16 December 2021
EMA/4079/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Saphnelo

International non-proprietary name: anifrolumab

Procedure No. EMEA/H/C/004975/0000

Note

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

List of abbreviations

1A7	murine isotype control antibody
293H	293 human embryonic kidney
9D4-Wt	parental monoclonal antibody for anifrolumab
ACR	American College of Rheumatology
ADA	anti-drug antibody(ies)
ADCC	antibody-dependent cell cytotoxicity
AE	adverse event(s)
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANA	anti-nuclear antibody
AS	Active Substance
AST	aspartate aminotransferase
AUC	area under the plasma concentration time curve
AUC	analytical ultracentrifugation
BSE	bovine spongiform encephalopathies
BICLA	British Isles Lupus Assessment Group-based Composite Lupus Assessment
B-IFNAR1	biotinylated interferon alpha receptor 1
BILAG	British Isles Lupus Assessment Group
BILAG-2004	British Isles Lupus Assessment Group 2004
BMI	body mass index
C1q	multivalent for attachment to the complement fixation sites of immunoglobulin
C3	third component of complement
C4	fourth component of complement
Cave	average anifrolumab concentrations
CDC	complement-dependent cytotoxicity
CDR	complementarity determining region
CE-SDS	capillary electrophoresis sodium dodecyl sulfate
CH50	total haemolytic complement
CI	confidence interval
cIEF	capillary isoelectric focusing
CL	clearance
CL/F	oral clearance
CLASI	Cutaneous Lupus Erythematosus Disease Area and Severity Index
Cmax	maximum concentration
CMV	cytomegalovirus
COS7 CV-1	African green monkey fibroblast cell line
CpG-A	cytosine triphosphate- guanine triphosphate oligodeoxynucleotide type A
CPM	counts per minute
CPP	critical proces parameter
CPS	counts per second
CQA	critical quality attribute
CRP	C-reactive protein
CSR	clinical study report
C-SSRS	Columbia Suicide Severity Rating Scale

Ctrough	trough concentration
CV	coefficient of variation
CV-EAC	Cardiovascular Event Adjudication Committee
CXCL10 / IP-1	interferon gamma-induced protein 10
CYP450	cytochrome P450
DAE	discontinuation of treatment with investigational product due to an adverse event
DB	day of birth
DC	dendritic cell
DNA-IC	DNA-containing immune complexes
dsDNA	double-stranded deoxyribonucleic acid
DP	drug product
DS	drug substance
DSC	differential scanning calorimetry
EAIR	exposure-adjusted incidence rate
EC50	half-maximal effective concentration
ECG	electrocardiogram
ECL	electrochemiluminescent
eCRF	electronic case report form
EDQM	European Directorate for the Quality of Medicines
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EOPCB	en of production cell bank
EPGN	epithelial mitogen
ePPND	Enhanced Pre- and Postnatal Developmental
EULAR	European Alliance of Associations for Rheumatology
EVA	ethylene-vinyl acetate
FACIT-F	Functional Assessment of Chronic Illness Therapy-fatigue
Fc	fragment crystallisable
FcRn	Fc receptor neonatal
FcγRI/IIA/IIB/IIIA	Fc gamma receptor I/IIA/IIB/IIIA
FDA	Food and Drug Administration
FMEA	failure mode and effects analysis
FP	Finished Product
FPP	finished pharmaceutical product
FTIR	fourier transform infrared spectroscopy
FUV CD	far UV circular dichroism
α-Gal	terminal Galα1-3Gal (alpha-Gal)
GCP	Good Clinical Practice
GD	Gestation Day
GLP	Good Laboratory Practices
GMP	good manufacturing practice
HCP	host cell protein
HPSEC	high performance size exclusion chromatography
HR	hazard ratio
IC	immune complex

IC50	concentration of a drug that is required for 50% inhibition
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	ion exchange chromatography
IFI202	interferon-activated protein 202
IFI44	interferon-induced protein 44
IFIT1	interferon-induced protein with tetratricopeptide repeats 1
IFN	interferon
IFNAR	type I interferon receptor
IFNAR1	subunit 1 of the type I interferon receptor
IFNAR2	subunit 2 of the type I interferon receptor
IFN-α/β/γ/κ/τ/ω	interferon-alpha/beta/gamma/kappa/theta/omega
IgG	immunoglobulin G
IgG1κ	human immunoglobulin GI kappa
IL-10Rβ	interleukin-10 receptor beta
IL-28Rα	interleukin-28 receptor alpha
IP	investigational product
IP-10	interferon gamma-induced protein 10
IPC	in-process control
IRF9	interferon regulatory factor 9
ISE	Integrated Summary of Efficacy
ISGF3	interferon stimulated gene factor 3
ISRE	interferon stimulated response element
ISRE-Luc	interferon stimulated response element-luciferase (ISRE-Luc)
ISS	Integrated Summary of Safety
IV	intravenous(ly)
KD	equilibrium dissociation constants
KLF10	TFG-β-inducible Krüppel-like factor 10
KLH	keyhole limpet hemocyanin
KPP	key process parameter
LC/MS	Liquid chromatography/mass spectrometry
LD28	lactation day 28
LIVCA	limit of in vitro cell age
LLOQ	lower limit of quantitation
LTE	long-term extension
mAb	monoclonal antibody(ies)
MACE	major adverse cardiovascular events
MC	microbial control
MCB	master cell bank
MCP	macrophage chemotactic protein
MCR	major clinical response
MCS	Mental Component Score
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MLE-12	murine epithelial SV40-transformed cells
MMP	matrix metalloproteinase
MRHD	maximum recommended human dose

MSD	Meso Scale Discovery
MVM	minute virus of mice
MSX	methionine sulfoximine
MX1	interferon-induced GTP-binding protein Mx
NANA	N-acetylneuraminic acid
nAb	neutralising antibody
NC	negative control
NGNA	N-glycolylneuraminic acid
NK	natural killer
NOAEL	no-observed-adverse-effect level
NSAID	non-steroidal anti-inflammatory drug
NUV CD	near UV circular dichroism
OAS	2'-5'-oligoadenylate synthetase
OCS	oral corticosteroids
OECD	Organization for Economic Co-operation and Development
OLE	open-label extension
PA	performance attribute
pAb	polyclonal antibody
PBMC	peripheral blood mononuclear cell
PCR	partial clinical response
PCR	polymerase chain reaction
PCS	Physical Component Score
PD	pharmacodynamic(s)
pDC	plasmacytoid dendritic cell
PDE	permitted daily exposure
PGA	Physician’s Global Assessment
Ph. Eur	European Pharmacopoeia
PHQ-8	Personal Health Questionnaire Depression Scale-8
PK	pharmacokinetic(s)
PKPD	Pharmacokinetic-pharmacodynamic
PPD	postpartum day
PRO	patient-reported outcomes
PRS	primary reference standard
PRV	Pseudorabies Virus
PS-80	polysorbate 80
PT	preferred term
PY	patient-years
Q4W	every 4 weeks
QoL	quality of life
qPCR	quantitative PCR
Q-TOF	quadrupole time-of-flight
Reo-3	Reovirus type 3
RH	relative humidity
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous(ly)

SD	standard deviation
SELENA	Safety of Estrogens in Lupus Erythematosus National Assessment
SF-36	Short Form-36
SLE	systemic lupus erythematosus
SLEDAI-2K	Systemic Lupus Erythematosus Disease Activity Index 2000
SMQ	Standardised MedDRA Query
SOC	System Organ Class
SPR	surface plasmon resonance
SRI	Systemic Lupus Erythematosus Responder Index
SRI(4)	Systemic Lupus Erythematosus Responder Index of ≥ 4
SSc	systemic sclerosis
STAT	signal transducer and activator of transcription (proteins)
t1/2	elimination half-life
TB	tuberculosis
TEM	transmission electron microscopy
TSE	Transmissible spongiform encephalopathies
TIMP	tissue inhibitor of metalloproteinase
TK	toxicokinetic(s)
TLDA	TaqMan low-density array
TLR	toll-like receptor
TM	triple mutation
Tmax	time when maximum concentration occurs
TNF	tumor necrosis factor
TNF-α	tumor necrosis factor alpha
TSE	transmissible spongiform encephalopathy
ULN	upper limit of normal
ULOQ	upper limit of quantitation
UPCR	urine protein/creatinine ratio
UV	ultraviolet
VAS	Visual analog scale
WCB	working cell bank
WFI	water for injections
WRS	working reference standard
Wt	wild type
XMuLV	Xenotropic Murine Leukemia Virus

1. Background information on the procedure

1.1. Submission of the dossier

The applicant AstraZeneca AB submitted on 8 October 2020 an application for marketing authorisation to the European Medicines Agency (EMA) for Saphnelo, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 25 January 2018.

The applicant applied for the following indication "*TRADENAME is indicated as an add-on therapy for the treatment of adult patients with moderate to severe systemic lupus erythematosus (SLE), despite standard therapy (see section 5.1)*."

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or studies.

1.3. Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0239/2020 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0239/2020 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 applicant 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.

1.4.2. New active Substance status

The applicant requested the active substance anifrolumab contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.5. Scientific advice

The applicant received the following Scientific advice on the development relevant for the indication

subject to the present application:

Date	Reference	SAWP co-ordinators
23 October 2014	EMEA/H/SA/2903/1/2014/III	Monique Wakelkamp, Markku Pasanen
26 May 2016	EMEA/H/SA/2903/2/2016/II	Minne Casteels, Mario Miguel Rosa
14 December 2017	EMEA/H/SA/2903/1/FU/1/2017/II	Fernando de Andrés Trelles, Minne Casteels
26 July 2018	EMEA/H/SA/2903/3/2018/III	Minne Casteels, André Elferink
20 September 2018	EMEA/H/SA/2903/4/2018/II	Minne Casteels, André Elferink

The Scientific advice pertained to the following quality, non-clinical, and clinical aspects:

The applicant received Scientific Advice from the CHMP on the development of anifrolumab on 23 October 2014 (EMEA/H/SA/2903/1/2014/III), 26 May 2016 (EMEA/H/SA/2903/2/2016/II), 14 December 2017 (EMEA/H/SA/2903/1/FU/1/2017/II), 26 July 2018 (EMEA/H/SA/2903/3/2018/III) and 20 September 2018 (EMEA/H/SA/2903/4/2018/II). The Scientific Advice pertained to the following quality, non-clinical, and clinical aspects:

- Acceptability of the manufacturing process.
- Acceptability of the non-clinical safety programme.

Acceptability of the immunogenicity assessment

- Acceptability of not conducting drug-drug interaction studies
- Acceptability of the dose selection, target population, *of the SLEDAI as the primary endpoint*, statistical testing strategy, management of SOC based on fixed criteria, CLASI to measure skin disease, definition of flare, inclusion of PROs, placebo-controlled design of the Phase III studies.
- • *Acceptability of the treatment concepts for low disease activity patients*

Introducing an endpoint of LLDAS (lupus low disease activity state) and its definition into a planned Phase III study with s.c. administered anifrolumab

Sufficiency of the safety database

As regards intravenous use, the advice has mostly been complied with. The following points are noted:

- The CHMP noted that patients proposed to be enrolled could not necessarily be characterised as patients failing an optimised SOC background therapy regimen and recommended that the patient population should consist of patients with active disease despite optimised standard therapy (not just steroids or requiring only observation). However, in studies 04 and 05, the minimum requirements for background medication did in fact permit enrolment of patients who were only receiving steroids, and the protocols did not include any particular requirements regarding optimisation of background therapy; on the other hand, actual presence of active disease at baseline was captured with minimum thresholds for SLEDAI and BILAG.
- Regarding OCS tapering, the CHMP recommended to start the tapering from Week 12 and that the OCS dose should be maintained at the Week 40 dose level between Weeks 41 and 52, i.e. not to permit increases or decreases as per the protocol.
- Due to differences in disease characteristics between paediatric and adult-onset SLE, the CHMP

recommended enrolling only adult-onset patients, unless the applicant can power the study sufficiently for both populations. This recommendation was not followed in studies 04 and 05, but the applicant has sufficiently justified the deviation.

- The CHMP recommended that the applicant consider a treatment period longer than 12 months for at least one study. Within the application, data is provided in terms of a 52-week treatment period from all three key studies, and the extension study 09 in which efficacy will be assessed over a 3 year treatment period is still ongoing.

- In the 2014 SA, the CHMP noted ADA positivity in >10% of subjects prior to exposure to the drug and almost two thirds of this ADA positivity could not be reproduced. The CHMP concluded that considerable matrix effects compared to the original validation data are obviously involved, and advised the applicant to evaluate the reason for this. This advice has been followed, although in the studies, the observed prevalence of ADA in drug-naïve scleroderma and SLE patients ranged from 2.3% to 5.7% and the incidence of ADA during the trials was higher in the placebo groups than the active groups. As a conclusion, the reported numbers of subjects with ADA are obviously unreliable. This uncertainty is reflected in the final SmPC.

1.6. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Outi Mäki-Ikola Co-Rapporteur: Armando Genazzani

The application was received by the EMA on	8 October 2020
The procedure started on	29 October 2020
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	18 January 2021
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	26 January 2021
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	2 February 2021
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	25 February 2021
The applicant submitted the responses to the CHMP consolidated List of Questions on	19 May 2021
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	28 June 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	08 July 2021
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	15 July 2021
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	22 July 2021
The applicant submitted the responses to the CHMP List of Outstanding Issues on	10 September 2021
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	29 September 2021
The CHMP Rapporteurs circulated the updated CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	07 October 2021
The CHMP agreed on a 2nd list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	14 October 2021
The applicant submitted the responses to the CHMP List of Outstanding Issues on	12 November 2021
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the 2nd List of Outstanding Issues to all CHMP and PRAC members on	01 December 2021
An AHEG was convened to address questions raised by the CHMP on The CHMP considered the views of the AHEG as presented in the	07 December 2021

minutes of this meeting.	
The CHMP Rapporteurs circulated the updated CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the 2nd List of Outstanding Issues to all CHMP and PRAC members on	09 December 2021
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 December 2021
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS)	16 December 2021

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The applicant has sought marketing authorisation for anifrolumab for the following indication:

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

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. Biologic features

The aetiology of SLE is considered multifactorial, with genetic, hormonal and environmental factors playing important parts. So far, no single abnormality of the immune system is viewed as solely responsible for the development of the disease. Activation of autoreactive B-cells, production of numerous autoantibodies and immune complex formation causing tissue injury and organ damage, are believed to play a central role in the pathogenesis. The interplay of a number of other factors including T-cells, antigen-presenting cells, cytokines, the complement system and apoptosis has also been considered important. Moreover, the disease pathogenesis of SLE includes activation of innate immunity, with increased production of type I interferons, including IFNα.

Type I interferons include 14 IFNα family members, IFNβ, IFNτ, IFNκ and IFNω. This cytokine family regulates immune functions of cellular components of both innate and adaptive immune systems, including dendritic cells, T cells, B cells, and natural killer cells. For example, type I interferons promote dendritic cell maturation, memory CD8+ T-cell proliferation, natural killer-cell activation, and B-cell differentiation.

According to the applicant, multiple lines of evidence indicate a role of type I interferons (IFNs) in the pathogenesis of SLE as well as in other IFN-driven autoimmune diseases. Type I IFNs stimulate dendritic cell maturation, autoantibody production, immune complex formation, organ inflammation, and the further production of type I IFNs that drive autoimmunity. Whereas healthy individuals switch off type I

IFN signalling in the absence of viral infections, the majority of SLE patients have sustained IFN signalling that leads to an over-expression of type I IFN-regulated genes (a type I IFN gene signature). Most adult patients with SLE (approximately 60% to 80%) express elevated levels of type I IFN-inducible genes, which have been associated with increased disease activity and severity. Given the central role of the IFN pathway in the pathogenesis of SLE, targeting type I IFN signalling is expected to provide a therapeutic benefit for SLE patients.

2.1.4. Clinical presentation, diagnosis and 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.

2.1.5. Management

Most of the current therapies for SLE are non-specific and inhibit broad inflammatory pathways. For mild disease, first line treatments include anti-malarials (hydroxychloroquine) and oral corticosteroids (OCSs; e.g., prednisone). NSAIDs are used for temporary symptom control, but, in contrast to glucocorticoids and immunosuppressants, have no impact on disease progression. Steroids remain a mainstay of treatment for mild to severe disease. Additional treatment options for moderate to severe disease include immunosuppressants, such as methotrexate, azathioprine, and mycophenolate mofetil. Each of these classes of agents are however associated with potentially significant toxicity and are sometimes poorly tolerated.

The only targeted therapy for SLE is belimumab (Benlysta), a monoclonal antibody targeting soluble human B Lymphocyte Stimulator protein. Belimumab blocks the binding of soluble BLyS, a B cell survival factor, to its receptors on B cells and inhibits B cell survival and differentiation into immunoglobulin-producing plasma cells. Belimumab is authorised in the EU since July 2011 as add-on therapy in adult patients with active, autoantibody-positive systemic lupus erythematosus (SLE) with a high degree of disease activity (e.g., positive anti-dsDNA and low complement) despite standard therapy. Benlysta has recently been indicated in combination with background immunosuppressive therapies for the treatment of adult patients with active lupus nephritis.

2.2. About the product

Anifrolumab is a human IgG1κ monoclonal antibody directed against subunit 1 of the type I interferon receptor (IFNAR1). Anifrolumab inhibits the binding of type I interferon to IFNAR1 blocking the biologic activity of type I IFNs. The constant domain of the IgG heavy chain on anifrolumab was intentionally modified to eliminate FcγRI, FcγRIIA and FcγRIIB, FcγRIIIA and C1q binding. These mutations also eliminate the potential for antibody-dependent cell cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC).

The applicant seeks marketing authorisation for the use of anifrolumab as an add on therapy for the treatment of adult patients with moderate to severe systemic lupus erythematosus, despite standard therapy.

The proposed posology for anifrolumab is 300 mg administered as an IV infusion at 4-week intervals (Q4W).

2.3. Quality aspects

2.3.1. Introduction

The finished product (FP) is presented as concentrate for solution for infusion containing 300 mg of anifrolumab as active substance (AS).

Other ingredients are histidine/ histidine hydrochloride monohydrate, lysine hydrochloride, trehalose dihydrate, polysorbate 80 (PS-80), and water for injections. The product is available in a clear type I glass vial with an elastomeric stopper and a grey flip-off aluminium seal. Each vial of 2.0 mL of concentrate contains 300 mg of anifrolumab (150 mg/mL).

2.3.2. Active substance

2.3.2.1. General information

The AS, anifrolumab (INN), is a human immunoglobulin GI kappa (IgG1κ) monoclonal antibody (mAb) directed against subunit 1 of the type I interferon receptor (IFNAR1).

The molecular mass of anifrolumab is approximately 148 kDa, including oligosaccharides. The antibody is composed of two identical heavy chains of 49 kDa each, and two identical light chains of 23 kDa each.

Anifrolumab inhibits the binding of type I interferon to IFNAR1 blocking the biologic activity of type I interferons (IFNs). The potency of anifrolumab is determined using a cell-based bioassay that measures the ability of anifrolumab to inhibit IFN-α induced signalling resulting from the binding of anifrolumab to IFNAR1.

The constant domain of the IgG heavy chain was intentionally modified (three amino acid changes) to eliminate Fc gamma receptor I/IIA/IIB/IIIA (FcγRI, FcγRIIA and FcγRIIB, FcγRIIIA) and C1q binding. These mutations also eliminate the potential for antibody-dependent cell cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC).

2.3.2.2. Manufacture, process controls and characterisation

Anifrolumab AS is manufactured and released by AstraZeneca Pharmaceuticals LP, Frederick Manufacturing Center, USA. Good Manufacturing Practice (GMP) compliance has been documented for all sites involved.

Description of manufacturing process and process controls

The anifrolumab AS manufacturing process consists of thawing of a working cell bank (WCB) vial and ending to storage. The process involves a serial cell culture expansion in seed bioreactors and a production bioreactor, harvest of the cell culture fluid followed by chromatographic purification, virus inactivation and reduction (by low pH and filtration), concentration and diafiltration, formulation, bulk filtration and controlled freeze. The AS is stored at -45°C to -35°C, and thawed (short term storage at 2-8°C) before shipping to the FP manufacturing site. Each production bioreactor lot leads to one AS lot. There is no pooling of harvests or purification process intermediates from different production bioreactor lots.

The manufacturing process has been clearly outlined in flow diagrams and a detailed summary of each processing and reprocessing step, including the process parameters, in-process controls (IPCs) and performance attributes are described for each step. The AS manufacturing process is considered acceptable.

Control of materials

Raw materials used in the manufacturing process for master cell bank (MCB), working cell banks (WCBs), and AS including excipients are presented. Many of the raw materials used in the manufacture are of compendial quality. In-house specifications for non-compendial raw materials have been presented. No material of human origin was used in host cell culture, cell line development, banking of the MCB and WCBs, or in AS manufacturing. Materials of animal origin used in cell line development, and materials of animal and other (non-animal) biological origins used in cell banking and AS manufacturing process are thoroughly described (see adventitious agents section). Transmissible spongiform encephalopathies (TSE)/bovine spongiform encephalopathies (BSE) risk assessment and available certificates for relevant animal-derived materials are discussed.

The steps involved in the isolation of anifrolumab from the hybridoma panel, anifrolumab expression plasmid (pMI393), host cell line, production cell line and preparation of the research cell bank have been adequately described.

The host cell line is well-characterised with a long history of safe and successful use in the manufacture of medical products.

A two-tiered cell bank system is used and the guidelines ICH Q5A for viral safety and ICH Q5B and ICH Q5D for expression construct in cell line and characterisation of cell substrates are followed. A MCB, two WCBs, two end of production cell bank (EOPCBs) and a limit of *in vitro* cell age (LIVCA) cell bank have been generated.

The cell banks were tested for identity, safety, purity, and cell substrate stability. Tests for identity, safety, and purity include sterility, mycoplasma, adventitious and endogenous virus, and species identification. In addition, the MCB, EOPCB, and LIVCA banks are tested for infectious retroviruses. The tests, specifications, and results are presented. Appropriateness of cell line for production was established by studying the phenotypic stability in a qualified scale-down production bioreactor model

and analysing the genetic stability of the cell line. The cell banking system and its characterisation and testing are adequately presented.

Future WCBs will be manufactured following the same process as the existing WCBs.

Control of critical steps and intermediates

Comprehensive control strategy for anifrolumab AS manufacture is in place. A systematic risk assessment is presented using a Failure mode and effects analysis (FMEA) approach to determine residual risk to the patients after accounting for all process and testing controls. Overall, the presented process parameters and outputs are appropriate. The applicant has presented acceptable ranges for critical process parameters (CPPs) and IPCs and action limits for microbial controls and performance attributes.

Hold times for anifrolumab process intermediates have been validated through a combination of a small-scale study of biochemical hold stability, and commercial scale studies demonstrating effective microbial control during the hold times.

Process validation

The commercial manufacturing process for anifrolumab AS has been validated at the commercial production scale. The validation covered all cell culture and purification steps.

Process parameters (PP) selected for monitoring in the validation studies included CPPs and key process parameters (KPPs) and process outputs (IPCs, Microbial Controls (MCs) and Performance attributes (PAs)). Validation was performed on consecutive process validation batches at the commercial scale.

Process validation study results met the pre-approved validation criteria, demonstrating that the AS manufacturing process is robust, adequately controlled, and consistent with regard to product quality, yield and impurity clearance.

In addition to the validation of the manufacturing process steps at the commercial scale, validation studies were conducted at small scale and commercial scale to address a number of other manufacturing considerations. Process intermediate hold times, resin sanitisation and storage, resin lifetime, filtration membrane lifetime, filter validation studies, AS shipping and reprocessing are appropriately validated.

Manufacturing process development

Different manufacturing processes have been described. Process 1 and Process 2 batches were used in non-clinical and clinical studies. The most relevant clinical studies are made using batches from Process 2.

The manufacturing site of anifrolumab AS was changed to Frederick Manufacturing Center for commercial manufacturing. Viral clearance in all process versions has been demonstrated to be acceptable.

A comparability study was performed to demonstrate that the Process 3 material, manufactured during the process validation campaign, is comparable to the product administered in clinical trials Prior to the comparability assessment of Process 3 and Process 1/2, two comparability studies were performed, to demonstrate that Process 2 material is comparable to Process 1 material and Process 3 material is comparable to Process 2 material.

As a conclusion, the three processes can be considered comparable and Process 3 data support an improvement of the manufacturing process as compared with Processes 1 and 2.

Characterisation

The characterisation on anifrolumab involved primary structure, higher order structure, carbohydrate structure, charge and size heterogeneity, and biological properties.

Impurities

Product-related impurities have been well characterised and studied. Subset of the impurities are controlled using AS and FP specifications while other impurities are well controlled by the manufacturing process to levels that adequately address risk to patients without the need for control by routine testing.

Process-related impurities include biologically derived macromolecules, hydrolysates, small molecules and synthetic macromolecules. Impurities that are considered critical quality attributes (CQAs)are monitored and controlled through AS release specification. Based on the control strategy risk assessment, it was determined that routine testing of other impurities would not be required.

2.3.2.3. Specification

The specifications for anifrolumab AS include general tests, identity, quantity, purity and impurities, biological activity and safety tests are controlled only at AS release. Tests for visible and sub-visible particles, extractable volume, sterility and container closure identity are tested only for the FP.

All test parameters proposed to be included in the anifrolumab AS specification have been discussed and justification has been provided for each parameter. Overall, the test parameters proposed to be included in the anifrolumab specification are considered appropriate and in line with relevant guidance.

Upon request some specifications have been tightened or further justified by the clinically qualified range and the expected change over the shelf life.

Analytical methods

Anifrolumab is tested using a combination of compendial and non-compendial analytical tests. Compendial methods Appearance-Clarity (Ph. Eur. 2.2.1), Appearance-Color (Ph. Eur. 2.2.2), pH (Ph. Eur. 2.2.3), and Osmolality (Ph. Eur. 2.2.35) were verified according to the corresponding compendial procedure. Compendial tests for endotoxin and bioburden are specific to anifrolumab and were verified to be suitable for microbial control of anifrolumab.

The non-compendial analytical methods have been validated according to ICH Q2 (R1). Full validation reports and validation summaries have been provided for all methods.

Batch analysis

Batch data has been provided for Process 1 batches, Process 2 batches and commercial scale Process 3 batches. The process, concentration and, manufacturing scale of the batches are presented. The results obtained from all the batches met their acceptance criteria. As a whole, the provided data confirms the consistency and uniformity of the AS across the manufacturing processes and they sufficiently demonstrate that the AS manufacturing process is under control.

Reference materials

Two-tiered reference standard system has been introduced for anifrolumab, involving primary and working reference standards.

The Primary Reference Standard (PRS), is used for routine AS and FP lot release and stability testing. The historical reference standards are adequately summarised in the dossier. The stability of the reference standard is also evaluated, in order to monitor every shift in performance. The current

reference standard is tested annually per protocol, trended quarterly, and the CoA is extended annually according to the stability/trending results.

Set of tests and acceptance criteria used for qualification of future reference standards are adequately described. The applicant states that a working reference standard (WRS), prepared in the same manner as the PRS, will be introduced for use in routine testing and sufficient portion of the PRS will be reserved for use as a Reference Standard to qualify future WRS and PRS. This ensures a link between current and future standards, as they are qualified against the existing primary standard.

Container closure

Details of the primary container closure system for anifrolumab AS and acceptable fill volume range has been provided. Protection from microbial ingress and evaluation of performance have been demonstrated. Extractables and leachables studies have been performed. Overall, appropriate description of the AS container closure system and its suitability for intended use has been provided.

2.3.2.4. Stability

The applicant has provided stability data at long term (-45°C to -35°C), short term (2-8°C: used post-thaw), accelerated (23-27°C /55-65% RH) and stress (38-42°C /70-80% RH) conditions as well as from multiple freeze-thaw cycles (3X) on the AS. The accelerated and stress stability studies are considered complete and well performed. Overall, the stability studies presented are largely compliant with the relevant guidelines. The number of batches under analysis is sufficient, the protocols are described, and the selected tests are adequate to monitor possible changes in the quality of the product.

The proposed shelf life for the anifrolumab AS is 60 months at the long-term storage condition of 45°C to -35°C, and 11 months at the short-term storage condition of 2-8°C (post thaw). This shelf-life can be considered acceptable as sufficient amount of real-time, real-condition stability data for the proposed shelf-life has been provided. Stability tests and testing intervals are mostly performed according to ICH Q5C and include adequate, stability indicating methods.

The provided data support the claimed shelf life and the proposed AS shelf life is agreed.

The post-approval stability protocol and stability commitment to continue stability studies of the AS through their scheduled duration of 60 months has been provided and are considered acceptable.

2.3.3. Finished medicinal product

2.3.3.1. Description of the product and Pharmaceutical development

The anifrolumab finished product is a sterile, preservative-free, concentrate for solution for infusion. It is supplied as a single-dose vial in one presentation: 300 mg of anifrolumab per vial with a 2.0 mL label-claim volume.

The FP contains 150 mg/mL anifrolumab in L-histidine/ L-histidine hydrochloride monohydrate, L-lysine hydrochloride, α,α-trehalose dihydrate, polysorbate 80, at pH 5.9.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation.

The FP is aseptically filled into type I glass vials and closed with an elastomeric stopper. The stoppered FP vial is then capped with an aluminum seal. The target filling volume provides an overfill which enables the labelled dose of 300 mg to be extracted from each vial. The primary packaging material complies

with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Pharmaceutical development

Formulation development

Based on the route of administration and dosing requirements, the anifrolumab FP formulation has been developed to stabilise the FP and to maintain FP quality for at least 36 months at 2-8°C. The formulation development of anifrolumab FP has been adequately described. The robustness of the formulation has been established via a multivariate formulation study. Rationale for the selection of excipients and concentrations used are provided. The applicant has confirmed the stability and robustness of the selected formulation.

Manufacturing process development

Process characterisation studies have been performed to investigate process parameter impact on product quality, to understand the risk and criticality of process parameters, and to define proven acceptable ranges. A process failure mode and effects analysis (pFMEA) was employed to facilitate overall process risk management for the FP manufacturing process. Detailed description of the development of the anifrolumab FP manufacturing process is provided. CPPs were identified based on results from the process characterisation studies.

Processing time limits have been characterised for AS thaw, temperature equilibration, mixing, in-process hold, and total wetted filter time.

Several changes to the anifrolumab FP manufacturing process were implemented during the manufacturing process development.

Different manufacturing processes are described for anifrolumab FP. Process 1 material has been used in non-clinical studies and Phase 1 and Phase 2 clinical studies. Process 2 material has been used in Phase 1, Phase 2, and Phase 3 clinical studies. Process 3 material has been used for process validation and stability studies, and in a Phase 3 clinical extension study. Comparability of Process 3 and Processes 1 and 2 was addressed. Based on the provided results, the manufacturing process changes have not impacted the quality or biological activity of anifrolumab. The manufacturing processes are considered comparable.

Container closure

The suitability of the primary packaging components has been demonstrated in terms of protection of the FP from environmental exposure, safety, compatibility with the FP, and performance. Elemental impurities testing is ongoing and data presented so far support the conclusion that there is no risk of inclusion of elemental impurities approaching the control limits as described in ICH Q3D.

Microbiological attributes

The microbiological quality and sterility of anifrolumab FP is ensured by pre-filtration bioburden level, sterile filtration and aseptic fill-finish process, use of depyrogenated and sterilised vials and stoppers, use of a validated capping and crimping process, and controlled by release testing for sterility and endotoxins, and container closure integrity testing during stability testing. The sterilising filter is tested for integrity as part of the manufacturing process. In addition, rabbit pyrogen testing was performed to demonstrate the FP is not pyrogenic.

Compatibility

Compatibility of diluted anifrolumab with polyvinyl chloride or polyolefin infusion bags and polyvinyl chloride administration set with polyether sulfone in-line filter has been demonstrated under worst-case conditions expected during infusions. The compatibility studies support the instructions for use and handling described in the SmPC section 6.3.

2.3.3.2. Manufacture of the product and process controls

Anifrolumab FP is released by AstraZeneca AB, Sweden. Adequate evidence of compliance with GMP has been provided.

Manufacturing process

The manufacturing process starts with the thawing of the AS at the AS manufacturing facility, followed by shipping of the thawed AS to the FP fill facility, and storage at 2-8°C prior to processing. The processing involves temperature equilibration, pooling and mixing of the AS, bioburden reduction filtration and in-process hold, sterile filtration, aseptic filling, stoppering and capping, visual inspection, bulk packing, shipping to secondary packaging and labelling or storage site, and ends with storage of FP vials at 2-8ºC. The manufacturing process is adequately described. Storage of the filled FP and the storage of the labelled and packed FP are overseen by the applicant's Quality Unit at approved sites.

Control of critical steps and intermediates

Control of critical FP manufacturing process steps is described through critical process parameters, in-process controls and in-process hold time. Control criteria and outcomes have been presented for each process control type. Ranges of the process parameters have been established during the manufacturing process development. Summary of in-process controls and criteria is provided. Process validation results verify that the proposed limits ensure that the manufacturing process is capable of consistently producing a FP product meeting the proposed release acceptance criteria. Descriptions of the analytical procedures used for in-process testing are provided.

Manufacturing process validation

Process validation data included process parameters, in-process controls and release specification testing. All process validation results were within the specifications and acceptance limits demonstrating that the manufacturing process is robust and that the in-process controls are suitable to monitor the manufacturing process. Maximum processing time / time out of refrigeration acceptable for commercial production has been based on stability data and maximum time that could be needed for processing of the FP. The longest hold time for bioburden reduced bulk has been validated during process validation.

The sterilisation procedures of filling equipment and container closure components have been qualified. Representative certificates of analysis have been provided for the sterile filters used in the manufacture of anifrolumab FP. Container closure integrity testing and container closure operational qualification, filter validation, and shipping qualification have been performed.

Control of excipients

The applicant states that all excipients, including water for injections (WFI), are of compendial grade and that none of the excipients are of animal or human origin. The information is considered acceptable.

Characterisation of impurities

No additional impurities are detected in the anifrolumab FP compared to the AS. For discussion on impurities, please, refer to section Characterisation (in the AS part). Absence of pyrogenic substances has been demonstrated. According to the applicant, a risk assessment considering potential elemental

impurities has been conducted in line with ICH Q3D, and the levels of metal impurities have been found to be below 30% control threshold of the permitted daily exposure (PDE) limits.

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.

2.3.3.3. Product specification

As the formulations of anifrolumab AS and FP are identical, many of the tests and most of their acceptance criteria are identical for anifrolumab AS and FP. FP-specific specifications were set for visible and sub-visible particles, extractable volume, sterility, identity by lateral flow assay, and container closure integrity. Overall, the specifications are in line with ICH Q6B and Ph. Eur. 2031 monoclonal antibodies for human use. The acceptance criteria have been established. Upon request some specifications have been tightened or further justified by the clinically qualified range and the expected change over the shelf life.

Analytical methods

The methods used for FP testing are either compendial test methods (appearance - clarity, appearance - color, endotoxin, osmolality, pH, sub-visible particles, visible particles, extractable volume, sterility) or in-house test methods. The methods are sufficiently described or an appropriate normative reference is reported.

Regarding the analytical methods specific for FP, all compendial methods following the Ph. Eur. have been verified, and in-house methods have been appropriately validated. For analytical methods common for FP and AS, please refer to the AS specification section.

Batch analysis

Batch analysis data are presented, including process validation batches, and batches used for clinical trials and stability. All batches met the acceptance criteria in place at the time of release and data are comparable between batches. The batch analysis results confirm consistency and uniformity of the product and indicate that the process is under control. FP batches have not been used in non-clinical studies.

