0
	Min	6	6	6	6	6	6
	Max	22	18	22	26	37	37
OCS dose (mg/day)							
< 10	n (%)	88 (50.0)	96 (56.5)	184 (53.2)	198 (43.1)	203 (43.6)	401 (43.4)
> = 10	n (%)	88 (50.0)	74 (43.5)	162 (46.8)	250 (54.5)	251 (53.9)	501 (54.2)
	n	176	170	346	448	454	902

		SC			IV		
	Statistic	**Anifrolumab 120 mg N = 176**	**Placebo N = 170**	**Total N = 346**	**Anifrolumab 300 mg N = 459**	**Placebo N = 466**	**Total N = 925**
	Mean	8.5	7.5	8.0	10.0	10.2	10.1
	SD	6.24	6.18	6.22	9.81	8.51	9.18
	Median	10.0	7.2	7.5	10.0	10.0	10.0
	Min	0	0	0	0	0	0
	Max	33	30	33	99	50	99
OCS dose (mg/day) excluding patients not taking OCS							
< 10	n (%)	61 (34.7)	60 (35.3)	121 (35.0)	127 (27.7)	141 (30.3)	268 (29.0)
> = 10	n (%)	88 (50.0)	74 (43.5)	162 (46.8)	250 (54.5)	251 (53.9)	501 (54.2)
	n	149	134	283	377	392	769
	Mean	10.1	9.6	9.8	11.9	11.8	11.9
	SD	5.51	5.38	5.44	9.58	8.06	8.83
	Median	10.0	10.0	10.0	10.0	10.0	10.0
	Min	1	2	1	1	1	1
	Max	33	30	33	99	50	99
Immunosuppressants	n (%)	104 (59.1)	84 (49.4)	188 (54.3)	232 (50.5)	229 (49.1)	461 (49.8)
Azathioprine (mg/day)	n (%)	36 (20.5)	30 (17.6)	66 (19.1)	96 (20.9)	85 (18.2)	181 (19.6)
	Mean	96.5	98.3	97.3	94.8	104.9	99.5
	SD	35.93	30.75	33.43	49.33	105.91	80.90
	Median	100.0	100.0	100.0	100.0	100.0	100.0
	Min	50	50	50	25	14	14
	Max	150	150	150	200	1000	1000
Methotrexate (mg/week)	n (%)	41 (23.3)	33 (19.4)	74 (21.4)	79 (17.2)	93 (20.0)	172 (18.6)
	Mean	16.0	15.6	15.8	14.2	15.3	14.8
	SD	5.04	8.14	6.56	5.62	10.64	8.70
	Median	15.0	15.0	15.0	15.0	15.0	15.0
	Min	6	3	3	1	3	1
	Max	25	53	53	25	105	105

		SC			IV		
	Statistic	**Anifrolumab 120 mg N = 176**	**Placebo N = 170**	**Total N = 346**	**Anifrolumab 300 mg N = 459**	**Placebo N = 466**	**Total N = 925**
Mycophenolate (g/day)[a]	n (%)	27 (15.3)	22 (12.9)	49 (14.2)	66 (14.4)	58 (12.4)	124 (13.4)
	Mean	1.5	1.4	1.5	1.4	1.4	1.4
	SD	0.50	0.57	0.54	0.68	0.57	0.63
	Median	1.5	1.3	1.4	1.2	1.4	1.4
	Min	1	0	0	0	0	0
	Max	2	2	2	4	2	4
Cyclosporine (mg/kg/day)	n (%)	0	0	0	0	0	0
Tacrolimus (mg/kg/day)	n (%)	0	0	0	0	0	0
Mizoribine (mg/day)	n (%)	0	0	0	4 (0.9)	3 (0.6)	7 (0.8)
	Mean				112.5	150.0	128.6
	SD				47.87	0.00	39.34
	Median				125.0	150.0	150.0
	Min				50	150	50
	Max				150	150	150
More than 1 immunosuppressant	n (%)	1 (0.6)	1 (0.6)	2 (0.6)	13 (2.8)	10 (2.1)	23 (2.5)
OCS in combination with immunosuppressants							
Yes	n (%)	90 (51.1)	70 (41.2)	160 (46.2)	193 (42.0)	203 (43.6)	396 (42.8)
No	n (%)	86 (48.9)	100 (58.8)	186 (53.8)	259 (56.4)	254 (54.5)	513 (55.5)
OCS dose (mg/day)	n	90	70	160	193	203	396
	Mean	10.5	10.5	10.5	12.6	11.7	12.1
	SD	5.96	5.96	5.94	9.78	8.62	9.20
	Median	10.0	10.0	10.0	10.0	10.0	10.0
	Min	3	3	3	1	1	1
	Max	33	30	33	90	50	90

n:Number of subjects in analysis for a continuous variable and number of subjects per category for a categorical variable; N Number of subjects per treatment group; N* Number of subjects with available SLEDAI-2K value (used as the denominator for percentage calculation.

For SC study, only first 220 randomized subjects have SLEDAI-2K data extracted for analyses). Baseline is defined as the last measurement prior to first double-blind dose administration.

The baseline demographic characteristic were balanced between the treatment groups also for the SC Safety Analysis Set (N=346) subpopulation. The median age was 44.0 vs. 42.0 years the anifrolumab vs placebo treatment groups respectively. No differences were seen in weight, height, or BMI. In the subgroups numbers were also similar between treatment groups with numbers higher for the female, white race, the Not Hispanic or Latino group and the geographic region of Europe. These demographic data were similar to that of the IV safety set. Slight differences were observed for race, ethnicity, and geographic region.

2.6.8.1. Patient exposure

Table 21: Disposition (TULIP SC Safety analysis set)

	TULIP SC Safety Analysis Set		
	Anifrolumab 120mg n (%)	Placebo n (%)	Total n (%)
Subjects started treatment	176 (100)	170 (100)	346 (100)
Subjects completed double-blind treatment	88 (50.0)	86 (50.6)	174 (50.3)
Subjects discontinued double-blind treatment	30 (17.0)	36 (21.2)	66 (19.1)
Adverse event	12 (6.8)	5 (2.9)	17 (4.9)
Withdrawal by subject	12 (6.8)	13 (7.6)	25 (7.2)
Lost to follow-up	0	2 (1.2)	2 (0.6)
Severe non-compliance to protocol	0	0	0
Lack of efficacy	1 (0.6)	4 (2.4)	5 (1.4)
Condition under investigation worsened	0	0	0
Development of study specific discontinuation criteria	1 (0.6)	1 (0.6)	2 (0.6)
Other	4 (2.3)	11 (6.5)	15 (4.3)
Subjects ongoing on double-blind treatment at data cut-off date	58 (33.0)	48 (28.2)	106 (30.6)
Subjects withdrawn from study during double-blind treatment period	27 (15.3)	35 (20.6)	62 (17.9)
Adverse event	3 (1.7)	2 (1.2)	5 (1.4)
Death	1 (0.6)	0	1 (0.3)
Withdrawal by subject	15 (8.5)	16 (9.4)	31 (9.0)
Lost to follow-up	1 (0.6)	3 (1.8)	4 (1.2)
Development of study specific withdrawal criteria	1 (0.6)	2 (1.2)	3 (0.9)
Lack of efficacy	0	0	0
Condition under investigation worsened	0	0	0
Severe non-compliance to protocol	0	0	0
Physician Decision	4 (2.3)	8 (4.7)	12 (3.5)
Other	2 (1.1)	4 (2.4)	6 (1.7)

Percentages are based on the number of subjects started treatment. Data cut-off date is 2024-07-23. NA: Not applicable.

In TULIP SC, anifrolumab 120 mg or placebo was administered SC using the APFS. The study is being conducted at 145 sites in 16 countries. As of the DCO, a total of 346 patients were randomized and

received at least one dose of IP and were included in the Safety Analysis Set: 176 patients received anifrolumab 120 mg SC QW and 170 patients received placebo during the DB period. The total PY of treatment exposure to anifrolumab 120 mg SC was 128.6 PY and was similar between the anifrolumab and placebo groups (Table *22*). A total of 88 patients were treated with anifrolumab SC and completed the 52-week DB treatment period. In the SC+IV Pool, the total PY of treatment exposure was 548.0 PY in the anifrolumab group. Table *22* shows the duration of exposure.

Table 22: Duration of Exposure – During Double-Blind Treatment (Safety Analysis Set)

	Statistic	**Anifrolumab 120mg N = 176**	**Placebo N = 170**	**Total N = 346**
Total PYs of exposure		128.56	124.69	253.25
Duration (days)	N	176	170	346
	Mean	266.8	267.9	267.3
	SD	136.84	132.36	134.46
	Median	359.0	362.0	362.0
	Min	1	1	1
	Max	448	462	462

Exposure duration is calculated as: (Last dosing date + 28 days) – first dosing date + 1. The total PY of exposure is the sum of duration of exposure (days) of all patients in the respective treatment group divided by 365.25 (days/year).

2.6.8.2. Adverse events

The incidence of any AE during the double-blind treatment period was 74.4% in the anifrolumab 120 mg SC group and 71.2% in the placebo group (Table *23*). Most AEs were mild to moderate in intensity.

The proportions of patients with SAEs were low and balanced between the anifrolumab and placebo groups with no PT predominating during the 52-week double-blind treatment period (Table *23*). The proportions of patients with AEs leading to IP discontinuation were low (5.1% in the anifrolumab group and 2.9% in the placebo group) with no PT predominating.

Table 23: Overall summary of adverse events – during double-blind treatment (SC vs IV Safety analysis set)

	SC				IV			
	Anifrolumab 120 mg (N = 176)		Placebo (N = 170)		Anifrolumab 300 mg (N = 459)		Placebo (N = 466)	
	n(%)	EAIR per 100 PY	n(%)	EAIR per 100 PY	n(%)	EAIR per 100 PY	n(%)	EAIR per 100 PY
Any AE	131 (74.4)	277.8	121 (71.2)	244.9	399 (86.9)	291.8	370 (79.4)	225.4
Any SAE	19 (10.8)	15.5	15 (8.8)	12.4	54 (11.8)	13.6	78 (16.7)	20.8
Any SAE with outcome death	1 (0.6)	0.8	0	0	2 (0.4)	0.5	0	0
Any AE leading to discontinuation of IP	9 (5.1)	7.1	5 (2.9)	4.0	19 (4.1)	4.6	24 (5.2)	6.0
Any AESI	41 (23.3)	38.3	37 (21.8)	36.7	52 (11.3)	13.1	39 (8.4)	10.1
non-opportunistic serious infections	11 (6.3)	8.8	6 (3.5)	4.9	22 (4.8)	5.4	26 (5.6)	6.6
opportunistic infections	0	0	0	0	1 (0.2)	0.2	1 (0.2)	0.3
MACE	2 (1.1)	1.6	1 (0.6)	0.8	1 (0.2)	0.2	3 (0.6)	0.8
malignancy	0	0	0	0	3 (0.7)	0.7	3 (0.6)	0.7
herpes zoster	7 (4.0)	5.6	2 (1.2)	1.6	28 (6.1)	6.9	6 (1.3)	1.5
tuberculosis including latent tuberculosis	1 (0.6)	0.8	1 (0.6)	0.8	4 (0.9)	0.9	1 (0.2)	0.2
injection site reaction	27 (15.3)	23.7	29 (17.1)	28.0	-	-	-	-

EAIR (per 100-patient year) is defined as the sum of subjects with the event/[sum across subjects' time at risk for the event /(365.25)]*100, where time at risk is time to first event for subjects who experienced the event during the analysis period and time during the analysis period for subjects who do not experience the event. Confidence interval of the difference is constructed based on Miettinen and Nurminen method. Possibly related is defined as reasonable possibility that the AE was caused by investigational product, as assessed by investigator. Double-blind treatment period starts on the date of first study intervention and ends on 28 days following the date of last dose of double-blind study intervention for subjects who do not go into OLE or date of first dose of open-label treatment-1 for subjects who go into OLE. Subjects with multiple occurrences in the same category are counted once per category regardless of the number of occurrences.

Adverse drug reactions

The following PTs and medical concepts were identified as ADRs of anifrolumab based on the IV clinical studies (i.e., considered to have a reasonable possibility of having a causal association with anifrolumab treatment): upper respiratory tract infection (grouped terms), bronchitis (grouped terms), herpes zoster, respiratory tract infection (grouped terms), hypersensitivity, anaphylactic

reaction, and infusion related reaction. Arthralgia has been included as an ADR in the SmPC section 4.8. with unknown frequency based on post-marketing information.

The most commonly reported adverse reactions during anifrolumab treatment were upper respiratory tract infection (31%), bronchitis (10%), infusionrelated reaction (9.4%) and herpes zoster (6.0%). The most common serious adverse reaction was herpes zoster (0.4%).

Data for the SC+IV Pool were evaluated to assess potential ADRs, irrespective of route of administration, during 52 weeks of treatment with anifrolumab. Frequencies of ADRs are summarized for the SC 220+IV Pool Safety Analysis Set (i.e., patients who completed the 52-week double blind treatment period or were prematurely discontinued in TULIP SC plus the IV Pool) to ensure comparable durations of exposure in TULIP SC and the IV Pool; different exposure times would confound the safety profile, as some events occur more frequently early on during treatment (Table *24*).

There were no events of anaphylaxis reported in the SC+IV Pool (the one anaphylactic event reported with anifrolumab was reported at the 150 mg dose and therefore is not included in the SC+IV Pool and SC220+IV Pool).

Table 24: Adverse Drug Reactions by System Organ Class and Preferred Term - during double-blind treatment (SC 220 + IV Safety analysis set)

	Anifrolumab 120 mg SC and 300 mg IV N = 569		**Placebo N = 576**	
System Organ Class Preferred Term (MedDRA version 27.0)	**n (%)**	**Classification**	**n (%)**	Classification
Infections and infestations				
Upper respiratory tract infection [b]	176 (30.9)	Very common	117 (20.3)	Very common
Bronchitis [c]	58 (10.2)	Very common	30 (5.2)	Common
Herpes zoster [a]	34 (6.0)	Common	8 (1.4)	Common
Respiratory tract infection [d]	17 (3.0)	Common	8 (1.4)	Common
Immune system disorders				
Hypersensitivity	14 (2.5)	Common	3 (0.5)	Uncommon
Anaphylactic reaction	0	Not known	0	Not known

Frequencies of occurrence of adverse reactions are defined as: very common (> = 10%), common (> = 1% to < 10%); uncommon (> = 0.1% to < 1%); rare (> = 0.01% to < 0.1%); very rare (< 0.01%); not known (cannot be estimated from available data). [a] grouped term that includes: PT Herpes zoster; [b] Grouped term that includes: PT Nasopharyngitis, PT Pharyngitis, PT Upper respiratory tract infection; [c] Grouped term that includes: PT Bronchitis, PT Bronchitis viral, PT Tracheobronchitis; [d] Grouped term that includes: PT Respiratory tract infection, PT Respiratory tract infection viral. n, Number of subjects per category; N Number of subjects per treatment group. The preferred term of 'Respiratory tract infection bacterial' was also included as an ADR for anifrolumab, but no cases were found in the SC 220 + IV Safety Analysis Set.

2.6.8.3. Serious adverse events, deaths and other significant events

AEs of special interest

In TULIP SC, consistent with the known safety profile of anifrolumab 300 mg IV Q4W, patients in the anifrolumab 120 mg SC QW group had an increased incidence of herpes zoster compared with the

placebo group during the 52-week DB treatment period (Table *25*). Most events were cutaneous localized, nonserious, mild or moderate in intensity, resolved with antiviral therapy, and did not lead to IP discontinuation. In the anifrolumab 120 mg SC QW group, 3 of the 7 events had an onset during the first 12 weeks of treatment. The incidence of herpes zoster infections with anifrolumab 120 mg SC QW treatment was similar to that seen with anifrolumab 300 mg IV Q4W treatment.

Table 25: Herpes zoster - during double-blind treatment (SC vs IV Safety analysis set)

						Placebo				
AESI category	**Anifrolumab**	**N**	**n (%)**	**Exposure years**	**EAIR per 100 PY**	**N**	**n (%)**	**Exposure years**	**EAIR per 100 PY**	**EAIR per 100 PY (Anifrolumab - Placebo) (95% CI)**
Any AE	120 mg SC	176	7 (4.0)	124.5	5.6	170	2 (1.2)	124.4	1.6	4.0 (-0.9, 10.2)
	300 mg IV	459	28 (6.1)	406.9	6.9	466	6 (1.3)	399.5	1.5	5.4 (2.7, 8.6)
Any SAE	120 mg SC	176	0	128.6	0	170	0	124.7	0	0.0 (-3.1, 3.0)
	300 mg IV	459	2 (0.4)	418.5	0.5	466	0	403.0	0	0.5 (-0.5, 1.7)
Any SAE with outcome death	120 mg SC	176	0	128.6	0	170	0	124.7	0	0.0 (-3.1, 3.0)
	300 mg IV	459	0	419.4	0	466	0	403.0	0	0.0 (-1.0, 0.9)
Any AE leading to discontinuation of IP	120 mg SC	176	1 (0.6)	128.5	0.8	170	0	124.7	0	0.8 (-2.3, 4.4)
	300 mg IV	459	2 (0.4)	419.3	0.5	466	0	403.0	0	0.5 (-0.4, 1.8)
Any cutaneous (localized) herpes zoster	120 mg SC	176	6 (3.4)	124.6	4.8	170	2 (1.2)	124.4	1.6	3.2 (-1.6, 9.1)
	300 mg IV	459	18 (3.9)	409.9	4.4	466	5 (1.1)	400.2	1.2	3.2 (0.9, 5.9)
Any cutaneous disseminated herpes zoster	120 mg SC	176	0	128.6	0	170	0	124.7	0	0.0 (-3.1, 3.0)
	300 mg IV	459	2 (0.4)	418.0	0.5	466	0	403.0	0	0.5 (-0.5, 1.7)
Any visceral disseminated herpes zoster	120 mg SC	176	1 (0.6)	128.5	0.8	170	0	124.7	0	0.8 (-2.3, 4.4)
	300 mg IV	459	0	419.4	0	466	0	403.0	0	0.0 (-1.0, 0.9)

EAIR is defined as the sum of subjects with the event/[sum across subjects' time at risk for the event /(365.25)] * 100, where time at risk is time to first event for subjects who experienced the event during the analysis period and time during the analysis period for subjects who do not experience the event. In the event that multiple studies are combined, the Miettinen and Nurminen weighted average EAIRs are presented for each treatment group. 95% CIs are calculated via the Miettinen and Nurminen method, stratified by study where applicable.
During double-blind treatment: Includes adverse events with an onset date on or after the date of first dose of IP up to and including 28 days following the date of last double-blind IP dose.
Subjects with multiple occurrences are counted once per AE category regardless of the number of occurrences. n Number of subjects per category; N Number of subjects per treatment group.
MedDRA version 27.0.

Tuberculosis (Including Latent Tuberculosis)

In TULIP SC, a total of 2 events of tuberculosis (including latent tuberculosis) were reported in the 52-week DB treatment period. There was one event of latent tuberculosis (assessed as not possibly related to IP and not an SAE) based on positive QuantiFERON test during screening in the anifrolumab 120 mg SC QW group. There was one event of extrapulmonary tuberculosis (assessed as possibly related to IP, categorized as an SAE, and led to IP discontinuation) in the placebo treatment group. No events of active tuberculosis were reported for the IV Pool.

MACE

In TULIP SC, 7 events reported for 7 patients during the 52-week DB treatment period plus follow-up were submitted to the CV-EAC; of these, a total of 3 patients had CV-EAC-confirmed MACE events: 2 in the anifrolumab 120 mg SC QW group (Myocardial infarction [non-fatal] and Stroke [non-fatal]) and 1 in the placebo group (Myocardial infarction [non-fatal]).

The incidence of CV-EAC-confirmed MACE during the 52-week DB treatment period plus follow-up period with anifrolumab 120 mg SC QW treatment was low and similar to that seen during the DB treatment period in TULIP SC and with anifrolumab 300 mg IV Q4W treatment.

Malignancy

In TULIP SC, no malignancies were reported during the 52-week DB treatment period. Incidences of malignancies with anifrolumab 300 mg IV Q4W were low.

Injection Site Reactions

In TULIP SC, the proportions of patients with AESIs of injection site reactions were similar in the anifrolumab 120 mg SC QW group (27 patients [15.3%]) and the placebo group (29 patients [17.1%]). All injection site reaction AESIs were nonserious, mild/moderate in intensity, and transient in nature. None resulted in discontinuation of IP. Most injection site reaction AEs were reported in the first 12 weeks of treatment in both treatment groups. According to the MAH, based on review of all available safety information, a reasonable possibility of a causal relationship between anifrolumab 120 mg administered SC QW and injection site reactions has not been established at this time.

Other significant events

Hypersensitivity and Anaphylaxis

Consistent with anifrolumab IV administration, there was a low rate of hypersensitivity reactions with anifrolumab 120 mg administered SC QW (2 patients) during the 52-week DB treatment period. There was 1 patient with a hypersensitivity AE that led to discontinuation of IP and was assessed by the investigator as possibly related to IP.

There were no events of anaphylactic reactions reported with anifrolumab 120 mg SC QW or 300 mg IV Q4W treatment. (One anaphylactic event was reported for anifrolumab 150 mg and therefore is not included in the IV Pool.)

Suicidal Ideation and Attempts

There was no evidence of an increased risk in suicidal ideation or behaviour in patients receiving anifrolumab compared with placebo, as assessed by the C-SSRS. There was no apparent increase in AEs of depression based on an evaluation of PTs.

Serious Adverse Events

In TULIP SC, there were no clinically meaningful differences in the frequency and event rate of SAEs (including events with the outcome of death) between the anifrolumab 120 mg SC QW and placebo groups during the 52-week DB treatment period (Table *26*). The SAEs of pneumonia (5 events in the anifrolumab 120 mg SC QW group and 1 event in the placebo group), extrapulmonary tuberculosis (placebo group), tubo-ovarian abscess (placebo group), cellulitis (placebo group), osteomyelitis (placebo group), and renal abscess (placebo group) were assessed as possibly related to IP by the Investigator.

The most common SOC with reported SAEs in TULIP SC was Infections and Infestations for both treatment groups during the 52-week DB treatment period (Table *26*). The only SAE PTs that were reported in more than one patient were pneumonia and dengue fever in the anifrolumab 120 mg SC QW group.

Incidences of SAEs with anifrolumab 120 mg SC QW treatment were similar to those observed with anifrolumab 300 mg IV Q4W treatment. The most frequently reported PT in TULIP SC and in the IV Pool was pneumonia (Table *26*).