Container closure

The container closure system for anifrolumab FP consists on Type I clear glass vials, sealed with elastomeric stoppers, and secured by aluminium seals with flip-off plastic buttons. Specifications for glass vial, stopper and aluminium seal are provided. The primary packaging components comply with the applicable Ph. Eur. monographs. Quality certificates are provided for the vials and stoppers. Schematic drawings of the container closure system have been provided.

Reference materials

The reference standard used for the FP is the same as that used for the AS. The conclusions described in the corresponding section of the AS can be also considered for the FP.

2.3.3.4. Stability of the product

A shelf life of 36 months when stored at 2-8°C is claimed for the finished product.
Overall, the stability studies for the anifrolumab FP are performed largely in accordance with ICH guidance. Data on stability studies performed at the long-term (2-8°C), accelerated (23-27°C), and at stressed storage conditions (38-42°C), as well as data for photostability and elemental impurities studies, are provided.

The provided data show that FP retains the physical, chemical and biological attributes at the long-term storage condition up to the indicated time-points. The claimed 36 months shelf-life is supported by the provided data. Statistical analysis of the FP stability data has been provided. Cumulative storage of up to 48 months at 2-8 °C has been accounted for in the specification calculations. The applicant confirms that the containers used in the stability studies are the same as those proposed for routine storage.

Based on available stability data, the shelf life of 36 months at the long-term storage condition of 2-8°C, is acceptable.

In-use stability results, performed as part of the compatibility studies, support the maximum intended hold times of 4h at 25ºC and 24h at 2-8ºC.

2.3.3.5. Adventitious agents

Anifrolumab is produced in cells using animal protein free medium and nutrient feeds. Cell banks and unprocessed bulk samples have been appropriately tested. The testing has covered sterility, mycoplasma, bacteriostasis, fungistasis, bovine- and porcine adventitious agents, mouse antibody production, minute virus of mice (MVM) assay, adventitious viruses, infectious retroviruses (co-cultivation and plaque assays) and transmission electron microscopy (TEM) with characterisation of retrovirus-like particles (Type A and C particles detected). Both *in vitro* (indicator cell lines) and *in vivo* (suckling and adult mice, guinea pigs, and embryonated hen egg) testing have been performed. Analytical reports of cell bank testing are provided in the dossier.

Testing of adventitious and endogenous viruses showed no contamination.

Viral clearance studies have been conducted in accordance with the guidance given in ICH Q5A. Sufficient numbers of manufacturing process steps have been assessed for clearance of viruses using verified scale-down models operating under worst-case conditions. Dedicated virus removal steps include low pH incubation and virus filtration. Samples of the clearance steps were measured using quantitative PCR (qPCR) or plaque assays using indicator cell lines to determine the number of infectious particles in the samples. A $\log_{10}$ reduction values were determined for each step and virus.

2.3.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

The manufacturing process, elucidation of structure and specifications for anifrolumab AS and FP have been appropriately presented. In response to the major objection, the applicant has performed a risk evaluation concerning the presence of nitrosamine impurities and found the risk of nitrosation or the presence of nitrosating reagents during the anifrolumab AS or FP manufacturing to be low.

Requests for further justification including e.g. tightening of AS and FP specifications have been adequately addressed. Comprehensive control strategy for anifrolumab manufacture is in place. Sufficient stability data to support the claimed shelf life for Saphnelo FP has been provided.

2.3.5. 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. Data has been presented to give reassurance on viral/TSE safety.

2.3.6. Recommendation(s) for future quality development

Not applicable

2.4. Non-clinical aspects

2.4.1. Introduction

The nonclinical development of anifrolumab was conducted in accordance with the ICH Guidelines, in particular ICH S6 (R1), and included the evaluation of its mechanism of action and its suppression of type I IFN induced signalling, gene expression and cellular responses, and the pharmacokinetics and toxicological profiles. Eleven nonclinical pharmacology studies including 2 nonclinical *in vivo* studies with a surrogate anti-IFNAR1 MAb were conducted to characterize the biochemical and functional properties of anifrolumab and to support the proof of concept of inhibition of type I IFNs in SLE. The PK of anifrolumab was characterised in all 6 nonclinical toxicity studies. The nonclinical safety profile of anifrolumab was characterised in single IV dose toxicity studies in cynomolgus monkeys, in repeat dose toxicity studies in cynomolgus monkeys for up to 39-weeks of duration, in a pre- and post-natal development study in cynomolgus monkeys, as well as in tissue cross-reactivity studies using healthy human and cynomolgus monkey tissues. Parameters for local tolerance, safety pharmacology, immunotoxicology, and indirect assessments of male and female fertility were included in the single and repeat dose toxicology studies and pre- and post-natal development study.

The code name of anifrolumab used in this application is MEDI-546.

The nonclinical development of anifrolumab can be considered to be in line with the recommendations given in the scientific advice. The potential secondary effects due to blockade of interferon signalling are being addressed by the available non-clinical and clinical data as well as carcinogenicity risk assessment.

All pivotal nonclinical safety studies were conducted in an Organization for Economic Co-operation and Development (OECD) member country in accordance with OECD GLP guidance. Study 7140-123 and Study 7140-142 were non-pivotal toxicology studies that were not performed to GLP.

The deviations and amendments were adequately described together with an impact assessment. In some studies, certain analyses were performed under non-GLP conditions but this is not considered to affect the integrity of the data.

2.4.2. Pharmacology

2.4.2.1. Primary pharmacodynamic studies

A series of *in vitro* and *in vivo* primary pharmacodynamics studies were performed with anifrolumab to determine binding affinity to human and cynomolgus monkey IFNAR1, mechanism of action, inhibition of type I IFN induced gene signature, suppression of downstream effects such as plasma cell and monocyte differentiation, and production of proinflammatory cytokines and chemokines, as well as binding to FcγRs and FcRn and antibody-mediated cell cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) activities. In addition, a murine surrogate anti-IFNAR antibody (5A3) was used to investigate pharmacodynamic activities in a murine disease models of lupus.

The structure of anifrolumab is modified by introducing mutations in three amino-acid residues, 234, 235 and 331 in the Fc region to prevent FcγRI and FcγRIIIA binding and the Fc-related effector functions, ADCC and CDC. Using two methods, an ELISA and surface plasmon resonance, it was shown that consistent with the anticipated effect of the modifications in the Fc region, anifrolumab binding to rFcγRI and rFcγRIIIA was either absent or significantly reduced. However, in an ADCC assay, anifrolumab had similar ADCC activity of 14-20% target cell lysis as the parental antibody 9D4-Wt. Thus, there remains an uncertainty if anifrolumab still has ADCC activity to the same level as the parental antibody 9D4. In another set of experiments, anifrolumab reduced the binding to FcγRI, FcγRIIa, FcγRIIb, FcγRIIIa-158F by 80%, 90%, 64% and 84%, respectively as compared to the parental antibody 9D4 bearing the wild-type Fc region. Anifrolumab did not exhibit detectable ADCC activity in freshly isolated B cells from healthy donors as compared to the positive control rituximab. Also, anifrolumab did not exhibit detectable CDC activity in Daudi B-cell line compared to rituximab. Despite the minimal binding of anifrolumab to rFcγRI and rFcγRIIIA the likelihood of having clinically relevant effector functions such ADCC, CDC or phagocytosis, seems low but is not excluded.

The KD of human FcRn to anifrolumab and the parental antibody 9D4 were determined by surface plasmon resonance. The KD for FcRn were calculated as 2.37 μM for 9D4, and 2.63 μM for anifrolumab. These data indicate that the triple mutation in the Fc region has no impact on FcRn binding, and hence, the normal endosomal retention and long half-life of the immunoglobulin molecule are retained.

Anifrolumab binding affinity to IFNAR1 was determined to be similar on human and cynomolgus monkey PBMCs. The average KD of anifrolumab on human PBMCs was 0.29 ± 0.29 nM, with 1448 ± 1183 IFNAR1 sites detected, and on cynomolgus monkey PBMCs 0.65 ± 0.74 nM, with 648 ± 353 IFNAR1 sites detected.

The mode of action for anifrolumab was demonstrated, i.e. binding of anifrolumab to its target molecule IFNAR1 on Daudi B cell surfaces competitively inhibited binding of the natural IFNAR1 ligand IFN-α2a. Rapid internalisation and inactivation of IFNAR1 was shown in monocytes following anifrolumab binding. This results in reduction of IFNAR1 receptor on the cell surface and inhibition of downstream signalling.

Binding of anifrolumab to IFNAR1 on human monocytes prevents downstream signalling by completely inhibiting STAT1 pTY701 phosphorylation in cells stimulated with up to 1,000 U of IFN-α2 or pDC supernatants.

The capacity of anifrolumab to inhibit type I IFN induced activation of ISRE was evaluated using human ISRE-luciferase reporter bioassays. Anifrolumab dose-dependently inhibited the ISRE-luciferase activity induced by recombinant human IFN-α2, and type I IFN induced by CpG-A or DNA-IC stimulation of human pDC. The anifrolumab IC50s for IFN-α2 for 100, 1,000, 10,000 and 100,000 U were 0.149, 0.528, 3.048 and 9.748 nM, respectively. The anifrolumab IC50s for CpG-A stimulated pDC media at dilutions of 1/1000, 1/100 and 1/10 were 0.021, 0.075, and 0.721 nM, respectively. The anifrolumab IC50s for

DNA-IC stimulated pDC media at dilutions of 1/1000, 1/100 and 1/10 were 0.060, 0.113 and 0.214 nM, respectively.

The capacity of anifrolumab to inhibit the different type I IFNs was evaluated. Anifrolumab potently inhibited all fourteen type I IFNs tested (IFN-α1, -α2, -α4, -α5, -α6, -α7, -α8, -α10¸-α14, -α16, -α17, -α21, IFN-B1, and IFN-ώ) with IC50s ranging from 0.004 to 0.3 nM. Anifrolumab also significantly inhibited ISRE signalling induced by endogenous type I IFNs in SLE patients' serum by 96% ($p < 0.0001$).

It was shown that the likelihood of having agonistic activity on IFNAR1 target molecule is low as anifrolumab did not induce luciferase activity above the negative control level in 293H ISRE-luciferase transfected cells.

The species-cross-reactivity was addressed in support of the selection of a relevant species for toxicity evaluation. Cynomolgus monkey type I IFNs exhibit high amino-acid sequence identity (81 to 95%) with the corresponding human type I IFNs. Unlike the mouse, cynomolgus monkey IFNAR1 exhibits high amino-acid sequence identity (90.8%) with the human IFNAR1. Similarly, the African green monkey IFNAR1 also exhibits high amino acid homology to both human and cynomolgus monkey IFNAR1. The critical binding epitope for anifrolumab in the IFNAR1 target sequence was identified within the subdomain 3. The amino acid sequences of the binding epitope are conserved between human, cynomolgus monkeys and African green monkeys whereas the murine and rabbit sequences exhibited low sequence homology in this region.

The capacity of anifrolumab to inhibit recombinant murine and cynomolgus monkey type I IFN was assessed using ISRE-luciferase reporter assays. Anifrolumab failed to inhibit ISRE activation induced by murine recombinant IFN-α. This was confirmed with the epitope mapping data demonstrating that replacing the human IFNAR1 sub-domain 3 with that from mouse prevented anifrolumab binding.

In contrast, it was shown that anifrolumab potently inhibited cynomolgus monkey recombinant IFN-α8, IFN-α16, IFN-α21, IFN-β and IFN-ω induced ISRE-luciferase activity in a non-human primate COS7 cell line transiently transfected with ISRE-luciferase. The capacity of anifrolumab to potently inhibit multiple cynomolgus type I IFNs induced ISRE activity was similar to that for recombinant human type I IFNs.

Cynomolgus monkey was selected as the pharmacologically relevant toxicology model for nonclinical safety assessment based on binding and neutralisation activity of anifrolumab in monkey cells.

The ability of anifrolumab to suppress the expression of a validated type I IFN gene signature based on the expression of 21 genes was demonstrated in CpG-A stimulated human PBMCs. Anifrolumab dose-dependently suppressed the CpG-A–induced interferon gene by an average of 86% compared with no antibody treatment.

The impact of anifrolumab on type I IFN induced monocyte activation, was evaluated by examining the upregulation of differentiation markers CD38 and CD123, and the production of IL-6, MCP-1 (CCL2), MCP-2 (CCL8) and IP10 (CXCL10). In stimulated CD14+ monocytes anifrolumab was able to inhibit the CD38 upregulation by 95.5% with an IC50 of 0.045 nM, and the CD123 upregulation by 73% with an IC50 of 0.06 nM relative to R3-47. Leukocyte IFN stimulation of monocytes increased the production of IL-6, IP-10, MCP-1 and MCP-2 by a mean of 3 to 19-fold, respectively, while the induction of cytokines and chemokines was 100% inhibited by anifrolumab. These results demonstrated that anifrolumab could inhibit the autocrine amplification of type I IFN production, and in turn suppress the costimulation and the production of proinflammatory cytokines, and plasma cell differentiation which could contribute to localised inflammation and tissue injury. However, in literature many cytokines implied in the pathogenesis of various autoimmune diseases, including SLE, could have a dual role.

According to Michael H. Lee, et al. 2019 murine lupus cDCs overproduce IL-10 and IL-27 as the result of an enhancement by the increased I-IFNs that are highly active in lupus. Importantly, they showed

that IL-10 and IL-27 levels correlate with the IFN signature in SLE patients. Indeed, they found that both IL27 and IL10 levels were significantly higher only in the SLE patients with a high I-IFN signature, while no significant difference in IL-27 and IL 10 levels was found between SLE patients and healthy controls who had similar levels of IFN-stimulated genes suggesting that in human SLE the I-IFN signature is associated with higher levels of IL-27 and IL-10. A causative link between I-IFNs, IL-27, and IL-10 has been previously proposed in normal immune cells (Iyer SS et al, 2010; McNab FW et al, 2014).

As reported by Meka RR et al, 2015, the mechanistic basis of the dual role of IL-27 in inflammation and autoimmunity is still not fully defined: IL-27 inhibits the production of pro-inflammatory cytokines IL-1, IL-6 and IL-17, but induces the production of anti-inflammatory cytokine IL-10. Additionally, IL-27 it's involved in the pathogenesis of autoimmunity, and with some exceptions, mostly anti-inflammatory effects have been described in different diseases while it is increasingly recognised that Interleukin-10, the prototypic anti-inflammatory cytokine, has a paradoxical pathogenic activity in the systemic autoimmune disease SLE. In conclusion Michael H. Lee, et al. 2019 suggest that I-IFN blockade, by suppressing IL-27 and IL-10, may have opposite effects on lupus disease; it may block the promotion of autoantibodies but also suppress anti-inflammatory mechanisms. Therefore, in order to better understand the crucial role of cytokine-mediated immunity in the pathological process of SLE the applicant was asked to provide a discussion regarding these evidences. An in-depth discussion based on literature has highlighted the importance of IL-27 and IL-10 in SLE pathogenesis. In any case, the specific role of these cytokines is not yet fully characterised, therefore, further studies, particularly in humans are needed to better understand their implications in the disease.

Anifrolumab blocks type I IFN induced monocyte differentiation and the induction of proinflammatory cytokines and chemokines as evidenced by dose-dependent inhibition of the upregulation of monocyte differentiation markers CD38 and CD123 by 95% and 73% relative to the isotype control antibody, respectively; and complete inhibition of induction of cytokines and chemokines IL-6, IP-10, MCP-1 and MCP-2 in monocytes.

The *in vivo* proof-of-concept was investigated in a mouse disease model of lupus, using a mouse surrogate anti-IFNAR1 mAb. The *in vivo* proof-of-concept was demonstrated in the spontaneous mouse model of SLE that develop disease that resembles several of the features of SLE in humans. The mouse surrogate anti-IFNAR1 mAb suppressed the expression of interferon-induced genes CXCL10/IP-10, IFIT1, IFI202b, and IFI44 to the normal level in this lupus model, and prevented induction of proteinuria, a hallmark of lupus. It should, however, be noted that the treatment with anti-IFNAR1 antibody was started prior to induction of proteinuria, and thus, the potential for reversing the existing proteinuria cannot be deduced from the data. Nevertheless, these results provide support the therapeutic rationale of blocking interferon signalling in SLE.

2.4.2.2. Secondary pharmacodynamic studies

No formal secondary pharmacodynamic studies have been conducted with anifrolumab. Anifrolumab was engineered to reduce binding to Fc receptors and complement and it did not exhibit detectable Fc-mediated CDC and ADCC activity. Also, anifrolumab does not exhibit IFNAR1 specific agonistic properties.

2.4.2.3. Safety pharmacology programme

No stand-alone safety pharmacology studies were performed with anifrolumab. In accordance with the ICH S6(R1) and ICH S7A guidelines, safety pharmacology endpoints were incorporated into the single and repeat-dose SC and IV toxicity toxicology studies in cynomolgus monkeys. There were no anifrolumab-related findings in assessments of the central nervous (clinical observations of behaviour), respiratory (rate), renal (urinalysis), and cardiovascular systems (heart rate, electrocardiogram, and

blood pressure). Additionally, microscopic pathology examinations did not show any anifrolumab-related adverse effects for key vital organs other than the arteritis observed in the 39-week study, probably a consequence of species-specific immunogenicity. Additionally, in the 39-week repeat dose toxicity study, at the end of dosing period, an anifrolumab-related trend for decreased blood pressures in animals given 60 mg/kg SC was observed.

2.4.2.4. Pharmacodynamic drug interactions

No nonclinical *in vivo* pharmacodynamic drug interactions studies have been conducted with anifrolumab. The absence of these studies is considered acceptable since it is not expected that blockade of physiological levels of type I IFN with anifrolumab will impact the activity of cytochrome P450 and lead to clinically meaningful drug-drug interactions that would warrant dose adjustment. With respect to modulation of anifrolumab metabolism by concomitant medications, pharmacokinetic drug interactions are not anticipated because of minimal involvement of CYP enzymes in anifrolumab's metabolism. Anifrolumab is an IgG1 mAb that is eliminated by target IFNAR-mediated elimination pathway and by the FcRn pathway. These elimination mechanisms are not dependent on CYP enzymes.

2.4.3. Pharmacokinetics

Stand-alone pharmacokinetic studies were not conducted. Pharmacokinetic properties of anifrolumab were evaluated in the single-dose and repeat-dose toxicity studies as well as in the pre- and postnatal developmental toxicity study.

The ELISA analytical methods for quantification of anifrolumab in cynomolgus monkey serum and milk were adequately validated or qualified. The ELISA assay for detecting anti-anifrolumab antibodies in cynomolgus monkey serum was formally validated and met the acceptance criteria. However, the assay seems to be sensitive to drug interference at anifrolumab concentrations present in the serum samples. Drug interference hampers reliable detection of anti-anifrolumab antibodies. Also, anti-anifrolumab antibody levels only at and above 2 µg/ml were detected in the presence of 2 µg/ml anifrolumab which is close to the detection limit for quantification of anifrolumab. This indicates that the assay is capable of measuring only high levels of anti-anifrolumab antibodies even in the presence of very low drug concentrations in the serum samples. The assay for measuring receptor occupancy is considered appropriately qualified for the purpose.

Following single IV administration of anifrolumab to cynomolgus monkeys, the C_{max} increased proportionally with dose in the 5-100 mg/kg dose range while more than dose-proportional increase in AUC was observed. The mean CL was 5.41, 4.11 and 2.58 mL/kg/d for the 5, 30 and 100 mg/kg doses, respectively. The elimination half-life $t_{1/2}$ of anifrolumab was significantly longer in the 100 mg/kg group animals than in the 5 and 30 mg/kg dose groups. No apparent gender differences in TK was observed in cynomolgus monkeys. No pre-existing anti-anifrolumab antibodies were detected. After single dose of anifrolumab, 11/15 animals had detectable ADA responses, with the frequency inversely proportional to the dose level administered and increasing at later time points. ADA titers ranged from 1:40 to 1:768,000 by the end of the study.

Following a single SC administration of 5 mg/kg anifrolumab to cynomolgus monkeys, the median T_{max} was 2 days post-dose. The mean systemic exposure (C_{max} and AUC) was higher in the SC group as compared to IV group at the same dose level. The mean CL/F and terminal t1/2 were 2.55 mL/kg/d and 13.2 d for the SC dose compared to 4.94 mL/kg/d and 8.42 d for the IV dose, respectively. No pre-existing ADA were detected in any of the animals. Post-treatment, all animals had detectable ADA at Day 29 regardless of dose with the titers being similar among the two dosing routes.

Following a single IV administration, Cmax increased in direct proportion to dose in the 0.03 to 1 mg/kg dose range in cynomolgus monkeys. A more than dose-proportional increase in AUC was observed. The mean CL was 140, 25.2 and 14.4 mL/kg/d for the 0.03, 0.3 and 1 mg/kg doses, respectively. No gender difference in TK was observed. Anti-anifrolumab antibodies were detected in 20/24 anifrolumab dosed animals. Positive titers in anifrolumab dosed animals ranged from 20 to 2 621 440. On Day 15, all animals in the 0.3 and 1 mg/kg groups tested positive for anti-anifrolumab antibodies, while 3/6 and 4/6 tested positive in the 0.003 and 0.03 mg/kg groups respectively.

In the 4-week repeat-dose study, C_{max} increased approximately in proportion with the dose in the 0.5 - 30 mg/kg dose range following the first IV administration in cynomolgus monkeys. More than dose proportional increase in Cmax and AUC(0-7d) was observed in the 5 - 30 mg/kg dose range. In Group 3 and 4 animals, more than dose proportional increase in C_{max} and $AUC_{(0-7d)}$ was observed. In recovery animals, the mean terminal ($t_{1/2}$) was 5.57 and 10.1 days for the 5 and 30 mg/kg groups, respectively. The shorter $t_{1/2}$ in the 5 mg/kg group recovery animals is likely due to the higher incidence of positive immunogenicity response in this group. No appreciable gender difference in drug exposure was observed. Following treatment, the incidence of positive immunogenicity response decreased with increasing dose. All animals (100%) in the 0.5 mg/kg dose group, 9/12 animals (75%) in the 5 mg/kg dose group, and 2/12 animals (17%) in the 30 mg/kg dose group had at least one positive immunogenicity response detected during the study period. The TK exposure in anifrolumab treated animals inversely correlated with the immunogenicity status and ADA titer.

In the 39-week repeat-dose study, following the first IV infusion administration of anifrolumab both $AUC_{(0-7d)}$ and C_{max} increased in an approximately dose-proportional manner in the tested range of 5 mg/kg to 50 mg/kg, consistent with linear pharmacokinetics. An approximate dose proportional increase was also observed following the first SC administration of anifrolumab in the tested range of 15 mg/kg to 60 mg/kg. The T_{max} for SC treated animals ranged from 2 to 7 days.

Following the dose 39 of anifrolumab via IV administration, the mean CL values at steady state of 2.55±0.569 and 2.47±0.653 mL/d/kg were estimated for animals dosed with 5 mg/kg and 50 mg/kg, respectively. Following the Dose 39 of anifrolumab via SC administration, the median time to T_{max} for SC treated animals was 2 and 2.5 days for animals in Groups 4 and 5, respectively. The average apparent clearance (CL/F) at steady state for animals receiving 15 mg/kg and 60 mg/kg was estimated as 2.98±0.615 and 3.08±1.05 mL/d/kg, respectively.

TK parameters following the last IV and SC doses (Dose 40) of anifrolumab were only calculated for the seronegative recovery animals. Following the last IV administration of anifrolumab, mean t1/2 values were estimated at 16.3 and 20.7±3.72 days following dosing with 5 mg/kg and 50 mg/kg anifrolumab, respectively. Following the last SC administration of anifrolumab, mean t1/2 was 15.7±2.80 and 19.4±2.84 days following dosing with 15 mg/kg and 60 mg/kg anifrolumab. The overall bioavailability was 78.7%.

Anifrolumab accumulated after repeated dosing by a factor of 3.77, 4.49, 6.12, and 5.29 in the 5mg/kg IV, 50 mg/kg IV, 15 mg/kg SC and 60 mg/kg SC groups, respectively. This is a likely consequence of saturation of the target.

Seven of twelve control animals (58%) in the control group showed positive titers during the treatment period. The ADA titers in the control animals ranged from borderline positive (1:10 and 1:20) to 1:655,000. Eight animals (67%, 4 males and 4 females) from Group 2 (5 mg/kg, IV) and three animals (25%, 1 male and 2 females) from Group 4 (15 mg/kg, SC) tested positive for anti-anifrolumab antibodies.

In the pre- and post-natal developmental toxicity study, following single IV infusion of anifrolumab, C_{max} and $AUC_{(0-14d)}$ was approximately dose-proportional in the tested range of 30 to 60 mg/kg in pregnant

adult female cynomolgus monkeys. Mean CL values of 3.14±0.460 and 2.87±0.900 mL/d/kg and the mean terminal $t_{1/2}$ values of 12.6±2.50 and 15.5±6.14 days were estimated for adult female cynomolgus monkeys dosed with 30 and 60 mg/kg, respectively. Following the fifth IV infusion of anifrolumab on GD76, a dose-proportional increase in C_{max} and $AUC_{(0\text{-}14d)}$ was observed in the dose range 30 to 60 mg/kg. Mean CL value of 3.67±0.746 and 3.59±0.811 mL/d/kg and the mean terminal $t_{1/2}$ values of 11.3±1.74 and 12.2±3.91 days were estimated following dosing with 30 and 60 mg/kg anifrolumab, respectively. Following the ninth IV infusion of anifrolumab on GD132, a dose-proportional increase in C_{max} and $AUC_{(0\text{-}14d)}$ was observed in the dose range 30 to 60 mg/kg. Mean CL value of 3.35±0.913 and 3.26±0.469 mL/d/kg and the mean terminal $t_{1/2}$ values of 11.4±2.07 and 13.4±2.96 days were estimated following dosing with 30 and 60 mg/kg anifrolumab, respectively. Following the last IV infusion of anifrolumab in the lactation period, a dose proportional increase in C_{max} and $AUC_{(0\text{-}14d)}$ was observed in the dose range 30 to 60 mg/kg. Mean CL value of 3.36±0.799 and 2.94±0.461 mL/d/kg and the mean terminal $t_{1/2}$ values of 16.2±7.21 and 17.5±5.43 days were estimated following dosing with 30 and 60 mg/kg anifrolumab, respectively. Accumulation ratio ranged from 1.6 to 1.8-fold for 30 mg/kg dose group, and 1.5 to 2.0-fold for 60 mg/kg dose group following the fifth (GD76), ninth (GD132) and last IV infusion of anifrolumab. Steady-state was reached by the ninth dose and that exposure to anifrolumab was maintained in adult females over the dosing period.

Exposure of infants to anifrolumab was demonstrated by detecting anifrolumab in the serum. Majority of the infants in the 30 mg/kg group (n=9) and all infants in the 60 mg/kg group (n=8) had detectable levels of anifrolumab in serum 30 days after birth. Infant anifrolumab concentrations were greater than dose proportional in the tested range of 30 to 60 mg/kg. The infant serum anifrolumab levels were considerably higher than corresponding adult female milk levels at time points after birth which demonstrate that anifrolumab is transferred via the placenta from maternal circulation into foetal circulation.

No tissue distribution and protein binding studies were conducted with anifrolumab, which is acceptable as it is an IgG, the distribution of anifrolumab is likely restricted to the extracellular fluid.

No metabolism studies were conducted which was considered acceptable to the CHMP as anifrolumab is a monoclonal antibody and therefore its expected metabolism is degradation to small peptides and amino acids. No active metabolite is expected for anifrolumab.

No specific studies to determine anifrolumab excretion were conducted which was considered acceptable to the CHMP as anifrolumab is a monoclonal antibody. Due to its large molecular size, anifrolumab and human immunoglobulins in general are not expected to be subject to renal filtration. There are two major elimination pathways of anifrolumab, the intrinsic clearance by the reticuloendothelial system in the same way as that for an endogenous IgG, and the elimination by the target antigen receptor (IFNAR1-mediated clearance). Excretion of anifrolumab into milk was evaluated in the pre- and post-natal developmental toxicity study. It was demonstrated that anifrolumab is excreted into milk.

Nonclinical *in vivo* drug-drug interaction studies were not conducted with anifrolumab. Based on its mode of action the likelihood of anifrolumab impacting on expression levels of metabolic enzymes, such as cytochrome P450s, is considered low. However, general considerations for anifrolumab pharmacokinetic drug interactions are discussed in the Clinical Section.

2.4.4. Toxicology

The toxicology programme consists of non-GLP and GLP-compliant single dose toxicity studies, GLP-compliant repeat-dose toxicity studies of 4- and 39-week duration, and a GLP-compliant pre- and post-natal developmental toxicity study. The clinical route of administration, i.e. intravenous as well as subcutaneous administration route were used in both single and repeat-dose toxicity studies.

Toxicokinetics, immunogenicity, as well as safety pharmacology and local tolerance were addressed in the toxicity studies. In addition, tissue-cross-reactivity studies with human and cynomolgus monkey tissue panels were conducted. A risk assessment based on the weight of evidence was provided to address carcinogenicity.

All *in vivo* toxicity studies were conducted in cynomolgus monkeys which can be considered as a relevant species for evaluation of safety of anifrolumab. Anifrolumab was pharmacologically active in cynomolgus monkeys, and it binds to IFNAR1 of cynomolgus monkeys and human with a similar affinity.

2.4.4.1. Single dose toxicity

Anifrolumab was well tolerated with no adverse findings observed following a single IV administration to male and female cynomolgus monkeys up to 100 mg/kg. The NOAEL was 100 mg/kg, the highest dose tested. However, an unusual unexpected hypersensitivity reaction and presence of IgG, IgE and IgM anti-drug antibodies in animals that received an additional dose of anifrolumab were observed. The clinical relevance and significance of this finding is not known. Nevertheless, a similar finding was not observed in repeat-dose toxicity studies up to 39-weeks of duration. In another non-GLP and a GLP-compliant single dose toxicity studies in cynomolgus monkeys, anifrolumab was well tolerated with no adverse effects observed following a single IV or SC dose of 5 mg/kg, and a single IV dose of up to 1 mg/kg. The receptor occupancy analysis and an *in vitro* genomic analysis of interferon gene signature confirmed pharmacological activity in this dose range.

2.4.4.2. Repeat dose toxicity

Repeat-dose toxicity of anifrolumab was evaluated in cynomolgus monkeys in 4-weeks and 39-weeks GLP toxicity studies with an additional recovery period of 7 or 12 weeks, respectively. In the 4-week repeat dose toxicity study, anifrolumab was well tolerated after weekly intravenous dosing for 4 weeks at dose levels up to 30 mg/kg. A non-adverse transient anifrolumab-related increase in the occurrence of dry faeces was noted in animals in the 5 and 30 mg/kg dose groups during the first 9 days. Similar findings were not noted in other repeat dose anifrolumab studies. The NOAEL in this study was 30 mg/kg/dose, the highest dose tested, which resulted in a mean $AUC_{(0\text{-}7d)}$ of 11,100 µg·d/mL and a mean C_{max} of 2,640 µg/mL.

Anifrolumab was generally well tolerated in the chronic 39-week repeat-dose toxicity study in cynomolgus following weekly administration at dose levels up to 50mg/kg intravenously and up to 60 mg/kg subcutaneously. Pharmacology-related findings in the lymphoid organs such as minimal increase in lymphoid follicle size in spleen and in some lymph nodes of dosed males and females of the high dose group animals at the end of the dosing and/or recovery phase. The minimal decrease in lymphocytes in the cortex and medulla of the thymus of dosed males was observed at the end of the dosing period. Decreased cortical lymphocytes persisted until the end of the recovery phase. At the end of dosing phase, attributed to anifrolumab, but of limited physiological importance, trend for decreased blood pressures in animals given 60 mg/kg SC and reversible increases in concentrations of C3 in males given 50 mg/kg IV were observed. One 60 mg/kg SC male testis had marked unilateral diffuse seminiferous tubular epithelium degeneration correlating with abnormal sperm parameters which differed markedly from all other terminal sacrifice animals. A recovery 50 mg/kg IV male had mild depletion of pachytene spermatocytes and spermatids correlating with normal motility and sperm numbers and indicating recovery toward normal spermatogenesis from the lack of sperm, likely correlating with seminiferous tubular degeneration in the motility samples taken mid-way through recovery.

Grade 1 to 3 focal arteritis characterised as intramural and perivascular infiltrates of lymphocytes and macrophages, without necrosis, giant cells, eosinophils, or granulomas in small- and medium-sized

arteries of several organs was noted in 5/24 males (21%), that received anifrolumab, but it was not evident in control males or in females regardless of treatment group (0/24, 0%). At the end of the dosing phase, 2 males in the 50 mg/kg IV group had anifrolumab-related arteritis in multiple organs. At the end of the recovery phase, 3 males had anifrolumab-related arteritis: one each given 5 mg/kg IV, 50 mg/kg IV, and 60 mg/kg SC. At the end of the recovery phase, arteritis was evident in more animals but was less pronounced and generally less widespread than in the dosing phase.

Anti-drug antibodies were detected in 11/48 (22.9%) animals treated with anifrolumab with higher incidence observed in animals receiving lower doses. Seven of twelve control animals (58%) showed positive titers ranging from borderline positive (1:10 and 1:20) to 1:655,000 during the treatment period.

In the 39-week repeat dose toxicity study, the NOAEL for females is 50 mg/kg IV (which resulted in a mean Cmax of 4,510 ± 1,200 µg/mL and mean AUC(0-7d) 21,600 ± 5,780 µg·d/mL) and 60 mg/kg SC (which resulted in a mean Cmax of 3,230 ± 1,120 µg/mL and mean AUC(0-7d) 19,500 ± 5,620 µg·d/mL). Based on the arterial inflammation observed, the NOAEL for males is less than 5 mg/kg IV and 15 mg/kg SC. If the observed arteritis is not factored into the NOAEL determination, the NOAEL of anifrolumab for males is at least 50 mg/kg IV and 60 mg/kg SC, the highest doses tested.

The comparison of animal to human systemic exposures (AUC and C_{max}) to allow establishing safety margins were provided at the CHMP's request. The requested safety margins were calculated based on the NOAEL levels with arteritis finding excluded and included. In the 39-week repeat-dose toxicity study, at the 50 mg/kg IV NOAEL (not taking arteritis into account), observed exposure consisted of $AUC_{(0\text{-}7d)}$ of 21600 µg·d/mL and C_{max} of 4510 mg/mL. This resulted in a margin of approximately 18 times the MRHD on an AUC at steady state basis, and 36 times the MRHD on a C_{max} at steady state basis for type I IFN gene signature test high subjects. For type I IFN gene signature test low subjects, this resulted in a margin of approximately 15 times the MRHD on an AUC at steady state basis, and 33 times the MRHD on a C_{max} at steady state basis. The safety margins calculated at NOAEL levels including arteritis resulted in lower exposure multiples, the C_{max} being 3 fold for both type I IFN high and low, and the AUC being 1.7 and 1.4 for both type I IFN high and low, respectively.

2.4.4.3. Genotoxicity

In line with the Guideline on the preclinical safety evaluation of biotechnology-derived pharmaceuticals (ICH S6 R1), the range and type of standard studies evaluating genotoxicity routinely conducted for pharmaceuticals are not applicable for anifrolumab. Therefore, no studies evaluating the genotoxic or mutagenic potential of anifrolumab have been conducted. Anifrolumab is a monoclonal antibody composed entirely of naturally occurring amino acids and contains no inorganic or synthetic organic linkers or other non-protein portions. Anifrolumab is a large protein molecule that is not expected to cross the nuclear or mitochondrial membrane and to interact directly with DNA or other chromosomal material inside the nucleus. Thus, it is highly unlikely that anifrolumab would react directly with DNA or other chromosomal material.

2.4.4.4. Carcinogenicity

Carcinogenicity studies with anifrolumab were not conducted. Anifrolumab does not bind to murine IFNAR1 and does not inhibit the biological activity of murine IFN-α. Therefore, a direct evaluation of anifrolumab carcinogenic risk in a 2-year rodent bioassay was not performed. Instead, a weight of evidence approach consisting of data from chronic toxicity studies with anifrolumab and literature data was presented to address the risk of carcinogenicity. Type I interferons have a role in the anti-tumour response. Thus, it is plausible that blockade of IFNAR1 responses would potentially increase the risk of

carcinogenicity. The repeat IV or SC dose non-clinical studies with anifrolumab for up to 39 weeks of duration showed no evidence of proliferative or pre-neoplastic effects in cynomolgus monkeys. In line with the recommendations in the Guideline on the preclinical safety evaluation of biotechnology-derived pharmaceuticals (ICH S6 R1), the potential risk can be mitigated by the risk management practices without performing additional *in vivo* studies in animal models.

2.4.4.5. Reproductive and developmental toxicity

A pre- and post-natal developmental toxicity study was conducted with anifrolumab in cynomolgus monkeys. Fertility or embryo-foetal developmental toxicity studies were not conducted.

In accordance with the ICH S6(R1) guideline, for situations in which nonhuman primates are the only relevant species for nonclinical safety testing, potential effects on organ weights and histopathology of the reproductive tract were evaluated as a surrogate endpoint for male and female fertility in a repeat-dose toxicity study in sexually mature primates. Assessment of indirect female fertility endpoints [menses cycle, organ weights (pituitary gland, ovaries and uterus), macroscopic and histopathology (pituitary gland, ovaries, uterus, cervix, vagina, and mammary gland)] were conducted in sexually mature cynomolgus monkeys during the 39-week repeat-dose toxicity study with weekly IV infusion (0, 5, or 50 mg/kg) or SC injection (0, 15, or 60 mg/kg). No anifrolumab related effect on menstruation was evident. There were no anifrolumab related changes in organ weights or macroscopic and microscopic pathology.

In the 39-week repeat-dose toxicity study, there were unilateral testicular seminiferous tubule degeneration and sperm changes noted for two anifrolumab-treated males. The associated data for the two males argues against these testicular findings being attributable to anifrolumab. This is consistent with available type I IFN literature suggesting that over-expression and not neutralisation of type I IFN could impair spermatogenesis.

A GLP-compliant pre- and post-natal development study was conducted in cynomolgus monkeys following IV administration of anifrolumab to pregnant cynomolgus monkeys which received every other week IV infusions of 0, 30, or 60 mg/kg anifrolumab from GD20 through approximately LD28, with subsequent monitoring of mothers and infants after delivery until PPD or BD for infants 180 ± 2. There were no anifrolumab-related adverse maternal, foetal, or infant effects. Two maternal animals in the 60 mg/kg group were euthanised on the day of emergency caesarean section due to dystocia they were but there were considered incidental and unrelated to anifrolumab as macroscopic changes were not observed.

High incidence of foetal loss was observed. The overall foetal loss (in utero foetal death and abortion before/on GD135) was 1/16 (6.3%), 5/17 (29.4%), and 3/16 (18.8%) females in the control, 30 and 60 mg/kg/week groups, respectively. The applicant considered this not significant, as the ratio of foetal loss was within the historical control range of 0 - 33.3% the average incidence being 14.2 ±10.2% (mean ±SD). The total embryo-foetal and infant loss ratios were 5/16 (31.3%), 7/17 (41.2%, and 8/16 (50%) for the control, and for the 30 and 60 mg/kg anifrolumab groups, respectively. The applicant argued that this is not relevant as it falls within the historical foetal loss ratio in the testing facility.

There were no anifrolumab-related changes in infants in clinical observations, body weights, survival, or in parameters of functional and morphological development including skeletal findings, behavioural assessment, anti-KLH antibody assay, haematology, serum chemistry, or flow cytometry analysis parameters. One infant in the control group was euthanised on DB16, and 2 infants in the 60 mg/kg group died on DB1, but there were no test article-related macroscopic changes observed for these infants. The applicant concluded the maternal and infant NOAEL to be 60 mg/kg, the highest dose tested.

2.4.4.6. Local Tolerance

Local tolerance of anifrolumab was assessed by clinical (dermal Draize scoring), macroscopic, and histopathology examinations of anifrolumab infusion/injection sites during the single and repeat-dose toxicity studies. No anifrolumab-related adverse changes were observed at the IV infusion or SC injection sites.

2.4.4.7. Other toxicity studies

Tissue cross-reactivity

The tissue cross-reactivity of anifrolumab in a panel of human tissues was as expected on the known IFNAR1 expression. A wide-spread anifrolumab-specific staining was detected in epithelium, endothelium, mesothelium, mononuclear cells, and spindloid/dendritic cells throughout the human tissue panel. In addition, anifrolumab staining of myenteric plexi in the gastrointestinal tract, glomerular tuft cells in the kidney, granulosa cells in the ovary, beta cells in the pancreas, chief cells of the parathyroid, endocrine cells and pituicytes in the pituitary, decidual cells in the placenta, and spermatogenic cells in the testis was observed. The cross-reactivity of anifrolumab was essentially similar in human and cynomolgus monkey tissues supporting the cynomolgus monkey as a relevant species for safety evaluation.

2.4.5. Ecotoxicity/environmental risk assessment

Anifrolumab is non-hazardous, biodegradable product. As such, the environmental risk in terms of use and disposal is considered to be negligible and in accordance with the guideline (CHMP 2006) ERA studies were not submitted. 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. This was acceptable to the CHMP.

2.4.6. Discussion on non-clinical aspects

The *in vitro* and *in vivo* pharmacological data were appropriate and sufficiently comprehensive. The studies with anifrolumab determined binding affinity to human and cynomolgus monkey IFNAR1, mechanism of action, inhibition of type I IFN induced gene signature, suppression of downstream effects such as plasma cell and monocyte differentiation, and production of proinflammatory cytokines and chemokines, as well as binding to FcγRs and FcRn and antibody-mediated cell cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) activities. In addition, a murine surrogate anti-IFNAR antibody (5A3) was used to investigate pharmacodynamic activities in a murine disease model of lupus.

The structure of anifrolumab is modified by introducing mutations in three amino-acid residues, 234, 235 and 331 in the Fc region to prevent FcγRI and FcγRIIIA binding and the Fc-related effector functions, ADCC and CDC. Consistent with the anticipated effect of the modifications it was shown that in the Fc region anifrolumab binding to rFcγRI and rFcγRIIIA was either absent or significantly reduced. However, the results from two sets of ADCC experiments gave slightly contradicting results. In the first experiment, anifrolumab had similar ADCC activity of 14-20% target cell lysis as the parental antibody 9D4-Wt. Thus, it remains uncertain if anifrolumab still has ADCC activity to the same level as the parental antibody 9D4. In the second set of experiments, anifrolumab reduced the binding to FcγRI, FcγRIIa, FcγRIIb, FcγRIIIa-158F by 80%, 90%, 64% and 84%, respectively as compared to the parental antibody 9D4 bearing the wild-type Fc region. In this study, anifrolumab did not exhibit detectable ADCC activity in freshly isolated B cells from healthy donors as compared to the positive control rituximab. Also,

anifrolumab did not exhibit detectable CDC activity in Daudi B-cell line compared to rituximab. Due to the minimal binding of anifrolumab to rFcγRI and rFcγRIIIA the likelihood of having clinically relevant effector functions such ADCC, CDC or phagocytosis, seems low but cannot be fully excluded. These results may have implications in safety as findings such as arteritis might result from cytotoxicity related to the effector functions of anifrolumab bound to target molecule on cell surfaces. See all discussions in Section 2.5.9.

The triple mutation in the Fc region has no impact on FcRn binding as the KD for FcRn binding affinities were 2.37 µM for 9D4, and 2.63 µM for anifrolumab. Hence, the normal endosomal retention and long half-life of the immunoglobulin molecule are retained.

The species-cross-reactivity was addressed in support of the selection of a relevant species for toxicity evaluation. Cynomolgus monkey type I IFNs exhibit high amino-acid sequence identity (81 to 95%) with the corresponding human type I IFNs. Unlike the mouse, cynomolgus monkey IFNAR1 exhibits high amino-acid sequence identity (90.8%) with the human IFNAR1. Similarly, the African green monkey IFNAR1 also exhibits high amino acid homology to both human and cynomolgus monkey IFNAR1. The critical binding epitope for anifrolumab in the IFNAR1 target sequence was identified within the subdomain 3. The amino acid sequences of the binding epitope are conserved between human, cynomolgus monkeys and African green monkeys whereas the murine and rabbit sequences exhibited low sequence homology in this region. Species-selectivity was corroborated with binding affinity and functional data showing that anifrolumab binding affinity to IFNAR1 was similar on human and cynomolgus monkey PBMCs. Also, anifrolumab failed to inhibit ISRE activation induced by murine recombinant IFN-α, and this was confirmed with the epitope mapping data demonstrating that replacing the human IFNAR1 sub-domain 3 with that from mouse prevented anifrolumab binding. In contrast, anifrolumab potently inhibited cynomolgus monkey recombinant IFN-α8, IFN-α16, IFN-α21, IFN-β and IFN-ω induced ISRE-luciferase activity in a non-human primate COS7 cell line transiently transfected with ISRE-luciferase. The capacity of anifrolumab to inhibit multiple cynomolgus type I IFNs induced ISRE activity was similar to that for recombinant human type I IFNs. Collectively, these data support the selection of cynomolgus monkey as the pharmacologically relevant toxicology model for nonclinical safety assessment.

The interferon gene signature of 21 interferon-induced genes was shown to be responsive to anifrolumab treatment using CpG-A stimulated human PBMCs. Anifrolumab dose-dependently suppressed the CpG-A–induced interferon gene by an average of 86% compared with no antibody treatment.

The disease-relevant functional activities such as inhibition of the auto-amplification of type I IFN production, suppression of the CD80 and CD83 co-stimulation, production of proinflammatory cytokines TNFα, IL-6 and IL-8, and differentiation of pDCs into plasma cells, as well as dose-dependent inhibition of the upregulation of monocyte differentiation markers CD38 and CD123 and complete inhibition of induction of cytokines and chemokines IL-6, IP-10, MCP-1 and MCP-2 in monocytes, were demonstrated for anifrolumab. Experimental evidence demonstrated that anifrolumab could inhibit the autocrine amplification of type I IFN production and in turn suppress the co-stimulation and the production of proinflammatory cytokines. Data from literature indicate that many cytokines implied in the pathogenesis of various autoimmune diseases, including SLE, could have a dual role. As reported by Meka RR et al, 2015, the mechanistic basis of the dual role of IL-27 in inflammation and autoimmunity is still not fully defined: IL-27 inhibits the production of pro-inflammatory cytokines IL-1, IL-6 and IL-17, but induces the production of anti-inflammatory cytokine IL-10. Additionally, Michael H. Lee, et al. 2019 suggest that I-IFN blockade, by suppressing IL-27 and IL-10, may have opposite effects on lupus disease; it may block the promotion of autoantibodies but also suppress anti-inflammatory mechanisms. At the CHMP's request an in-depth discussion based on literature has highlighted the importance of IL-27 and IL-10 in SLE pathogenesis. In any case, the specific role of these cytokines is not yet fully characterised,

therefore, further studies, particularly in humans are needed to better understand their implications in the disease.

The data generated with a mouse surrogate anti-IFNAR1 mAb in the *in vivo* proof-of-concept lupus disease models, supported the therapeutic rationale for blockade of type I interferon signalling in the treatment of SLE.

No formal secondary pharmacodynamic studies have been conducted with anifrolumab. Anifrolumab was engineered to reduce binding to Fc receptors and complement and did not exhibit detectable Fc-mediated CDC and ADCC activity. Also, anifrolumab does not exhibit IFNAR1 specific agonistic properties. It was recommended in the EMA CHMP scientific advice, that secondary effects, i.e. anti-proliferative, anti-viral and immune-modulatory effects, due to blocking of interferon stimulated effects by anifrolumab should be addressed. The CHMP considered that these aspects were sufficiently covered by the available non-clinical and clinical data as well as carcinogenicity risk assessment. Based on the weight of evidence, treatment with anifrolumab is likely associated with an increased carcinogenicity risk that has been followed throughout the clinical development programme and addressed in the RMP (see Section 2.7), and thus, no further animal studies are necessary (SmPC section 5.3). The potential risk of increased susceptibility to viral infections was not addressed in non-clinical studies. However, an increase of herpes zoster and influenza virus infections has been observed in patients treated with anifrolumab and thus, no further non-clinical studies are considered necessary by the CHMP. Effects to the immune functions were included in the repeat dose toxicity study studies.

In the 39-week repeat dose toxicity study, at the end of dosing period, an anifrolumab-related trend for decreased blood pressures in animals given 60 mg/kg SC was observed. The applicant considered this observation to be of limited physiological relevance. The CHMP agreed as significant changes in blood pressure were not detected in patients who received anifrolumab.

The pharmacokinetics of anifrolumab after single and repeated doses was evaluated as part of the single and repeat-dose toxicity studies. These data are considered appropriate and sufficient to characterize the PK profile in cynomolgus monkeys. Anifrolumab appeared to be immunogenic in cynomolgus monkeys. The accuracy and predictivity of the PK data was not hampered by the fact that frequent ADAs were detected on the animals of the control group.

Anifrolumab was generally well tolerated in cynomolgus after single and repeated dosing for up to 39 weeks of duration at dose levels up to 50mg/kg intravenously and up to 60 mg/kg subcutaneously. Pharmacology-related findings in the lymphoid organs such as minimal increase in lymphoid follicle size in spleen and in some lymph nodes of dosed males and females of the high dose group animals at the end of the dosing and/or recovery phase. The minimal decrease in lymphocytes in the cortex and medulla of the thymus of dosed males was observed at the end of the dosing period. Decreased cortical lymphocytes persisted until the end of the recovery phase.

Grade 1 to 3 focal arteritis was observed in several organs in 5/24 males (21%) that received anifrolumab while none of the control males or females regardless of treatment group were affected (0/24, 0%). At the end of the dosing phase, 2 males given 50 mg/kg IV had anifrolumab-related arteritis in multiple organs. The applicant argues that the observed arteritis is a result of a species-specific, chronic immune-mediated reaction due to immunogenicity and associated with immune-complex deposition. According to the applicant, vasculitis background incidence of 6% has been noted in the literature for this species (Chamanza et al, 2006), and the Testing Facility had a historical incidence of 2/167 (1.2%) for a diagnosis of "inflammation, vascular" in studies of $\geq$ 26 weeks in duration. The applicant provided further consideration to various aspects, such as effector functions related to the Fc-region, antagonistic and agonistic effects, lack of arteritis in IFNAR-deficient mice or in long-term toxicity study with a related IFN-α antibody sifalimumab, and the level of aggregates in the drug product, that could contribute to arteritis. At the CHMP's request, the applicant provided further information on the relationship between

incidence of ADAs and arteritis in cynomolgus monkeys and discussed the potential for clinically relevant effector functions. The CHMP concluded that the potential for drug-related arteritis cannot be completely excluded but is low (see also Section 2.5.9).

There was a finding of seminiferous tubular epithelium degeneration and marked changes in sperm parameters in males which received 60 mg/kg subcutaneously. These findings were considered as incidental by the CHMP and likely not clinically relevant, and the risk to male fertility seems unlikely.

A justification for not performing embryo-foetal developmental toxicity evaluation with anifrolumab was not provided. Some parameters including crown-rump length, femur length and biparietal diameter, and foetal heart rate measurements via ultrasound for addressing the embryo-foetal development were included in the pre- and post-natal developmental toxicity study, and they appeared to be within the normal range. However, high incidence of embryo-foetal loss was observed in the pre- and post-natal developmental toxicity study. Anifrolumab treatment of mothers started on GD20, and thus, the effects on early embryonic events are not evaluable. Consequently, it is not known if anifrolumab treatment has a harmful effect on early embryonic development or maintenance of pregnancy. See discussions below on SmPC / RMP implications.

In the pre- and post-natal developmental toxicity study, there was a clear imbalance in embryo-fetal loss ratios between the control and the anifrolumab- treatment groups being 6.3%, 29.4% and 18.8% for the control, 30 mg/kg and 60 mg/kg dose groups, respectively. High incidence of embryo-fetal loss was observed within 2-3 weeks after start of anifrolumab dosing of the mothers. The applicant argues that this is not relevant as it falls within the historical foetal loss ratio in the testing facility; hence, the observed increased embryo-fetal loss ratios in the anifrolumab-treated groups should be interpreted as a chance finding. This was not fully agreed by the CHMP as the number of animals are sufficient for hazard identification, and consequently the relationship to the anifrolumab cannot be excluded based on the available data (see Section 5.3 of the SmPC).

The nonclinical Enhanced Pre- and Postnatal Developmental (ePPND) study, although in line with the current guidance, is not considered sufficient to exclude the potential anifrolumab-related harmful effects on reproduction. The dosing started on GD20 and consequently, early events are missed. Moreover, data beyond GD20 from mothers that experienced an embryo-fetal loss or other that external observations from dead foetuses are not presented. The applicant referred to two literature reports published in 1994 and 1995 related to IFNAR1-deficient mice, and concluded that type I interferons do not affect reproduction. However, a role for type I interferons has since then been implicated in pregnancy, maternal-fetal tolerance and development. Also, due to target expression in the vasculature and placenta, anifrolumab might have vascular effects that could impact the maintenance of pregnancy.

Although the infants that survived until the birth-day 180 appeared to develop normally, there is a concern that anifrolumab may harmfully impact reproduction. The CHMP agreed that the conducted studies, i.e. ePPND study and assessment of female fertility aspects in the 39-week repeat-dose toxicity study, are considered to be in line with the current guidelines [ICH S5(R3) and ICH S6(R1)]. However, a limited amount of data is available from the mothers that experienced pregnancy loss as well as from the dead fetuses or infants. A comprehensive literature review was also submitted on the role of type I interferons and IFNAR1 in pregnancy highlighting the harmful effects of increased interferon levels during pregnancy. This is also true for SLE, as the patients often suffer from pregnancy complications. However, much less is known on the effects of interferon signalling blockade during pregnancy. There seems to be species variability in the involved interferons and not much is known about the species-specificity. Nevertheless, as the target molecule IFNAR1 is expressed in the human placenta and vasculature, as also demonstrated with the tissue-binding data with anifrolumab, and the known role and importance of balanced interferon signalling in establishment and maintenance of pregnancy, there is a theoretical risk to reproduction due to interference of balanced immune modulation. It should be noted that the available

data do not inform about the effect of anifrolumab on early pregnancy i.e. recognition, implantation and induction of maternal-foetal immune tolerance. Once the immune tolerance has been induced, effects due to blockade of signalling through IFNAR1 later during pregnancy may not be detected in an ePPND study. Due to limitations of the NHP model, lack of other pharmacologically responsive species, possible species-differences, and the underlying confounding disease background in SLE patients, the CHMP concluded that further animal studies are unlikely to provide clinically meaningful data to inform about the risk to reproduction in this patient population. However, at the CHMP's request, the SmPC sections 4.6. and 5.3 were update to more accurately reflect the nonclinical reproductive toxicity data and adequately communicate the risk. Saphnelo is not recommended during pregnancy and in women of childbearing potential not using contraception, unless the possible benefit justifies the potential risk.

Genotoxicity and carcinogenicity studies have not been conducted with anifrolumab. This is acceptable as anifrolumab is not expected to cause genotoxicity. The weight of evidence suggests that blockade of type I interferon response may increase the risk of malignancies. This risk is reflected in Section 5.3 of the SmPC and is followed by the routine risk management activities (see Section 2.7).

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.

2.4.7. Conclusion on the non-clinical aspects

Anifrolumab is a human immunoglobulin G1 kappa monoclonal antibody that binds to subunit 1 of the type I interferon receptor (IFNAR1) with high specificity and affinity. This binding inhibits type I IFN signalling thereby blocking the biologic activity of type I IFNs. Anifrolumab also induces the internalisation of IFNAR1, thereby reducing the levels of cell surface IFNAR1 available for receptor assembly. Blockade of receptor mediated type I IFN signalling inhibits IFN responsive gene expression as well as downstream inflammatory and immunological processes. Inhibition of type I IFN blocks plasma cell differentiation and normalises peripheral T cell subsets, restoring the balance between adaptive and innate immunity that is dysregulated in SLE. Overall, the pharmacological data provided adequate evidence that anifrolumab is capable of inhibiting type I interferon responses relevant for the interferon-related pathology of SLE and support the therapeutic rationale.

The selection of cynomolgus monkey as pharmacologically relevant species for safety evaluation was adequately demonstrated and confirmed by the binding and functional data.

The pharmacokinetics data are considered appropriate to characterise the PK profile in cynomolgus monkeys. The toxicological programme is considered appropriate and sufficient to characterise the toxicity profile of anifrolumab. Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology or repeated dose toxicity studies in cynomolgus monkeys.

Anifrolumab is a monoclonal antibody, as such genotoxicity and carcinogenicity studies have not been conducted. In rodent models of IFNAR1 blockade, increased carcinogenic potential has been observed. The clinical relevance of these findings is unknown. This risk is reflected in Section 5.3 of the SmPC and is followed by the routine risk management activities (see Section 2.7).

Animal studies show no adverse effects of anifrolumab on indirect measures of fertility. However, the risk to reproduction cannot be excluded based on the available nonclinical data. Given that it is unlikely that further animal studies would provide clinically meaningful data to inform about the risk in SLE patients, a revision of the SmPC sections 4.6 and 5.3 of the SmPC was requested by the CHMP to correctly describe the nonclinical reproductive toxicity data. Saphnelo is not recommended during pregnancy and

in women of childbearing potential not using contraception, unless the possible benefit justifies the potential risk.

In conclusion, the application for anifrolumab in the treatment of adult patients with SLE is considered approvable from the nonclinical point of view.

2.5. Clinical aspects

2.5.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

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

- **Tabular overview of clinical studies**

Table 1 Tabular overview of clinical studies

Type of study	Study identifier	Location of study report in Module 5	Objectives of the study	Study design and type of control	Anifrolumab, dosage regimen, route of administration	No. of subjects randomized/ treated	Healthy subjects or diagnosis of patients	Treatment duration	Study status/type of report
Phase I									
Safety	MI-CP180	5.3.3.2	Primary: Safety and tolerability Secondary: PK, immunogenicity, PD	Phase I; SAD/MAD OL	9 cohorts (0.1 to 20 mg/kg), single dose, IV 3 cohorts (0.3, 1.0, and 5.0 mg/kg), multiple dose, IV	Total:34/34 0.1 mg/kg single dose: 1/1 0.3 mg/kg single dose: 4/4 1.0 mg/kg single dose: 4/4 3.0 mg/kg single dose: 4/4 10 mg/kg single dose: 4/4 20 mg/kg single dose: 4/4 0.3 mg/kg multiple dose: 4/4 1.0 mg/kg multiple dose: 4/4 5.0 mg/kg multiple dose: 5/5	Adults (≥ 18 years) with scleroderma	Single dose and 12-week (84 days) follow-up after dose Multiple dose: 4 weeks (4 doses on Days 0, 7, 14, and 21) and 12- week (84 days) follow-up after last dose	Complete/ Full CSR
Safety/ PK	D3461C00006 "study 06"	5.3.3.1	Primary: PK, safety, and tolerability Secondary: immunogenicity	Phase I; RD/DB/PC	300 mg or placebo, 600 mg or placebo, SC; 300 mg or placebo, IV	Total: 30/30 300 mg SC: 6/6 300 mg IV: 6/6 600 mg SC: 6/6 Placebo: 4/4 for each of the 3 cohorts	Healthy volunteers aged 18-55 years	Single dose 12-week (85 days) follow-up after dose	Complete/ Full CSR
Phase II									
Efficacy	CD-IA-MEDI-546-1013 "study 1013"	5.3.5.1	Primary: Efficacy Secondary: Safety, PK, PD, and immunogenicity	Phase II; RD/DB/PC	300 mg, 1000 mg, or placebo Q4W, IV	Total: 307/305 300 mg: 100/99 1000 mg: 104/105 Placebo: 103/101	Adults (18-65 years) with moderate to severe SLE who are receiving standard of care	52 weeks (13 doses)[a] 12-week (85 days) follow-up after last dose	Complete/ Full CSR and CSR addendum
Safety	CD-IA-MEDI-546-1145 "study 1145"	5.3.5.2	Primary: Safety and tolerability Secondary: Immunogenicity	Phase II; OL extension	1000 mg, then all patients switched to 300 mg[b], Q4W, IV	Total:218/218 1000 mg: 218/218 300 mg: 191 patients switched from 1000 mg group	Patients who completed study 1013	156 weeks (up to 40 doses)[c] 12- week (85 days) follow-up after last dose	Complete/ Full CSR
Safety	D3461C00002 "study 02" (Japan only)	5.3.5.2	Primary: Safety and tolerability Secondary: PK, PD, and immunogenicity	Phase II; OL/DE	Stage I: 100, 300, or 1000 mg Stage II: All patients switched to 300 mg[d] Q4W, IV	Total: 20/17 Stage I: 100 mg: 6 300 mg: 5 1000 mg: 6 Stage II: 100 mg: 4 300 mg: 3 1000 mg:2	Adults (18-65 years) with SLE who are receiving standard of care	Stage I: 52 weeks (13 doses)[a] Stage II: 156 weeks (40 doses)[c] 12-week (85 days) follow-up after last dose in Stages I and II	Complete/ Full CSR
PK	D3461C00008 "study 08"	5.3.4.2	Primary: PK and PD Secondary: Safety and tolerability, immunogenicity	Phase II; RD/DB/PC	150 or 300 mg or placebo, Q2W, SC	Total: 36/36 150 mg: 14/14 300 mg: 13/13 placebo for 150 mg: 5/5 placebo for 300 mg: 4/4	Adults (18-70 years); type I IFNGS test high SLE patients with active skin manifestations while receiving standard of care	52 weeks (26 doses)[a] 8-week (56 days) follow-up after last dose	Complete/ Full CSR

Type of study	Study identifier	Location of study report in Module 5	Objectives of the study	Study design and type of control	Anifrolumab, dosage regimen, route of administration	No. of subjects randomized/ treated	Healthy subjects or diagnosis of patients	Treatment duration	Study status/type of report
Phase II									
Efficacy	D3461C00007 "study 07"	5.3.5.4	Primary: UPCR Secondary: CRR Safety and tolerability	Phase II; RD/DB/PC	300 mg, 900 mg, then 300 mg or placebo, Q4W, IV	Total: 147/145 300 mg: 46/45 900 mg to 300 mg: 52/51 Placebo: 49/49	Adults (18-70 years) with active proliferative lupus nephritis	52 weeks (13 doses)[a] 300 mg group: 13 doses 900 mg/300 mg group: 3 doses 900 mg, then 10 doses 300 mg Placebo group: 13 doses Extension period: 52 weeks (13 doses)[f] 12-week (84 days) follow-up after last dose	Ongoing, Data up to 26 March 2020 are included/ Full CSR pending
Phase III									
Efficacy	D3461C00005 "study 05"	5.3.5.1	Primary: SRI(4) Secondary: PK, PD, immunogenicity, and QOL Safety and tolerability	Phase III; RD/DB/PC	150 mg, 300 mg, or placebo Q4W, IV	Total:457/457 150 mg: 93/93 300 mg: 180/180 Placebo: 184/184	Adults (18-69 years) with moderate to severe SLE who are receiving standard of care	52 weeks (13 doses)[a] 12-week (84 days) follow-up after last dose	Complete/ Full CSR
Efficacy	D3461C00004 "study 04"	5.3.5.1	Primary: BICLA Secondary: PK, PD, immunogenicity, and QOL Safety and tolerability	Phase III; RD/DB/PC	300 mg or placebo, Q4W, IV	Total:365/362 300 mg: 181/180 Placebo: 184/182	Adults (18-69 years) with moderate to severe SLE who are receiving standard of care	52 weeks (13 doses)[a] 12-week (84 days) follow-up after last dose	Complete/ Full CSR
Safety	D3461C00009 "study 09"	5.3.5.1	Primary: Safety and tolerability	Phase III; RD/DB/PC	300 mg or placebo, Q4W, IV Patients in study 04 and 05 continued on 300 mg; placebo patients from study 04 and 05 randomized 1:1 to 300 mg or placebo	Total: 556/556 300 mg: 443/443 Placebo: 113/113	Patients who completed study 04 and study 05	156 weeks (39 doses)[g] 12-week (84 days) follow-up after last dose	Ongoing, Data up to 01 August 2019 are included/ Full CSR pending

[a] Last dose at Week 48.

[b] Initially, all patients were administered 1000 mg, which was later amended to 300 mg following the population modeling of study 1013 interim data.

[c] Last dose at Week 156.

[d] All patients in the 100 mg group in Stage II received 300 mg anifrolumab from Day 1. Two patients in the 1000 mg group in Stage II received 1000 mg anifrolumab from Day 1 and discontinued the study before the planned switch to 300 mg anifrolumab.

[e] Last dose at Week 50.

[f] Last dose at Week 100.

[g] Last dose at Week 152.

BICLA, British Isles Lupus Assessment Group-based Composite Lupus Assessment; CRR, complete renal response; DB, double blind; IFNGS, interferon gene signature; IV, intravenous; MAD, multiple ascending dose; OL, open label; PC, placebo controlled; PD, pharmacodynamics; PK, pharmacokinetics; Q2W, every 2 weeks, Q4W, every 4 weeks; QOL, quality of life; RD, randomized; SAD, single ascending dose; SC, subcutaneous; SLE, systemic lupus erythematosus; SRI(4), Systemic Lupus Erythematosus Responder Index ≥4; UPCR, urine protein to creatinine ratio.

2.5.2. Clinical pharmacology

2.5.2.1. Pharmacokinetics

The PK, PD, and immunogenicity of anifrolumab has been characterised from 8 clinical studies (2 phase I, 2 phase II, 2 phase III, and 2 long-term extension studies) that evaluated the IV route of administration. Single-dose and multiple-dose pharmacokinetics of anifrolumab after IV infusion was studied in patients with scleroderma (study MI-CP180) and single dose pharmacokinetics was evaluated in healthy volunteers (D3461C00006, hereafter referred as study 06). Three phase II clinical studies (CD-IA-MEDI-546-1013, CD-IA-MEDI-546-1145, D3461C00002, hereafter referred as study 1013, 1145 and 02, respectively) and two phase III clinical studies (D3461C00004, D3461C00005, hereafter referred as study 04 and 05, respectively) were conducted in patients with the target indication, i.e. an adult population with moderate to severe systemic lupus erythematosus (SLE). In addition, the applicant has provided a population PK modelling report, an exposure-response modelling report and a summary of pooled immunogenicity data from phase III studies related to clinical pharmacology to support the marketing authorisation of anifrolumab. The phase III study D3461C00009 is ongoing and its interim results were included in the population PK analysis.

There were no subjects over 65 years of age in study 06; three patients above 65 years of age participated in the scleroderma study MI-CP180. The age group distribution of patients participating in Phase III SLE studies (studies 04 and 05) is summarised in Table 42.

In the clinical studies 1013, 02, 04, 05 and 1145 (long-term extension to study 1013) the patients with SLE were tested at screening for their 4-gene type I IFN gene signature which are the most highly expressed type I IFN genes in the target SLE patient population. The 4 type I interferon-inducible (target) genes (IFI27, IFI44, IFI44L, and RSAD2) relative to 3 reference (housekeeping) genes (18S, ACTB, and GAPDH) were used to classify a patient as type I IFN gene signature test high or type I IFN gene signature test low at baseline. These 4-gene type I IFN gene signature test results (IFNGS high or low) were used to stratify SLE patients at randomisation in order to ensure balance among treatment groups and facilitate subgroup analyses.

Bioanalytical methods

The ECL based immunoassay for determination of anifrolumab concentrations in human serum is based on capturing anifrolumab with biotinylated IFNAR1 (B-IFNAR1) bound to a streptavidin-coated MSD plate. The captured anifrolumab is detected with a sulfo-TAG labeled monoclonal antibody directed against the triple mutation (TM). In general, the validations followed the principles laid down in EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2** Guideline on bioanalytical method validation.

Pharmacokinetic data analysis

The applicant has used non-compartmental methods to calculate the PK parameters (C_{max}, AUC, $t_{1/2}$ and CL) for anifrolumab after single dose and multiple dose administration in patients with scleroderma (study MI-CP180) and in a small Phase II study in Japanese patients with SLE (study 02). In addition, the PK parameters (C_{max}, AUC, T_{max}, CL) after single dose administration of 300 mg IV in healthy volunteers were determined in the study 06, where the number and frequency of samples were sufficient to characterise the concentration-time profile for anifrolumab. In the studies MI-CP180 and study 02, more frequent and later time points would have improved the determination of the terminal elimination phase. Pharmacokinetics of anifrolumab was evaluated following sparse sampling for PK analyses in patients with the target indication, i.e. an adult population with moderate to severe systemic lupus erythematosus (SLE), in the phase II (study 1013, 1145) and phase III clinical studies (study 04 and 05). The reported PK parameters were C_{max} and C_{trough}.

The population PK modelling report

The objectives of the analysis were:

- To characterize the PK properties of anifrolumab in healthy volunteers and adult patients with moderate to severe SLE;
- To evaluate the potential impact of demographics, baseline laboratory values, SLE disease characteristics, and commonly used SLE medications on the PK of anifrolumab in healthy volunteers and adult patients with moderate to severe SLE.
- To evaluate the difference in PK between Process 2 clinical and Process 3 commercial materials used in study 09.

The population PK analysis included pooled PK data from both SLE patients and healthy volunteers. The PK data for SLE patients came from 2 phase II studies (studies 1013 and 02) and 2 phase III studies (studies 04 and 05). The PK data for healthy volunteers were from the IV arm of the phase I bioavailability study (study 06). The model was developed with data from studies 06, 1013, 02, and 05, and then externally validated with study 04. All PK samples, except for PK samples collected in the 60-day follow-up period in study 1013 and the Stage II treatment period in study 02, collected in the first year of treatment were used.

A target mediated drug disposition PK model with parallel elimination pathways by the reticuloendothelial system and IFNAR-mediated internalisation and intracellular degradation was adopted to describe anifrolumab PK following IV infusion in SLE subjects. The model was simplified by setting internalisation rate constant of anifrolumab-IFNAR1 complex to the degradation rate constant of IFNAR1 and fixed to 77.4 d^{-1}, a value estimated in confocal imaging studies (Wang et al 2013, doi: 10.1038/clpt.2013.35). As a result, the total receptor concentration remained constant over time. Free anifrolumab was measured, and the model was used to predict free anifrolumab concentrations.

The relationship between continuous covariates and PK parameters was modelled using the power function, centred by the median of the covariate, and the categorical covariates were modelled using the fractional change function of the covariate factor.

The following baseline covariates were considered for inclusion in the PK model:

- Demographic covariates: body weight, sex, age, race, region, and ethnicity
- Liver function: ALT, AST, and total bilirubin
- Renal function: eGFR and UPCR
- Immunogenicity: ADA by screening assay
- Disease related and other covariates: type I IFN gene signature test status, concomitant medication usage (OCS, antimalarial, azathioprine, methotrexate, mycophenolate mofetil mycophenolic acid, and mizoribine)

The covariates were selected based on scientific interest, mechanistic plausibility, and prior knowledge. The covariate-PK relationships were evaluated for CL, Vc, and R0 parameters. Covariates that were missing or not evaluable for more than 15% of the patients in the pooled analysis were excluded from further covariate analysis.