Table 26: Serious adverse events (at least 2 patients in any treatment group) - during double-blind treatment (SC vs IV Safety analysis set)

						Placebo				
Preferred Term (MedDRA version 27.0)	**Anifrolumab**	**N**	**n (%)**	**Exposure years**	**EAIR per 100 PY**	**N**	**n (%)**	**Exposure years**	**EAIR per 100 PY**	**EAIR per 100 PY (Anifrolumab - Placebo) (95% CI)**
Any SAE	120 mg SC	176	19 (10.8)	122.4	15.5	170	15 (8.8)	120.8	12.4	3.1 (-6.7, 13.1)
	300 mg IV	459	54 (11.8)	397.9	13.6	466	78 (16.7)	376.0	20.8	-7.1 (-13.2, -1.3)
Pneumonia	120 mg SC	176	4 (2.3)	127.6	3.1	170	1 (0.6)	124.3	0.8	2.3 (-1.7, 7.3)
	300 mg IV	459	8 (1.7)	417.3	1.9	466	9 (1.9)	400.4	2.3	-0.4 (-2.6, 1.7)
Dengue fever	120 mg SC	176	3 (1.7)	126.6	2.4	170	0	124.7	0	2.4 (-0.7, 7.0)
	300 mg IV	459	0	419.4	0	466	0	403.0	0	0.0 (-1.0, 0.9)
Systemic lupus erythematosus	120 mg SC	176	1 (0.6)	127.9	0.8	170	1 (0.6)	124.6	0.8	-0.0 (-3.8, 3.7)
	300 mg IV	459	7 (1.5)	416.4	1.7	466	14 (3.0)	399.4	3.5	-1.9 (-4.4, 0.4)
Anaemia	120 mg SC	176	0	128.6	0	170	0	124.7	0	0.0 (-3.1, 3.0)
	300 mg IV	459	0	419.4	0	466	2 (0.4)	402.2	0.5	-0.5 (-1.8, 0.4)
Angioedema	120 mg SC	176	0	128.6	0	170	0	124.7	0	0.0 (-3.1, 3.0)
	300 mg IV	459	2 (0.4)	418.6	0.5	466	0	403.0	0	0.5 (-0.5, 1.8)
Appendicitis	120 mg SC	176	0	128.6	0	170	0	124.7	0	0.0 (-3.1, 3.0)
	300 mg IV	459	3 (0.7)	418.7	0.7	466	0	403.0	0	0.7 (-0.2, 2.1)
Asthma	120 mg SC	176	0	128.6	0	170	0	124.7	0	0.0 (-3.1, 3.0)
	300 mg IV	459	2 (0.4)	418.7	0.5	466	1 (0.2)	403.0	0.3	0.2 (-0.9, 1.5)
Atrial fibrillation	120 mg SC	176	0	128.6	0	170	0	124.7	0	0.0 (-3.1, 3.0)

						Placebo				
Preferred Term (MedDRA version 27.0)	**Anifrolumab**	**N**	**n (%)**	**Exposure years**	**EAIR per 100 PY**	**N**	**n (%)**	**Exposure years**	**EAIR per 100 PY**	**EAIR per 100 PY (Anifrolumab - Placebo) (95% CI)**
	300 mg IV	459	0	419.4	0	466	2 (0.4)	402.2	0.5	-0.5 (-1.8, 0.4)
Chest pain	120 mg SC	176	0	128.6	0	170	0	124.7	0	0.0 (-3.1, 3.0)
	300 mg IV	459	2 (0.4)	418.8	0.5	466	1 (0.2)	403.0	0.3	0.2 (-0.9, 1.5)
Gastroenteritis	120 mg SC	176	0	128.6	0	170	0	124.7	0	0.0 (-3.1, 3.0)
	300 mg IV	459	2 (0.4)	419.0	0.5	466	3 (0.6)	401.3	0.8	-0.3 (-1.8, 1.1)
Gastroenteritis viral	120 mg SC	176	0	128.6	0	170	0	124.7	0	0.0 (-3.1, 3.0)
	300 mg IV	459	2 (0.4)	418.4	0.5	466	0	403.0	0	0.5 (-0.5, 1.7)
Herpes zoster	120 mg SC	176	0	128.6	0	170	0	124.7	0	0.0 (-3.1, 3.0)
	300 mg IV	459	2 (0.4)	418.5	0.5	466	0	403.0	0	0.5 (-0.5, 1.7)
Influenza	120 mg SC	176	0	128.6	0	170	0	124.7	0	0.0 (-3.1, 3.0)
	300 mg IV	459	2 (0.4)	418.3	0.5	466	1 (0.2)	402.2	0.3	0.2 (-1.0, 1.5)
Ischaemic stroke	120 mg SC	176	0	128.6	0	170	0	124.7	0	0.0 (-3.1, 3.0)
	300 mg IV	459	0	419.4	0	466	2 (0.4)	401.1	0.5	-0.5 (-1.9, 0.4)
Pyrexia	120 mg SC	176	0	128.6	0	170	0	124.7	0	0.0 (-3.1, 3.0)
	300 mg IV	459	0	419.4	0	466	2 (0.4)	402.1	0.5	-0.5 (-1.8, 0.4)
Radius fracture	120 mg SC	176	0	128.6	0	170	0	124.7	0	0.0 (-3.1, 3.0)
	300 mg IV	459	0	419.4	0	466	2 (0.4)	402.3	0.5	-0.5 (-1.8, 0.4)
Sepsis	120 mg SC	176	0	128.6	0	170	0	124.7	0	0.0 (-3.1, 3.0)

						Placebo				
Preferred Term (MedDRA version 27.0)	**Anifrolumab**	**N**	**n (%)**	**Exposure years**	**EAIR per 100 PY**	**N**	**n (%)**	**Exposure years**	**EAIR per 100 PY**	**EAIR per 100 PY (Anifrolumab - Placebo) (95% CI)**
	300 mg IV	459	0	419.4	0	466	2 (0.4)	401.5	0.5	-0.5 (-1.8, 0.4)
Urinary tract infection	120 mg SC	176	0	128.6	0	170	0	124.7	0	0.0 (-3.1, 3.0)
	300 mg IV	459	2 (0.4)	418.2	0.5	466	1 (0.2)	402.8	0.2	0.2 (-1.0, 1.5)
Vasculitis	120 mg SC	176	0	128.6	0	170	0	124.7	0	0.0 (-3.1, 3.0)
	300 mg IV	459	0	419.4	0	466	2 (0.4)	403.0	0.5	-0.5 (-1.8, 0.4)

EAIR is defined as the sum of subjects with the event/[sum across subjects' time at risk for the event /(365.25)] * 100, where time at risk is time to first event for subjects who experienced the event during the analysis period and time during the analysis period for subjects who do not experience the event. In the event that multiple studies are combined, the Miettinen and Nurminen weighted average EAIRs are presented for each treatment group. 95% CIs are calculated via the Miettinen and Nurminen method, stratified by study where applicable. During double-blind treatment: Includes adverse events with an onset date on or after the date of first dose of IP up to and including 28 days following the date of last double-blind IP dose. Subjects with multiple occurrences of the same preferred term are counted once regardless of the number of occurrences. Table is sorted by decreasing frequency on preferred term level in Anifrolumab 120 mg treatment group
n Number of subjects per category; N Number of subjects per treatment group.

In TULIP SC, SAEs by SOC and PT with anifrolumab 120 mg SC in the 52-week DB treatment period plus follow-up and in the OLE period through the IA DCO were generally consistent with those observed during the 52-week DB treatment period.

Deaths

As of the DCO for TULIP SC, one death occurred in the anifrolumab 120 mg SC QW group due to the AE PT gastrointestinal infection. The event was assessed as not possibly related to IP by the Investigator and considered to be related to the patient's underlying conditions. A structured patient narrative was provided in the CSR.

ADRs of special interest, serious ADRs and deaths causally related to the medicinal product

According to the MAH incidence of ADRs, with anifrolumab 120 mg administered SC QW was consistent with the established safety profile of anifrolumab 300 mg Q4W administered by IV infusion. Collated data namely on the subgroups on AESI, SAE and deaths were not presented.

The single event of death was assessed as not possibly related to the IMP.

2.6.8.4. Laboratory findings

Consistent with anifrolumab 300 mg IV Q4W, there were no clinically meaningful differences between treatments in clinical laboratory values with anifrolumab 120 mg SC QW during the 52-week DB treatment period.

There was no clinically meaningful worsening in hematology, clinical chemistry, and urinalysis values during 52 weeks of treatment with anifrolumab 120 mg SC QW. Mean hematology values were generally similar between the anifrolumab 120 mg SC QW and placebo groups at baseline and at Week 52, with the exception of mean change from baseline in lymphocyte levels showing improvement in the anifrolumab group. There were no other clinically meaningful differences noted between the treatment groups in categorical shifts and no other differences in the frequency or pattern of potentially clinically significant treatment-emergent changes from baseline in hematology variables at 52 weeks.

Mean clinical chemistry values were generally similar between the anifrolumab 120 mg SC QW and placebo groups at baseline and at Week 52. There were no clinically meaningful differences noted between the treatment groups in categorical shifts and no other differences in the frequency or pattern of potentially clinically significant treatment-emergent changes from baseline in clinical chemistry variables at 52 weeks.

There were no Hy's Law cases (AST or ALT ≥ 3 × ULN and total bilirubin ≥ 2 × ULN) reported during the 52-week treatment period.

No trends were observed between the anifrolumab 120 mg SC QW and placebo groups in the pattern and frequency of patients shifting from negative to positive values in urinalysis tests during the 52-week DB treatment period.

2.6.8.5. In vitro biomarker test for patient selection for safety

N/A

2.6.8.6. Safety in special populations

For ages 65 and older, only the ≥ 65 age category is shown in Table *27*, since there were no patients randomized in TULIP SC or the IV studies who were older than 70 years of age (based on inclusion criteria adults 18 to 70 years of age in TULIP SC and the Phase 3 IV studies and 18 to 65 years in the Phase 2 IV study). Therefore, all 36 patients included in this category are 65 to 70 years of age.

Table 27: Overall summary of adverse events by age – during double-blind treatment (SC + IV safety analysis set)

	Anifrolumab 120 mg SC + 300 mg IV		Placebo	
AE Category	< 65 (N = 611)	> = 65 (N = 24)	< 65 (N = 624)	> = 65 (N = 12)
Any AE	510 (83.5)	20 (83.3)	481 (77.1)	10 (83.3)
Any SAE	69 (11.3)	4 (16.7)	90 (14.4)	3 (25.0)
Any SAE with outcome death	2 (0.3)	1 (4.2)	0	0
Any AE leading to discontinuation of IP	26 (4.3)	2 (8.3)	29 (4.6)	0
Any severe AE	54 (8.8)	1 (4.2)	44 (7.1)	1 (8.3)
Any related AE	208 (34.0)	7 (29.2)	166 (26.6)	3 (25.0)
Any AESI	90 (14.7)	3 (12.5)	75 (12.0)	1 (8.3)
Non-opportunistic serious infections	31 (5.1)	2 (8.3)	32 (5.1)	0
Opportunistic infections	1 (0.2)	0	1 (0.2)	0
MACE	3 (0.5)	0	4 (0.6)	0
Malignancy	3 (0.5)	0	3 (0.5)	0
Herpes zoster	35 (5.7)	0	8 (1.3)	0
Tuberculosis including latent TB	5 (0.8)	0	2 (0.3)	0
Injection site reaction	26 (4.3)	1 (4.2)	28 (4.5)	1 (8.3)

Per the inclusion criteria, subjects aged 18 – 70 years old were enrolled in the study. Therefore, age groups of < 65 and > = 65 years are presented as no subjects older than 70 were enrolled. During double-blind treatment: The table includes adverse events with an onset date on or after the date of first dose of IP up to and including 28 days following the date of last double-blind IP dose. For subjects who go into open-label treatment, including events up until the date of first dose of open-label treatment-1. Subjects with multiple occurrences in the same category are counted once per category regardless of the number of occurrences. IP Investigational product; MACE Major acute cardiovascular events; n Number of subjects per category; N Number of subjects per treatment group. MedDRA version 27.0

As claimed by the MAH, there are no AE data available from TULIP SC for the indicated special populations of hepatically impaired, renally impaired or pregnant patients. Both hepatically impaired and renally impaired patients were excluded from TULIP SC (and other anifrolumab studies) to protect potentially vulnerable patients and to avoid factors that may confound a complete understanding of the safety data.

Anifrolumab is eliminated by a target-mediated non-linear pathway through binding to IFNAR1 as well as a non-specific linear pathway in the reticuloendothelial system. Generally, clearance of monoclonal antibodies by the liver is considered to be a minor pathway. Therefore, there is no scientific rationale to suspect that the safety profile of patients with moderate to severe hepatic impairment may differ significantly to that characterized so far for the general target population.