Among the covariates tested, body weight status was identified to be the most statistically significant covariate on anifrolumab CL, followed by type I IFN gene signature test status on CL; IFN gene signature status was found to have a larger drop in objective functional value on linear CL than R0. After accounting for type I IFN gene signature test status in CL, the addition of IFN gene signature status on R0, was not

found to be significant. In addition to IFN gene signature status on CL, baseline body weight on CL was also found to be a statistically significant covariate. Body weight was also found to be a statistically significant covariate on Vc. Age, eGFR, total bilirubin, and albumin were not found to be significant on CL. Further, the final model was updated with a time-varying component in CL. An empirical sigmoidal time-dependent function was added to the linear CL.

$$CL = \theta_{CL}\left(\times \theta_{CL,IFN\ status}\ if\ type\ I\ IFN\ test\ low\right) exp\left(\frac{TMAX \cdot time}{TC50+time}\right)\left(\frac{Body\ weight}{69.1}\right)^{\theta_{CL,wt}} \eta_{CL}$$

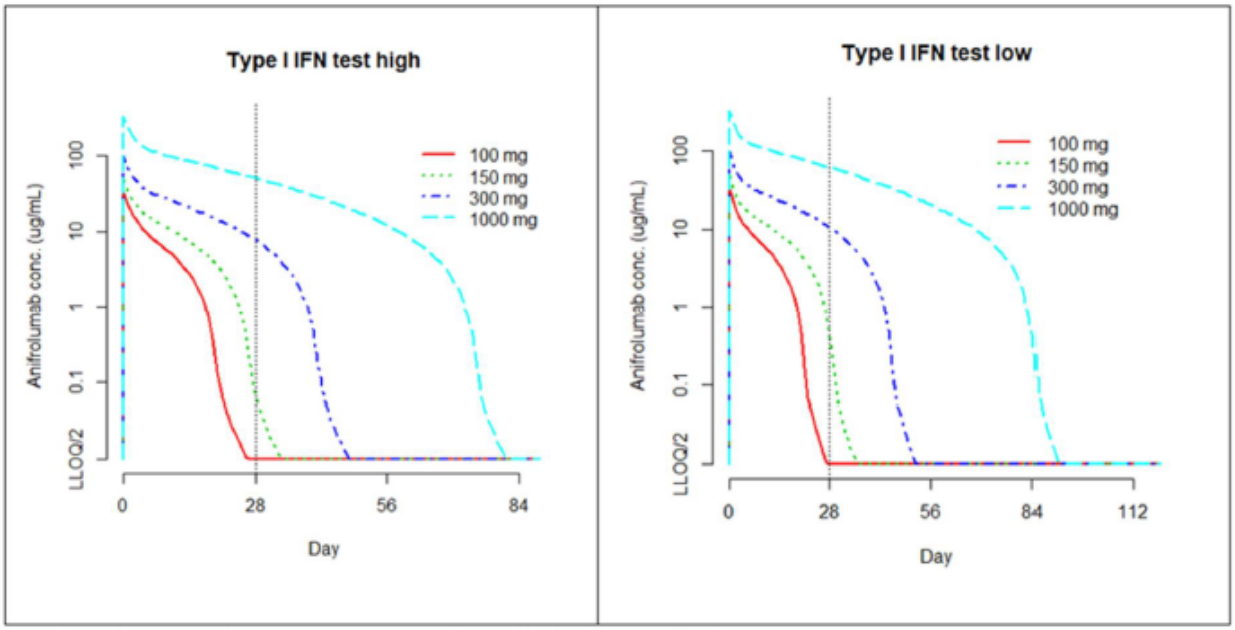
The estimation of PK parameters was prematurely terminated due to rounding errors. The applicant was subsequently requested to provide robust confidence intervals for the parameters, and the applicant proceeded to calculate robust confidence intervals using bootstrap. Briefly, 500 resampled datasets were generated, and models fitted to these datasets. From these, 81 models converged successfully, and 338 model fittings were terminated due to rounding errors; these models were used for the calculation of bootstrap confidence intervals, while the remaining models were discarded. The reported typical values for CL, V_c, and V_p were 0.189 L/day, 3.27 L, and 3.77 L, respectively. The IIV of anifrolumab was moderate with population CV% estimate of 52.7%, 19.9%, 26.1%, and 38.2%, respectively, for CL, Vc, R0, and time to maximum plasma concentration. The PK parameters estimated from the model, and their bootstrap-based confidence intervals (Table 2) show the median model-predicted concentration-time profiles following a single-dose administration of 100 to 1000 mg, where doses ≤ 150 mg exhibited a rapid decline in anifrolumab concentration within 28 days and hence provided sub-optimal PK exposure in every 4-week dosing regimen. The population PK model was validated via Visual Predictive Checks both against the model-building data, and against external data not included in model-building phase.

Table 2 Summary of PK parameters from the final PK model with time-varying linear clearance and external validation data included

Parameters	Point Estimate	%RSE	Bootstrap median (90% CI)
Systemic clearance (CL) (L/day)	0.193	2.34%	0.201 (0.175 - 0.233)
Volume of distribution, central (V_C) (L)	2.93	1.31%	3.14 (2.91 - 3.37)
Intercompartmental clearance (Q) (L/day)	0.937	7.68%	0.929 (0.0581 - 1.13)
Volume of distribution, peripheral (V_P) (L)	3.30	1.58%	2.65 (0.945 - 3.25)
Steady-state constant (K_{SS}) (nmol/L)	0.712	6.78%	0.727 (0.536 - 1.82)
Baseline IFN-αR1 level (R_0) (nmol/L)	0.0999	2.69%	0.0955 (0.0591 - 0.109)
Internalisation rate constant (k_{int}) (day^{-1})	77.4 (Fixed)	--	77.4 (Fixed)
Baseline 4-gene signature status on CL	0.793	4.53%	0.749 (0.656 - 0.838)
Body weight on CL	0.601	10.75%	0.603 (0.448 - 0.854)
Body weight on V_C	0.764	7.02%	0.562 (0.0125 - 0.76)
Maximal possible change in the log of clearance (T_{max})	-0.155	16.97%	-0.384 (-1.59) - (-0.112)
Time to reach half the maximal change in log clearance (TC_{50})	380	14.05%	414 (292 – 4633)
Variance (CL)	0.109 (CV = 33.01%)	4.68%	0.0986 (0.0585 - 0.13)
Variance (V_C)	0.0723 (CV = 26.89%)	2.92%	0.0733 (0.0567 - 0.0988)

Variance (R_0)	0.0882 (CV = 29.70%)	4.69%	0.0846 (0.0233 - 0.178)
Variance (T_{max})	0.146 (CV = 38.21%)	6.68%	0.16 (0.11 - 9.83)
Additive error	20.1	0.73%	20.1 (8.13 – 300)
Proportional error	0.305	0.50%	0.297 (0.267 - 0.317)

CV, coefficient of variation; EST, estimate; %RSE, percent relative standard error (100% × SE/EST); PK, pharmacokinetic; SE, standard error.



IFN, interferon; IV, intravenous; LLOQ, lower limit of quantification (0.02 µg/mL).

Figure 1 Model-predicted concentration-time profiles following a single dose of anifrolumab IV administration (typical body weight of 70 kg)

Absorption

The applications concern a concentrate for solution to be administered as intravenous infusion, thus, there is no absorption of the active substance.

Absorption and bioavailability after subcutaneous administration of single dose has been evaluated in a Phase I study in healthy volunteers (6 subjects per dose group). After subcutaneous administration, exposure to anifrolumab increased approximately dose-proportionally when the dose was increased from 300 mg to 600 mg (C_{max} = 36.22 and 63.86 µg/mL, respectively, and AUC_{inf} = 784.6 and 1828 day*µg/mL, respectively). After a single dose of 300 mg anifrolumab given IV, mean C_{max} was 82.44 µg/mL, T_{max} median 0.03 days (min.-max. 0.03-1.03 days) and mean CL 0.3396 L/day (SD 0.05459). The total exposure of IV administration by AUC_{inf} was approximately 16% greater compared to the SC administration (906.5 and 784.7 day*µg/mL after 300 mg dose as IV and SC, respectively). The serum concentration-time profiles are presented in the Figure 2.

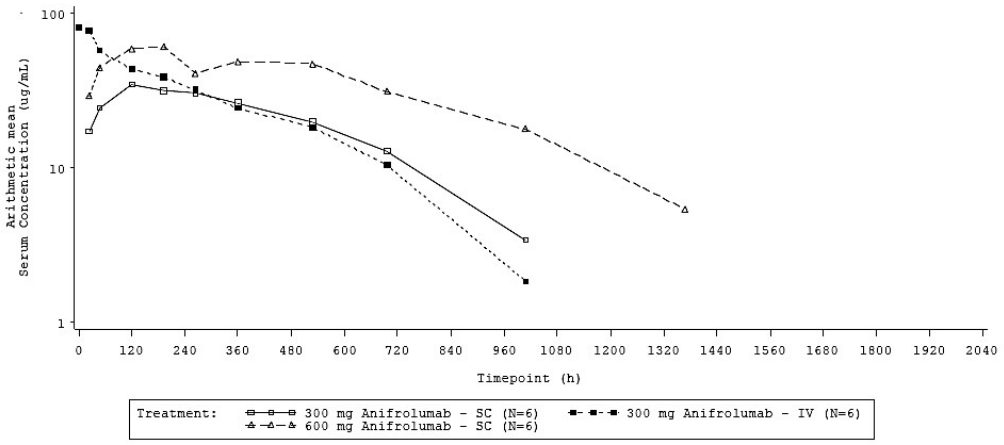


Figure 2 Anifrolumab concentration-time profiles after intravenous and subcutaneous administration on semi-logarithmic scale (study 06).

Bioequivalence

The proposed anifrolumab drug product is 150 mg/ml concentrate for solution for infusion intended for administration of 300 mg of anifrolumab as an intravenous infusion over a 30-minute period, every 4 weeks. The applicant has not conducted bioequivalence studies. The comparability of the product batches manufactured using different processes has been performed by quality testing. Process 3 commercial material was first introduced in the study 09 at the end of 2018. In the population PK analysis report, the applicant has conducted 2 exploratory analyses to compare the indented commercial drug product produced by process 3 with the clinical study batches produced by process 2. The final analysis dataset consisted of 4366 PK samples: 3865 (91.5%) from clinical material and 373 (8.5%) from commercial material. The applicant analysed the change in anifrolumab concentrations over time for subjects taken Process 2 clinical material and Process 3 commercial material. However, only 8.5% of patients taken the commercial formulation respect to 91.5% that taken the clinical formulation. Although considering the paucity of PK data for process 3, the exploratory analyses performed to assess the difference between Process 2 and Process 3 commercial materials used in study 09, no significant differences are evident among exposures reached with the two manufacturing processes. The provided exploratory analyses as supportive analysis of comparability are sufficient to the CHMP.

Distribution

Anifrolumab pharmacokinetics was observed to follow target meditated disposition distribution (TMDD) characterised by non-linear more than dose proportional increase of exposure by increasing single doses from 0.1 mg/ml to 10 mg/kg in the study MI-CP180 in patients with scleroderma (Table 3). A dose-proportional increase in maximum concentration (C_{max}) was observed, but an increase in area under the concentration-time curve (AUC) was more than dose proportional between 0.1 and 10.0 mg/kg. However, AUC increased dose proportionally between 10.0 and 20.0 mg/kg. Systemic clearance (CL) decreased from 40.8 to 4.67 mL/kg/day when the dose was increased from 0.1 to 20.0 mg/kg, due to the saturation of the subunit 1 of the type I interferon receptor (IFNAR1) mediated clearance pathway.

Table 3 Anifrolumab serum PK parameters following single dose IV administration of anifrolumab in scleroderma patients (study MI-CP180)

Parameter	Anifrolumab					
	0.1 mg/kg (N = 1)	**0.3 mg/kg (N = 4)**	**1.0 mg/kg (N = 4)**	**3.0 mg/kg (N = 4)**	**10.0 mg/kg (N = 4)**	**20.0 mg/kg (N = 4)**
AUC_{inf} (day·µg/mL), mean (SD)	2.45	12.4 (4.91)	102 (14.1)	497 (105)	2610 (728)	4870 (1750)
C_{max} (µg/mL), mean (SD)	1.97	6.7 (1.47)	23.3 (2.22)	72.4 (13.7)	213 (44.0)	394 (83.5)
CL (ml/kg/d), mean (SD)	40.8	27.4 (11.0)	9.94 (1.44)	6.26 (1.43)	4.07 (1.13)	4.67 (2.18)
$t_{1/2}$ (days), mean (SD)	0.84	1.24 (0.358)	2.96 (0.593)	4.07 (1.23)	7.70 (2.26)	11.8 (2.06)

In the dose-escalation study 02 in Japanese patients with SLE, single dose and multiple dose pharmacokinetics of anifrolumab was investigated in Stage I after administration 100 mg, 300 mg or 1000 mg with IV infusion. The serum concentration-time profiles on semi-logarithmic scale indicated rapid distribution phase followed by slow linear elimination phase and thereafter, rapid non-linear elimination with steep decline at lower concentrations in the Japanese SLE patients (study 02). The PK parameters after single dose and multiple dose administration are summarised in Table 4. The mean C_{max} for anifrolumab increased less than proportion to dose while the AUC_{last} increased more than dose proportionally after the first doses of 100 mg, 300 mg and 1000 mg IV, respectively. After last dose on Day 337, the mean $C_{max\ ss}$ and AUC_{τ} for anifrolumab increased more than in proportion to dose being 25.0, 95.7 and 414.3 µg/mL and 152.3 (39.2), 1035.5 (488.0) and 5814.6 (2164.1) day*µg/ml for doses 100, 300 mg and 1000 mg at steady state, respectively. Mean C_{trough} increased more than dose-proportionally from 14.8 to 99.4 µg/mL when the dose increased from 300 to 1000 mg. The concentration time profile after single dose administration of 300 mg IV suggest that elimination rate starts to increase before the next dose on Day 28. After the last dose on Day 337, the dosing interval of 28 days is on the linear part of the concentration-time profile. The dose groups were not stratified for the type I IFN gene signature at screening, and the majority of the patients belonged to type I IFN gene signature high. Moreover, the number of patients was low and the dose groups differed in terms of body weight.

Table 4 PK parameters of anifrolumab after single dose and multiple dose administration once every 4 weeks for 337 days (48 weeks) in Japanese SLE patients (Study 02).

PK parameter		**Anifrolumab**		
Single dose on day 1	**Summary statistics**	**100 mg IV (N=6)**	**300 mg IV (N=5)**	**1000 mg (N=6)**
Cmax (µg/ml)	Arithmetic mean (SD)	42.4 (11.3)	75.5 (9.5)	259.2 (50.6)
AUClast (day*µg/ml)		224.6 (39.1)	702.2 (262.5)	3179.1 (444.0)
AUCinf day*µg/ml l)		231.7 (40.5)	786.2 (280.2)	4350.9 (588.1)
CL (l/day)		0.445 (0.091)	0.417 (0.129)	0.234 (0.033)
t1/2 (day)		3.77 (1.42)	5.97 (2.63)	15.86(2.64)
Multiple dose, after last dose on day 337		**100 mg IV (N=2)**	**300 mg IV (N=5)**	**1000 mg (N=3)**
AUCτ (day*µg/ml)	Arithmetic mean (SD)	152.3 (39.2)	1035.5 (488.0)	5814.6 (2164.1)
CLss (l/day)		0.679 (0.175)	0.356 (0.181)	0.194 (0.089)
Cmax, ss (µg/ml)		25.0 (2.2)	95.7 (24.6)	414.3 (82.1)
Cmin, ss (µg/ml)		0.1 (N=1)	14.8 (12.7)	99.4 (51.7)
t1/2 (day)		3.64 (1.57)	5.33 (1.28)	15.52 (8.83)

Based on the population PK analyses, the estimated central and peripheral volumes of distribution for anifrolumab were 2.93 L with 26.9 % CV inter-individual variability and 3.3 L, respectively, which are typical for IgG. Body weight was observed to affect the central volume of distribution (V_c) with the power parameter (exponent) estimate of 0.764, i.e. patients with higher body weight were found to have significantly higher V_c.

Elimination

As a monoclonal antibody anifrolumab is eliminated through non-specific linear pathway with reticuloendothelial system (RES) as well as target-mediated non-linear pathway through binding to IFN-receptor on cell surface followed by internalisation and subsequent intracellular degradation. Renal and hepatic elimination do not play significant role in elimination or excretion of monoclonal antibodies. No data on excretion or metabolism of anifrolumab have been provided and these data are not required.

The estimated typical linear CL for anifrolumab was 0.193 l/day with 33.0% CV inter-individual variability based on the population PK modelling. The reported clearance is typical for this kind of molecule. The median CL decreases slowly over time, with 8.4% after one year of treatment. The population PK model identified body weight and type 1 IFN gene signature test status as significant covariates for anifrolumab CL, i.e. patients with higher body weight and type I IFNGS test high patients were found to have significantly higher CL.

In preclinical studies, anifrolumab has been observed to bind to Fc Gamma Neonatal Receptor (FcRn) which protects it from degradation in endosomes and should prolong elimination half-life. In the non-compartmental analysis of study MI-CP180, the elimination half-life of anifrolumab increased with increasing dose being approximately 12 days after IV administration of 20 mg/kg dose in patients with scleroderma. In the phase III clinical studies 1013, 04 and 05, the serum concentrations of anifrolumab were followed up to 12 weeks after the last dose on week 48. The majority of the patients had their remaining concentrations eliminated to concentrations below LLOQ during this period. Based on

population PK analysis, serum concentrations were below detection in the majority (95%) of patients approximately 16 weeks after the last dose of anifrolumab, when anifrolumab has been dosed for one year.

Dose proportionality and time dependency

The pharmacokinetics of anifrolumab in the patients with moderate to severe SLE has been investigated at three dose levels; 150 mg and 300 mg IV infusion in the phase III study 05 and 300 mg and 1000 mg IV infusion in the phase II study 1013. The PK was characterised by C_{max} and C_{trough} values in these studies. The doses 100 mg, 300 mg and 1000 mg were administered in the Phase II study in Japanese patients with SLE and concentration time profiles were followed with more dense sampling and exposure calculation of AUC-values.

The applicant has not provided evaluation of dose-proportionality in the dossier. Based on the provided PK data, the post-dose concentrations (C_{max}) are almost dose-proportional but the C_{trough} increase more than in proportion to the dose after administration of 150 mg, 300 mg or 1000 mg q4w in the clinical studies. More than dose-proportional increase in AUC_{inf} was observed in the clinical study MI-CP180 in patients with scleroderma and in Japanese patients with SLE (study 02). The non-linear PK and more than dose proportional increase in exposure is typical for cell membrane receptor-binding monoclonal antibodies. The population PK model was characterised by TMDD, which implies that exposure is not dose-proportional.

Time dependency

In the study 1013, the mean (SD) C_{trough} after first 300 mg dose on day 29 were 6.82 µg/ml (5.31) and 11.5 µg/ml (7.38) for type I IFN gene signature test high and low patients, respectively. There was minimal accumulation in C_{max} after multiple dosing with an accumulation ratio of 1.36 at the 300-mg dose level and 1.43 at the 1000-mg dose level by D169 after administration every four weeks (6 doses). However, mean C_{trough} doubled after six multiple doses with an accumulation ratio of 2.49 at the 300-mg dose level and 2.29 at the 1000-mg dose level by D169 and triples with an accumulation ratio of 3.06 at the 300-mg dose level and 3.02 at the 1000-mg dose level at Day 365. The patients with type I IFN gene signature high had mean C_{trough} 17.0 µg/ml while the patients with type I IFN gene signature low had slightly higher C_{trough} 23.3 µg/ml.

The accumulation ratios based on median post-dose concentration (Day 1 vs Week 48) after multiple dosing ranged from 1.14 to 1.28 and from 1.05 to 1.08 in type I IFN gene signature test high and low patients in studies 05 and 04, respectively. In both studies 04 and 05, lower serum C_{trough} of anifrolumab were observed in patients with baseline type I IFN gene signature test high compared to patients with type I IFN gene signature test low across all visits. At 48 weeks after dosing of 300 mg IV, the geometric mean (CV%) $C_{through}$ were 6.99 mg/ml (1847.3%) and 21.69 µg/ml (382.0%) for type I IFN gene signature test high and low patients, respectively, in the study 05, and 9.95 µg/ml (1311.2 %) and 16.73 µg/ml (160.0 %) for type I IFN gene signature test high and low patients, respectively, in the study 04. In the clinical study 05, a higher inter-individual variability in anifrolumab exposure was observed in the anifrolumab 150 mg group as compared to the patients in the anifrolumab 300 mg group. The anifrolumab PK exhibited time-varying CL where in most patients the CL slowly decreased i.e., the concentrations slowly increased, over time. Based on the population PK analysis, the median decrease in CL was 8.4% at the end of the first year and the maximum predicted decrease was 16.4%. Minor to moderate differences between subgroups by type I IFN gene signature test status and between studies were observed as the median asymptotic decrease in CL was numerically higher in type I IFN test high patients compared with type I IFN test low patients/healthy subjects (~17% vs 14% to 15%, respectively), and were higher in study 1013 versus study 05 and 04 (~23% vs 14% to 16%, respectively). In applicant's opinion, the decrease in CL over time could be an indicator of disease improvement, as higher CL was observed in patients with higher level of inflammation or active disease.

Additionally, approximately 15% of patients exhibited increasing CL over time, with a dose-related increase observed in the proportion of patients with increasing CL. No particular reason related to a patient characteristic could be identified for the increasing clearance. Anti-drug antibodies (ADA) effect on anifrolumab PK could not be observed because of limited number of ADA positive patients detected in the clinical studies (see Section 2.6.8 Clinical Safety).

Special populations

Type I IFN gene signature status

In the clinical studies, lower serum C_{trough} of anifrolumab were observed in patients with baseline type I IFN gene signature test high compared to patients with type I IFN gene signature test low across all visits. The population PK model identified type 1 IFN gene signature test status as a significant covariate for anifrolumab CL with an exponent of 0.793, i.e. patients with type I IFNGS test high patients were found to have higher CL. In the population PK model, patients who were type I IFN gene signature test low had ~21% lower CL as compared with type I IFN gene signature test high patients. The effect of IFNGS test status on CL did not warrant dose adjustment for IFNGS high or low patients based on the efficacy and safety in phase III studies. Majority of the SLE patients in studies 04 and 05 (82.6%) had type I IFNGS test high at baseline.

Weight

In a population PK analysis, body weight was found to predict CL with an exponent of 0.6 for CL, and 0.76 for central volume of distribution. The population PK analysis showed that the median CL in patients < 50 kg and ≥ 90 kg were ~22% lower and ~19% higher, respectively, than the typical CL of 0.193 L/day with typical body weight of 69.1 kg. The applicant has justified, that despite the significant effect of body weight on CL, there was no relevant clinical impact of body weight on efficacy, as morbidly obese patients with BMI > 35 kg/m^2 still demonstrated a positive BICLA rate difference at Week 52 with respect to placebo in both studies 04 and 05. Similarly, the safety profile of anifrolumab is generally similar in patients with BMI ≥ 28 kg/m^2 compared with those < 28 kg/m^2 for up to 52 weeks of treatment.

Impaired renal function and impaired hepatic function

Separate clinical studies in subjects with impaired renal function or impaired hepatic function have not been conducted and these are not necessary because hepatic and renal elimination of monoclonal antibodies is negligible.

Based on the population PK analysis, the CL of anifrolumab in patients with mild (60-89 mL/min/1.73 m^2) and moderate (30-59 mL/min/1.73 m^2) decrease in estimated glomerular filtration rate (eGFR) were comparable to those with normal renal function (≥90 mL/min/1.73 m^2). The clinical studies did not include patients with severe decrease in eGFR or with severe end stage renal disease (<30 mL/min/1.73 m^2).

Patients with high urine protein/creatinine ratio (UPCR) appeared to have higher CL, however this covariate relationship was deemed as clinically insignificant. The exclusion criteria for UPCR was > 2 mg/mg (or > 226.30 mg/mmol). The pooled dataset included 664 patients with UPCR median 6.56 mg/mmol (min, max = 1.47, 380.98 mg/mmol). The number of SLE patients with high UPCR values was low, thus, significant effect of UPCR on CL may not be observed in this population and the effect of high UPCR on CL remain unclear. Based on the population PK analysis, baseline hepatic function tests (AST, ALT, and total bilirubin) have no clinically relevant impact on the CL of anifrolumab. No clinically relevant relationship between serum bilirubin and CL, and between serum albumin and CL, were found during population PK analysis.

Gender, race, age

Gender was not identified as significant covariate on CL, when adjusted for body weight in the population PK analysis. The majority of the patients with SLE were female, i.e. 92.5% (620/670) of the patients included in the population PK analysis. Based on the population PK analysis, race lacked apparent impact on CL of anifrolumab.

The provided population PK analyses indicated that age had no clinically relevant impact on the CL of anifrolumab. The population PK analyses included data on patients with median age of 41 years, range: 18 to 69 years. There were 20 (3%) patients ≥ 65 years of age. There is no clinical data on patients aged <18 years old.

Pharmacokinetic interaction studies

Patients were treated concomitantly with several medicinal products in the clinical studies, thus, their effect on anifrolumab PK has been evaluated by population PK analysis. The permitted standard of care medication for SLE included oral corticosteroids (OCS) (prednisone, prednisolone or equivalent), intra-muscular or intra-articular corticosteroids, antimalarials, slow-acting immunosuppressants (methotrexate, mycophenolate, mofetil/mycophenolic acid, and azathioprine), prescription NSAIDs, analgesics/non-prescription NSAIDs, and topical therapy. Based on the population PK analysis, standard of care therapy had no impact on the CL of anifrolumab. Pharmacodynamic interactions have not been studied.

Drug-Drug Interactions

The applicant has not conducted specific drug-drug interaction studies with anifrolumab because anifrolumab elimination is not dependent on CYP enzymes. Pro-inflammatory cytokines may suppress CYP 450 activity during chronic inflammation like SLE. Anifrolumab treatment in study 1013 reduced the median baseline levels of TNF-α and IL-10 by 15% to 20% in SLE patients. Thus, therapeutic monitoring is recommended for patients treated with narrow therapeutic index medicines that are CYP substrate and the dose is individually adjusted (e.g. warfarin).

2.5.2.2. Pharmacodynamics

Clinical Exposure-Response Modelling Report

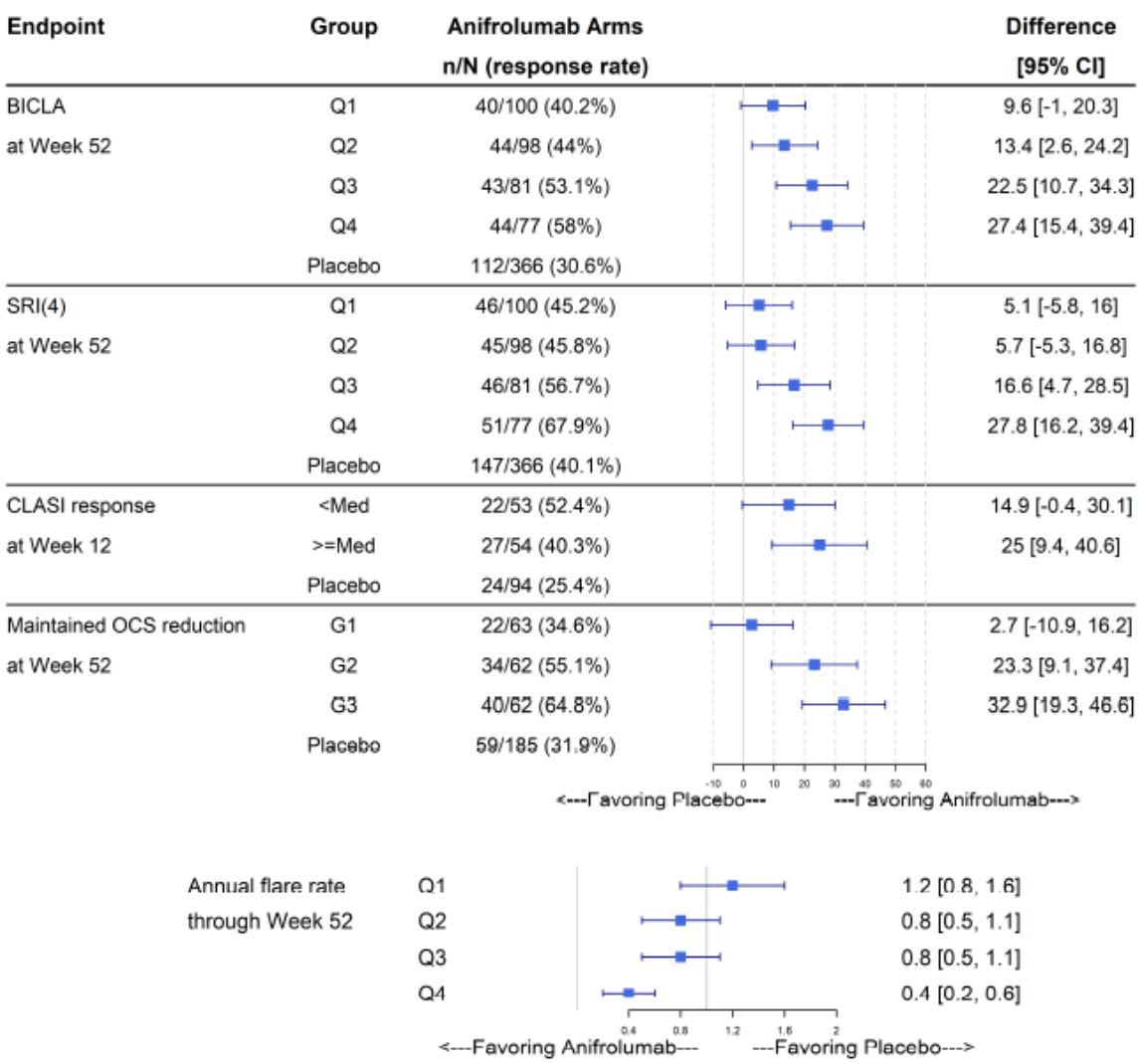
The objectives of the analysis were:

- To evaluate the relationship of drug exposure and the primary and key secondary study endpoints:
    - The proportion of patients with a BICLA response at Week 52 in all patients and in the subgroup of patients with high type I IFN gene signature test at screening
    - The proportion of patients with a SRI(4) response at Week 52 in all patients and in the subgroup of patients with high type I IFN gene signature test at screening
    - CLASI responders at Week 12 for the subgroup of patients with baseline CLASI activity score of ≥ 10 (i.e., moderate to severe skin disease)
    - The proportion of patients who achieved an OCS dose ≤ 7.5 mg/day at Week 40, which was maintained through Week 52 in the subgroup of patients with baseline OCS ≥ 10 mg/day
    - Annualised flare rate through Week 52
- To evaluate the relationship of drug exposure and safety, specifically, the incidence of the following treatment-emergent AEs:

    - Herpes zoster
    - Serious infections
    - Hypersensitivity, anaphylaxis, and investigator-reported AEs of infusion-related reactions
    - Malignancy
- To evaluate the relationship of drug exposure and PD (neutralisation of the 21-gene type I IFN PD signature)

Exposure-efficacy analysis: The exposure-efficacy analysis evaluated PK exposure and the key efficacy outcome measures. The PK exposure was stratified by quartiles or other cutoffs (eg, tertiles/median) as appropriate based on sample size. The proportion of patients achieving BICLA or SRI(4) in the PK exposure groups were compared with the placebo group using the AME approach by taking into account the stratification factors (SLEDAI-2K score at screening [< 10 points vs ≥ 10 points], Week 0 OCS dose [< 10 mg/day vs ≥ 10 mg/day prednisone or equivalent], and type I IFN gene signature test result at screening [high vs low]), wherever applicable. The same approach was used to evaluate the exposure-efficacy relationship between individual PK exposure and the proportion of patients with baseline OCS ≥ 10 mg/day prednisone or equivalent who achieved an OCS dose ≤ 7.5 mg/day prednisone or equivalent at Week 40 and maintained to Week 52, and the exposure-efficacy for the proportion of CLASI responders at Week 12.

In the pooled phase III (studies 04 and 05) population, an overall positive benefit in BICLA response at Week 52 was consistently observed for the anifrolumab 300 mg group compared with placebo across all quartiles and tertiles (Figure 3). Overall benefits were also observed in SRI(4) and key secondary endpoints of sustained OCS reduction, CLASI response, and flare rates. Additional logistic regression analyses of the BICLA response rate and SRI(4) response rate were performed by evaluating the significance of a continuous Cave in type I IFN test high patients who completed treatment (150 mg and 300 mg) and exhibited a slight positive exposure-response trend in the absence of discontinuation. The analysis found a significant positive correlation between Cave and BICLA response rate at Week 52. The 150 mg group was in the suboptimal region of the exposure-response curve, whereas the 300 mg group was at the plateau of the exposure-response curve that would minimize the impact of PK variability on efficacy. Furthermore, the highest dose in study 1013 (1000 mg) was projected to provide incremental benefit.



Response rates and rate difference for BICLA, SRI(4), CLASI, and OCS reduction were calculated using the AME approach based on logistic regression models by treating quartile/median groups along with placebo group as one covariate, and stratification factors by SLEDAI-2K score at screening (< 10 points vs ≥ 10 points), Week 0 OCS dose (< 10 mg/day vs ≥ 10 mg/day prednisone or equivalent), and type I IFN gene signature test result at screening (high vs low), whenever applicable.

AME, average marginal effect; BICLA, British Isles Lupus Assessment Group-based Composite Lupus Assessment; CI, confidence interval; CLASI, Cutaneous Lupus Erythematosus Disease Area and Severity Index; G, tertile; IFN, interferon; Med, median; n, number of patients; N, number of patients in group; OCS, oral corticosteroids; P, placebo; Q, quartile; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000; SRI(4), Systemic Lupus Erythematosus Responder Index ≥ 4.

Figure 3 Exposure-efficacy analyses of primary and key secondary endpoints for anifrolumab 300 mg in the pooled phase III population – all-comers (full exposure-response analysis set)

Exposure-safety analysis: Graphical analyses of adverse effect incidences during treatment and individual predicted Cave quartiles were generated for all patients by study and treatment group. The same analysis set used for efficacy (the full exposure-response analysis set) was used in the exposure-response analyses of safety parameters.

There was an increased incidence of herpes zoster in patients who received anifrolumab when compared with placebo in the pooled phase III population; however, there was no evidence that higher

concentrations would lead to higher incidence of herpes zoster within each anifrolumab dose group (150 or 300 mg).

The overall incidence rate of non-opportunistic serious infections in the anifrolumab 300 mg group was lower compared with placebo in the pooled phase III population (3.9% vs 4.9%).

The incidence of infusion-related reactions in the anifrolumab group was numerically higher compared with the placebo group in the pooled phase III population; however, there was no evidence that higher C_{max} was associated with higher incidence.

A numerical increase in the incidence of hypersensitivity was observed in the anifrolumab 150 and 300 mg groups. The incidence was comparable between the anifrolumab 150 mg and 300 mg groups in the pooled phase III population; there was no evidence of exposure-driven hypersensitivity.

There was a low rate of malignancy, and there was no evidence of exposure-driven malignancy.

PK-PD analysis: The PKPD model focused on the 21-gene type I IFN PD signature in patients who had high (4-gene) type I IFN gene signature test at screening. A dose-related neutralisation/suppression of the type I IFN PD signature was observed across studies where doses ≥ 300 mg exhibited rapid onset of PD neutralisation at Week 4 and a median PD neutralisation of > 80% in type I IFN gene signature test high patients, whereas in the anifrolumab 150 mg group, there was a slow onset of PD effect and a median PD neutralisation of < 60% reached at Week 52.

The PD of anifrolumab (21-gene type I IFN PD signature) was described by an indirect response model in which the type I IFN-inducible gene production (kin) was inhibited by free anifrolumab. Since the PD endpoint was the percent neutralisation of the type I IFN PD signature compared with baseline, the PKPD analysis set was limited to patients with high type I IFN gene signature at screening. The observed data were adequately captured by the 95% prediction interval.