Similarly, there is no scientific rationale, based on anifrolumab' s clearance mechanisms, to suspect the safety profile of anifrolumab in patients with severe renal impairment (due to lupus nephritis or any other cause) may differ from the general target population. Additionally, although patients with severe renal disease were not included in the SLE clinical program, patients with mild or moderate renal disease

(n = 427) were enrolled in the completed Phase III IV studies. There were no differences in PK observed for patients with mild to moderate renal disease compared to patients with normal renal function.

For these reasons, neither hepatic nor renal impairment are considered missing information in the RMP.

For ethical reasons, as indicated by the MAH, pregnant patients have been excluded from anifrolumab studies, including TULIP SC. A small number of patients reported pregnancies in the anifrolumab program, but as patients were discontinued from IP once their pregnancy was known, there are no data of patients taking anifrolumab throughout the entirety of their pregnancy, and there are no data on the effect of anifrolumab on patients who are breastfeeding or their offspring. Just 2 pregnancies were reported in the double-blind period of TULIP SC, both in the placebo group. Pregnancy is considered missing information in the RMP and a post-authorization pregnancy study is being conducted.

Intrinsic Factors

The AE and SAE profile of anifrolumab 120 mg SC QW was generally consistent across pre-defined subgroups (sex, age, race, BMI, disease-related factors, and ADA status) based on analyses of AEs by category, common AEs, and SAEs, although there were small numbers of patients in some subgroups.

Adverse Events by Anti-drug Antibody Status

Based on MAH, anifrolumab administered SC is poorly immunogenic in patients with moderate to severe SLE. There was no apparent effect of ADA-positive status on the overall incidence of AEs in TULIP SC, but due to very small numbers of ADA-positive patients, it was not possible to draw firm conclusions.

Extrinsic Factors

The AE and SAE profile of anifrolumab 120 mg SC QW was generally consistent across the pre-defined geographic region subgroups (Asia Pacific, Europe, Latin America, US/Canada, Rest of World) and concomitant medication use at baseline (immunosuppressant use) based on analyses of AEs by category, common AEs, and SAEs.

ADRs in special populations

According to the MAH incidences of ADRs, with anifrolumab 120 mg administered SC QW was consistent with the established safety profile of anifrolumab 300 mg Q4W administered by IV infusion. Collated data on the subgroups of special populations were not presented.

2.6.8.7. Immunological events

In the Device PK bridging study, ADA titer, ADA positivity, and nAb positivity at baseline, on Day 29 and Day 57 were assessed. Overall, the immunogenicity of anifrolumab SC was very low in both devices (AI or APFS) and there were no differences in relation to device used for administration, with total 3 (1.7%) participants ADA positive on Day 57 (1/90 [1.1%] AI device group; 2/90 [2.2%] APFS device group). Titers for the 3 ADA-positive participants were low, but all detected ADAs (3/180) showed neutralizing capabilities.

In the TULIP SC study, Pre dose sample for ADAs were planned to be collected at Week 0, 12, 24, 36, 52, 104. The data cut-off date for PK, PD, and immunogenicity assessments was 28 May 2024. At the time of data cut-off date, only the data from first 220 patients were available for PK, PD, and immunogenicity assessments. All treatment-emergent-ADA-positive patients were positive during the double-blind treatment period. Among ADA-positive patients who received anifrolumab, no patients were

classified as treatment-emergent nAb-positive in the study, suggesting that the detected ADAs lacked neutralizing properties in this study (Table *28*).

Table 28: Summary of Anti-Drug Antibody Responses During Double-blind Treatment and Follow-up (Safety Analysis Set)

ADA category	Statistic	Anifrolumab 120mg N = 176	Placebo N = 170
ADA prevalence (ADA positive at baseline and/or post-baseline)	n/Nobs [a] (%)	11/110 (10.0)	10/110 (9.1)
	Median	80.0	120.0
	Min, max	39, 320	39, 2560
ADA incidence (TE-ADA positive)	n/Nobs [b] (%)	6/107 (5.6)	7/105 (6.7)
	Median	160.0	160.0
	Min, max	39, 320	39, 1280
Treatment-induced ADA positive	n/Nobs [b] (%)	6/107 (5.6)	7/105 (6.7)
	Median	160.0	160.0
	Min, max	39, 320	39, 1280
Treatment-boosted ADA positive	n/Nobs [b] (%)	0/107	0/105
	Median	-	-
	Min, max	-, -	-, -
Non-TE-ADA positive	n/Nobs [b] (%)	5/107 (4.7)	3/105 (2.9)
	Median	40.0	39.0
	Min, max	40, 80	39, 2560
Both baseline and post-baseline positive	n/Nobs [b] (%)	2/107 (1.9)	2/105 (1.9)
	Median	60.0	39.0
	Min, max	40, 80	39, 39
Only baseline positive	n/Nobs [c] (%)	3/110 (2.7)	1/109 (0.9)
	Median	40.0	2560.0
	Min, max	40, 80	2560, 2560
ADA persistently positive	n/Nobs [b] (%)	3/107 (2.8)	2/105 (1.9)
	Median	80.0	200.0
	Min, max	39, 320	80, 320
ADA transiently positive	n/Nobs [b] (%)	3/107 (2.8)	5/105 (4.8)
	Median	160.0	160.0
	Min, max	160, 320	39, 1280
TE-ADA positive with maximum post-baseline titer > median of maximum post-baseline titers	n/Nobs [b] (%)	2/107 (1.9)	3/105 (2.9)
	Median	320.0	640.0
	Min, max	320, 320	320, 1280

ADA category	Statistic	Anifrolumab 120mg N = 176	Placebo N = 170
nAb prevalence (nAb positive at baseline and/or post-baseline)	n/Nobs [a] (%)	0/110	0/110
	Median	-	-
	Min, max	-, -	-, -
nAb incidence (treatment-induced nAb positive)	n/Nobs [b] (%)	0/107	0/105
	Median	-	-
	Min, max	-, -	-, -

[a] Nobs is the number of patients with an ADA result at baseline and/or post-baseline. [b] Nobs is the number of patients with an ADA result at baseline and at least one post-baseline assessment. [c] Nobs is the number of patients with an ADA result at baseline. For IA, only first 220 randomized subjects are considered with data cut-off of May 28 2024. Summary statistics are calculated based on the maximum post-baseline titer for each ADA-positive patient within each treatment group, with the exception of the following categories: only baseline positive (based on the baseline titer) and ADA and nAb prevalence (based on the maximum titer, baseline or post-baseline). Post-baseline assessments include assessments on or after date of first dose. Baseline is the last non-missing value prior to administration of the first dose of IP. Percentages are based on Nobs. Titers of borderline positive measurements reported as < = 40 (limit of detection) are imputed as 39.

Median ADA titers in the anifrolumab group were similar to or lower than those in placebo (range of 40.0 to 320.0 anifrolumab; 39.0 to 2560.0 placebo) and close to the MRD of 40. The ADA titer did not consistently increase over time, suggesting that maturation of ADA did not occur***.***

Due to the low level of immunogenicity the effect of ADA on PK, efficacy or safety could not be conclusively assessed (for further information see specific sections for PK on clinical pharmacology discussion 2.6.3., and discussion on clinical ***efficacy 2.6.7. and discussion on clinical safety 2.6.9.)***

2.6.8.8. Safety related to drug-drug interactions and other interactions

No drug interaction studies were conducted.

Immunisations/Immune response

In a previous variation application, the MAH submitted the final study report for the NAÏVE study D3461C00023/ESR-20-21053. This study was concluded to fulfil the Post-Authorisation Safety Category 3 study, pending only a commitment to update the Saphnelo PI texts. This PI text update is now provided within this variation.

The NAÏVE study was a phase I, non-randomised, multi-centre, open-label, parallel group study to evaluate the potential impact of anifrolumab administered intravenously (IV) on the effectiveness of immune responses to seasonal influenza vaccination in women or men of any race between the ages of 18 and 70 years with active moderate to severe manifestations of SLE.

2.6.8.9. Discontinuation due to adverse events

In TULIP SC, during the 52-week DB treatment period, proportions of patients with AEs leading to discontinuation of treatment were low in the anifrolumab 120 mg SC QW and placebo groups with no PT predominating (Table *29*). One additional AE leading to IP discontinuation (PT: lupus nephritis) was identified as missing in the anifrolumab group after the interim clinical data lock.

Incidences of AEs leading to discontinuation of anifrolumab 120 mg SC QW treatment were similar to those observed with anifrolumab 300 mg IV Q4W treatment (Table *29*).

Table 29: All adverse events leading to discontinuation of IP - during double-blind treatment (SC vs IV Safety analysis set)

						Placebo				
Preferred Term (MedDRA version 27.0)	**Anifrolumab**	**N**	**n (%)**	**Exposure years**	**EAIR per 100 PY**	**N**	**n (%)**	**Exposure years**	**EAIR per 100 PY**	**EAIR per 100 PY (Anifrolumab - Placebo) (95% CI)**
Any AE leading to IP discontinuation	120 mg SC	176	9 (5.1)	127.4	7.1	170	5 (2.9)	124.2	4.0	3.0 (-3.2, 9.9)
	300 mg IV	459	19 (4.1)	418.1	4.6	466	24 (5.2)	401.3	6.0	-1.4 (-4.8, 1.8)
Acute myocardial infarction	120 mg SC	176	1 (0.6)	128.5	0.8	170	0	124.7	0	0.8 (-2.3, 4.4)
	300 mg IV	459	0	419.4	0	466	0	403.0	0	0.0 (-1.0, 0.9)
Cerebrovascular accident	120 mg SC	176	1 (0.6)	128.5	0.8	170	0	124.7	0	0.8 (-2.3, 4.4)
	300 mg IV	459	0	419.4	0	466	0	403.0	0	0.0 (-1.0, 0.9)
Gastric ulcer	120 mg SC	176	1 (0.6)	128.5	0.8	170	0	124.7	0	0.8 (-2.3, 4.4)
	300 mg IV	459	0	419.4	0	466	0	403.0	0	0.0 (-1.0, 0.9)
Gastrointestinal infection	120 mg SC	176	1 (0.6)	128.5	0.8	170	0	124.7	0	0.8 (-2.3, 4.4)
	300 mg IV	459	0	419.4	0	466	0	403.0	0	0.0 (-1.0, 0.9)
Herpes zoster	120 mg SC	176	1 (0.6)	128.5	0.8	170	0	124.7	0	0.8 (-2.3, 4.4)
	300 mg IV	459	2 (0.4)	419.3	0.5	466	0	403.0	0	0.5 (-0.4, 1.8)
Hypersensitivity	120 mg SC	176	1 (0.6)	128.5	0.8	170	0	124.7	0	0.8 (-2.3, 4.4)
	300 mg IV	459	0	419.4	0	466	1 (0.2)	402.9	0.3	-0.3 (-1.4, 0.7)
Osteonecrosis	120 mg SC	176	1 (0.6)	127.9	0.8	170	0	124.7	0	0.8 (-2.3, 4.4)
	300 mg IV	459	0	419.4	0	466	0	403.0	0	0.0 (-1.0, 0.9)
Pneumonia	120 mg SC	176	1 (0.6)	128.5	0.8	170	0	124.7	0	0.8 (-2.3, 4.4)
	300 mg IV	459	1 (0.2)	419.4	0.2	466	2 (0.4)	402.9	0.5	-0.3 (-1.6, 0.9)
Rheumatoid arthritis	120 mg SC	176	1 (0.6)	128.5	0.8	170	0	124.7	0	0.8 (-2.3, 4.4)
	300 mg IV	459	0	419.4	0	466	0	403.0	0	0.0 (-1.0, 0.9)
Acute sinusitis	120 mg SC	176	0	128.6	0	170	0	124.7	0	0.0 (-3.1, 3.0)
	300 mg IV	459	1 (0.2)	419.4	0.2	466	0	403.0	0	0.2 (-0.7, 1.3)

						Placebo				
Preferred Term (MedDRA version 27.0)	**Anifrolumab**	**N**	**n (%)**	**Exposure years**	**EAIR per 100 PY**	**N**	**n (%)**	**Exposure years**	**EAIR per 100 PY**	**EAIR per 100 PY (Anifrolumab - Placebo) (95% CI)**
Adnexa uteri cyst	120 mg SC	176	0	128.6	0	170	0	124.7	0	0.0 (-3.1, 3.0)
	300 mg IV	459	0	419.4	0	466	1 (0.2)	402.9	0.2	-0.2 (-1.4, 0.7)
Angioedema	120 mg SC	176	0	128.6	0	170	0	124.7	0	0.0 (-3.1, 3.0)
	300 mg IV	459	1 (0.2)	419.3	0.2	466	0	403.0	0	0.2 (-0.7, 1.4)
Atrial fibrillation	120 mg SC	176	0	128.6	0	170	0	124.7	0	0.0 (-3.1, 3.0)
	300 mg IV	459	0	419.4	0	466	1 (0.2)	403.0	0.3	-0.3 (-1.4, 0.7)
Bronchitis	120 mg SC	176	0	128.6	0	170	0	124.7	0	0.0 (-3.1, 3.0)
	300 mg IV	459	1 (0.2)	419.4	0.2	466	0	403.0	0	0.2 (-0.7, 1.3)
Cervical dysplasia	120 mg SC	176	0	128.6	0	170	0	124.7	0	0.0 (-3.1, 3.0)
	300 mg IV	459	1 (0.2)	419.3	0.2	466	2 (0.4)	402.7	0.5	-0.3 (-1.6, 0.9)
Diverticulitis	120 mg SC	176	0	128.6	0	170	0	124.7	0	0.0 (-3.1, 3.0)
	300 mg IV	459	1 (0.2)	419.3	0.2	466	0	403.0	0	0.2 (-0.7, 1.3)
Ecchymosis	120 mg SC	176	0	128.6	0	170	0	124.7	0	0.0 (-3.1, 3.0)
	300 mg IV	459	1 (0.2)	419.4	0.2	466	0	403.0	0	0.2 (-0.7, 1.3)
Extrapulmonary tuberculosis	120 mg SC	176	0	128.6	0	170	1 (0.6)	124.6	0.8	-0.8 (-4.5, 2.2)
	300 mg IV	459	0	419.4	0	466	0	403.0	0	0.0 (-1.0, 0.9)
Face oedema	120 mg SC	176	0	128.6	0	170	0	124.7	0	0.0 (-3.1, 3.0)
	300 mg IV	459	1 (0.2)	419.2	0.2	466	0	403.0	0	0.2 (-0.7, 1.4)
Follicular lymphoma	120 mg SC	176	0	128.6	0	170	0	124.7	0	0.0 (-3.1, 3.0)
	300 mg IV	459	1 (0.2)	419.4	0.2	466	0	403.0	0	0.2 (-0.7, 1.4)
Gastroenteritis	120 mg SC	176	0	128.6	0	170	0	124.7	0	0.0 (-3.1, 3.0)
	300 mg IV	459	0	419.4	0	466	1 (0.2)	402.8	0.3	-0.3 (-1.4, 0.7)
Headache	120 mg SC	176	0	128.6	0	170	0	124.7	0	0.0 (-3.1, 3.0)
	300 mg IV	459	1 (0.2)	419.4	0.2	466	0	403.0	0	0.2 (-0.7, 1.4)

						Placebo				
Preferred Term (MedDRA version 27.0)	**Anifrolumab**	**N**	**n (%)**	**Exposure years**	**EAIR per 100 PY**	**N**	**n (%)**	**Exposure years**	**EAIR per 100 PY**	**EAIR per 100 PY (Anifrolumab - Placebo) (95% CI)**
Hypertensive emergency	120 mg SC	176	0	128.6	0	170	0	124.7	0	0.0 (-3.1, 3.0)
	300 mg IV	459	0	419.4	0	466	1 (0.2)	403.0	0.3	-0.3 (-1.4, 0.7)
Influenza like illness	120 mg SC	176	0	128.6	0	170	0	124.7	0	0.0 (-3.1, 3.0)
	300 mg IV	459	0	419.4	0	466	2 (0.4)	402.9	0.5	-0.5 (-1.8, 0.4)
Infusion related reaction	120 mg SC	176	0	128.6	0	170	0	124.7	0	0.0 (-3.1, 3.0)
	300 mg IV	459	0	419.4	0	466	1 (0.2)	402.9	0.3	-0.3 (-1.4, 0.7)
Lupus nephritis	120 mg SC	176	0	128.6	0	170	0	124.7	0	0.0 (-3.1, 3.0)
	300 mg IV	459	0	419.4	0	466	1 (0.2)	402.9	0.2	-0.2 (-1.4, 0.7)
Lupus vasculitis	120 mg SC	176	0	128.6	0	170	1 (0.6)	124.6	0.8	-0.8 (-4.5, 2.2)
	300 mg IV	459	0	419.4	0	466	0	403.0	0	0.0 (-1.0, 0.9)
Migraine	120 mg SC	176	0	128.6	0	170	0	124.7	0	0.0 (-3.1, 3.0)
	300 mg IV	459	1 (0.2)	419.4	0.2	466	0	403.0	0	0.2 (-0.7, 1.4)
Myasthenia gravis	120 mg SC	176	0	128.6	0	170	0	124.7	0	0.0 (-3.1, 3.0)
	300 mg IV	459	1 (0.2)	419.4	0.2	466	0	403.0	0	0.2 (-0.7, 1.4)
Mycobacterium avium complex infection	120 mg SC	176	0	128.6	0	170	0	124.7	0	0.0 (-3.1, 3.0)
	300 mg IV	459	1 (0.2)	419.3	0.2	466	0	403.0	0	0.2 (-0.7, 1.4)
Myelitis transverse	120 mg SC	176	0	128.6	0	170	0	124.7	0	0.0 (-3.1, 3.0)
	300 mg IV	459	1 (0.2)	419.3	0.2	466	0	403.0	0	0.2 (-0.7, 1.3)
Myocardial ischaemia	120 mg SC	176	0	128.6	0	170	0	124.7	0	0.0 (-3.1, 3.0)
	300 mg IV	459	0	419.4	0	466	1 (0.2)	403.0	0.3	-0.3 (-1.4, 0.7)
Nephritis	120 mg SC	176	0	128.6	0	170	0	124.7	0	0.0 (-3.1, 3.0)
	300 mg IV	459	1 (0.2)	419.2	0.2	466	0	403.0	0	0.2 (-0.7, 1.4)
Optic neuritis	120 mg SC	176	0	128.6	0	170	0	124.7	0	0.0 (-3.1, 3.0)
	300 mg IV	459	0	419.4	0	466	1 (0.2)	402.7	0.3	-0.3 (-1.4, 0.7)

						Placebo				
Preferred Term (MedDRA version 27.0)	**Anifrolumab**	**N**	**n (%)**	**Exposure years**	**EAIR per 100 PY**	**N**	**n (%)**	**Exposure years**	**EAIR per 100 PY**	**EAIR per 100 PY (Anifrolumab - Placebo) (95% CI)**
Pulmonary alveolar haemorrhage	120 mg SC	176	0	128.6	0	170	0	124.7	0	0.0 (-3.1, 3.0)
	300 mg IV	459	0	419.4	0	466	1 (0.2)	402.9	0.3	-0.3 (-1.4, 0.7)
Retinal disorder	120 mg SC	176	0	128.6	0	170	0	124.7	0	0.0 (-3.1, 3.0)
	300 mg IV	459	1 (0.2)	419.2	0.2	466	0	403.0	0	0.2 (-0.7, 1.3)
Skin wound	120 mg SC	176	0	128.6	0	170	1 (0.6)	124.6	0.8	-0.8 (-4.5, 2.2)
	300 mg IV	459	0	419.4	0	466	0	403.0	0	0.0 (-1.0, 0.9)
Syncope	120 mg SC	176	0	128.6	0	170	0	124.7	0	0.0 (-3.1, 3.0)
	300 mg IV	459	1 (0.2)	419.3	0.2	466	0	403.0	0	0.2 (-0.7, 1.3)
Systemic lupus erythematosus	120 mg SC	176	0	128.6	0	170	0	124.7	0	0.0 (-3.1, 3.0)
	300 mg IV	459	0	419.4	0	466	6 (1.3)	402.6	1.5	-1.5 (-3.3, -0.5)
Thrombocytopenia	120 mg SC	176	0	128.6	0	170	1 (0.6)	124.5	0.8	-0.8 (-4.5, 2.2)
	300 mg IV	459	0	419.4	0	466	0	403.0	0	0.0 (-1.0, 0.9)
Upper respiratory tract infection	120 mg SC	176	0	128.6	0	170	0	124.7	0	0.0 (-3.1, 3.0)
	300 mg IV	459	1 (0.2)	419.4	0.2	466	0	403.0	0	0.2 (-0.7, 1.4)
Urticaria	120 mg SC	176	0	128.6	0	170	1 (0.6)	124.6	0.8	-0.8 (-4.5, 2.2)
	300 mg IV	459	0	419.4	0	466	0	403.0	0	0.0 (-1.0, 0.9)
Uterine cancer	120 mg SC	176	0	128.6	0	170	0	124.7	0	0.0 (-3.1, 3.0)
	300 mg IV	459	0	419.4	0	466	1 (0.2)	402.9	0.3	-0.3 (-1.4, 0.7)
Varicose vein	120 mg SC	176	0	128.6	0	170	0	124.7	0	0.0 (-3.1, 3.0)
	300 mg IV	459	0	419.4	0	466	1 (0.2)	403.0	0.3	-0.3 (-1.4, 0.7)

EAIR is defined as the sum of subjects with the event/[sum across subjects' time at risk for the event /(365.25)] * 100, where time at risk is time to first event for subjects who experienced the event during the analysis period and time during the analysis period for subjects who do not experience the event. In the event that multiple studies are combined, the Miettinen and Nurminen weighted average EAIRs are presented for each treatment group. 95% CIs are calculated via the Miettinen and Nurminen method, stratified by study where applicable. During double-blind treatment: Includes adverse events with an onset date on or after the date of first dose of IP up to and including 28 days following the date of last double-blind IP dose. Subjects with multiple occurrences of the same preferred term are counted once regardless of the number of occurrences. Table is sorted by decreasing frequency on preferred term level in Anifrolumab 120 mg treatment group n Number of subjects per category; N Number of subjects per treatment group.

2.6.8.10. Post marketing experience

Anifrolumab is approved for the treatment of moderate to severe SLE in over 65 countries. A summary of safety data from post-marketing sources is presented in the Periodic Benefit-Risk Evaluation Report/EU Periodic Safety Update Reports provided to regulatory agencies on a regular basis. The cumulative global post-marketing patient exposure to anifrolumab is estimated to be 16,124 PY, from 30 July 2021 to 30 June 2024.

The MAH has safety reporting procedures that are designed to meet regulatory requirements worldwide. Safety surveillance activities for anifrolumab are conducted on an ongoing basis and include an analysis of data in clinical studies, published literature, data in MAH's safety database, and data available from other sources.

2.6.8.1. Human Factors Engineering (HFE)

Accessorised prefilled syringe (APSF)

Medical devises document summarises the Human Factors Engineering (HFE) process related to design and development of the APFS, which includes formative evaluations, user interface design iterations, summative evaluation, and integration with Risk Management (RM).