The parameter estimates of the model are tabulated in Table 5. Based on the IC_{50} estimate of 6.56 nM, the IC_{80} was approximately 26.24 nM (3.88 µg/mL with anifrolumab molecular weight of 148 kDa), where the median of Week 24 C_{trough} of 300 mg in patients with type I IFN gene signature test high was ~16 µg/mL and ~83% of the patients had troughs exceeding the IC_{80}. Conversely, there was only ~27% of the Week 24 troughs in type I IFN gene signature test high patients who received 150 mg that exceeded IC_{80} concentrations, further confirming that 150 mg is a suboptimal dose.

Table 5 Parameter estimates of PKPD model

Parameters	Parameter Estimates	Standard error
I_{max}	0.94	0.00355
IC_{50} (nM)	6.56	0.90
Baseline type I IFN 21-gene fold change, GS_0	13.1	0.395
Elimination rate constant, k_{out} (d^{-1})	0.746	0.479
Var(η_{IC50})	2.80	0.381
Var(η_{GS0})	0.466	0.0309
σ^2	0.182	0.00617

GS_0, baseline gene signature; IC_{50}, potency, anifrolumab concentration corresponding to half maximum inhibition of PD signature production; IFN, interferon; I_{max}, maximal change in PD signature production relative to baseline; PD, pharmacodynamic; PK, pharmacokinetic; Var(η_{IC50}), inter-subject variability of IC50; Var(η_{GS0}), inter-subject variability of GS_0; σ^2, residual variability.

PD-efficacy analysis: In the assessment of the relationship between neutralisation of the type I IFN PD signature and efficacy in type I IFN test high patients, individual median of PD suppressions from baseline at steady-state levels were correlated with both BICLA and SRI(4) at Week 52. In the pooled phase III population, including the anifrolumab 150 mg group, higher efficacy was associated with higher percent PD neutralisation in a graphical analysis.

2.5.3. Discussion on clinical pharmacology

An ECL based immunoassay is used for determination of anifrolumab concentrations in human serum. The assay is based on capturing anifrolumab with biotinylated IFNAR1 (B-IFNAR1) bound to a streptavidin-coated MSD plate. The captured anifrolumab is detected with a sulfo-TAG labeled monoclonal antibody directed against the triple mutation (TM). In general, the validations followed the principles laid down in EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2** Guideline on bioanalytical method validation.

Pharmacokinetics of anifrolumab after single dose and multiple dose IV administration was evaluated by non-compartmental analysis in patients with scleroderma (study MI-CP180) and in a small Phase II study in Japanese patients with SLE (study 02). In addition, the PK parameters (C_{max}, AUC, T_{max}, CL) after single dose administration of 300 mg IV in healthy volunteers were determined in study 06, where the number and frequency of samples were sufficient to characterise the concentration-time profile for anifrolumab. In the studies MI-CP180 and 02, more frequent and later time points would have improved the determination of the terminal elimination phase. Additionally, in study 02, the dose groups were not stratified for the type I IFNGS at screening, the number of patients was low and the dose groups differed in terms of body weight. Both type I IFNGS and body weight were identified as significant covariates for CL, body weight also for V_c in the population PK analyses. PK data included in the non-compartmental analyses is limited and subjected to variabilities, thus, reliable conclusions on exposure cannot be made solely based on these data. Despite these deficiencies, nonlinear more rapid elimination at lower concentrations could be identified in the non-compartmental analyses. These data together with the C_{max} and C_{trough} values from the SLE patients in the phase II and phase III clinical studies were included in the population PK analyses to further characterise the PK and covariate effects on PK.

A population PK model has been fitted to PK data from several, but not all, available clinical trials. The model has two compartments, a linear first-order clearance, and a target-mediated clearance pathway which describes anifrolumab elimination after it has bound to IFNAR and the drug-receptor complex has been internalised to the cell. This way, the model captures the nonlinearity of anifrolumab clearance. The peripheral distribution processes are mainly informed by an IV arm of a phase I study, which included six healthy volunteers. The other available clinical data consisted mostly of C_{max} and trough concentrations over several dosing cycles. The C_{max} is informative of central volume of distribution, and trough concentrations are informative of overall clearance. The identification of linear and target-mediated clearances is possible because data are available over a range of doses, and because of the densely sampled PK data from the IV arm of a phase I study.

Standard software and algorithms have been used to fit the population PK model. However, the final population PK model minimisation has ended prematurely due to rounding errors, which means that the parameter estimates are not the true maximum likelihood estimates. While a population PK model is always an approximation of reality, typically the reported PK parameter estimates are the ones that best describe the data, given the model. Within the current population PK model, there is no such guarantee. However, the model was able to reasonably describe the observed data, as was shown via Visual Predictive Checks for both the model-building data (internal validation), and studies 1145 and 09 data, which were not used during model fitting (external validation). Furthermore, the model did converge successfully when study 04 data were not included within the model; this suggests that the model

convergence issues are not a result of overparameterisation, and the data are adequate to identify the parameters. As such, information from the population PK model is accepted by the CHMP as part of this marketing authorisation application, even if the reported parameter estimates are not a result of successful model convergence.

Anifrolumab is administered by intravenous infusion. Based on population pharmacokinetic analysis, the estimated central and peripheral volumes of distribution for anifrolumab were 2.93 L (with 26.9% CV inter-individual variability) and 3.3 L, respectively for a 69.1 kg patient (SmPC section 5.2). These values are typical for an IgG molecule.

Anifrolumab is a protein, therefore specific metabolism studies have not been conducted. Anifrolumab is eliminated by target IFNAR mediated elimination pathway and reticuloendothelial system where anifrolumab is expected to be degraded, into small peptides and individual amino acids, by proteolytic enzymes that are widely distributed in the body (SmPC section 5.2). Renal and hepatic elimination do not play significant role in elimination or excretion of monoclonal antibodies. No data on excretion or metabolism of anifrolumab have been provided and these data are not required.

Anifrolumab PK is characterised by target-mediated drug disposition and non-linear PK in the dose range of 100 mg to 1000 mg as observed by the non-compartmental analysis in study MI-CP180 and study 02. Increasing the dose will result in an exposure increase that is higher than the increase in dose. In addition to dose-dependent exposure, anifrolumab showed time-dependency in clearance observed as gradual increase of $C_{through}$ during the first years of treatment in the phase II study 1013. The linear CL of anifrolumab decreases as a function of time, with a maximum clearance of approximately 16% and about 8% decrease in clearance occurring one year after the start of treatment, in a typical patient. According to the population PK report, although a typical patient showed decreasing CL over time, a portion of patients (15%) showed increasing CL of anifrolumab over time. The median increase in clearance (4.8% with 10^{th} and 90^{th} percentiles 0% and 19%) in the portion of patients treated with 300 mg in the studies 04 and 05 was not significant and apparent effect on PD suppression was not observed. No particular reason related to a patient characteristic could be identified for the increasing clearance.

Specific dose finding studies have not been conducted but the dose selection was based on model informed decisions. The doses 150 mg, 300 mg and 1000 mg IV were administered in the phase II and III studies. The 150 mg dose was included to investigate dose response. The data with 1000 mg dose supports the safety evaluation of anifrolumab in addition to saturation of the target mediated elimination pathway. The selected dose of 300 mg seemed to produce sustained mean C_{trough} concentrations with the q4w dosing regimen compared to 150 mg q4w. The percent neutralisation of the type I IFN PD signature was approximately 70% on day 29 after administration of first 300 mg dose IV in SLE patients with type I IFNGS high, the mean C_{trough} being 6.82 µg/ml (SD 5.31) in the study 1013. The applicant has reported in the exposure-response-model, that anifrolumab concentration corresponding to 80% of the maximum inhibition of PD signature production (IC80) was 3.88 µg/ml. The IC_{80} parameter has high inter-individual variability, and it seems that 300mg q4w is not able to fully suppress the PD signature in all patients.

The recommended dose is 300 mg, administered as an intravenous infusion over a 30-minute period, every 4 weeks (SmPC section 4.2). In case of missed dose, a minimum interval of 14 days should be maintained between doses. This interval is half the dosing interval and prevents unnecessary high serum concentrations and accumulation of anifrolumab exposure. Based on population PK analysis, serum concentrations were below detection in the majority (95%) of patients approximately 16 weeks after the last dose of anifrolumab, when anifrolumab has been dosed for one year.

Inter-individual variability was estimated in the population PK model for CL (CV = 52.72%), central volume of distribution (CV= 19.92%), baseline receptor concentration (CV = 26.09%) and for the magnitude of maximal time-dependent decrease in CL (CV = 38.21%).The inter-individual variability of

the C_{trough} and even C_{max} concentrations was high and there are both concentrations below the limit of quantitation (LOQ) of the analytical method (LOQ=0.02 µg/ml) when looking at the range of the concentrations. The applicant has not identified any particular reasons for these unexpected concentrations related to demographic data or bioanalytical method. The bioanalytical method validation for specificity did not indicate non-specific binding of anifrolumab to matrix components in serum of SLE patients. Otherwise, non-specific binding to blood components has not been studied.

Only body weight and IFN gene signature were identified as predictors of anifrolumab PK in the population pharmacokinetic analyses. The SLE patients belonging to type I IFN gene signature high had lower serum trough concentrations (C_{trough}) as patients with type I IFN gene signature low. The geometric mean (CV%) $C_{through}$ were 6.99 µg/ml (1847.3%) and 21.69 µg/ml (382.0%) for type I IFN gene signature test high and low patients, respectively, in the study 05, and 9.95 µg/ml (1311.2 %) and 16.73 µg/ml (160.0 %) for type I IFN gene signature test high and low patients, respectively, in the study 04 at 48 weeks after dosing of 300 mg. The type I IFNGS status was identified as significant covariate on CL in the population PK analysis, but no dose adjustment is needed for IFNGS high or low patients.

The applicant does not consider dose modifications based on body weight necessary. The PK-PD simulations indicate that a proportion of patients are expected to have trough concentrations below 1.00 µg/mL, and this proportion increases as weight increases. Also, there seems to be a significant proportion of patients who are predicted to have practically no PD suppression and the proportion increases with increasing bodyweight. However, random variability has a large impact on PD suppression; also patients with low bodyweight are somewhat likely to gain negligible PD suppression due to random variability. In this light, the impact of bodyweight seems negligible when compared to overall PD variability, and no relevant benefit is anticipated from shortening the dose interval for the heaviest individuals. It is noted that the proposed 300mg Q4W dose does not seem to produce a reliable PD suppression in all the patients; however, the bodyweight-independent dosing recommendation is supported by the CHMP (SmPC section 5.2).

No specific clinical studies have been conducted to investigate the effect of renal impairment on anifrolumab because anifrolumab is not cleared renally. Based on population PK analyses, anifrolumab clearance was comparable in SLE patients with mild (60-89 mL/min/1.73 m2) and moderate decrease in eGFR (30-59 mL/min/1.73 m2) values and patients with normal renal function (≥90 mL/min/1.73 m2). SLE patients with a severe decrease in eGFR or end stage renal disease (<30 mL/min/1.73 m2) were excluded from the clinical trials.

Patients with UPCR >2 mg/mg were excluded from the clinical trials. Based on population PK analyses, increased urine protein/creatinine ratio (UPCR) did not significantly affect anifrolumab clearance (SmPC section 5.2).

No specific clinical studies have been conducted to investigate the effect of hepatic impairment on anifrolumab. As an IgG1 monoclonal antibody, anifrolumab is principally eliminated via catabolism and is not expected to undergo metabolism via hepatic enzymes, as such changes in hepatic function are unlikely to have any effect on the elimination of anifrolumab. Based on population pharmacokinetic analyses, baseline hepatic function biomarkers (ALT and AST ≤2.0 × ULN, and total bilirubin) had no clinically relevant effect on anifrolumab clearance (SmPC section 5.2).

The applicant has not conducted specific drug-drug interaction studies with anifrolumab because anifrolumab elimination is not dependent on CYP enzymes. This was considered acceptable to the CHMP. Pro-inflammatory cytokines may suppress CYP 450 activity during chronic inflammation like SLE. Anifrolumab treatment in study 1013 reduced the median baseline levels of TNF-αand IL-10 by 15% to 20% in SLE patients. Thus, therapeutic monitoring is recommended for patients treated with narrow therapeutic index medicines that are CYP substrate and the dose is individually adjusted (e.g. warfarin). Due to uncertainties in timing of the use of concomitant medication in relation to the study medication

and to sample collection during the studies, the result of the population PK modelling is considered as general observation for no significant major interactions. Based on population PK analyses, concomitant use of oral corticosteroids, antimalarials, immunosuppressants (including azathioprine, methotrexate, mycophenolate and mizoribine), NSAIDS, ACE inhibitors, HMG-CoA reductase inhibitors did not significantly influence the PK of anifrolumab. This is adequately reflected in Section 5.2 of the SmPC.

The applicant has conducted exposure-response, exposure-safety, PK/PD and PD-response analyses.

An apparent exposure-response relationship was noted for the 300mg dose (Figure 3). Higher exposure correlated with higher probability of response. However, this apparent relationship is largely caused by subjects who discontinued the study and were thus labelled as non-responders. Because these subjects discontinued early, their average anifrolumab concentrations were lower than the anifrolumab concentrations of subjects who completed the study, thus causing an apparent correlation between low anifrolumab concentrations and non-response.

The applicant has claimed that the exposures achieved from 300mg dose are in the flat part of the exposure-response curve, based on a logistic regression curve of log(1+Cave) as a predictor of response probability, where C_{ave} is the average anifrolumab concentration over treatment duration. This claim is met with reservations by the CHMP, because with log-transformation, the linearity or flatness of the exposure-response curve will depend on the parameterisation and units, i.e. if log(1+Cave) is the predictor of response, then different results will be obtained if C_{ave} is for example in mg/mL units as compared to µg/mL units.

With regard to exposure-safety, the occurrence of select adverse events (herpes zoster occurrence; serious infections; hypersensitivity, anaphylaxis, and investigator-reported AEs of infusion-related reactions; malignancy) was numerically higher in anifrolumab-treated patients than in placebo-treated patients for some of the adverse effect categories. However, apart from the placebo versus treatment comparison, increasing anifrolumab exposure was not associated with an increasing risk of adverse events.

The PK/PD model captures the relationship between free anifrolumab concentrations and PD response, defined as the relative activity of 21 genes that are inducible by type I IFN. The IC_{80} value from the model, which describes the concentration required to elicit 80% of maximum response, was 3.88µg/mL. The IC_{80} parameter had a high inter-individual variability, with a coefficient of variation of 392%. The PK/PD model only included data from IFNGS high patients because only these patients had an overexpression of type I IFN gene signature. For IFNGS low patients, only minimal PD suppression was seen because these patients had no overexpression of the PD signature. A modest graphical PD-efficacy trend was noted, and no further analyses were conducted.

Overall, the above analyses were considered acceptable to the CHMP.

2.5.4. Conclusions on clinical pharmacology

Despite the limited PK data of anifrolumab and some deficiencies, nonlinear more rapid elimination at lower concentrations could be identified in the non-compartmental analyses implying target-mediated drug disposition for anifrolumab.

The dense PK data from phase I and phase II studies together with the C_{max} and C_{trough} values from the SLE patients in the phase II and phase III clinical studies were included in the population PK analyses to further characterise the PK and covariate effects on PK. The PK model has two compartments, a linear first-order clearance, and a target-mediated clearance pathway which describes anifrolumab elimination after it has bound to IFNAR and the drug-receptor complex has been internalised to the cell. This way, the model captures the nonlinearity of anifrolumab clearance. The PK of anifrolumab and covariate effects

on PK has been characterised by the population PK modelling. The population PK model is considered an acceptable source of PK information by the CHMP, even though the model has not successfully converged to maximum likelihood estimates.

From population PK modelling the estimated typical systemic clearance (CL) was 0.193 L/day with a 33.0% CV inter-individual variability. The median CL decreases slowly over time, with an 8.4% reduction after 1 year of treatment. Based on population PK analysis, serum concentrations were below detection in the majority (95%) of patients approximately 16 weeks after the last dose of anifrolumab, when anifrolumab has been dosed for one year. Due to saturation of IFNAR1-mediated clearance at higher doses, exposure increases are greater-than-dose-proportional (SmPC section 5.2).

The type I IFNGS status and body weight were identified as significant covariate on CL in the population PK analysis, but no dose adjustment is needed for IFNGS high or low patients or based on body weight. There was no clinically meaningful difference in systemic clearance based on age, race, ethnicity, region, gender, IFN status or body weight that requires dose adjustment.

No dose adjustment is required in patients with renal or hepatic impairment.

In adult patients with SLE, administration of anifrolumab at doses ≥300 mg, via intravenous infusion every 4 weeks, demonstrated consistent neutralisation (≥80%) of a 21 gene type I interferon pharmacodynamic (PD) signature in blood. This suppression occurred as early as 4 weeks post-treatment and was either maintained or further suppressed over the 52-week treatment period. Following withdrawal of anifrolumab at the end of the 52-week treatment period in the SLE clinical trials, the type I IFN PD signature in blood samples returned to baseline levels within 8 to 12 weeks. Anifrolumab 150 mg IV, showed <20% suppression of the gene signature at early timepoints, that reached a maximum of <60% by the end of the treatment period.

The CHMP considered that the applicant has sufficiently addressed the issues on PK, PK/PD or PD-response analyses of anifrolumab.

The proposed dosing regimen of 300 mg, administered as an intravenous infusion over a 30-minute period, every 4 weeks was considered acceptable to the CHMP.

2.5.5. Clinical efficacy

A tabular overview of clinical studies conducted to support the application is provided in Table 1.

The key studies for assessment of safety and efficacy within the programme comprised:

- Two completed 52-week, randomised, double-blind, placebo controlled, Phase III studies: D3461C00004 or 'Study 04' (TULIP 2), and D3461C00005 or 'Study 05' (TULIP 1)
- An ongoing 3-year, double-blind, placebo-controlled, long-term extension study containing patients rolled over from studies 04 and 05 (D3461C00009 or 'Study 09'). Interim safety data from study 09 are reported in the Summary of Clinical Safety while exploratory efficacy endpoints, including SLEDAI-2K scores over time, will be reported when the study is complete; anticipated in Q2 2022.
- One completed 52-week Phase II study: CD-IA-MEDI-546-1013 or 'Study 1013' (MUSE)
- A completed 3-year, open-label extension study containing patients rolled over from study 1013 (study CD-IA-MEDI-546-1145 or 'Study 1145')

Within the submission, the applicant has presented Study 04 as a pivotal study, with Studies 05 and 1013 providing supportive evidence of efficacy. Considering that the original aim was for both Study 04

and Study 05 to serve as pivotal studies (but with Study 05 failing on its original primary endpoint), the efficacy section of the AR presents all key studies in an integrated manner without separate consideration of the applicant's classification regarding the status of the studies.

2.5.5.1. Dose response study

The Phase II study 1013, which could also be considered a dose response study, is discussed within the main studies below. Dose selection for Study 1013 was based on PK/PD modelling and simulation as well as a PK/PD analysis of a Phase I study in scleroderma patients.

For the Phase III studies 04 and 05, selection of a dose of 300 mg Q4W was based on safety and efficacy results from the interim analysis of Study 1013. In the interim analysis, clinically meaningful benefit was observed with the 300 mg dose, with no incremental benefit at 1000 mg. In addition, a higher proportion of patients reporting herpes zoster reactivations was observed at 1000 mg compared to 300 mg. In Study 05, a dose of 150 mg was also evaluated; according to the applicant, this dose was included to elucidate dose response and to provide additional justification for the 300 mg dose. However, due to the lack of a consistent pattern of efficacy, the applicant is not seeking marketing authorisation for a posology of 150 mg.

2.5.5.2. Main studies

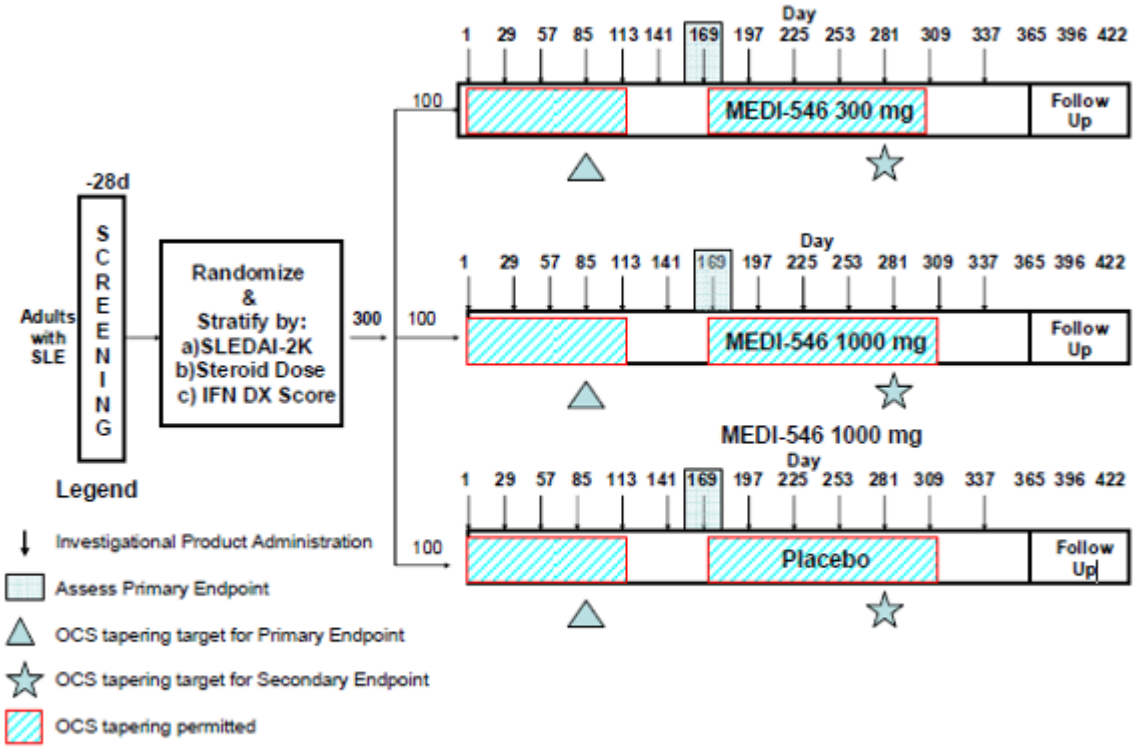
Demonstration of clinical efficacy is based on three large-scale randomised double-blind studies. As the methodology across the three studies was very similar, the Methods and Results sections present the studies together, with differences between the studies highlighted as relevant.

Methods

Study CD-IA-MEDI-546-1013 (Study 1013; MUSE) "A Phase 2, Randomized Study to Evaluate the Efficacy and Safety of MEDI-546 in Subjects with Systemic Lupus Erythematosus".

Study 1013 was a randomised, double-blind, placebo-controlled, parallel-group multicentre study to evaluate the efficacy and safety of two intravenous treatment regimens of anifrolumab (300 mg and 1000 mg Q4W) in adult subjects with chronic, moderately-to-severely active SLE with an inadequate response to standard of care treatment for SLE.

The general design of Study 1013 is depicted in Figure 4.



-28d = -28 days; IFN DX =4-gene type I interferon test; OCS = oral corticosteroids; SLE = systemic lupus erythematosus; SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index 2000

Figure 4 Study design for Study 1013

Study D3461C00004 (Study 04; TULIP 2) "A Multicentre, Randomised, Double-blind, Placebo-controlled, Phase 3 Study Evaluating the Efficacy and Safety of Anifrolumab in Adult Subjects with Active Systemic Lupus Erythematosus".

Study 04 was a randomised, double-blind, placebo-controlled, parallel-group multicentre study to evaluate the efficacy and safety of anifrolumab 300 mg Q4W in adult subjects with chronic, moderately-to-severely active SLE with an inadequate response to standard of care treatment for SLE.

The general design of Study 04 is depicted in Figure 5.

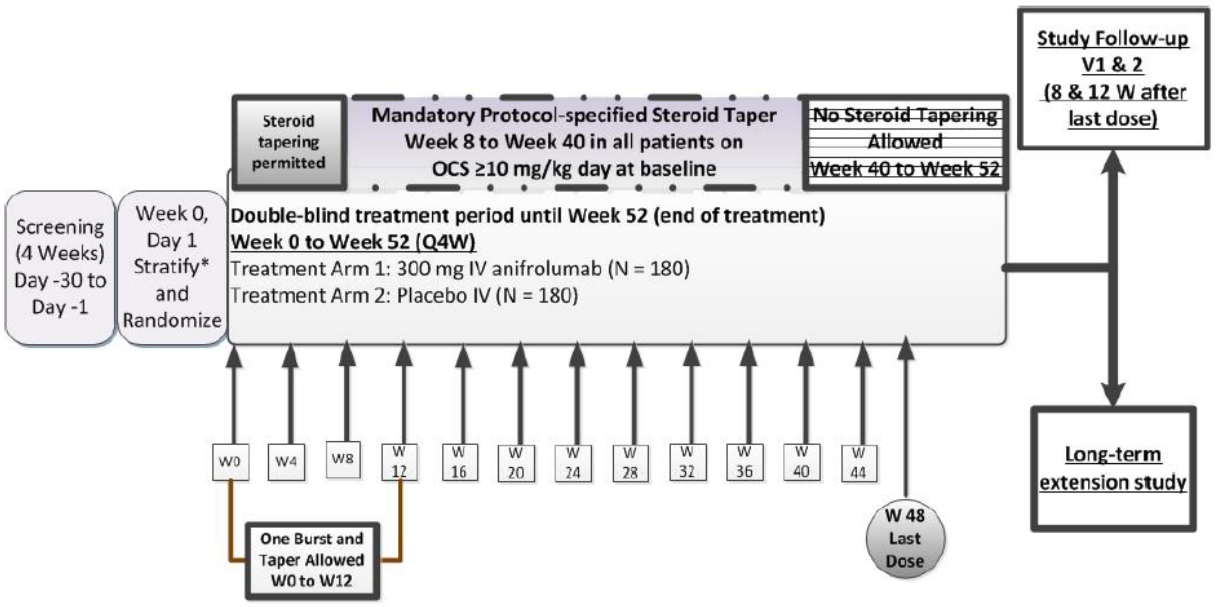
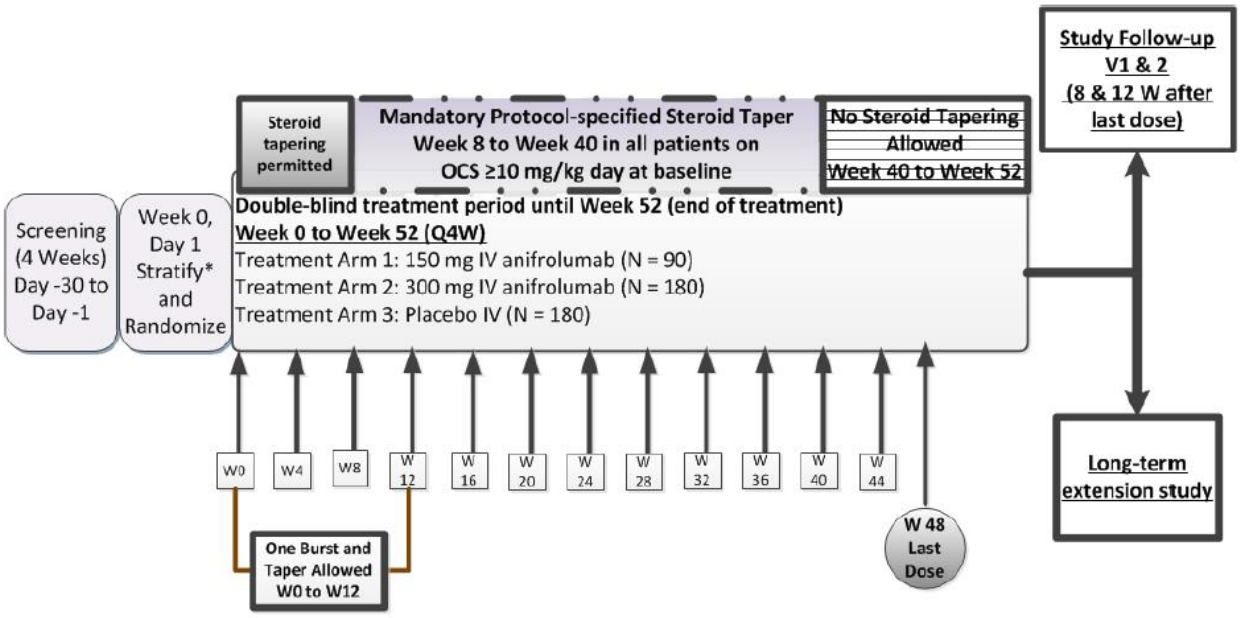


Figure 5 Study design for Study 04

Study D3461C00005 (Study 05; TULIP 1) "A Multicentre, Randomised, Double-blind, Placebo-controlled, Phase 3 Study Evaluating the Efficacy and Safety of Two Doses of Anifrolumab in Adult Subjects with Active Systemic Lupus Erythematosus".

Study 05 was a randomised, double-blind, placebo-controlled, parallel-group multicentre study to evaluate the efficacy and safety of two intravenous treatment regimens of anifrolumab (150 mg and 300 mg Q4W) in adult subjects with chronic, moderately-to-severely active SLE with an inadequate response to standard of care treatment for SLE.

The general design of Study 05 is depicted in Figure 6.



* Stratification:
SLEDAI Score (< or ≥10 points)
OCS Dose (< or ≥10 mg)
IFN Test (Low or High)

IFN = interferon; IV = intravenous; N = number of patients; OCS = oral corticosteroid; SLEDAI = Systemic Lupus Erythematosus Disease Activity Index
Q4W = every 4 weeks; V = Visit; W = Week

Figure 6 Study design for Study 05

Study Participants

Similar eligibility criteria were applied in all three studies. The studies enrolled adult patients of both genders; the main disease-relevant inclusion criteria were:

- Diagnosis of paediatric or adult SLE at least 24 weeks prior to screening
- Fulfilling at least 4 of the 11 American College of Rheumatology (ACR) classification criteria for SLE, one of which must be:
    - Positive antinuclear antibody (ANA) test at screening with a titre of ≥ 1:80; OR
    - Elevated anti-double-stranded DNA (anti-dsDNA) antibodies at screening; OR
    - Elevated anti-Smith antibodies at screening
- Currently receiving at least one of the following medications:
    a. oral prednisone or equivalent <= 40 mg/day with a stable dose for at least 2 weeks prior to Day 1
    b. any of the following medications administered for a minimum of 12 weeks and at a stable dose for a minimum of 8 weeks prior to signing of the informed consent through Day 1:
        - Azathioprine ≤ 200 mg/day
        - Antimalarial (e.g., chloroquine, hydroxychloroquine, quinacrine)
        - Mycophenolate mofetil ≤ 2.0 g/day / mycophenolic acid
        - Oral, SC, or intramuscular methotrexate ≤ 25 mg/week
        - Mizoribine ≤150 mg/day (Studies 04 and 05 only)

- At Screening, confirmation of the following by an adjudication group:
    - SLEDAI-2K Criteria: SLEDAI-2K score ≥6 points and "Clinical" SLEDAI-2K score ≥4 points. The "Clinical" SLEDAI-2K is the SLEDAI-2K assessment score without the inclusion of points attributable to any urine or laboratory results including immunologic measures:
        - Includes points from the following clinical components: arthritis, myositis, rash, alopecia, mucosal ulcers, pleurisy, pericarditis, or vasculitis
        - Excludes points attributed to a fever, an SLE headache, and organic brain syndrome
    - BILAG-2004 Level Criteria: At least 1 of the following:
        - BILAG-2004 level A disease in ≥1 organ system
        - BILAG-2004 level B disease in ≥2 organ systems
    - PGA score ≥1.0 on a 0 to 3 visual analogue scale (VAS) at Screening

The main exclusion criteria were:

- Use of biological agents, including B-cell depleting therapies and belimumab, with product-specific minimum wash-out periods outlined in the protocols
- Regular use of >1 nonsteroidal anti-inflammatory drug (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)
- History of, or current diagnosis of, a clinically significant non SLE-related vasculitis syndrome
- Active severe or unstable neuropsychiatric SLE
- Active severe SLE-driven renal disease
- Diagnosis (within 1 year of signing the ICF) of mixed connective tissue disease or any history of overlap syndromes of SLE and systemic sclerosis; an overlap with myositis or rheumatoid arthritis at screening was permitted provided the patients also met the criteria for SLE.
- History of or current diagnosis of catastrophic or severe anti-phospholipid syndrome within 1 year prior to signing the ICF
- History of, or current, inflammatory joint or skin disease other than SLE
- History or evidence of suicidal ideation (severity of 4 [active: method and intent, but no plan] or 5 [active: method, intent, and plan]) within the past 6 months; or any suicidal behaviour within the past 12 months
- Known history of a primary immunodeficiency, splenectomy, or any underlying condition that predisposed the patient to infection, or a positive result for human immunodeficiency virus (HIV) infection
- Confirmed positive test for hepatitis B serology for Hepatitis B surface antigen, OR Hepatitis B core antibody (HBcAb) AND hepatitis B virus (HBV) DNA detected above the lower limit of quantitation
- Positive test for hepatitis C antibody
- Any severe herpes infection at any time prior to Week 0

- Any herpes zoster, cytomegalovirus, or Epstein-Barr virus infection that had not completely resolved within 12 weeks prior to signing the ICF
- Opportunistic infection requiring hospitalisation or IV antimicrobial treatment within 3 years of randomisation
- Clinically significant chronic infection (i.e., osteomyelitis, bronchiectasis, etc.) within 8 weeks prior to signing the ICF (chronic nail infections were allowed); any infection requiring hospitalisation or treatment with IV anti-infectives not completed at least 4 weeks prior to signing the ICF; or any infection requiring oral anti-infectives (including antivirals) within 2 weeks prior to Day 1
- History of cancer, apart from squamous or basal cell carcinoma of the skin treated with documented success of curative therapy ≥3 months prior to Week 0 (Day 1); or cervical carcinoma in situ treated with apparent success with curative therapy ≥1 year prior to Week 0 (Day 1)
- Pregnancy or breastfeeding. Anifrolumab has not been studied in patients who are pregnant or breastfeeding. Pregnancy avoidance methods were instituted for women of childbearing potential and for non-sterilised, sexually active men with female partners of childbearing potential.
- Any live or attenuated vaccine within 8 weeks prior to signing the ICF (administration of killed vaccines was acceptable; the applicant recommended investigators ensured all patients were up to date on required vaccinations, including influenza [inactivated/recombinant] vaccine prior to study entry)
- Bacillus Calmette-Guerin (BCG) vaccine within 1 year of signing the ICF.
- Laboratory tests:
    - AST, AST >2.0 × upper limit of normal (ULN) Total bilirubin >ULN (unless due to Gilbert's syndrome)
    - Serum creatinine >2.0 mg/dL (or >181 µmol/L); Urine protein/creatinine ratio >2.0 mg/mg (or >226.30 mg/mmol)
    - Neutrophil count <1000/µL (or <1.0 × 109/L); Platelet count <25000/µL (or <25 × 109/L)
    - Haemoglobin <8 g/dL (or <80 g/L), or <7 g/dL (or <70 g/L) if related to patient's SLE such as in active haemolytic anaemia
- Glycosylated haemoglobin >8% (or >0.08) at screening (diabetic patients only)

Treatments

In Study 1013, patients received anifrolumab at doses of 300 mg or 1000 mg, or matching placebo.

In Study 04, patients received anifrolumab at a dose of 300 mg, or matching placebo.

In Study 05, patients received anifrolumab at doses of 150 mg or 300 mg, or matching placebo.

In all studies, dosing was at 4-week intervals, with the last dose administered at Week 48.

For Study 1013, anifrolumab was supplied in vials as a 100 mg/mL solution. For studies 04 and 05, anifrolumab was supplied in vials as a 150 mg/mL solution. The investigational product was diluted with 0.9% saline and administered as an intravenous infusion over 60 minutes in Study 1013, and over at least 30 minutes in studies 04 and 05.