The Notified Body Opinion described the Assessment of the General Safety and Performance Requirements (GSPR) of clinical issues regarding the device. The evaluated documents included, among other documents: Hazard Assessment anifrolumab APFS, Summary of Human Factors Engineering for Notified Body Anifrolumab APFS, Instructions for Use for Anifrolumab Accessorised Pre-filled Syringe, Summary of Post Market Data and Literature for Similar Prefilled Syringes Anifrolumab Accessorised Prefilled Syringe, Risk Management Plan for Accessorised Pre-Filled Syringe for MEDI-546 and Risk Management Summary Report for an Accessorised Pre-Filled Syringe for anifrolumab 120mg/0.8ml (anifrolumab) 120 mg / 0.8 ml.

Three formative evaluations were performed.

A formative study was conducted to compare three SSI APFS variants, one equipped with a manual safety feature (BO UltraSafe Needle Guard Device) and two equipped with automatic NSD (BO UltraSafe Passive Needle Guard and BD UltraSafe Plus Needle Guard) by using simulated use assessment. The participants consisted of 12 HCPs and 6 adult SLE patients. Participants were asked to perform simulated injections with three devices without training.

APFS Formative Usability Study #1 was conducted to demonstrate safe and effective use of the commercial design of anifrolumab APFS by adult SLE patients in a non-clinical (e.g., home) environment. The study was conducted to assess the usability of the APFS, including its secondary packaging and labeling. Participants in the study included 9 adult SLE patients, 4 of which were injection naive and 5 which were injection experienced.

A second APFS Formative Usability Study #2 was conducted using simulated use and knowledge-based assessments to evaluate the IFU and packaging changes. Participants in the study included 35 patients with chronic diseases.

As outcome of the formative studies conducted design modifications were implemented in the user interface, and IFU.

The HF validation study with 45 participants including adult patients and caregivers in simulated conditions was conducted and use-related risks analysis (URRA) was performed.

A review of known use problems with similar devices was conducted by reviewing complaint databases, product recalls, safety reports and literature. Known issues identified were mitigated with design modifications.

Potential clinical hazards and hazardous associated with the use of the anifrolumab APFS were identified by a cross-functional risk management team, including clinical and patient safety representatives, and documented.

The applicant claims that the results of summative evaluation show that the device user interface has been optimized and the residual user related risks have been mitigated as far as possible. The design of the device user interface supports users in safely, accurately, and effectively administering a dose.

Risk management activities including clinical risks, and usability were conducted with a positive outcome considering the device part risk benefit. In addition, the manufacturer conducted postmarked clinical activities with acceptable sources, no additional risks were identified by the manufacturer.

Autoinjector (AI)

The Notified Body Opinion described the Assessment of the General Safety and Performance Requirements (GSPR) of clinical issues regarding the AI device. The evaluated documents included, among other documents: Risk Management Summary Report, Summary of Human Factors Engineering for Notified Body, Instructions for Use (IFU), Human-factors-anifrolumab-ai, General-safety-and-performance-requirements-mdr-(eu)-2017-745-anifrolumab-ai, Risk-management-plan-ai, hazard-assessment, General Safety and Performance Requirements (MDR (EU) Anifrolumab Autoinjector containing an overview of the applicable and non-applicable General Safety and Performance Requirements.

Summary of Post Market Data and Literature for Similar devices reviews Known Use Problems with Similar Devices, complaints data search (MAUDE and MedSun- covering a 3 years period), Published Regulatory Review Summaries: Use Errors Reported in Regulatory Review Summaries, literature (range of issues with autoinjectors in general), DESIGN MODIFICATIONS IMPLEMENTED IN RESPONSE TO KNOWN ISSUES incl. an overview of updates done within the instruction for use and reference to those literature data.

Two formative studies have been performed:

Study #1 evaluated two revisions of IFUs accompanying an Ypsomed YpsoMate AI by intended untrained user populations (3 HCP, 3 caregivers and 16 patients) in two different phases. Based on this result the instruction for use was improved.

Study #2 Formative Human Factors Study for Platform: to Demonstrate safe and effective use of the commercial design of the anifrolumab N=19 untrained adult participants. Based on the result the instruction for use was updated.

The outcomes of the formative evaluations were incorporated into the Use-Related Risk Assessment (URRA) and used to inform the selection of the device and the design and content of the commercial labelling and packaging that were used for summative evaluation.

A total of 32 participants, including adult patients and caregivers were included in the Summative Study. Adult patients (ages 18 years and older) with moderate to severe SLE performing self-administration, caregivers of patients with SLE performing administration to patients and Healthcare Professionals (HCPs) were considered. Intended that patients and caregivers will use theAI in a non-clinical environment, most commonly at home.

Anifrolumab AI development and risk management was conducted with consideration of the target patient population. Device use by lay users, including use by patients and caregivers, was evaluated in the formative and summative studies. SLE, RA and OA patients (6 injection naïve and 5 injection experienced) were recruited in these studies. RA/OA patients can be considered the worst case in terms of physical capabilities when compared to SLE patients due to the dexterity impairments associated with RA/OA. The results of the HF summative study fed into the evaluation of errors associated with performing use steps in the use FMEA. Additionally, the device was designed with redundant feedback mechanisms, including visual and auditory indications of delivery progress during an injection to support users delivering a full dose, including those with audible impairments. During the HF summative study, the device was validated with the final device design, and results were incorporated into the use FMEA.

Residual Risk for Health Care Professionals (HCP) and Home Use was reviewed and the process risk assessment covering the complete activity of the treatment by the patient and the health care personal. As an outcome from the human engineering study no separate training is needed for using the auto injector.

2.6.9. Discussion on clinical safety

Within this extension application, the MAH is proposing a new route of administration, Saphnelo (anifrolumab) 120 mg SC QW *as an add on therapy for the treatment of adult patients with moderate to severe, active autoantibody positive systemic lupus erythematosus (SLE), despite standard therapy.* The safety data derive mainly from the single, pivotal, phase 3 study, randomized, double-blind, multicenter, parallel-group, placebo-controlled TULIP SC study. This study was on-going during the procedure and final results are expected in the last quarter of the current year 2025. This variation was based on an interim analysis (IA) of a study sample of 346 SLE patients of the planned 367 (94%) safety population (for detailed discussion on the IA, see the efficacy section 2.6.5).

The MAH has provided a commitment of submitting the final full 52 week safety results of this study, a discussion and an update of the PI, once available (1Q2026).

TULIP SC study (D3465C00001)

This pivotal Phase 3 study (fixed dose 120 mg weekly) targeted a similar average belimumab exposure as the 300 mg IV dose, which is marketed, and a SLE population consistent with the population studied in the phase 3 IV studies. Accordingly, the same potential and identified risks, as well as AEs of special interest (AESI) that apply to the IV product were also prospectively defined for the SC development programme, now complemented with those inherent to the new mode of administration, which included local and systemic injection related reactions. This approach was endorsed by the CHMP.

The analysis of safety data was based on the 52-week double-blind treatment period, including all available data up to the data cut off for the IA (23 July 2024), irrespective of whether they are ongoing in the study, have completed the 52-week double-blind treatment period, or have withdrawn from the study early (Safety Analysis Set, N = 346). All safety analyses for the 52-week double blind treatment period were performed using the Safety Analysis Set, which included all patients who received at least one dose of the IMP. All patients (N = 367) were randomized prior to the IA clinical data-lock. Limited safety data from the open-label extension (OLE) period is also available.

To confirm that the safety of anifrolumab 120 mg SC QW was consistent with the established profile for anifrolumab 300 mg IV Q4W for up to 52 weeks of double-blind treatment, pooled safety data from 2 Phase III studies D3461C00004 and D3461C00005, and one Phase II study CD-IA-MEDI-546-1013 (hereafter referred to as studies 04, 05, and 1013, respectively) are presented side-by-side with the

TULIP SC data. This approach of evaluating safety in the context of the previous IV studies was endorsed by the CHMP.

The SC Safety Analysis Set included patients with a wider range of exposure times than those included in the IA FAS, the analysis set for assessment of efficacy (N = 220), as not all patients had completed the double-blind treatment period or withdrawn from the study early. Thus, a subset of AE analyses were also conducted for the population of 220 patients only (referred to as the SC 220 Safety Analysis Set). This was to confirm conclusions drawn from the comparison of SC and IV EAIR (exposure adjusted AEs) in a population where most patients had completed the 52 week double-blind treatment period.

Exposure

Anifrolumab 120 mg was administered by subcutaneous (SC) injection in a 1 mL APFS with 0.8 mL fill volume. The safety assessment was based on an IA of the 346 (94%) patients in TULIP SC study. The maximum planned duration of the double-blind treatment period was 52 weeks. The total PY of treatment exposure to anifrolumab 120 mg SC was 128.56 PY and was similar between the anifrolumab and placebo groups (median duration of exposure 359.0 and 362.0 days, respectively). Thus, drug exposure was similar across study groups in the pivotal clinical study, enabling meaningful comparisons. The overall extent of exposure at the approved or intended dosing regimen was considered adequate to assess the overall safety profile of SC administered anifrolumab 120 mg QW, considering the previously established safety profile for anifrolumab administered IV Q4W. The MAH provided a commitment within this procedure to submit the final CSR of the pivotal study TULIP SC once available (1Q2026) including an update of the SC anifrolumab SmPC.

Baseline information

The baseline demographic characteristic were in general well balanced between the treatment groups also for the IA Safety Analysis Set (N=346) subpopulation. An imbalance in the disease related baseline data was observed. Considering only slight differences in the SLE disease severity between the study groups, and a clear imbalance in the use of SLE-related treatments was seen, with higher use in the anifrolumab treatment group. Further analyses (summaries of AEs by category for the TULIP SC safety analysis set by baseline SLEDAI-2K, immunosuppressant use, and OCS dose) and detailed discussion revealed no clear untoward effect of these baseline imbalances on the safety results and inferences made, and no further text amendments were deemed necessary to section 4.4 of the currently presented SmPC.

Adverse events

The overall incidence of AE during the double-blind treatment period of the TULIP SC study was similar between the treatment groups, 74.4% in the anifrolumab 120 mg SC group and 71.2% in the placebo group. Most AEs were mild to moderate in intensity. Consistently with previous data and the mode of action of anifrolumab the most common AEs (frequency > 5%) were nasopharyngitis (10.8% patients), COVID-19 (9.1% patients), and upper respiratory infection (8.0% patients) in anifrolumab 120 mg SC group compared with nasopharyngitis (9.4% patients), injection site erythema (8.8% patients), bronchitis (7.6% patients) and urinary tract infection (7.6% of patients) in placebo group.

Related adverse events

Overall, also the incidence and type of ADR in the SC safety study appeared similar to that of the IV safety profile. No new ADRs , inherent to the new route of administration, wereidentified from the data available.

AESIs

In line with the known anifrolumab safety profile, the incidence of serious infections was higher in the anifrolumab treatment group than in the placebo group. Two events of serious infections resulted in discontinuation in the anifrolumab treatment group. No opportunistic infections were reported.

Also consistent with the known safety profile of anifrolumab 300 mg IV, patients in the anifrolumab SC group had an increased incidence of herpes zoster. Most events were cutaneous, localised, nonserious, mild or moderate in intensity, resolved with antiviral therapy, and did not lead to investigational product discontinuation.

A total of 2 AESIs of tuberculosis were reported, one in the anifrolumab 120 mg SC group (latent tuberculosis), the only one of the two considered related to the study treatment, and one in the placebo group (extrapulmonary tuberculosis).

The 3 MACE events reported, 2 in the anifrolumab group (acute myocardial infarction, cerebrovascular accident) and one in the placebo group (acute myocardial infarction) were judged not to be related to the IMP.

No malignancies were reported during the 52-week double-blind treatment period.

Overall, the above-mentioned findings on these AESIs are adequately reflected in the proposed SC PI (please see Saphnelo SmPC).

The numbers of patients with the AESI of injection site reactions (ISR) were similar in the anifrolumab group and the placebo group. All injection site reaction AESIs were nonserious, mild/moderate in intensity, and transient in nature. None resulted in discontinuation of investigational product. However, most of the ISR reported meeting narrative criteria, were considered related to the anifrolumab treatment. This AESI inherent to the new route of administration is currently judged not related to the IMP.

The rate for hypersensitivity reactions with anifrolumab 120 mg SC was low (2 patients in the anifrolumab 120 mg SC group and no patients in the placebo group). One of the hypersensitivity AEs led to discontinuation of IP and was assessed by the investigator as possibly related to IP (see discontinuations below). This was incorrectly stated in the SC SmPC, but the text was subsequently corrected. In the anifrolumab SC SmPC a threshold of 5% was used for ADRs inclusion. The MAH explained that also the rarer TEAEs have undergone causality assessment and there is no need for revision of the PI texts. This was agreed on by the CHMP. There were no events of anaphylactic reactions in this patient sample.

Serious adverse events

The proportions of patients with SAEs were low and similar between the anifrolumab and placebo groups with no clustering seen during the 52-week treatment period. The most common system organ class (SOC) with reported SAEs was "Infections and infestations" in both the anifrolumab 120 mg SC and in the placebo groups.

Deaths

Up to the date of the interim clinical data lock, one outcome of death (PT, gastrointestinal infection) was reported in the anifrolumab treatment group and none in the placebo group. The event (was assessed as not possibly related to anifrolumab treatment by the Investigator and considered to be related to the patient's underlying conditions. However, as SC administration is designed for at-home use, and any risk of unrecognised or unmanaged serious infection poses greater concern. The MAH discussed this case in further detail and justified acceptably that further precautionary texts were not considered necessary in the PI.

Laboratory and other findings

The clinical laboratory results as well as observations related to vital signs for the study pivotal study was consistent with the IV formulation and no clinically meaningful. There were no new safety concerns.

Safety in special populations

- Intrinsic Factors: The AE and SAE profile of anifrolumab 120 mg SC QW was generally consistent across pre-defined subgroups (sex, age, race, BMI, disease-related factors, and ADA status) based on analyses of AEs by category, common AEs, and SAEs, although there were small numbers of patients in some subgroups.

Adverse Events by Anti-drug Antibody Status: Anifrolumab administered SC is poorly immunogenic in patients with moderate to severe SLE. There was no apparent effect of ADA-positive status on the overall incidence of AEs in TULIP SC, but due to very small numbers of ADA-positive patients, it is not possible to draw firm conclusions.

Extrinsic Factors: The AE and SAE profile of anifrolumab 120 mg SC QW was generally consistent across the pre-defined geographic region subgroups (Asia Pacific, Europe, Latin America, US/Canada, Rest of World) and concomitant medication use at baseline (immunosuppressant use) based on analyses of AEs by category, common AEs, and SAEs.

ADRs in special populations: According to the MAH incidences of ADRs, with anifrolumab 120 mg administered SC QW was consistent with the established safety profile of anifrolumab 300 mg Q4W administered by IV infusion. Collated data on the subgroups of special populations were not presented.

The ADRs identified for anifrolumab are not based on route of administration and are based on an evaluation of all studied populations. Based on all assessments and the rationale presented there is no reason to believe that any special population would be at any increased risk for any of the ADRs identified.

Discontinuations

The proportions of patients with AEs leading to IP discontinuation were low, and slightly higher in the treatment group (5.1% in the anifrolumab group and 2.9% in the placebo group). By PT, they were single occurrence, thus untoward clustering was not evident. From further clarification by the MAH, no new safety concerns arose.

Immunisations/Immune response

The MAH has, within this extension application, also provided a text update of sections 4.4 and 4.5 of the Saphnelo SmPC, to inform healthcare practitioners of the availability of the results from the NAÏVE study (a Post-Authorisation Safety Category 3 study). The provided results of this study showed that overall, acknowledging the possible limitations of the study, the humoral antibody responses, as measured by HAI titres and anti-influenza virus vaccine IgG concentrations, following the quadrivalent influenza virus vaccination appear similar between patients with moderately to severely active SLE who initiated anifrolumab at baseline in addition to SoC (n=19), or received SoC only (n=6).

Thetext update was a commitment from a previous variation EMEA/H/C/004975/II/0020. The proposed texts concerning the results of the NAÏVE study are acceptable verbatim and the commitment is recommended for approval. As per EMA advice during the previous variation, an update of the RMP to remove this Category 3 study following its completion, can be done at the next regulatory procedure affecting the RMP, after approval of this variation application.

ADA levels in SC studies

Taken together, data from both SC studies (TULIP SC and the Device bridging study) are consistent with the previously reported low immunogenicity risk profile of anifrolumab in IV studies and they demonstrate a low immunogenicity of anifrolumab also when it is administered subcutaneously.

Due to the low level of immunogenicity the effect of ADA on PK, efficacy or safety could not be conclusively assessed (for further information see specific sections for PK on clinical pharmacology discussion 2.6.3., and discussion on clinical efficacy 2.6.7. and discussion on clinical safety 2.6.9.)

Post-marketing experience

Overall, AEs received from post-marketing sources were generally consistent with those observed in clinical studies of anifrolumab. Arthralgia has been included as an ADR in the prescribing information (with unknown frequency) based on post-marketing information. On the data from the reporting period of the latest PSUR period, it was concluded that the benefit/risk profile of belimumab continued to be positive.

Other

The safety profile of anifrolumab 120 mg SC QW appeared generally consistent with the established safety profile of anifrolumab 300 mg IV Q4W, acknowledging the inherent limitations of post hoc, between-study comparisons.

The results of the safety analysis on the subset of AE analyses (the analysis set for assessment of efficacy; N = 220), conducted for the population of 220 patients only (the SC 220 Safety Analysis Set) overall appeared to support the conclusions drawn from the comparison of SC and IV EAIR in a population where most patients had completed the 52 week double-blind treatment period i.e. in the patients with a wider range of exposure times (Safety Analysis Set).

Human Factors Engineering (HFE)

Risk review concluded positive benefit-risk profile for Accessorized prefilled syringe (APSF). Design verification and HFE activities demonstrated that the design input requirements, user needs, and intended uses have been met and that the product is safe and effective for its intended use. Device normal conditions of use was included in IFU.

Based on the outcome of the human factors evaluation of the autoinjector no training will be defined for the patients or caregivers besides the instructions outlined in the IFU. Human Factors summative study concluded that the AI can be used by the intended users without serious use errors or problems, for the intended use and under the expected use conditions.

The MAH provided the medical device document (module 3.2.R) and notified body opinion for an Accessorised prefilled syringe (APSF) and Autoinjector (AI). These documents describe the engineering and optimization of the devices, user interface, instructions of use and risk minimisation of the use. Risk review concluded positive benefit-risk profile. Based on these the APSF and AI can be used safely and effectively by the intended user populations in the expected use environments. No training will be defined for the patients or caregivers besides the instructions outlined in the IFU.

From the safety database all the adverse reactions reported in clinical studies and post-marketing have been included in the Summary of Product Characteristics.

2.6.10. Conclusions on the clinical safety

In the pivotal phase 3 TULIP SC study, anifrolumab 120 mg SC QW appeared well tolerated during 52 weeks of treatment, in adult patients with moderate to severe, active SLE. No new safety concerns or ADRs were identified. The safety profile of anifrolumab 120 mg SC QW appeared generally consistent with the established safety profile of anifrolumab 300 mg IV Q4W, acknowledging the inherent limitations of post hoc, between-study comparisons.

As these results are based on an IA, the MAH provided a commitment of submitting the final full 52 weeks safety results of this study, a discussion on the results and an update of the PI, once available (1Q2026*)*.

The commitment of a Saphnelo SmPC text update (EMEA/H/C/004975/II/0020) with the results of a Post-Authorisation Safety Category 3 study, the NAÏVE study, has been submitted within this procedure and is considered acceptable and recommended for approval.

From a safety perspective the application for marketing authorisation for anifrolumab 120 mg SC QW in the proposed indication is approvable.

2.7. Risk Management Plan

2.7.1. Safety concerns

Summary of safety concerns

Table 30: Summary of safety concerns

Summary of safety concerns	
Important potential risks	Malignancy Serious infection
Missing information	Use in pregnant and breastfeeding women

2.7.2. Pharmacovigilance plan

Table 31: Ongoing and additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 – Required additional pharmacovigilance activities				
D3461R00028 A Non-Interventional Multi- Database Post Authorisation Study to Assess Pregnancy- Related Safety Data from Women with SLE Exposed to Anifrolumab Ongoing	The aim of this study is to describe the congenital malformations, adverse pregnancy and birth outcomes in pregnancies/offspring from women with moderate/severe SLE exposed to anifrolumab during pregnancy and to compare with outcomes in women with moderate/severe SLE who are exposed to other SOC but not anifrolumab. Adverse outcomes related to infant growth up to one year of age will also be investigated.	Use in pregnant women	Study protocol submission	August 2022
			Completion of the feasibility study	March 2023
			Interim report 1	Q4 2027
			Interim report 2	Q4 2030
			Final report submission	Q1 2032
D3461R00046 A non-interventional multi- country post-authorisation safety study (PASS) to assess the incidence of serious infections & malignancies in systemic lupus erythematosus (SLE) patients exposed to anifrolumab.	To compare hazard rates of new malignancies (as a composite outcome) in moderate/severe SLE patients initiating anifrolumab versus comparable moderate/severe SLE patients who do not initiate anifrolumab (exposed to SLE SOC). To compare hazard rates of the first occurrence of a serious infection (as a composite outcome) in moderate/severe SLE patients initiating anifrolumab versus comparable moderate/severe SLE patients who do not initiate anifrolumab (exposed to SLE SOC). To describe the demographic and clinical characteristics of patients in	Serious infection and malignancies	Study protocol submission	August 2022
			Completion of feasibility study (Stage 1)	March 2023
			Interim report 1 (serious infections and malignancy)	Q2 2027
			Final report of study results (serious infections)	Q4 2028
			Interim report 2 (malignancy)	Q2 2030

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 – Required additional pharmacovigilance activities				
Ongoing	each study cohort (malignancy cohort and serious infection cohort) at index date, by exposure status (exposed to anifrolumab vs. exposed to SLE SOC). To compare hazard rates of new pre-specified malignancy sub-types (separately) in moderate/severe SLE patients initiating anifrolumab versus comparable moderate/severe SLE patients who do not initiate anifrolumab (exposed to SLE SOC). To compare hazard rates of the first occurrence of opportunistic serious infections, other serious infections, pneumonia (overall), fatal and non-fatal pneumonia (separately) in moderate/severe SLE patients initiating anifrolumab versus comparable moderate/severe SLE patients who do not initiate anifrolumab (exposed to SLE SOC), where feasible (ie, if sample size is sufficient). To compare the hazard rates of recurrent infections leading to hospitalisation in moderate/severe SLE patients initiating anifrolumab and in comparable moderate/severe SLE patients who do not initiate anifrolumab (exposed to SLE SOC), when feasible.		Final report of study results (malignancies)	Q4 2032

2.7.3. Risk minimisation measures

Table 32: Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety concern	Risk minimization measures	Pharmacovigilance activities
Important potential risks		
Malignancy	Routine risk minimization measures: • SmPC Section 4.4 • Package leaflet Section 2	Routine pharmacovigilance activity: • Targeted safety questionnaire Additional pharmacovigilance activities: • Study D3461R00046 - A non-interventional multi-country post-authorisation safety study (PASS) to assess the incidence of serious infections & malignancies in systemic lupus erythematosus (SLE) patients exposed to anifrolumab.
Serious infection	Routine risk minimization measures: • SmPC Section 4.4 • Package leaflet Section 2	Additional pharmacovigilance activities: • Study D3461R00046 - A non-interventional multi-country post-authorisation safety study (PASS) to assess the incidence of serious infections & malignancies in systemic lupus erythematosus (SLE) patients exposed to anifrolumab.
Missing information		
Use in pregnant and breastfeeding women	Routine risk minimization measures: • SmPC Section 4.6 • Package leaflet Section 2	Additional pharmacovigilance activity: • D3461R00028, A Non-Interventional Multi-Database Post-Authorisation Study to Assess Pregnancy-Related Safety Data from Women with SLE Exposed to Anifrolumab

2.7.4. Conclusion

The CHMP considered that the risk management plan version 6.1 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.9. Product information

2.9.1. User consultation

The results of the user consultation for Saphnelo 120 mg solution for injection in pre-filled syringe submitted by the MAH show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

The bridging report for the pre-filled pen submitted by the MAH has been found acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Systemic lupus erythematosus (SLE) is a complex, chronic, and heterogeneous autoimmune disease of unknown etiology that affects multiple organ systems.