Regarding concomitant medications, an attempt to taper oral corticosteroids (OCS) was included in the protocol as follows:

- In studies 04 and 05, for patients receiving baseline ≥ 10 mg/day oral prednisone or equivalent, tapering attempts were mandated between Week 8 and Week 40 until achieving a dose ≤ 7.5 mg/day. Tapering was also encouraged for patients receiving OCS < 10 mg/day at baseline. OCS dosages were required to be stable for the last 12 weeks before the primary endpoint assessment at Week 52.
- In study 1013, OCS tapering was encouraged based on disease activity, after randomisation except within 8 weeks of the primary (Week 24) and secondary (Week 52) endpoint assessments. A steroid tapering milestone to ≤ 10 mg/day was a component of the primary and secondary endpoints—combined with the SRI(4) measure of disease activity. Steroid tapering to ≤ 7.5 mg/day was the target used to evaluate the secondary objective of reduced OCS use.

Objectives

The primary objective in all three studies was to evaluate the effects of anifrolumab on overall disease activity. Two primary endpoints, as outlined in more detail below, were used. Secondary objectives were chosen to further characterise the reduction in overall disease activity, in particular the ability to reduce OCS use, the effect on organ-specific endpoints (cutaneous SLE activity and joints), and flare rates.

Statistical analyses were based on demonstrating superiority against a placebo control.

Outcomes/endpoints

The efficacy endpoints used in the key studies and their hierarchy, as presented within the application, are outlined in Table 6.

Table 6 Assessments and endpoints to assess the efficacy of anifrolumab in the proposed indication—study 04, study 05, and study 1013

Assessment	Endpoint	Study 04	Study 05	Study 1013[a]
Overall disease activity	**BICLA response at Week 52**	Primary endpoint	Secondary endpoint	Secondary endpoint
	BICLA response at Week 52 for the subgroup of type 1 IFNGS test-high patients	Key secondary endpoint	Exploratory endpoint	Exploratory endpoint
	SRI(4) response at Week 52	Secondary endpoint	Primary endpoint	Secondary endpoint
Oral corticosteroid use	**Maintained OCS tapering at Week 52**	Key secondary endpoint	Key secondary endpoint	Secondary endpoint
Cutaneous SLE activity	**CLASI response at Week 12**	Key secondary endpoint	Key secondary endpoint	Secondary endpoint
Joints	**Joints at Week 52**	Key secondary endpoint	Secondary endpoint[b]	Exploratory endpoint[b]
Flares	**Annualized flare rate**	Key secondary endpoint	Key secondary endpoint	Exploratory endpoint[c]

[a] Note that the primary endpoint in study 1013 was SRI(4) response with OCS tapering at Week 24. In order to assess the effect of anifrolumab on overall disease activity out to Week 52 in this application, and to align with the endpoints used to assess this in studies 04 and 05, data for SRI(4) response at Week 52 is presented for study 1013, which was a secondary endpoint in the study.

[b] The definition of the joint endpoint in study 05 was slightly different to that in studies 04 and 1013; for further details see Section 4.1.6.4

[c] The definition of the flare endpoint in study 1013 was different to that in studies 04 and 05; for further details see Section 4.1.6.5

'Key secondary' endpoints are adjusted for multiplicity control.

'Secondary' endpoints are prespecified in the protocol and not adjusted for multiplicity control.

'Exploratory' endpoints are not prespecified in the protocol.

BICLA, British Isles Lupus Assessment Group-based Composite Lupus Assessment; CLASI, Cutaneous Lupus Erythematosus Disease Area and Severity Index; IFNGS, Interferon gene signature; OCS, Oral corticosteroids; SLE, Systemic lupus erythematosus; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000; SRI, Systemic Lupus Erythematosus Responder Index; SRI(4) ≥ 4 point reduction in SLEDAI-2K score in the SRI.

Due to the heterogeneity and complexity of SLE, composite endpoints are often used to evaluate disease activity across multiple organ systems. Two composite endpoints, BICLA and SRI, have been used in clinical trials and both were used in the anifrolumab studies.

The disease activity instruments used for assessment of BICLA and SRI(4) response are BILAG-2004, SLEDAI-2K and PGA.

BILAG-2004 is an ordinal scale index with 97 organ-specific items in 9 systems (constitutional, mucocutaneous, neuropsychiatric, musculoskeletal, cardiorespiratory, gastrointestinal, ophthalmic, renal, and haematology) that is able to capture changes in clinical manifestations. It records disease activity occurring over the immediate past 4 weeks, as compared with the previous 4 weeks, whereby organ manifestations are assessed as not present, improving, same, worse, or new. It is based on the principle of a physician's intention to treat and categorises disease activity across the 9 systems as levels A to E, (where 'A' indicates severe disease, 'B' is moderate activity, 'C' is mild stable disease, 'D' is resolved activity, and 'E' indicates the organ was never involved). These levels can be translated into numeric scores. A BILAG-2004 index including at least one 'A' or two 'B's is considered to reflect moderate to severe disease requiring therapy.

The BILAG-2004 gives equal weight to all affected body systems and is capable of measuring incremental improvements or worsening within a body system. For example, a 50% improvement, such as a clinically meaningful reduction from 30% to 15% of the skin surface involved with a skin eruption, the BILAG-2004 level for that organ would change from A (severe activity) to B (moderate activity). The BILAG-2004 requires improvement in all baseline manifestations within a system to result in a change in that system's BILAG-2004 level. For example, a patient with skin eruption and severe mucosal ulceration at baseline must show improvement in both to result in a change in the BILAG-2004 mucocutaneous index level.

The SLEDAI-2K consists of a list of 24 defined organ manifestations covering 9 organ systems (central nervous system, vascular, renal, musculoskeletal, serosal, mucocutaneous, immunologic, constitutional, and haematologic). These manifestations are assessed as being 'present' or 'absent' in the previous 28 days and attributable to SLE. Organ involvement scoring is weighted differently (eg, rash, alopecia, and low complement are each scored 2, musculoskeletal and renal activities are scored 4, and central nervous system activity is scored 8). The summation of the weighted organ manifestations into a final score ranges from 0 to 105. A SLEDAI-2K score of 6 or more has shown to be consistent with moderate to severe disease requiring therapy, and scores greater than 20 are rare. A clinically meaningful improvement is defined as a reduction in SLEDAI-2K of 4 units. With each domain scored in a binary fashion as present or absent, a SLEDAI-2K score reduction is only recorded on complete resolution of a disease manifestation. For example, a notional 50% improvement in multiple organ systems would not result in any change in SLEDAI-2K.

The PGA is a physician-rated global assessment of disease activity utilising a modification of the classic VAS (0-3 scale), with 0 = no, 1 = mild, 2 = moderate, and 3 = severe disease; for example, "3" refers to the most severe possible disease and does not reflect the most severe seen in a given patient. This is a global assessment factoring in all aspects of the patient's SLE disease activity and represents the physician's (trained and certified) overall assessment of average SLE disease severity.

In the anifrolumab programme, the applicant included two intercurrent events (no discontinuation of investigational product, and no use of restricted medications beyond the protocol-allowed threshold) as components of the composite estimand. Consequently, a BICLA responder was defined as a patient meeting all of the following criteria:

- Reduction of all BILAG-2004 baseline A items to B/C/D and baseline B items to C/D, plus no worsening in other organ systems; worsening is defined as one or more new A items or 2 or more new B items
- No worsening from baseline in SLEDAI-2K (defined as an increase from baseline of > 0 points in SLEDAI-2K)
- No worsening of the physician-rated global estimate of disease activity from baseline (defined by ≥ 0.30 points on a PGA VAS [0-3 scale])
- No discontinuation of investigational product
- No use of restricted medications beyond the protocol-allowed threshold before assessment

An SRI(4) responder was defined as a patient meeting all of the following criteria:

- 4-point or greater improvement of SLEDAI-2K from baseline
- No new organ system affected as defined by one or more new BILAG-2004 level A or 2 or more new level B items compared with baseline (ie, no new level A and no more than one new level B score)
- No worsening of the physician-rated global estimate of disease activity from baseline (defined by ≥ 0.30 points on a PGA VAS [0-3 scale])
- No discontinuation of investigational product
- No use of restricted medications beyond the protocol-allowed threshold before assessment

Study withdrawal (i.e. a patient withdrawing completely from the study, leading to true absence of data from time of withdrawal onward) was also considered an intercurrent event leading to categorisation of the patient as a non-responder subsequent to withdrawal.

When the Phase III studies 04 and 05 were initiated in 2015, SRI(4) response at 52 weeks was chosen as the primary endpoint to measure changes in overall disease activity. According to the applicant, the decision was based on the positive results achieved with SRI(4) in the phase II study 1013, as well as the fact that it had been previously accepted by the regulatory authorities as the basis of approval of belimumab for SLE. BICLA response at 52 weeks was a pre-specified secondary/exploratory endpoint in all 3 studies, although it was not included in the multiplicity control.

The first Phase III study (Study 05) was unblinded in August 2018, and the full set of pre-specified analyses became available in September 2018. Study 05 did not meet its primary endpoint, SRI(4) at 52 weeks. However, improvements in overall disease activity were observed in terms of BICLA response and other secondary endpoints, and in consultation with an external Steering Committee for the TULIP programme, the applicant subsequently changed the primary endpoint of Study 04 to BICLA response. According to the applicant, the review was conducted and decisions made while study 04 was blinded and after all patients had completed the 52-week treatment period, and no data from the blinded study 04 were reviewed for this purpose nor used to inform the decisions.

The applicant has justified the appropriateness of the change based on the following premises:

- Reduction in disease activity in BICLA is measured by the BILAG-2004 index, which captures more disease-related elements than the SLEDAI index, which is used to measure disease activity in SRI(4). Thus BICLA captures more of the clinical diversity of SLE disease activity than SRI(4).
- The BILAG-2004 is a more sensitive measure to changing severity of organ involvement as it captures incremental improvements or worsening within a body system, whereas SLEDAI-2K score reduction reflects only complete resolution of a disease manifestation.

- It is stringent, as it requires improvement in all organs affected at baseline, with no new flares in the remaining body systems.
- It weighs organ systems equally according to the physician's intention to treat. Importantly, for the typical SLE trial population, skin and joints are given equal weighting to each other and to all other organs.

A number of secondary endpoints were defined for further characterisation of changes in disease activity. Key secondary endpoints were multiplicity controlled, other secondary endpoints were tested outside of the confirmatory framework.

- BICLA (Study 04) and SRI(4) (Study 05) at Week 52 in the type I IFN gene signature test-high subgroup was used as a key secondary endpoint to evaluate the effect of anifrolumab in this subgroup.
- To assess whether anifrolumab could permit a tapering of oral corticosteroids (OCS), the proportion of patients with baseline OCS $\geq$ 10 mg/day who could achieve a target OCS dose $\leq$ 7.5 mg/day prednisone or equivalent by Week 40 and maintain it through Week 52 was analysed as a key secondary endpoint in studies 04 and 05 and as a secondary endpoint in Study 1013.
  It should be noted that in studies 04 and 05, OCS tapering was mandated per protocol, whereas in Study 1013, OCS tapering was only recommended. The primary endpoint in Study 1013 was SRI(4) combined with the ability to taper OCS.
- To evaluate the effect of anifrolumab on inflammatory cutaneous lupus lesions, the proportion of patients with $\geq$ 50% reduction in Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) score at Week 12 in patients with moderate to severe skin disease (CLASI $\geq$ 10) at baseline was analysed as a key secondary endpoint in studies 04 and 05 and as a secondary endpoint in Study 1013.
- A reduction in swollen and tender joint counts was analysed as an exploratory endpoint in Study 1013, a secondary endpoint in Study 05 and escalated as a key secondary endpoint for Study 04. The definition of response was slightly different from study to study.
- In studies 04 and 05, a moderate to severe flare was defined as either 1 or more new BILAG-2004 A item or 2 or more new BILAG-2004 B items compared to the previous visit (i.e., a worsening from an E, D, or C score to a B score in at least 2 organ systems or a worsening from an E, D, C, or B to an A score in any 1 organ system compared to the previous visit). The effect of anifrolumab on the annualised flare rate through Week 52 was a key secondary endpoint in studies 04 and 05.
- Higher thresholds of disease improvement (SRI[5] to SRI[8]) were evaluated as secondary endpoints. Intercurrent events were not considered for these endpoints.
- Two concepts of a sustained response ["major clinical response" (MCR) and "partial clinical response" (PCR)] were also evaluated as secondary endpoints. MCR was defined as a patient with BILAG-2004 C scores or better at Week 24 with no new A or B scores, and maintenance of response with no new BILAG-2004 A or B scores between Week 24 and Week 52. PCR was defined as a patient with a maximum of one BILAG-2004 B score or better at Week 24, and maintenance of response without a new BILAG-2004 A or more than one new BILAG-2004 B item out to Week 52. Intercurrent events were not considered for these endpoints.
- A number of patient-reported outcomes were also evaluated among the secondary endpoints. These included:

    - Short Form 36 version 2 (SF-36-v2)
    - Functional Assessment of Chronic Illness Therapy-FATIGUE (FACIT-F)
    - Euro quality of life 5 dimensions (EQ-5D-5L)
    - Lupus quality of life (Lupus QoL)
    - Patient global assessment (PtGA)
    - Work Productivity and Activity Impairment - Lupus (WPAI-Lupus)
    - Medical Resource Use Questionnaire
- Pain numerical rating scale (Pain NRS)

As outlined above, the applicant's definitions for BICLA and SRI(4) response were composite estimands that included an intercurrent event of "No use of restricted medications beyond the protocol-allowed threshold". Following a review of the study 05 data (prior to unblinding of study 04), the applicant considered that some of these rules had not been interpreted correctly and made corrections and adjustments to the restricted medication rules. In terms of the number of patients affected by the revision, the clearly most significant change was related to NSAID's; with the original rules, 21 patients in the anifrolumab 300 mg group and 9 patients in the placebo group were considered non-responders, whereas no patients in either group were considered non-responders based on the revised rules.

Randomisation and blinding (masking)

Block randomisation using an interactive voice/web response system (IXRS) was used to randomise patients in 1:1 ratio to receive a fixed IV dose of 300 mg anifrolumab or placebo in Study 04 and in 1:2:2 ratio to receive a fixed IV dose of 150 mg anifrolumab, 300 mg anifrolumab or placebo in Study 05.

The randomisation was stratified using the following factors:

- SLEDAI-2K score at screening (<10 points versus ≥10 points)
- Week 0 (Day 1) OCS dose (<10 mg/day versus ≥10 mg/day prednisone or equivalent) as reported by the investigator
- Results of the type I IFN gene signature test (high versus low)

The random allocation sequence was generated globally (not by centre) considering 8 strata. Block randomisation using an interactive voice/web response system was used to randomise patients in permuted blocks:

- Study 1013: in a 1:1:1 ratio (300 mg anifrolumab, 1000 mg anifrolumab, or placebo) with a block size of 3.
- Study 04: in a 1:1 ratio (300 mg anifrolumab or placebo) with a block size of 4.
- Study 05: in a 1:2:2 ratio (150 mg anifrolumab, 300 mg anifrolumab, or placebo) with a block size of 5.

All key studies (studies 1013, 04 and 05) were double-blind.

Statistical methods

Analysis populations

Full analysis set

The full analysis set was used as the primary population for reporting efficacy and safety data. This comprises all subjects randomised into the study who receive at least 1 dose of investigational product and was analysed according to randomised treatment (modified Intention-To-Treat).

Primary Efficacy Analyses

The primary estimand in study 04 was the difference between anifrolumab 300 mg and placebo in the proportion of patients achieving BICLA response at Week 52. As outlined above, the primary estimand was derived using a composite strategy that included three intercurrent events (use of restricted medication; investigational product discontinuation; withdrawal from study), and the occurrence of any of these led to the categorisation of the patient as a non-responder. The estimand was measured by the primary efficacy endpoint (difference in the proportion of BICLA responders between the anifrolumab 300 mg and placebo groups at Week 52). The primary objective of study 05 was constructed in the same way as study 04, however, evaluated using SRI(4).

In study 04, the null hypothesis that the proportion of patients achieving a BICLA response on anifrolumab 300 mg is equal to that on placebo was evaluated. The alternative hypothesis was that the proportion of patients achieving a BICLA response on anifrolumab 300 mg is not equal to that on placebo, ie,

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

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

The null and alternative hypotheses for study 05 were constructed similarly for SRI(4) response.

A stratified Cochran-Mantel-Haenszel test with the same stratification factors as for the randomisation, i.e., disease activity at screening (SLEDAI-2K < 10 points versus ≥ 10 points), Day 1 OCS dose (< 10 mg/day versus ≥ 10 mg/day prednisone or equivalent), and results of the type I IFN gene signature test at screening (high versus low) were used for the assessment of the primary objective in both studies.

To enable the comparison of studies 04 and 05, efficacy endpoints that included assignment of patients as non-responders based on use of restricted medications were re-derived for study 05 using the same restricted medication rules used in study 04.

Several sensitivity analyses were planned in the SAP of Study 04 to assess the impact of intercurrent events and missing data.

The key secondary endpoints in Studies 04 and 05 were not the same. If the primary endpoint was statistically significant, then the key secondary endpoints were tested and the weighted Holm procedure with pre-defined weights used in order to strongly control the family-wise error rate at the 2-sided 5% level. The weights were chosen based on a combination of estimated power for the individual key secondary endpoints and their relative clinical importance. The actual weights were not identical between the two studies.

The key secondary endpoints were analysed similarly, with the exception of the effect on the annualised flare rate, which was analysed using a negative binomial regression model. The model included the covariates of treatment group and the stratification factors. The logarithm of the follow-up time was used as an offset variable in the model to adjust for patients having different exposure times.

There were no interim analyses in either of the two studies.

Results

Participant flow

In Study 1013, 307 patients were randomised and 305 patients received investigational product (99, 104, and 102 patients in the anifrolumab 300 mg, anifrolumab 1000 mg, and placebo groups, respectively); 84.0% patients in the anifrolumab 300 mg group, 81.7% patients in the anifrolumab 1000 mg group, and 74.8% patients in the placebo group completed the study.

In Study 04, 365 patients were randomised and 362 patients received investigational product (180 and 182 patients in the anifrolumab 300 mg and placebo groups, respectively); 85.0% of patients in the anifrolumab 300 mg group and 71.4% of patients in the placebo group completed study treatment. The most common reason for study withdrawal was "Withdrawal by Patient".

In Study 05, 457 patients were randomised and received investigational product (93, 180, and 184 patients in the anifrolumab 150 mg, anifrolumab 300 mg, and placebo groups, respectively); 80.6% of patients in the anifrolumab 150 mg group, 80.0% patients in the anifrolumab 300 mg group, and 79.3% patients in the placebo group completed study treatment.

In studies 04 and 05, the percentage of screened patients who were not randomised were 44% and 46%, respectively. The most common reasons for not meeting the randomisation criteria were 1) not fulfilling the SLE disease activity criteria, 2) prohibited concomitant medication use, and 3) screening laboratory test results.

Patient disposition in Study 1013 is displayed in Table 7, and patient disposition in studies 04 and 05 is displayed in Table 8.

Table 7 Patient disposition (randomised patients in study 1013)

Patient disposition	Number (%) of patients			
	Anifrolumab 300 mg	Anifrolumab 1000 mg	Placebo	Total
Patients randomized	100	104	103	307
Patients in the full analysis set[a]	99	104	102	305
Patients who completed the study[b]	84 (84.0)	85 (81.7)	77 (74.8)	246 (80.1)
Patients who did not complete the study[b]	16 (16.0)	19 (18.3)	26 (25.2)	61 (19.9)
Reasons for not completing the study				
Death	0	1 (1.0)	0	1 (0.3)
Lost to follow-up	2 (2.0)	2 (1.9)	4 (3.9)	8 (2.6)
Withdrawal of consent	3 (3.0)	8 (7.7)	11 (10.7)	22 (7.2)
Other	11 (11.0)	8 (7.7)	11 (10.7)	30 (9.8)
Sponsor decision	1	4	4	9
Patient choice/patient moved	1	1	2	4
Investigator decision	1	0	0	1
AE/SAE	1	1	2	4
Received prohibited medication	0	0	1	1
Missed first follow-up visit/did not complete all 3 follow-up visits	5	2	2	9
Inadequate venous access	2	0	0	2

Derived from Table 10.1.1-1 and Table 11.1-1 in study 1013 CSR in Module 5.3.5.1.

[a] Referred to as 'mITT population' in the study 1013 CSR

[b] Patients who discontinued investigational product also discontinued the study per protocol

AE Adverse event; CSR Clinical study report; mITT Modified intent-to-treat; SAE Serious adverse event.

Table 8 Patient disposition (all patients in study 04 and study 05)

Patient disposition	Number (%) of patients						
	Study 04			Study 05			
	Anifrolumab 300 mg	Placebo	Total	Anifrolumab 150 mg	Anifrolumab 300 mg	Placebo	Total
Patients enrolled [a]	NA	NA	649	NA	NA	NA	847
Patients randomized [b]	181	184	365 (56.2)	93	180	184	457 (54.0)
Patients in the full analysis set [c]	180	182	362	93	180	184	457
Patients who completed the study [d]	156 (86.7)	136 (74.7)	292 (80.7)	76 (81.7)	146 (81.1)	148 (80.4)	370 (81.0)
Patients withdrawn from the study	24 (13.3)	46 (25.3)	70 (19.3)	17 (18.3)	34 (18.9)	36 (19.6)	87 (19.0)
Patients who completed Week 52 [e]	162 (90.0)	145 (79.7)	307 (84.8)	80 (86.0)	153 (85.0)	157 (85.3)	390 (85.3)
Patients withdrawn from the study before Week 52	18 (10.0)	37 (20.3)	55 (15.2)	13 (14.0)	27 (15.0)	27 (14.7)	67 (14.7)
Patients who completed investigational product [f]	153 (85.0)	130 (71.4)	283 (78.2)	75 (80.6)	145 (80.6)	146 (79.3)	366 (80.1)
Patients discontinued investigational product	27 (15.0)	52 (28.6)	79 (21.8)	18 (19.4)	35 (19.4)	38 (20.7)	91 (19.9)
Adverse event	5 (2.8)	14 (7.7)	19 (5.2)	6 (6.5)	13 (7.2)	8 (4.3)	27 (5.9)
Condition under investigation worsened	2 (1.1)	4 (2.2)	6 (1.7)	1 (1.1)	1 (0.6)	4 (2.2)	6 (1.3)
Lack of efficacy	2 (1.1)	12 (6.6)	14 (3.9)	3 (3.2)	3 (1.7)	9 (4.9)	15 (3.3)
Lost to follow-up	2 (1.1)	3 (1.6)	5 (1.4)	0	0	2 (1.1)	2 (0.4)
Severe non-compliance to protocol	0	1 (0.5)	1 (0.3)	2 (2.2)	0	2 (1.1)	4 (0.9)
Withdrawal by patient	7 (3.9)	16 (8.8)	23 (6.4)	5 (5.4)	15 (8.3)	13 (7.1)	33 (7.2)
Other	9 (5.0)	2 (1.1)	11 (3.0)	1 (1.1)	3 (1.7)	0	4 (0.9)
Patients continued to study 09 [g]	133 (73.9)	104 (57.1)	237 (65.5)	69 (74.2)	126 (70.0)	129 (70.1)	324 (70.9)

Source: Table 1.1.1.1, Appendix 2.7.3.6.1 in Module 5.3.5.3.

[a] Informed consent received.

[b] Percentages are based upon all enrolled patients.

[c] The full analysis set comprises all randomized patients who received at least one dose of investigational product. In study 04, one patient in the anifrolumab 300 mg group and 2 patients in placebo group who were randomized, did not receive treatment with investigational product.

[d] Completion of the studies is based upon the number of patients who completed Week 52 (Visit 14) and either continued to study 09, the long-term extension study, or completed Follow-up Visit 2 regardless of number of doses of investigational product that were received.

[e] Completion of Week 52 is based upon the number of patients completing up to and including Week 52 (Visit 14) regardless of number of doses of investigational product that were received.

[f] Completion of investigational product is based upon the number of patients completing treatment with investigational product up to and including Week 48 (Visit 13.)

[g] Continuation to study 09, the long-term extension study, is based on the Week 52 status of the eCRF.

If not stated otherwise, percentages are based upon all patients in the full analysis set within the respective study and treatment group.

Note that for study 05, there are some slight differences between the results in this table and the corresponding results in the study 05 CSR. This is because of slight differences in the final-lock database and the Week 52-lock database used for the CSR.

N Number of patients in treatment group; NA Not applicable; eCRF Electronic case report form.

In Study 04, the overall number of study withdrawals before Week 52 was higher in the placebo group (n = 37, 20.3%) than in the anifrolumab 300 mg group (n = 18, 10.0%) whereas withdrawals were balanced between treatment arms in Study 05; n = 27, 14.7% vs n = 27, 15.0% for placebo vs anifrolumab 300 mg, respectively). The higher number of withdrawals in the placebo group as compared with anifrolumab 300 mg group in Study 04 was mainly driven by more patients in the placebo group withdrawing due to withdrawal by patient (17 vs 9 for placebo vs anifrolumab as compared to 10 vs 13 in Study 05) as well as due to an adverse event (7 vs 3 patients on placebo vs anifrolumab 300 mg as compared to 5 vs 10 in the corresponding groups in Study 05) (Table 9).

Table 9 Patients Status at Week 52 and Reasons for Withdrawal from Study (Study 04 and Study 05, Full Analysis Sets)

	Number (%) of patients			
	Study 04		Study 05	
	Anifrolumab 300 mg (N = 180)	Placebo (N = 182)	Anifrolumab 300 mg (N = 180)	Placebo (N = 184)
Patients who completed Week 52[a]	162 (90)	145 (79.9)	153 (85.0)	157 (85.3)
Patients withdrawn from the study before Week 52	18 (10.0)	37 (20.3)	27 (15.0)	27 (14.7)
Adverse event	3 (1.7)	7 (3.8)	10 (5.6)	5 (2.7)
Condition under investigation worsened	0 (0.0)	4 (2.2)	1 (0.6)	1 (0.5)
Lack of efficacy	1 (0.6)	6 (3.3)	2 (1.1)	6 (3.3)
Lost to follow-up	1 (0.6)	2 (1.1)	0 (0.0)	0 (0.0)
Severe non-compliance to protocol	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.5)
Withdrawal by patient	9 (5.0)	17 (9.3)	13 (7.2)	10 (5.4)
Other	4 (2.2)	0 (0.0)	1 (0.6)	4 (2.2)

[a] Completion of Week 52 is based upon the number of patients completing up to and including Week 52 (Visit 14) regardless of number of doses of IP that were received

IP, Investigational product

In both Study 04 and 05, more patients in placebo groups withdrew from study due to lack of therapeutic response, i.e., lack of efficacy or condition worsened, as compared with anifrolumab-treated patients. According to the applicant, the AE leading to withdrawal in placebo groups was an SLE flare in 3 of 7 patients in Study 04 and 2 of 5 patients in Study 05, whereas no particular type of AE was found that could explain the higher number of study withdrawals in anifrolumab 300 mg group as compared with placebo group in Study 05 or as compared with anifrolumab 300 mg group in Study 04.

A structured, blinded internal review of each individual patient who withdrew from Study 04 and 05 due to "withdrawal by patient" was undertaken by the applicant and showed that the majority of placebo patients in both Study 04 and 05 displayed signs of lack of therapeutic response at the time of study withdrawal. To investigate this further, and based on the assumption that patients who lack treatment response are more likely to use restricted medications and discontinue IP and subsequently withdraw from study, the proportion of patients with worsening in disease activity on SLEDAI-2K, BILAG and/or PGA at IP discontinuation was assessed in relation to reason for discontinuation. This analysis showed that the proportions of placebo patients who discontinued IP due to "withdrawal by patient" (Table 10) and had worsening on at least one of the disease activity scales were very similar in Study 04 (8 of 16, 50%) and Study 05 (6 of 13, 46%). Thus, despite the number of study withdrawals in Study 04 being higher among placebo patients than in the anifrolumab 300 mg group, the proportion of placebo patients with worsening of disease at withdrawal was very similar to the proportion seen in placebo patients in Study 05.

Table 10 Disposition of Efficacy Components at the Time of IP Discontinuation for Patients who Discontinued IP due to 'Withdrawal by Patient' (Study 04 and Study 05, Full Analysis Sets)

	Number (%) of patients			
	Study 04		Study 05	
	Anifrolumab 300 mg (N = 7)	Placebo (N = 16)	Anifrolumab 300 mg (N = 15)	Placebo (N = 13)
No post baseline assessment prior to IP discontinuation	0	1 (6.3)	1 (6.7)	2 (15.4)
Last assessment prior to IP discontinuation [a]				
Restricted medication started before clinical assessments [b]	1 (14.3)	3 (18.8)	3 (20.0)	1 (7.7)
All clinical criteria met [a]	0	1 (6.3)	1 (6.7)	1 (7.7)
At least one clinical criteria failed	1 (14.3)	2 (12.5)	2 (13.3)	0
BILAG worsening [c,d]	1 (14.3)	2 (12.5)	1 (6.7)	0
SLEDAI-DK worsening [c,e]	0	0	1 (6.7)	0
PGA worsening [c,f]	1 (14.3)	1 (6.3)	0	0
No restricted medication started before clinical assessments [b]	6 (85.7)	12 (75.0)	11 (73.3)	10 (76.9)
All clinical criteria met [a]	2 (28.6)	6 (37.5)	3 (20.0)	4 (30.8)
At least one clinical criteria failed	4 (57.1)	6 (37.5)	8 (53.3)	6 (46.2)
BILAG worsening [c,d]	4 (57.1)	5 (31.3)	7 (46.7)	6 (46.2)
SLEDAI-DK worsening [c,e]	0	1 (6.3)	1 (6.7)	2 (15.4)
PGA worsening [c,f]	0	0	0	0

[a] date of assessment(s) ≤ date of last IP administration
[b] start date of restricted medication < date of assessment(s)
[c] The same patient may have more than one criterion met.
[d] BILAG worsening defined as one or more new BILAG-2004 A or 2 or more new BILAG-2004 B items compared to baseline.
[e] SLEDAI-2K worsening defined as an increase from baseline of > 0 points in SLEDAI-DK.
[f] PGE worsening defined as an increase ≥ 0.30 points on a 3-point PGA VAS
Percentages are based upon all patients who have discontinued IP for that reason in the Full Analysis Set.
BILAG, British Isles Lupus Assessment Group; IP, investigational product; N, number of subjects in treatment group; PGA, Physician's Global Assessment; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000; VAS, visual analog scale.

Baseline data

Demographic characteristics across the three studies are displayed in Table 11. Mean age was 39 to 43 years, and over 90% of patients in each study were female. The majority of patients in studies 04 and 05 were white; both 04 and 05 also enrolled a substantial number of Black patients, and over 16% of patients in Study 04 were Asian. A large proportion of patients in Study 1013 were mestizos/mestizas enrolled in Latin America (represented in the "Other" category in the Table). While ACR classification criteria for SLE were used in the studies, over 98% of patients receiving anifrolumab 300 mg or placebo in the Phase III studies also met the 2019 EULAR/ACR classification criteria for SLE.

Table 11 Demographic characteristics for the anifrolumab 300 mg and placebo groups in studies 04, 05 and 1013 (full analysis sets)

Demographic Characteristic		Study 04		Study 05		Study 1013	
		Anifrolumab 300 mg (N = 180)	Placebo (N = 182)	Anifrolumab 300 mg (N = 180)	Placebo (N = 184)	Anifrolumab 300 mg (N = 99)	Placebo (N = 102)
Age (years)	n	180	182	180	184	99	102
	Mean	43.1	41.1	42.0	41.0	39.1	39.3
	SD	11.95	11.47	11.99	12.30	11.9	12.9
	Median	44.0	42.0	40.5	41.0	38.0	39.0
	Minimum	18	19	18	18	19	18
	Maximum	69	66	68	69	65	65
Age subgroups[a], n (%)	< 18 years	0	0	0	0	NA	NA
	≥ 18 to < 65 years	175 (97.2)	181 (99.5)	169 (93.9)	178 (96.7)	NA	NA
	≥ 65 years	5 (2.8)	1 (0.5)	11 (6.1)	6 (3.3)	NA	NA
Sex, n (%)	Female	168 (93.3)	170 (93.4)	165 (91.7)	171 (92.9)	93 (93.9)	93 (91.2)
	Male	12 (6.7)	12 (6.6)	15 (8.3)	13 (7.1)	6 (6.1%)	9 (8.8%)
BMI[b], n (%)	≤ 28 kg/m^2	107 (59.4)	114 (62.6)	98 (54.4)	109 (59.2)	NA	NA
	> 28 kg/m^2	73 (40.6)	68 (37.4)	82 (45.6)	75 (40.8)	NA	NA
Race[c], n (%)	White	110 (61.1)	107 (58.8)	125 (69.4)	137 (74.5)	35 (35.4)	41 (40.2)
	Black or African American	17 (9.4)	25 (13.7)	29 (16.1)	23 (12.5)	19 (19.2)	12 (11.8)
	Asian	30 (16.7)	30 (16.5)	11 (6.1)	5 (2.7)	3 (3.0)	13 (12.7)
	Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0
	American Indian or Alaska Native	4 (2.2)	1 (0.5)	0	1 (0.5)	4 (4.0)	0
	Other	11 (6.1)	11 (6.0)	15 (8.3)	18 (9.8)	37 (37.4)	35 (34.3)
	Missing/multiple categories checked	8 (4.4)	8 (4.4)	0	0	1 (1.0)	1 (1.0)
Geographic region[d], n (%)	Asia-Pacific	27 (15.0)	26 (14.3)	11 (6.1)	6 (3.3)	2 (2.0)	10 (9.8)
	Europe	51 (28.3)	46 (25.3)	64 (35.6)	76 (41.3)	20 (20.2)	25 (24.5)
	Latin America	35 (19.4)	32 (17.6)	24 (13.3)	25 (13.6)	39 (39.4)	37 (36.3)
	USA/Canada	64 (35.6)	68 (37.4)	75 (41.7)	72 (39.1)	37 (37.4)	28 (27.5)
	Rest of world	3 (1.7)	10 (5.5)	6 (3.3)	5 (2.7)	1 (1.0)	2 (2.0)

Derived from Table 1.1.3.1 and Table 1.1.3.5, Appendix 2.7.3.6.1 in Module 5.3.5.3; Table 11.2.1-1 in study 1013 CSR in Module 5.3.5.1; Table 0001.143.3, Appendix 2.7.3.6.5 in Module 5.3.5.3.

[a] Study 1013: ≤ 45 years, 67.7% anifrolumab 300 mg and 70.6% placebo group; > 45 years 32.3% anifrolumab 300 mg and 29.4% placebo

[b] Study 1013 Mean (SD) BMI: 26.58 (5.87) anifrolumab 300 mg group; 26.12 (6.64) placebo group

[c] Study 1013 Race 'other': patients from Latin America [mestizo or mestiza] who did not identify with the race definitions provided

[d] **Asia-Pacific**: Australia, Japan, New Zealand, South Korea, Singapore, Taiwan
Europe: Belgium, Bulgaria, Czech Republic, France, Germany, Hungary, Italy, Lithuania, Poland, Romania, Russia, Spain, Ukraine, United Kingdom
Latin America: Argentina, Brazil, Chile, Colombia, Mexico, Peru
Rest of world: India, Israel, South Africa

Percentages are based upon all patients in the full analysis set within the respective study and treatment group.

BMI Body mass index; CSR Clinical study report; n Number of patients in analysis; N Number of patients in treatment group; NA Not available; SD Standard deviation; USA United States of America.