Clinical manifestations of SLE include, but are not limited to, constitutional symptoms such as fatigue and fever, alopecia, rashes, serositis, arthritis, nephritis, vasculitis, lymphadenopathy, splenomegaly, hemolytic anemia, cognitive dysfunction, and other nervous system involvement. These disease manifestations cause a significant burden of illness and can lead to reduced physical function, loss of employment, and considerable health-related quality of life impairments. Increased hospitalizations and side effects of medications, including chronic oral corticosteroids (OCS) and other immunosuppressive treatments, add to the disease burden in SLE. There is considerable morbidity and reduced quality of life for many patients with SLE, and it is associated with cumulative and irreversible organ damage and early mortality.

The sought indication for SC anifrolumab was: "*Saphnelo is indicated as an add on therapy for the treatment of adult patients with moderate to severe, active autoantibody positive systemic lupus erythematosus (SLE), despite standard therapy.*", which is identical to the approved wording for IV anifrolumab.

3.1.2. Available therapies and unmet medical need

Until the approval of the 2 available targeted therapies for SLE (belimumab, IV or SC and IV anifrolumab), treatments were based on non-targeted therapies such as OCS and other immunosuppressive drugs. These remain a major component of SLE therapy. However, chronic steroid use, nonsteroidal anti-inflammatory drugs, and immunosuppressive agents have known safety concerns that contribute to long-term morbidity and mortality in SLE patients.

There continues to be a need for improvement in SLE treatment through enhanced convenience for patients. The current application was a line extension for SC anifrolumab to the already approved IV administered anifrolumab.

3.1.3. Main clinical studies

The anifrolumab SC clinical programme included a single, pivotal, global, multicenter, randomized, double-blind (DB), placebo-controlled, Phase III study (TULIP SC). TULIP SC was an ongoing study during the procedure evaluating the safety and efficacy of anifrolumab SC administered by accessorised pre-filled syringe (APFS) in adults with moderate to severe SLE despite receiving standard of care.

3.2. Favourable effects

The primary endpoint, i.e. BICLA response rate at week 52 was 59.4% for anifrolumab and 43.9% for placebo (15.5% treatment difference, 95% CI 2.3, 28.6; p=0.0211). The results of the sensitivity and supplementary analyses were consistent with those of the primary analysis.

Overall, the secondary endpoints were numerically in favour of anifrolumab, supporting the beneficial effect of SC anifrolumab in the treatment of adult patients with moderate to severe, active autoantibody-positive SLE, despite standard therapy.

3.3. Uncertainties and limitations about favourable effects

The efficacy analysis is based on an IA of the first 220 patients of TULIP SC study. In the chosen IA strategy, only the primary endpoint was formally tested, while the key secondary endpoints will be tested in the multiple testing procedure when the full data on all 367 patients is available. Despite that the key secondary endpoints were all numerically in favour of SC anifrolumab this weakens the robustness and comprehensiveness of the efficacy results. Further efficacy results will become available when the MAH will submit the complete study report for all patients of the TULIP SC study by Q1 2026.

3.4. Unfavourable effects

Interim safety analysis (N= 346/367) of the pivotal phase 3 TULIP SC study (SC Safety Analysis Set)

Based on the 128.56 PY of treatment exposure to anifrolumab 120 mg SC (median duration of exposure 359.0 days), with 88 patients treated for one year, the overall incidence of AE during the double-blind treatment period of the TULIP SC study was 74.4% in the anifrolumab 120 mg SC group and 71.2% in the placebo group. Most AEs were mild to moderate in intensity.

The most common AEs (frequency > 5%) were nasopharyngitis (10.8% patients), COVID-19 (9.1% patients), and upper respiratory infection (8.0% patients) in anifrolumab 120 mg SC group compared with nasopharyngitis (9.4% patients), injection site erythema (8.8% patients), bronchitis (7.6% patients) and urinary tract infection (7.6% of patients) in placebo group.

The incidence of non-opportunistic serious infections was 6.3% (exposure-adjusted incidence rate [EAIR]: 8.84 per 100 PY) in the anifrolumab group and 3.5% (EAIR: 4.89 per 100 PY) in the placebo (EAIR difference of 3.95; 95% CI: -2.90, 11.50). Two events of non-opportunistic serious infections resulted in discontinuation of IMP.

No opportunistic infections were reported during the 52-week DB treatment period.Incidence of herpes zoster was (4.0% [EAIR: 5.62 per 100 PY]) in the anifrolumab treatment group compared with placebo

(1.2% [1.61 per 100 PY]). Most events were cutaneous, localized, nonserious, mild or moderate in intensity, resolved with antiviral therapy, and did not lead to IMP discontinuation.

In all, 2 events of tuberculosis (including latent tuberculosis) were reported in the 52-week DB treatment period, one in the anifrolumab 120 mg SC group (latent tuberculosis) and one in the placebo group (extrapulmonary tuberculosis).

In all, 3 MACE events were reported, 2 in the anifrolumab 120 mg SC group (adjudication outcomes: acute myocardial infarction, cerebrovascular accident) and one in the placebo group (adjudication outcome: acute myocardial infarction).

The proportions of patients with AESI of injection site reactions were similar in the anifrolumab group (27 patients [15.3%]) and in the placebo group (29 patients [17.1%]). All injection site reaction AESIs were nonserious, mild or moderate in intensity, and transient in nature, mostly considered related to the anifrolumab treatment by the investigator.

The most common system organ class (SOC) with reported SAEs was Infections and infestations in the anifrolumab 120 mg SC (6.8%) and in the placebo groups (3.5%).

No malignancies were reported during the 52-week double-blind treatment period.

One outcome of death (PT, gastrointestinal infection) was reported in the anifrolumab treatment group and none in the placebo group.

The clinical laboratory results as well as observations related to vital signs for the study pivotal study was consistent with the IV formulation and none considered clinically meaningful. There were no new safety concerns.

3.5. Uncertainties and limitations about unfavourable effects

The current submission is based on data from an interim analysis of the pivotal study TULIP SC study therefore data remains limited. Acknowledging the inherent limitations of between-study comparisons data showed that safety profile of anifrolumab 120 mg SC QW is generally consistent with the established safety profile of anifrolumab 300 mg IV Q4W. Further safety data will become available when the MAH will submit the complete study report for all patients of the TULIP SC study by Q1 2026.

3.6. Effects Table

Table 33: Effects Table for anifrolumab 120 mg SC QW for the treatment of moderate to severe SLE [data cut-off: 23 July 2024 for the interim analysis)].

Effect	Short Description	Unit	Ani 120 SC	Placebo	Uncertainties/ Strength of evidence	References
Favourable Effects						
BICLA RR	BICLA response rate at Week 52	%	59.4	43.9	difference 15.5% (95 CI 2.3, 28.6); p=0.0211, IA of 220 patients	TULIP SC
BICLA RR with low/reduced OCS	BICLA response rate at Week 52 with maintained low (or reduced) OCS use	%	59.4	39.5	difference 19.9% (95% CI 6.9, 32.9); nominal p=0.0027, IA of 220 patients	TULIP SC
Time to sustained BICLA response	Time to BICLA response sustained through Week 52	% of response	39.8	22.8	HR 2.038 (95% CI 1.248, 3.408); nominal p=0.0052, IA of 220 patients	TULIP SC
Time to first flare	Time to first flare through Week 52	% of flare	39.3	46.6	HR 0.757 (95% CI 0.499, 1.141); nominal p= 0.1841, IA of 220 patients	TULIP SC
Unfavourable Effects **						
Number of patients	N=346 in all		n=176	n=170		
AEs, all		n (%)	(74.4)	(71.2)	52 week double-blind period	TULIP SC
AEs, most common	Nasopharyngitis	n (%)	19 (10.8)	16 (9.4)		TULIP SC
Any SAE		n (%)	19 (10.8)	15 (8.8)		TULIP SC
Serious Infections		n (%)	11 (6.3)	6 (3.5)	Two events resulted in discontinuation of IP	TULIP SC
Deaths		n (%)	1 (0.6)	0	The single death was due to gastroenteritis	TULIP SC
Discontinuations due to AEs		n (%)	9 (5.1)	5 (2.9)		TULIP SC
Local injection site reactions		n (%)	27 (15.3)	29 (17.1)	No ADAs detected	TULIP SC
Post-injection systemic reactions	Hypersensitivity reactions	n (%)	2 (1.1)	0	No ADAs detected	TULIP SC

Effect	Short Description	Unit	Ani 120 SC	Placebo	Uncertainties/ Strength of evidence	References
	Anaphylactic reactions	n (%)	0	0	One anaphylactic event was reported for IV anifrolumab 150 mg in study 5	TULIP SC

Abbreviations:
Notes: ** Data reflect the IA (n=346/367) population, the Safety Analysis Set, of the pivotal TULIP SC study

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The efficacy of SC anifrolumab was evaluated in a single phase 3 study, TULIP SC. Given the approval of IV anifrolumab, a single study was considered sufficient for the assessment of efficacy of SC anifrolumab in the same target population and the same indication. The primary endpoint BICLA response is a valid composite index to assess SLE disease activity and acceptable from the regulatory point of view as it is in line with the Guideline on clinical investigation of medicinal products for the treatment of systemic lupus erythematosus and lupus nephritis (EMA/CHMP/51230/2013 corr 1). The response rate of BICLA response at week 52 was 59.4% for SC anifrolumab and 43.9% for placebo, resulting in a 15.5% treatment difference. The efficacy observed with the sc formulation is comparable to the efficacy seen in pivotal IV anifrolumab studies, i.e. 16.3% treatment difference in the IV study 04 and 17.0% treatment difference in the IV study 05.

The key secondary endpoints were all numerically in favour of SC anifrolumab, including BICLA response at week 52 with maintained low (or reduced) use of OCS, time to BICLA response sustained through week 52, and time to flare through week 52. It was considered a major weakness that these endpoints were not hypothesis tested for the IA in the multiple testing procedure, which was planned only at the time of the final analysis.

In conclusion, the efficacy data as a whole, suggested a modest, but clinically relevant efficacy for SC anifrolumab that is broadly similar to the efficacy seen with the approved IV anifrolumab. SC administration will introduce a relevant new option for anifrolumab to be administered by the patient or by caregiver.

With respect to safety, in the single pivotal phase 3 TULIP SC study, anifrolumab 120 mg SC QW appeared well tolerated in adult patients with moderate to severe active SLE during 52 weeks of treatment. No new safety concerns or no new ADRs were identified. The safety profile of anifrolumab 120 mg SC QW appeared generally consistent with the established safety profile of anifrolumab 300 mg IV Q4W, acknowledging the inherent limitations of between-study comparisons.

3.7.2. Balance of benefits and risks

The benefit/risk balance of SC anifrolumab is positive.

3.7.3. Additional considerations on the benefit-risk balance

None

3.8. Conclusions

The overall benefit /risk balance of 120mg SC anifrolumab is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of, Saphnelo 120mg, solution for injection for subcutaneous use is favourable in the following indication(s):

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

The CHMP therefore recommends the extension(s) of the marketing authorisation for Saphnelo subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.