Baseline disease characteristics are displayed in Table 12, and an overview of affected organ systems based on the BILAG-2004 index is displayed in Table 13. The majority of patients enrolled in the Phase III studies had adult-onset SLE: in Study 04, SLE was paediatric-onset in 14 patients on anifrolumab and 12 patients on placebo, and adult-onset in 166 patients on anifrolumab and 170 patients on placebo. In Study 05, SLE was paediatric-onset in 12 patients on anifrolumab 300 mg and 12 patients on placebo, and adult-onset in 168 patients on anifrolumab 300 mg and 172 patients on placebo.

Table 12 Baseline disease characteristics for the anifrolumab 300 mg and placebo groups in studies 04, 05 and 1013 (full analysis sets)

SLE disease characteristic at baseline[a]		Study 04		Study 05		Study 1013	
		Anifrolumab 300 mg (N = 180)	Placebo (N = 182)	Anifrolumab 300 mg (N = 180)	Placebo (N = 184)	Anifrolumab 300 mg (N = 99)	Placebo (N = 102)
SLEDAI-2K score	< 10 points, n (%)	51 (28.3)	51 (28.0)	55 (30.6)	49 (26.6)	40 (40.4)	41 (40.2)
	≥ 10 points, n (%)	129 (71.7)	131 (72.0)	125 (69.4)	135 (73.4)	59 (59.6)	61 (59.8)
	n	180	182	180	184	99	102
	Mean (SD)	11.4 (3.64)	11.5 (3.88)	11.3 (4.04)	11.5 (3.50)	10.7 (3.7)	11.1 (4.4)
	Median	11.0	10.0	10.0	10.5	10.0	10.0
	Min, max	6, 25	4, 26	4, 32	6, 24	6, 24	6, 29
Clinical SLEDAI-2K score	n	180	182	180	184	99	102
	Mean (SD)	8.9 (2.94)	8.9 (2.83)	9.0 (2.93)	8.9 (2.63)	8.9 (NA)	9.0 (NA)
	Median	8.0	8.0	8.0	8.0	NA	NA
	Min, max	4, 18	4, 18	4, 20	4, 18	NA	NA
BILAG-2004 global score	n	180	182	180	184	99	102
	Mean (SD)	18.6 (4.72)	19.0 (5.00)	19.8 (6.28)	18.9 (5.45)	19.6 (5.7)	19.8 (5.8)
	Median	17.0	18.0	18.0	17.5	18.0	20.0
	Min, max	3, 33	9, 33	2, 40	4, 33	9, 36	2, 36
BILAG organ system scoring (Overall)	At least one A, n (%)	81 (45.0)	95 (52.2)	93 (51.7)	84 (45.7)	52 (52.5)	49 (48.0)
	No A and at least 2 Bs, n (%)	91 (50.6)	78 (42.9)	79 (43.9)	84 (45.7)	41 (41.4)	48 (47.1)
	No A and < 2Bs, n (%)	8 (4.4)	9 (4.9)	8 (4.4)	16 (8.7)	6 (6.1)	5 (4.9)
PGA score	n	180	182	180	184	99	102
	Mean (SD)	1.68 (0.411)	1.76 (0.397)	1.87 (0.399)	1.84 (0.383)	1.86 (0.39)	1.77 (0.44)
	Median	1.60	1.70	1.90	1.90	1.90	1.80
	Min, max	0.8, 2.8	0.9, 2.6	1.0, 2.7	0.6, 2.8	0.9, 2.6	0.8, 2.8
CLASI activity score	< 10, n (%)	131 (72.8)	142 (78.0)	122 (67.8)	130 (70.7)	72 (72.7)	76 (74.5)
	≥ 10, n (%)	49 (27.2)	40 (22.0)	58 (32.2)	54 (29.3)	27 (27.3)	26 (25.5)
	0, n (%)	6 (3.3)	12 (6.6)	6 (3.3)	6 (3.3)	0	1 (1.0)
	> 0, n (%)	174 (96.7)	170 (93.4)	174 (96.7)	178 (96.7)	99 (100)	101 (99.0)
	n	180	182	180	184	99	102
	Mean (SD)	8.3 (7.94)	7.6 (7.75)	8.5 (7.26)	8.1 (6.66)	7.5 (6.3)	6.7 (5.1)
	Median	6.0	5.5	6.0	6.0	5.0	5.0
	Min, max	0, 51	0, 52	0, 41	0, 35	1, 36	0, 26
Active joint count	0, n (%)	22 (12.2)	19 (10.4)	18 (10.0)	15 (8.2)	NA	NA
	> 0, n (%)	158 (87.8)	163 (89.6)	162 (90.0)	169 (91.8)	NA	NA
	n	180	182	180	184	99	102
	Mean (SD)	5.7 (5.58)	7.1 (6.49)	7.1 (5.74)	6.3 (4.49)	11.4 (7.2)	10.0 (7.0)
	Median	4.0	5.0	6.0	6.0	11.0	7.5
	Min, max	0, 28	0, 28	0, 25	0, 23	0, 28	0, 28
Swollen joint count[b]	0, n (%)	20 (11.1)	18 (9.9)	16 (8.9)	14 (7.6)	NA	NA
	> 0, n (%)	160 (88.9)	164 (90.1)	164 (91.1)	170 (92.4)	NA	NA
	n	180	182	180	184	99	102
	Mean (SD)	6.2 (5.65)	7.4 (6.55)	7.4 (5.79)	7.0 (4.80)	8.6 (6.0)	8.3 (6.4)
	Median	5.0	6.0	6.0	6.0	7.0	6.0
	Min, max	0, 28	0, 28	0, 25	0, 23	0, 25	0, 26

SLE disease characteristic at baseline[a]		Study 04		Study 05		Study 1013	
		Anifrolumab 300 mg (N = 180)	Placebo (N = 182)	Anifrolumab 300 mg (N = 180)	Placebo (N = 184)	Anifrolumab 300 mg (N = 99)	Placebo (N = 102)
Tender joint count[b]	0, n (%)	12 (6.7)	10 (5.5)	11 (6.1)	8 (4.3)	0	NA
	> 0, n (%)	168 (93.3)	172 (94.5)	169 (93.9)	176 (95.7)	99 (100)	NA
	n	180	182	180	184	99	102
	Mean (SD)	9.0 (7.07)	11.0 (7.89)	11.7 (7.50)	10.6 (7.17)	12.2 (7.1)	10.5 (7.4)
	Median	7.0	10.0	10.5	10.0	11.0	8.0
	Min, max	0, 28	0, 28	0, 28	0, 28	2, 28	0, 28
Time from initial SLE diagnosis to randomization (months)	n	180	182	180	184	99	102
	Mean (SD)	130.2 (109.28)	107.7 (99.16)	116.2 (97.00)	103.4 (90.29)	95.91 (76.77)	90.59 (86.29)
	Median	94.5	78.0	88.0	79.5	71.40	65.75
	Min, max	6, 555	6, 494	0, 450	4, 503	7.1, 360.9	6.9, 403.5
Results of 4-gene type I IFN gene signature test at screening	High, n (%)	150 (83.3)	151 (83.0)	148 (82.2)	151 (82.1)	75 (75.8)	76 (74.5)
	Low, n (%)	30 (16.7)	31 (17.0)	32 (17.8)	33 (17.9)	24 (24.2)	26 (25.5%)
Anti-dsDNA levels[c]	Positive, n (%)	86 (47.8)	73 (40.1)	81 (45.0)	82 (44.6)	56 (72.7)	66 (80.5)
	Negative, n (%)	94 (52.2)	109 (59.9)	99 (55.0)	102 (55.4)	21 (27.3%)	16 (19.5%)
	Missing, n (%)	0	0	0	0	22	20
ANA	Normal (titer < 1:80), n (%)	12 (6.7)	12 (6.6)	11 (6.1)	14 (7.6)	1 (1.0%)	3 (2.9%)
	Abnormal (titer ≥ 1:80), n (%)	160 (88.9)	165 (90.7)	164 (91.1)	165 (89.7)	98 (99.0%)	99 (97.1%)
	Missing, n (%)	8 (4.4)	5 (2.7)	5 (2.8)	5 (2.7)	0	0
Complement C3 level[d]	Normal, n (%)	108 (60.0)	110 (60.4)	122 (67.8)	119 (64.7)	71 (71.7)	59 (57.8)
	Abnormal, n (%)	72 (40.0)	72 (39.6)	58 (32.2)	65 (35.3)	28 (28.3)	43 (42.2)
Complement C4 level[d]	Normal, n (%)	131 (72.8)	136 (74.7)	145 (80.6)	145 (78.8)	78 (78.8)	77 (75.5)
	Abnormal, n (%)	49 (27.2)	46 (25.3)	35 (19.4)	39 (21.2)	21 (21.2)	25 (24.5)
Complement CH50 level[d]	Normal, n (%)	165 (91.7)	166 (91.2)	160 (88.9)	169 (91.8)	NA	NA
	Abnormal, n (%)	15 (8.3)	16 (8.8)	20 (11.1)	15 (8.2)	NA	NA
	Missing, n (%)	0	0	0	0	NA	NA

Derived from Table 1.1.4.1, Appendix 2.7.3.6.1 in Module 5.3.5.3; Table 11.2.2-1, Table 14.2.2.7.1, Table 14.2.2.7.3, Table 14.2.2.7.5, Table 14.2.2.8.5, Table 14.2.2.8.7, and Table 14.2.2.22.2 in study 1013 CSR in Module 5.3.5.1; Table 0001.143.1, Appendix 2.7.3.6.5 in Module 5.3.5.3.

[a] All characteristics are measured at baseline unless otherwise indicated.

[b] Study 1013, number of patients with ≥ 2 swollen and ≥ 2 tender joint counts at baseline: 95(96.0%) anifrolumab 300 mg group and 93 (91.2%) placebo group

[c] The Farr assay, the most specific method for detecting dsDNA auto-antibodies, was used in study 1013—an abnormal anti-dsDNA (Farr assay) was defined as value ≥ 5 IU/mL

[d] 'Abnormal' refers to 'low'

Baseline is defined as the last measurement prior to randomization and investigational product administration on Day 1.

Percentages are based upon all patients in the full analysis set within the respective study and treatment group.

ANA Anti-nuclear antibody; BILAG British Isles Lupus Assessment Group; C3 Third component of complement; C4 Fourth component of complement; CH50 Total hemolytic complement; CLASI Cutaneous Lupus Erythematosus Disease Area and Severity Index; dsDNA Double-stranded deoxyribonucleic acid; IFN Interferon; min Minimum; max Maximum; n Number of patients in analysis; N Number of patients in treatment group; NA Not available; PGA Physician's Global Assessment; SD Standard deviation; SLEDAI-2K Systemic Lupus Erythematosus Disease Activity Index 2000.

Table 13 Baseline BILAG-2004 items for the anifrolumab 300 mg and placebo groups in studies 04, 05 and 1013 (full analysis sets)

BILAG-2004 item	BILAG-2004 scoring	Study 04		Study 05		Study 1013	
		Anifrolumab 300 mg N = 180	Placebo N = 182	Anifrolumab 300 mg N = 180	Placebo N = 184	Anifrolumab 300 mg N = 99	Placebo N = 102
Constitutional	A n (%)	0	0	1 (0.6)	0	1 (1.0)	1 (1.0)
	B n (%)	15 (8.3)	6 (3.3)	9 (5.0)	11 (6.0)	6 (6.1)	10 (9.8)
	C, D or E n (%)	165 (91.7)	176 (96.7)	170 (94.4)	173 (94.0)	92 (92.9)	91 (89.2)
Mucocutaneous	A n (%)	31 (17.2)	36 (19.8)	53 (29.4)	39 (21.2)	22 (22.2)	18 (17.6)
	B n (%)	124 (68.9)	118 (64.8)	107 (59.4)	119 (64.7)	62 (62.6)	69 (67.6)
	C, D or E n (%)	25 (13.9)	28 (15.4)	20 (11.1)	26 (14.1)	15 (15.2)	15 (14.7)
Neuropsychiatric	A n (%)	1 (0.6)	0	0	1 (0.5)	0	0
	B n (%)	0	2 (1.1)	8 (4.4)	2 (1.1)	0	2 (2.0)
	C, D or E n (%)	179 (99.4)	180 (98.9)	172 (95.6)	181 (98.4)	99 (100.0)	100 (98.0)
Musculoskeletal	A n (%)	56 (31.1)	60 (33.0)	58 (32.2)	55 (29.9)	36 (36.4)	29 (28.4)
	B n (%)	102 (56.7)	101 (55.5)	101 (56.1)	112 (60.9)	58 (58.6)	66 (64.7)
	C, D or E n (%)	22 (12.2)	21 (11.5)	21 (11.7)	17 (9.2)	5 (5.1)	7 (6.9)
Cardiorespiratory	A n (%)	1 (0.6)	1 (0.5)	2 (1.1)	3 (1.6)	0	0
	B n (%)	13 (7.2)	17 (9.3)	14 (7.8)	6 (3.3)	4 (4.0)	8 (7.8)
	C, D or E n (%)	166 (92.2)	164 (90.1)	164 (91.1)	175 (95.1)	95 (96.0)	94 (92.2)
Gastrointestinal	A n (%)	0	1 (0.5)	0	0	0	0
	B n (%)	1 (0.6)	2 (1.1)	0	1 (0.5)	0	0
	C, D or E n (%)	179 (99.4)	179 (98.4)	180 (100)	183 (99.5)	99 (100.0)	102 (100.0)
Ophthalmic	A n (%)	0	0	1 (0.6)	0	0	0
	B n (%)	0	1 (0.5)	0	0	1 (1.0)	0
	C, D or E n (%)	180 (100)	181 (99.5)	179 (99.4)	184 (100)	98 (99.0)	102 (100.0)
Renal	A n (%)	1 (0.6)	4 (2.2)	1 (0.6)	3 (1.6)	1 (1.0)	2 (2.0)
	B n (%)	9 (5.0)	13 (7.1)	14 (7.8)	12 (6.5)	10 (10.1)	9 (8.8)
	C, D or E n (%)	170 (94.4)	165 (90.7)	165 (91.7)	169 (91.8)	88 (88.9)	91 (89.2)
Hematological	A n (%)	0	0	0	0	0	0
	B n (%)	1 (0.6)	0	1 (0.6)	1 (0.5)	0	4 (3.9)
	C, D or E n (%)	179 (99.4)	182 (100)	179 (99.4)	183 (99.5)	99 (100.0)	98 (96.1)
Overall	At least one A n (%)	81 (45.0)	95 (52.2)	93 (51.7)	84 (45.7)	52 (52.5)	49 (48.0)
	No A and at least 2 Bs n (%)	91 (50.6)	78 (42.9)	79 (43.9)	84 (45.7)	41 (41.4)	48 (47.1)
	No A and < 2Bs n (%)	8 (4.4)	9 (4.9)	8 (4.4)	16 (8.7)	6 (6.1)	5 (4.9)

Derived from Table 11.1.9 in study 04 CSR; Table 11.1.9 in study 05 CSR; Table 14.2.2.4.19, study 1013 CSR in Module 5.3.5.1.

BILAG-2004 British Isles Lupus Assessment Group 2004; N Number of patients in treatment group; n Number of patients in analysis.

SLE medications at baseline are summarised in Table 14 for studies 04 and 05, and in Table 15 for Study 1013. While concomitant use of biological agents was not permitted during the studies, prior use of biologics was reported in a proportion of patients; in studies 04 and 05, the most commonly used biologics were belimumab (9.6% of patients), epratuzumab (6.7% of patients), and rituximab (1.9% of patients).

Table 14 SLE-related treatments at baseline for the anifrolumab 300 mg and placebo groups — study 04 and study 05 (full analysis sets)

SLE-related treatments at baseline [a]		Study 04		Study 05	
		Anifrolumab 300 mg (N = 180)	Placebo (N = 182)	Anifrolumab 300 mg (N = 180)	Placebo (N = 184)
OCS [b]	n (%)	180 (100)	182 (100)	180 (100)	184 (100)
OCS dose (mg/day) [c]	< 10 n (%)	93 (51.7)	99 (54.4)	77 (42.8)	82 (44.6)
	≥ 10 n (%)	87 (48.3)	83 (45.6)	103 (57.2)	102 (55.4)
	Mean (SD)	8.32 (7.151)	8.90 (8.041)	10.69 (11.910)	9.89 (8.326)
	Median	7.75	7.50	10.00	10.00
	Min, max	0.0, 40.0	0.0, 40.0	0.0, 99.0	0.0, 40.0
OCS dose (mg/day) excluding patients not taking OCS [b]	n (%)	141 (78.3)	151 (83.0)	150 (83.3)	153 (83.2)
	< 10 n (%)	54 (30.0)	68 (37.4)	47 (26.1)	51 (27.7)
	≥ 10 n (%)	87 (48.3)	83 (45.6)	103 (57.2)	102 (55.4)
	Mean (SD)	10.62 (6.384)	10.73 (7.633)	12.83 (11.950)	11.89 (7.712)
	Median	10.00	10.00	10.00	10.00
	Min, max	1.0, 40.0	1.0, 40.0	2.0, 99.0	2.5, 40.0
OCS only [b, d]	n (%)	31 (17.2)	17 (9.3)	25 (13.9)	21 (11.4)
OCS dose (mg/day)	Mean (SD)	11.53 (5.905)	12.94 (9.447)	11.54 (5.934)	13.45 (5.835)
	Median	10.00	10.00	10.00	10.00
	Min, max	5.0, 25.0	5.0, 40.0	3.0, 25.0	5.0, 25.0
OCS in combination with immunosuppressants and/or anti-malarials [b]	n (%)	110 (61.1)	134 (73.6)	125 (69.4)	132 (71.7)
OCS dose (mg/day)	Mean (SD)	10.37 (6.516)	10.45 (7.367)	13.09 (12.821)	11.64 (7.960)
	Median	10.00	10.00	10.00	10.00
	Min, max	1.0, 40.0	1.0, 40.0	2.0, 99.0	2.5, 40.0
Time on OCS up to randomization (months) [e]	Mean (SD)	26.77 (52.053)	23.63 (47.990)	25.04 (49.455)	21.28 (37.155)
	Median	6.24	7.59	6.77	6.64
	Min, max	0.0, 333.4	0.0, 397.7	0.4, 309.5	0.4, 204.1
Anti-malarials	n (%)	119 (66.1)	133 (73.1)	124 (68.9)	134 (72.8)
Anti-malarials only [e]	n (%)	17 (9.4)	20 (11.0)	15 (8.3)	18 (9.8)
Anti-malarials in combination with OCS and/or immunosuppressants	n (%)	102 (56.7)	113 (62.1)	109 (60.6)	116 (63.0)
Immunosuppressants	n (%)	88 (48.9)	86 (47.3)	85 (47.2)	91 (49.5)
AZATHIOPRINE	n (%)	30 (16.7)	27 (14.8)	32 (17.8)	34 (18.5)
AZATHIOPRINE dose (mg/day)	Mean (SD)	100.83 (50.208)	92.59 (39.110)	97.66 (43.700)	102.21 (40.995)
	Median	100.00	100.00	100.00	100.00
	Min, max	50.0, 200.0	50.0, 200.0	50.0, 200.0	50.0, 200.0
METHOTREXATE	n (%)	34 (18.9)	35 (19.2)	22 (12.2)	38 (20.7)
METHOTREXATE dose (mg/week)	Mean (SD)	15.18 (5.585)	13.77 (5.527)	16.48 (4.980)	15.33 (4.764)
	Median	15.50	15.00	15.00	15.00
	Min, max	2.5, 25.0	2.5, 25.0	7.5, 25.0	2.5, 25.0
MYCOPHENOLATE [f]	n (%)	23 (12.8)	23 (12.6)	31 (17.2)	22 (12.0)
MYCOPHENOLATE dose (g/day)	Mean (SD)	1.43 (0.600)	1.35 (0.534)	1.37 (0.668)	1.27 (0.528)
	Median	1.50	1.44	1.47	1.00
	Min, max	0.4, 2.0	0.5, 2.0	0.4, 2.2	0.5, 2.0

SLE-related treatments at baseline [a]		Study 04		Study 05	
		Anifrolumab 300 mg (N = 180)	Placebo (N = 182)	Anifrolumab 300 mg (N = 180)	Placebo (N = 184)
MIZORIBINE	n (%)	4 (2.2)	3 (1.6)	0	0
MIZORIBINE dose (mg/day)	Mean (SD)	112.50 (47.871)	150.00 (0.000)	NA	NA
	Median	125.00	150.00	NA	NA
	Min, max	50.0, 150.0	150.0, 150.0	NA	NA
More than 1 immunosuppressant	n (%)	3 (1.7)	2 (1.1)	0	3 (1.6)
NSAIDS	n (%)	41 (22.8)	45 (24.7)	31 (17.2)	35 (19.0)

Derived from Table 1.1.7.1, Appendix 2.7.3.6.1 in Module 5.3.5.3.

[a] Baseline defined as the last measurement prior to randomization and investigational product dose administration on Day 1

[b] OCS contains prednisone or equivalent. It is defined as oral medications listed in the WHO-DD SDG "Corticosteroids"

[c] Includes patients not taking OCS at baseline. Their dose is considered to be 0 mg/day at baseline

[d] OCS not taken in combination with immunosuppressants and/or anti-malarials

[e] Anti-malarials not taken in combination with OCS and/or immunosuppressants

[f] Mycophenolate or mycophenolic acid

Percentages are based on all patients in the full analysis sets within the respective study and treatment group.

SLE-related medications at baseline are defined as all medications with therapy reason given as "disease under study" or "disease under study, clinical failure of study therapy", with an intake at the date of first dose of investigational product.

Note that for study 05, there are some slight differences between the results in this table and the corresponding results in the study 05 CSR. This is because of slight differences in the final-lock database and the Week 52-lock database used for the CSR.

max Maximum; min Minimum; n Number of patients in analysis; N Number of patients in treatment group; NA Not applicable; NSAIDs Non-steroidal anti-inflammatories; OCS Oral corticosteroids; SD Standard deviation; SDG Standardized Drug Grouping; SLE Systemic lupus erythematosus; WHO-DD World Health Organization Drug Dictionary.

Table 15 SLE-related treatments at baseline for the anifrolumab 300 mg and placebo groups — study 1013 (full analysis set)

SLE-related treatments at baseline[a]		Anifrolumab 300 mg (N = 99)	Placebo (N = 102)
OCS dose (mg/day) (prednisone or equivalent) excluding patients not taking OCS	n (%)	79 (79.8)	88 (86.3)
	Mean (SD)	11.345 (6.376)	12.841 (8.149)
	Median	10.000	10.000
	Min, max	1.25, 30.00	2.50, 40.00
OCS dose ≥ 10 mg/day	n (%)	55 (55.6)	64 (62.7)
Anti-malarials	n (%)	76 (76.8)	75 (73.5)
Immunosuppressants	n (%)	51 (51.5)	46 (45.1)
Azathioprine	n (%)	23 (23.2)	19 (18.6)
Methotrexate	n (%)	19 (19.2)	16 (15.7)
Mycophenolate	n (%)	11 (11.1)	11 (10.8)
NSAIDs	n (%)	NA	NA

Derived from Table 11.2.2-1 in 1013 CSR, Table 0001.143.2, Appendix 2.7.3.6.5 in Module 5.3.5.3.

[a] Corticosteroids and other immunomodulatory medications used on or after screening visit and before study Day 1 are counted once for each patient

max Maximum; min Minimum; n Number of patients in analysis; N Number of patients in treatment group; NA Not available; NSAIDs Non-steroidal anti-inflammatories; OCS oral corticosteroid; SD standard deviation; SLE systemic lupus erythematosus.

Numbers analysed

The analysis sets for the studies were defined as follows:

- The all patients analysis set was used for reporting patient disposition and screening failures and comprised all patients enrolled in the study.
- The full analysis set was used as the primary population for reporting efficacy data and comprised all patients randomised into the study who received at least one dose of investigational product.

Patients were analysed according to randomised treatment. The full analysis sets comprised 362 patients in study 04 (180 anifrolumab 300 mg, 182 placebo), 457 patients in study 05 (180 anifrolumab 300 mg, 184 placebo, and 93 anifrolumab 150 mg), and 305 patients in study 1013 (99 anifrolumab 300 mg, 104 placebo, and 104 anifrolumab 1000 mg).

The analysis set used for the phase III pool was the combined study 04 and study 05 full analysis sets, excluding patients randomised to anifrolumab 150 mg (a total of 360 patients in the anifrolumab 300 mg group and 366 patients in the placebo group).

Outcomes and estimation

A summary of results within the three key studies, based on the endpoint hierarchy as revised after the change of primary endpoint for Study 04, is displayed in Table 16. A forest plot of main results across the three studies, regardless of hierarchy, is shown in Figure 7. Results for each individual efficacy endpoint across the three studies are presented further below. All data are based on the applicant's originally defined composite estimand, unless indicated otherwise.

Table 16 Efficacy results for Study 04, Study 05, and Study 1013 based on endpoint hierarchy following change of primary endpoint for Study 04 (full analysis set)

Endpoint		Anifrolumab 300 mg n/N (response rate)	Placebo n/N (response rate)	Effect measure[a] with CI[b]	Nominal p-value	Adjusted p-value	Significant following multiplicity
Study 04							
Primary	BICLA at Week 52	86/180 (47.8)	57/182 (31.5)	16.3 (6.3, 26.3)	0.0013	NA	Yes
Key secondary	BICLA in IFN test-high patients at Week 52	72/150 (48.0)	46/151 (30.7)	17.3 (6.5, 28.2)	0.0018	0.0022	Yes
	Maintained OCS tapering at Week 52	45/87 (51.5)	25/83 (30.2)	21.2 (6.8, 35.7)	0.0040	0.0135	Yes
	CLASI response at Week 12	24/49 (49.0)	10/40 (25.0)	24.0 (4.3, 43.6)	0.0168	0.0392	Yes
	Joint reduction at Week 52	30/71 (42.2)	34/90 (37.5)	4.7 (-10.6, 20.0)	0.5469	0.5469	No
	Annualized flare rate[c]	0.43	0.64	0.67 (0.48, 0.94)	0.0202	0.0809	No
Study 05							
Primary	SRI(4) at Week 52 (original)	65/180 (36.20)	74/184 (40.4)	-4.2 (-14.2, 5.8)	0.412	NA	No
	SRI(4) at Week 52 (post hoc)[d]	84/180 (46.9)	79/184 (43.0)	3.9 (-6.3, 14.1)	0.455	NA	NA
Key secondary	SRI(4) in IFN test-high patients at Week 52 (post hoc)[d]	71/148 (48.2)	63/151 (41.8)	6.4 (-4.8, 17.7)	0.261	NA	NA
	Maintained OCS tapering at Week 52 (post hoc)[d]	50/103 (48.8)	33/102 (32.1)	16.7 (3.5, 29.8)	0.013	NA	NA
	CLASI response at Week 12 (post hoc)[d]	25/58 (43.6)	14/54 (24.9)	18.7 (1.4, 36.0)	0.034	NA	NA
	SRI(4) at Week 24 (post hoc)[d]	83/180 (46.4)	79/184 (43.1)	3.3 (-6.7, 13.4)	0.515	NA	NA
	Annualized flare rate[c]	0.60	0.72	0.83 (0.60, 1.14)	0.258	NA	NA
Study 1013							
Primary	SRI(4) + OCS tapering at Week 24	34/99 (34.3)	18/102 (17.6)	2.38 (1.33, 4.26)	0.014	NA	Yes, alpha 0.1 pre-specified
	SRI(4) + OCS tapering in IFN test-high patients at Week 24	27/75 (36.0)	10/76 (13.2)	3.55 (1.72, 7.32)	0.004	NA	Yes, alpha 0.1 pre-specified
Secondary	SRI(4) + OCS tapering at Week 52	51/99 (51.5)	26/102 (25.5)	3.08 (1.86, 5.09)	< 0.001	NA	NA
	SRI(4) + OCS tapering in IFN test-high patients at Week 52	39/75 (52.0)	15/76 (19.7)	4.30 (2.34, 7.91)	< 0.001	NA	NA
	Maintained OCS tapering at Week 52	31/55 (56.4)	17/64 (26.6)	3.59 (1.87, 6.89)	0.001	NA	NA
	Maintained OCS tapering in IFN test-high patients at Week 52	26/44 (59.1)	13/53 (24.5)	4.40 (2.12, 9.16)	< 0.001	NA	NA

Derived from: Table 11.2.1 study 04 CSR in Module 5.3.5.1; Table 11.2.1 and Table 11.2.1a study 05 CSR in Module 5.3.5.1; Table 11.4.1.1-1, Table 11.4.1.1-2, Table 11.4.1.1-3 study 1013 CSR in Module 5.3.5.1.

[a] For all binary endpoints in studies 04 and 05, the effect measure is the difference in proportions; in study 1013 they are odds ratios. For the annualized flare endpoints in studies 04 and 05, the effect measure is a rate ratio.

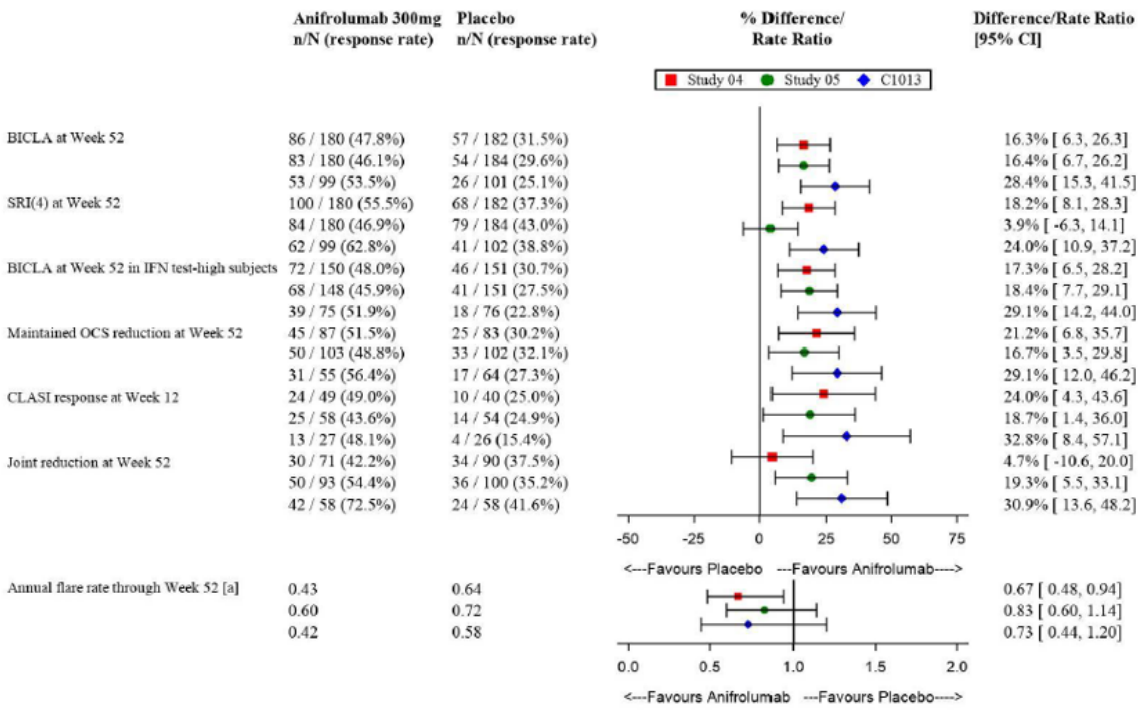
[b] For studies 04 and 05, 95% CI. For study 1013, 90% CI.

[c] For the flare endpoint, rate is presented for each treatment group.

[d] Post hoc results incorporate the revised restricted medication rules for study 05.

Full analysis set include all patients randomized who received at least one dose of investigational product, analyzed according to randomized treatment. Note that this was referred to as a 'modified Intent-to-treat' population in study 1013 CSR.

BICLA British Isles Lupus Assessment Group-based Composite Lupus Assessment; CI Confidence interval; CLASI Cutaneous Lupus Erythematosus Disease Area and Severity Index; IFN interferon; N number of patients in treatment group; n number of patients with response; NA not applicable; OCS oral corticosteroids; SLEDAI-2K Systemic Lupus Erythematosus Disease Activity Index 2000; SRI Systemic lupus erythematosus Responder Index; SRI(4) ≥ 4-point reduction in SLEDAI-2K score in the SRI.



Source: Figure 0000.175.1, Appendix 2.7.3.6.8 in Module 5.3.5.3.

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

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

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

Full analysis set includes all patients randomized who received at least one dose of investigational product, analyzed according to randomized treatment. Note that this was referred to as a 'modified Intent-to-treat' population in study 1013 CSR.

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

Study 04 restricted medication rules are applied to studies 04 and 05. For additional information, see Section 1.2.1.7.

For the definition of each endpoint, see Section 1.2.1.7.

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

BICLA British Isles Lupus Assessment Group-based Composite Lupus Assessment; CI Confidence interval; CLASI Cutaneous Lupus Erythematosus Disease Area and Severity Index; IFN Interferon; N Number of patients in treatment group; n Number of patients with response; OCS Oral corticosteroids; SLEDAI-2K Systemic Lupus Erythematosus Disease Activity Index 2000; SRI Systemic lupus erythematosus Responder Index; SRI(4) ≥ 4 point reduction in SLEDAI-2K score in the SRI.

Figure 7 Forest plot of efficacy data in main clinical studies 04, 05 and 1013 (Full analysis sets)

BICLA Response

As discussed above, BICLA response at Week 52 was initially designated a secondary endpoint for all key studies. When Study 05 failed on SRI(4) and favourable results were seen for BICLA, the applicant changed the endpoint hierarchy for Study 04 and designated BICLA response as its primary endpoint.

BICLA response rates across the three studies are displayed in Table 17. In Study 04, BICLA response rate was 47.8% for anifrolumab 300 mg and 31.5% for placebo. In study 05, the response rates were 47.1% for anifrolumab 300 mg and 30.2% for placebo. In the Phase II study 1013, BICLA response rates were 53.3% for anifrolumab 300 mg and 25.1% for placebo. Due to the change in endpoints, BICLA could only be formally tested in Study 04, and the difference in response rates of 16.3 percentage points (95% CI 6.3 to 26.3) was statistically significant with a p value of 0.001. In Study 05, the difference in response rates between anifrolumab 300 mg and placebo was 17.0 percentage points (95% CI 7.2 to 26.8), and in Study 1013, the difference between anifrolumab 300 mg and placebo was 28.4 percentage points (95% CI 15.3 to 41.5); however, the statistical testing in Study 05 and Study 1013 was done outside of the confirmatory framework.

Table 17 BICLA response rate at Week 52—study 04, study 05, and study 1013 (full analysis sets)

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

Derived from: Table 2.1.1.1, Appendix 2.7.3.6.1 in Module 5.3.5.3; Table 0001.138.3, Appendix 2.7.3.6.8 in Module 5.3.5.3; Table 14.2.2.1.1.3, study 1013 CSR in Module 5.3.5.1.

[a] BICLA response at Week 52 is not part of the multiplicity procedure in studies 05 and 1013, and cannot be interpreted in terms of statistical significance. The p-value for study 1013 is based on the pre-specified logistic regression model for comparison of anifrolumab 300 mg versus placebo, adjusted for randomization stratification factors.

BICLA response is defined in Section 1.2.1.7.

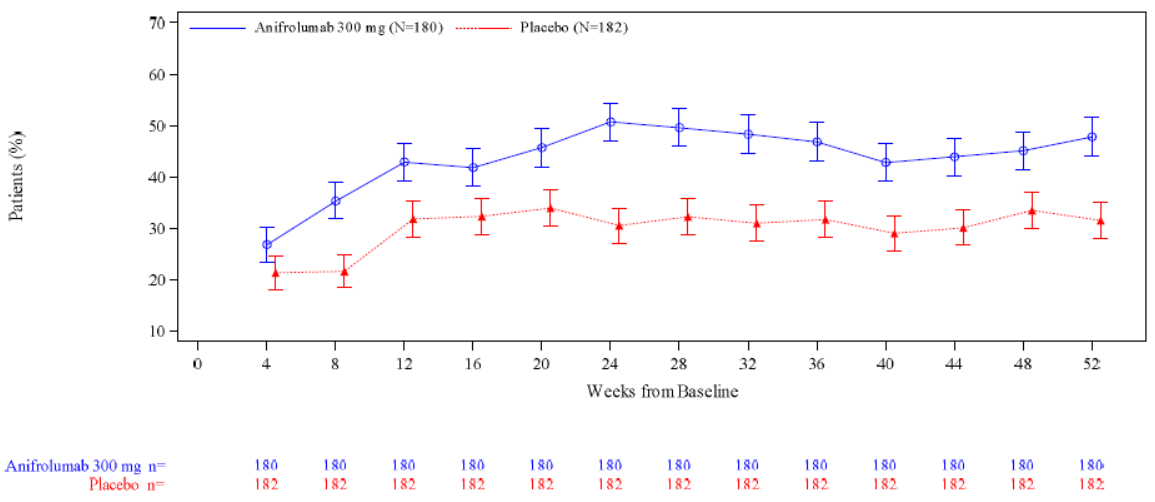
Study 04 and study 05 results are based on the study 04 restricted medications rules. For additional information, see Section 1.2.1.7. Study 1013 results are based on the study 1013 rules for restricted medications.

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

The responder rates and the difference in estimates and associated 95% CI, are calculated using a stratified CMH approach, with stratification factors SLEDAI-2K score at screening, Day 1 OCS dose, and type I IFN gene signature test result at screening.

BICLA British Isles Lupus Assessment Group-based Composite Lupus Assessment; CI Confidence interval; CMH Cochran-Mantel-Haenszel; IFN Interferon; n Number of patients in analysis; NA Not available; N Number of patients in treatment group; OCS Oral corticosteroids; SLEDAI-2K Systemic Lupus Erythematosus Disease Activity Index 2000.

The time courses of the BICLA response in Study 04 and Study 05 are displayed in Figure 8 and Figure 9.



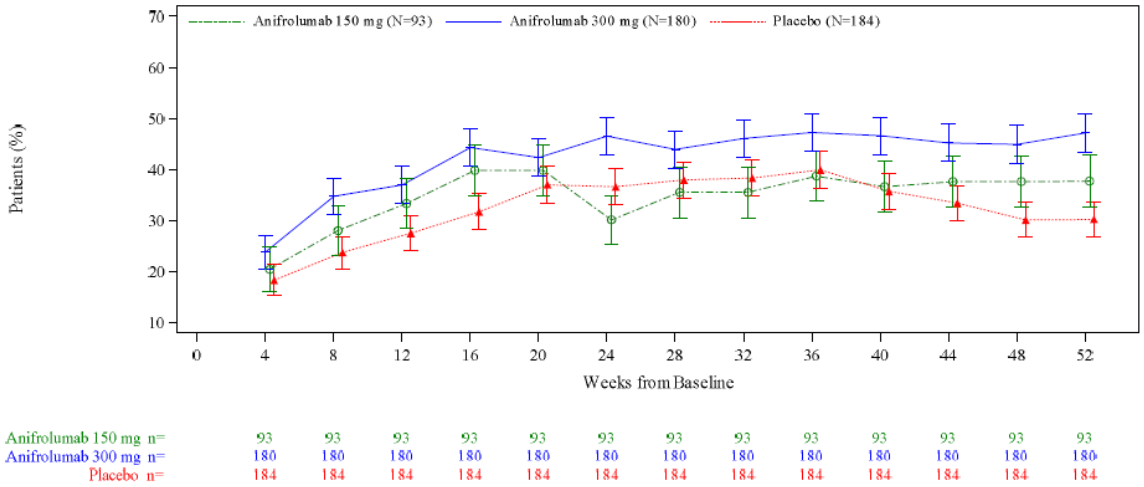
Source: Figure 2.1.4.2, Appendix 2.7.3.6.2 in Module 5.3.5.3.

BICLA response is defined in Section 1.2.1.7.

The responder rates are calculated using a stratified CMH approach, with stratification factors SLEDAI-2K score at screening, Day 1 OCS dose, and type I IFN gene signature test result at screening.

BICLA British Isles Lupus Assessment Group-based Composite Lupus Assessment; CMH Cochran-Mantel-Haenszel; IFN Interferon; n Number of patients in analysis; N Number of patients in treatment group; OCS Oral corticosteroids; SLEDAI-2K Systemic Lupus Erythematosus Disease Activity Index 2000.

Figure 8 BICLA response estimates and standard errors by time point, stratified CMH approach—study 04 (full analysis set)



Source: Figure 2.1.4.3, Appendix 2.7.3.6.2 in Module 5.3.5.3.

BICLA response is defined in Section1.2.1.7.

Results are based on the study 04 rules for restricted medications. For additional information, see Section 1.2.1.7.

The responder rates are calculated using a stratified CMH approach, with stratification factors SLEDAI-2K score at screening, Day 1 OCS dose, and type I IFN gene signature test result at screening.

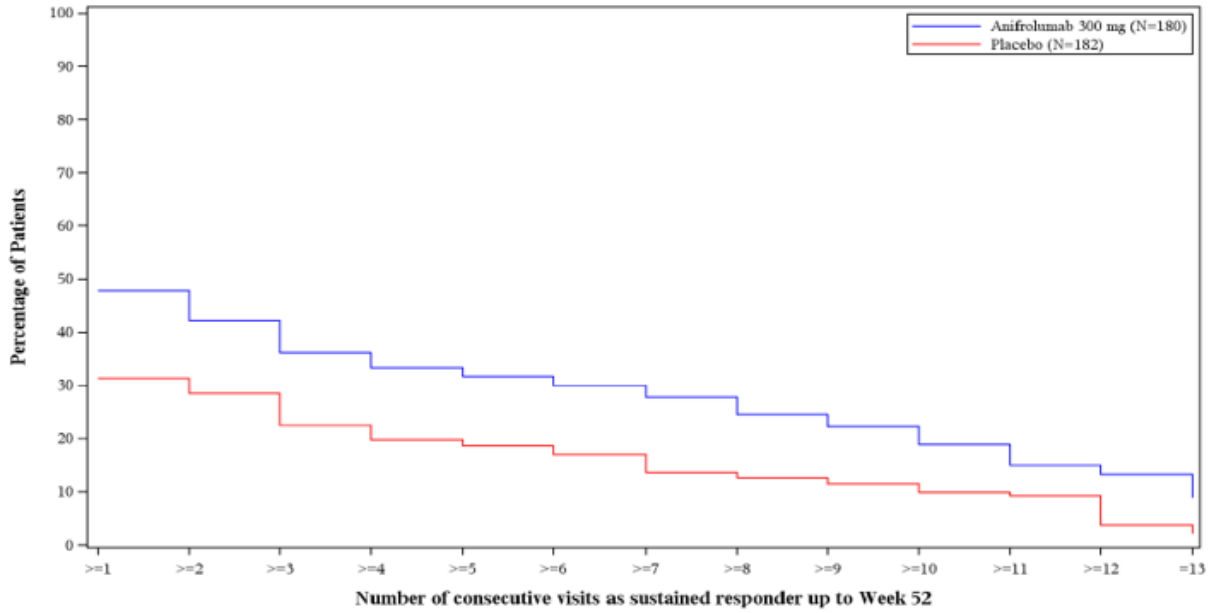
BICLA British Isles Lupus Assessment Group-based Composite Lupus Assessment; CMH Cochran-Mantel-Haenszel; IFN Interferon; n Number of patients in analysis; N Number of patients in treatment group; OCS Oral corticosteroids; SLEDAI-2K Systemic Lupus Erythematosus Disease Activity Index 2000.

Figure 9 BICLA response estimates and standard errors by time point, stratified CMH approach—study 05 (full analysis set)

Sustained BICLA Response

Since individual patients can transition between a responder and a non-responder status from one study visit to the next, the applicant was requested to provide analyses describing sustained responses over longer periods of time. A summary of the proportion of patients who achieved a sustained BICLA response through Week 52 is displayed in Figure 10 (the starting point for each treatment is the proportion of patients with a Week 52 response, and e.g. a patient who responded at Week 4 and maintained consecutive responses through Week 52 would be identified as having a sustained response for 13 visits). The proportion of BICLA responders at Week 52 with a sustained response duration of greater than or equal to 3, 6, 9, and 12 months is shown in Table 18.

Study 04



Study 05

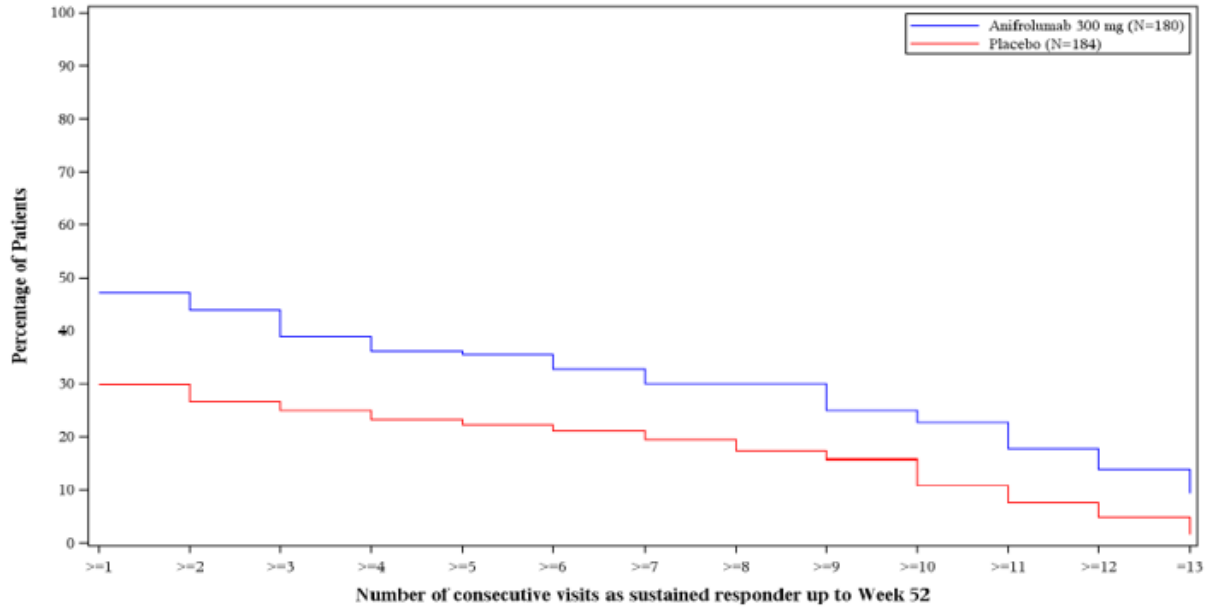


Figure 10 BICLA response sustained among week 52 BICLA responders, number of consecutive visits as responder (Full analysis sets: Study 04 and Study 05)

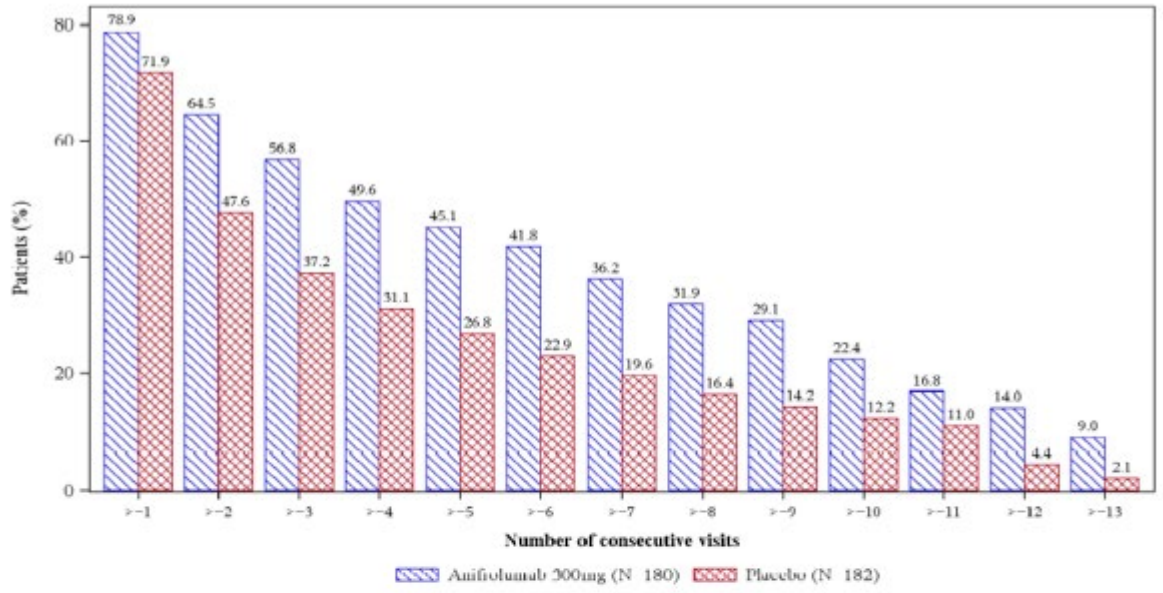
Table 18 Sustained BICLA response, up to and including Week 52

	Study 04		Study 05	
	Anifrolumab 300 mg (N = 180)	**Placebo (N = 182)**	**Anifrolumab 300 mg (N = 180)**	**Placebo (N = 184)**
Consecutive visits in sustained BICLA response, up to and including Week 52, n (%)				
Sustained BICLA response, Week 36 to 52 (at least 3 months)	57 (31.7)	34 (18.7)	64 (35.6)	41 (22.3)
Sustained BICLA response, Week 24 to 52 (at least 6 months)	44 (24.4)	23 (12.6)	54 (30.0)	32 (17.4)
Sustained BICLA response, Week 12 to 52 (at least 9 months)	27 (15.0)	17 (9.3)	32 (17.8)	14 (7.6)
Sustained BICLA response, Week 4 to 52 (12 months)	16 (8.9)	4 (2.2)	17 (9.4)	3 (1.6)

BICLA: British Isles Lupus Assessment Group-based Composite Lupus Assessment; N: number of patients in treatment group; n, number of patients in analysis.
Source: Table 0000.389.15, Appendix A

Corresponding data for sustained BICLA response for all patients is depicted in Figure 11.

Study 04



Study 05

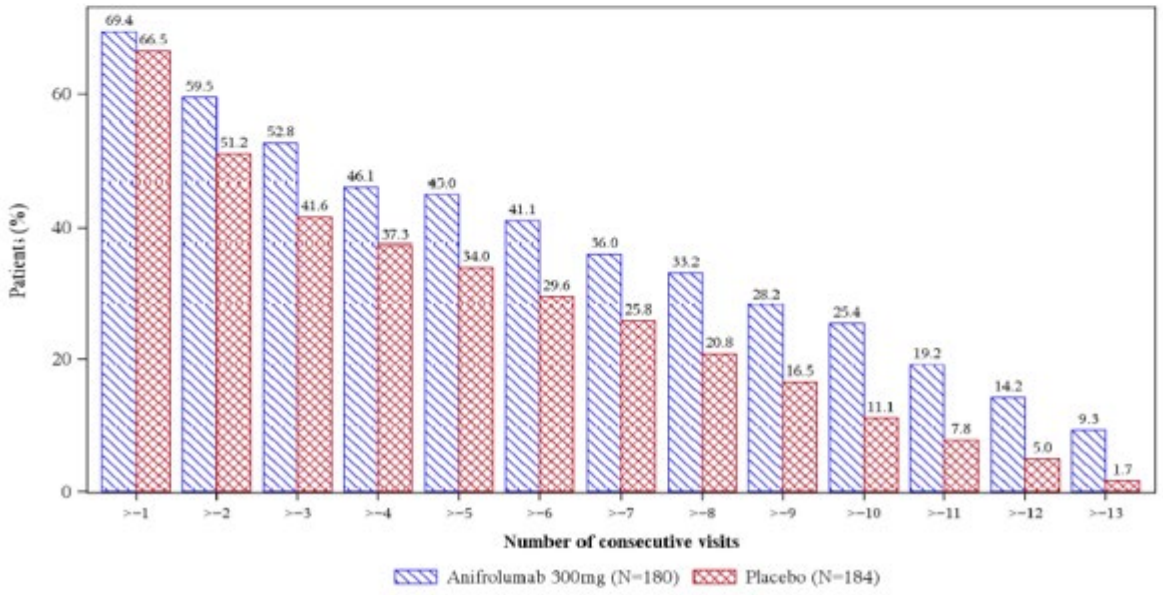


Figure 11 Sustained BICLA response at any time, number of consecutive visits as responder, stratified Cochran-Mantel-Haenszel approach (full analysis set: Study 04 and Study 05)

SRI(4) Response

The applicant initially selected SRI(4) response as the primary endpoint for all key studies. For Study 1013, the primary analysis for SRI(4) response was at Week 24, and SRI(4) at Week 52 was a secondary endpoint. For studies 04 and 05, SRI(4) at Week 52 was the primary endpoint. When Study 05 failed on SRI(4), the endpoint hierarchy for Study 04 was changed, with SRI(4) being demoted to a secondary endpoint.

SRI(4) results across the three studies are displayed in Table 19. Whereas a statistically significant treatment effect had been seen in Study 1013, the difference between treatments was only marginal

and not statistically significant for Study 05; it should furthermore be noted that the results were even less favourable when using the original rules for restricted medications, with the difference in response rates favouring placebo (see Table 19).

In stark contrast, a clear treatment effect favouring anifrolumab was seen in Study 04. The difference between the treatment groups was 18.2 percentage points (95% CI 8.1, 28.3) and associated with a nominal p value of <0.001; however, as SRI(4) had been demoted to a secondary endpoint in Study 04, it was tested outside of the confirmatory framework.

Table 19 SRI(4) response rate at Week 52—study 04, study 05, and study 1013 (full analysis sets)

	Study 04		Study 05			Study 1013	
SRI(4) response at Week 52	**Anifrolumab 300 mg (N = 180)**	**Placebo (N = 182)**	**Anifrolumab 150 mg (N = 93)**	**Anifrolumab 300 mg (N = 180)**	**Placebo (N = 184)**	**Anifrolumab 300 mg (N = 99)**	**Placebo (N = 102)**
n	180	182	93	180	184	99	102
Number (%) responders	100 (55.5)	68 (37.3)	45 (48.4)	88 (49.0)	79 (43.0)	62 (62.8)	41 (38.8)
Comparison with placebo							
Difference in response rate	18.2			6.0		24.0	
95% CI of difference in response rate	8.1, 28.3			-4.2, 16.2		10.9, 37.2	
Nominal p-value[a]	< 0.001			0.248		< 0.001	

Source: Table 2.3.1.3, Appendix 2.7.3.6.1 in Module 5.3.5.3; Table 0001.138.3, Appendix 2.7.3.6.8 in Module 5.3.5.3; Table 14.2.1.1.1.7, study 1013 CSR in Module 5.3.5.1.

[a] SRI(4) response at Week 52 is the primary endpoint in study 05. It is not part of the multiplicity procedure in study 04 and cannot be interpreted in terms of statistical significance. The p-value for study 1013 is based on the pre-specified logistic regression model for comparison of anifrolumab 300 mg versus placebo, adjusted for randomization stratification factors.

Study 04 and 05 results are based on the study 04 rules for restricted medications. For additional information, see Section 1.2.1.7. Study 1013 results are based on the study 1013 rules for restricted medications.

SRI(4) response is defined in Section 1.2.1.7.

The responder/non-responder rates, the difference in estimates and associated 95% CI are calculated using a stratified CMH approach, with stratification factors SLEDAI-2K score at screening, Day 1 OCS dose, and type I IFN gene signature test result at screening. The nominal p-values presented are based on this CMH model.

CI Confidence interval; CMH Cochran-Mantel-Haenszel; IFN Interferon; n Number of patients in analysis; N Number of patients in treatment group; OCS Oral corticosteroids; SLEDAI-2K Systemic Lupus Erythematosus Disease Activity Index 2000; SRI Systemic Lupus Erythematosus Responder Index.

Components of the BICLA and SRI(4) response

The applicant has provided separate analyses concerning the individual components underlying the BICLA and SRI(4) responses. The individual components of the BICLA response at Week 52 are outlined in Table 20, and a corresponding summary of the SRI(4) components is shown in Table 21.

Table 20 Individual components of BICLA at Week 52—study 04, study 05, and study 1013 (full analysis sets)

Individual components of BICLA	Number (%) patients					
	Study 04		Study 05		Study 1013	
	Anifrolumab 300 mg (N = 180)	Placebo (N = 182)	Anifrolumab 300 mg (N = 180)	Placebo (N = 184)	Anifrolumab 300 mg (N = 99)	Placebo (N = 101)
BICLA responder[a]	86 (47.8)	57 (31.3)	85 (47.2)	55 (29.9)	53 (53.5)	26 (25.7)
BILAG-2004 improvement[b]	88 (48.9)	59 (32.4)	85 (47.2)	58 (31.5)	53 (53.5)	26 (25.7)
No worsening of SLEDAI-2K[b]	122 (67.8)	94 (51.6)	121 (67.2)	104 (56.5)	73 (73.7)	60 (59.4)
No worsening of PGA[b]	122 (67.8)	95 (52.2)	117 (65.0)	105 (57.1)	76 (76.8)	61 (60.4)
No discontinuation of investigational product	153 (85.0)	130 (71.4)	145 (80.6)	146 (79.3)	87 (87.9)	70 (69.3)
No use of restricted medications beyond protocol-allowed thresholds	144 (80.0)	123 (67.6)	140 (77.8)	128 (69.6)	81 (81.8)	86 (85.1)

Source: Table 2.1.3, Appendix 2.7.3.6.1 in Module 5.3.5.3; Table 11.2.9.1, Appendix 2.7.3.6.5 in Module 5.3.5.3.

[a] The BICLA responder rates are the raw proportions, unlike other tables that present the CMH model-based BICLA responder rates

[b] Patients who discontinued investigational product or used medications beyond protocol-allowed threshold are considered non-responders

Study 04 and 05 results are based on the study 04 rules for restricted medications. For additional information, see Section 1.2.1.7. Study 1013 results are based on the study 1013 rules for restricted medications.

BICLA response is defined in Section1.2.1.7.

BILAG British Isles Lupus Assessment Group; CMH Cochran-Mantel-Haenszel; N Number of patients in treatment group; PGA Physician's Global Assessment; SLEDAI-2K Systemic Lupus Erythematosus Disease Activity Index 2000.

Table 21 Individual components of SRI(4) at week 52 - studies 04, 05 and Phase III pool (full analysis set)

	Number (%) of patients						
	Study 04		Study 05			Phase III pool	
	Anifrolumab 300 mg (N=180)	Placebo (N=182)	Anifrolumab 150 mg (N=93)	Anifrolumab 300 mg (N=180)	Placebo (N=184)	Anifrolumab 300 mg (N=360)	Placebo (N=366)
>=4 point reduction in SLEDAI-2k [a]	101 (56.1)	71 (39.0)	45 (48.4)	89 (49.4)	80 (43.5)	190 (52.8)	151 (41.3)
No worsening of BILAG [a]	125 (69.4)	94 (51.6)	62 (66.7)	119 (66.1)	105 (57.1)	244 (67.8)	199 (54.4)
No worsening of PGA [a]	122 (67.8)	95 (52.2)	61 (65.6)	117 (65.0)	105 (57.1)	239 (66.4)	200 (54.6)
No discontinuation of investigation product	153 (85.0)	130 (71.4)	75 (80.6)	145 (80.6)	146 (79.3)	298 (82.8)	276 (75.4)
No use of restricted medications beyond protocol allowed threshold	144 (80.0)	123 (67.6)	72 (77.4)	140 (77.8)	128 (69.6)	284 (78.9)	251 (68.6)
SRI(4) responder	100 (55.6)	68 (37.4)	45 (48.4)	88 (48.9)	79 (42.9)	188 (52.2)	147 (40.2)

[a] Patients who discontinued IP or used medications beyond protocol allowed threshold are considered non-responders and not included in this category.
Phase III pool includes study 04 and study 05 (excluding the 150 mg group from study 05).
SRI(4) response is defined in section 7.1.3 in statistical analysis plan. The definition of restricted medications used is from study 04, therefore the study 05 summaries may differ from the summary presented in the individual study CSR.
N Number of patients in treatment group. n Number of patients in analysis. SLEDAI-2K Systemic Lupus Erythematosus Disease Activity Index 2000. BILAG British Isles Lupus Assessment Group. PGA Physician's Global Assessment. IP Investigational Product. SRI Systemic Lupus Erythematosus Responder Index.

BICLA and SRI(4) responses in the Phase III studies were also analysed without consideration of the attributes "no use of restricted medication" and "no discontinuation of investigational product". The results are displayed in Table 22 and Table 23, respectively.

Table 22 BICLA and SRI(4) response rates at Week 52, excluding restricted medication use—study 04 and study 05 (full analysis sets)

Response rates at Week 52 (%)	Study 04			Study 05		
	Anifrolumab 300 mg N = 180	Placebo N = 182	Difference in response rates (95% CI)	Anifrolumab 300 mg N = 180	Placebo N = 184	Difference in response rates (95% CI)
SRI(4)	55.5	37.3	18.2 (8.1, 28.3)	49.0	43.0	6.0 (-4.2, 16.2)
Modified SRI(4) excluding the (component of) restricted medication use	66.6	49.2	17.4 (7.4, 27.4)	58.5	55.5	3.1 (-7.1, 13.2)
BICLA	47.8	31.5	16.3 (6.3, 26.3)	47.1	30.2	17.0 (7.2, 26.8)
Modified BICLA excluding the (component of) restricted medication use	55.1	38.6	16.6 (6.4, 26.7)	54.4	39.4	15.0 (4.9, 25.0)

Derived from: Table 2.1.2 and Table 2.3.1.3, Appendix 2.7.3.6.1 in Module 5.3.5.3; Table 0001.181.1, Appendix 2.7.3.6.8 in Module 3.5.3.5; Figure 0005.138.4, Appendix 2.7.3.6.8 in Module 5.3.5.3; Table 11.2.1.7, study 04 CSR in Module 5.3.5.1.

Study 04 restricted medication rules are applied to studies 04 and 05 in the non-modified SRI(4) and BICLA endpoints. For additional information, see Section 1.2.1.7.

For the definition of the SRI(4) and BICLA endpoints, see Section 1.2.1.7.

Responder rates, and the difference in estimates and associated 95% CI, are calculated using a stratified CMH approach, with stratification factors SLEDAI-2K score at screening, Day 1 OCS dose, and type I IFN gene signature test result at screening.

BICLA British Isles Lupus Assessment Group-based Composite Lupus Assessment; CI Confidence interval; CMH Cochran-Mantel-Haenszel; IFN Interferon; N Number of patients in treatment group; OCS Oral corticosteroid; SLEDAI-2K Systemic Lupus Erythematosus Disease Activity Index 2000; SRI Systemic lupus erythematosus Responder Index; SRI(4) ≥ 4-point reduction in SLEDAI-2K score in the SRI.

Table 23 BICLA and SRI(4) response rates at Week 52, multiple imputation excluding discontinuation of IP—study 04 and study 05 (full analysis sets)

Response rates at Week 52 (%)	Study 04			Study 05		
	Anifrolumab 300 mg N = 180	Placebo N = 182	Difference in response rates (95% CI)	Anifrolumab 300 mg N = 180	Placebo N = 184	Difference in response rates (95% CI)
SRI(4)	55.5	37.3	18.2 (8.1, 28.3)	49.0	43.0	6.0 (-4.2, 16.2)
Modified SRI(4) excluding the (component of) discontinuation of IP	64.7	50.8	13.8 (2.8, 24.9)	58.4	51.9	6.5 (-4.6, 17.6)
BICLA	47.8	31.5	16.3 (6.3, 26.3)	47.1	30.2	17.0 (7.2, 26.8)
Modified BICLA excluding the (component of) discontinuation of IP	55.2	43.0	12.2 (1.0, 23.4)	56.3	35.9	20.4 (9.4, 31.4)

Derived from: Table 2.1.2 and Table 2.3.1.3, Appendix 2.7.3.6.1 in Module 5.3.5.3; Table 11.2.10.3 and Table 11.2.10.4, Appendix 2.7.3.6.3 in Module 3.5.3.5.

All observed data were used in this analysis, and patients with missing observations were imputed using multiple imputation. For patients discontinuing investigational product, imputation was based on patients with non-missing observations by treatment group, as only limited data were observed post discontinuation. This implies an underlying assumption that patients who discontinue investigational product were similar to patients who complete treatment, making this a conservative analysis.

Study 04 restricted medication rules are applied to studies 04 and 05. For additional information, see Section 1.2.1.7.

For the definition of the SRI(4) and BICLA endpoints, see Section 1.2.1.7.

Responder rates, and the difference in estimates and associated 95% CI, are calculated using a stratified CMH approach, with stratification factors SLEDAI-2K score at screening, Day 1 OCS dose, and type I IFN gene signature test result at screening.

BICLA British Isles Lupus Assessment Group-based Composite Lupus Assessment; CI Confidence interval; CMH Cochran-Mantel-Haenszel; IFN Interferon; IP Investigational product; N Number of patients in treatment group; OCS Oral corticosteroid; SLEDAI-2K Systemic Lupus Erythematosus Disease Activity Index 2000; SRI Systemic lupus erythematosus Responder Index; SRI(4) ≥ 4-point reduction in SLEDAI-2K score in the SRI.

Additional sensitivity analyses

Additional analyses were undertaken to evaluate the effect of intercurrent events on BICLA and SRI(4) response. As outlined above, there were 3 intercurrent events incorporated into endpoints in studies 04 and 05:

- IP discontinuation: a component of the primary estimand and refers to premature discontinuation of IP prior to the Week 48 visit. This event could be indicative of lack of efficacy or tolerability; therefore, the patient is deemed a non-responder from the time of this event onward.
- Restricted medication use: a component of the primary estimand and refers to use of restricted medications on or prior to the Week 52 visit. This event could be indicative of lack of efficacy; therefore, the patient is deemed a non-responder from the time of this event onward.

- Study withdrawal: this event refers to situations for which no further data can be observed for a patient. The intercurrent event of study withdrawal includes (1) premature study withdrawal (due to investigator or patient decision), (2) lost to follow-up, and (3) death prior to Week 52. This event marks the beginning of true missing data and therefore the patient is considered a non-responder from time of withdrawal onward.

In studies 04 and 05, patients were encouraged to remain in the study even if they discontinued IP or restricted medication use occurred; therefore, data could continue to be observed after these events. Since the intercurrent event strategy only imputes non-response when an intercurrent event is observed, the impact of intercurrent events focused on reasons for non-response at Week 52.

The impact assessment of non-responders followed a hierarchical flow:

1. Non-responders who prematurely withdrew from the study prior to Week 52 were deemed non-responders due to study withdrawal since no clinical data are available to determine response status.
2. Non-responders who completed through Week 52 and met all clinical criteria (responder for BILAG-2004, SLEDAI-2000, and PGA) were deemed non-responders due to intercurrent events as follows: IP discontinuation only, restricted medication use only, or both IP discontinuation and restricted medication use.
3. Non-responders completing through Week 52 who did not meet all clinical criteria were deemed non-responders due to the clinical criteria not met, irrespective of intercurrent events of IP discontinuation or restricted medication use, since failure to respond on all clinical criteria would result in non-response at Week 52 regardless of intercurrent event status.

The impact of intercurrent events was assessed based on imputation of non-response, using the treatment policy estimand which ignores the IP discontinuation and restricted medication use, and by performing a completers analysis in which the impact of IP discontinuation and premature withdrawal are removed by only assessing patients who completed the double-blind period on treatment.

Since the impact assessment on non-responders and the non-response rate is different for BICLA and SRI(4), the impact for these endpoints was assessed separately. Study 1013 was not included in these impact assessments, as the study protocol did not continue to collect data for the double-blind treatment period once a patient used restricted medication or discontinued IP.

Impact of Intercurrent Events on BICLA Response Status

The impact of the intercurrent events on the BICLA response rates at Week 52 are presented for study 04 and study 05 in Table 24.

Table 24 Disposition of BICLA response at Week 52 (Study 04 and Study 05, full analysis sets)

	Number (%) of patients			
	Study 04		Study 05	
	Anifrolumab 300 mg (N = 180)	Placebo (N = 182)	Anifrolumab 300 mg (N = 180)	Placebo (N = 184)
BICLA responder	86 (47.8)	57 (31.3)	85 (47.2)	55 (29.9)
BICLA nonresponder[a]	94 (52.2)	125 (68.7)	95 (52.8)	129 (70.1)
Withdrew from study prior to Week 52	18 (10.0)	37 (20.3)	27 (15.0)	27 (14.7)
Completed Week 52 and met all clinical criteria	15 (8.3)	23 (12.6)	15 (8.3)	17 (9.2)
Discontinuation of IP only	1 (0.6)	3 (1.6)	0	0
Use of restricted medication only	13 (7.2)	13 (7.1)	13 (7.2)	17 (9.2)
Discontinued IP and used restricted medication	1 (0.6)	7 (3.8)	2 (1.1)	0
Completed Week 52 and failed at least one clinical criteria[b]	61 (33.9)	65 (35.7)	53 (29.4)	85 (46.2)
No BILAG-2004 improvement	58 (32.2)	63 (34.6)	52 (28.9)	80 (43.5)
Worsening of SLEDAI-2K	3 (1.7)	1 (0.5)	0	3 (1.6)
Worsening of PGA	0	1 (0.5)	1 (0.6)	2 (1.1)

[a] Reasons for nonresponse were determined sequentially in the order shown.
[b] Reasons may include patients who have also discontinued IP or used restricted medications.
BICLA response is defined as reduction of all baseline BILAG-2004 A and B scores and no worsening in other organ systems, no increase > 0 on SLEDAI-2K from baseline, and no increase ≥ 0.30 on PGA VAS from baseline. Clinical criteria: BILAG-2004, SLEDAI-2K, PGA.
BICLA, British Isles Lupus Assessment Group-based Composite Lupus Assessment; BILAG-2004, British Isles Lupus Assessment Group 2004; IP, Investigational product; PGA, Physician's Global Assessment; N, Number of patients in treatment group; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000.
Source: Table 0000.292.3.

In studies 04 and 05, the key factors contributing to BICLA non-response across studies and treatment groups (listed in order of magnitude) were:

- No BILAG improvement
- Study withdrawal
- Restricted medication use

In study 04, study withdrawal resulted in the largest difference in the proportion of BICLA non-responders, with 20.3% of patients in the placebo group withdrawing from the study prior to Week 52 compared with 10.0% of patients in the anifrolumab 300 mg group. Reasons for withdrawal in study 04 occurring in a higher proportion in the placebo group compared with the anifrolumab 300 mg group included withdrawal by patient (9.2% vs 5.0%), adverse event (3.8% vs 1.7%), lack of efficacy (3.3% vs 0.6%), condition under investigation worsened (2.2% vs 0), lost to follow-up (1.1% vs 0.6%), and severe noncompliance to protocol (0.5% to 0). In the applicant's opinion, this distribution of events is consistent with inadequate treatment effect and/or treatment-limiting AEs. The only reason for withdrawal that affected a higher proportion of patients in the anifrolumab 300 mg group vs the placebo group was the category 'other', which occurred in 2.2% of anifrolumab-treated patients compared with 0 placebo-treated patients.

In study 05, the largest difference in the proportion of non-responders was due to clinical criteria not being met, with 46.2% of patients in the placebo group vs 29.4% in the anifrolumab 300 mg group. The

proportions of non-responders due to study withdrawal or IP discontinuation/restricted medication use were similar between the treatment groups.

Impact of Intercurrent Events on SRI(4) Response Status

The impact of the intercurrent events on the SRI(4) response rates at Week 52 is presented for studies 04 and 05 in Table 25.

Table 25 Disposition of SRI(4) response at Week 52 (Study 04 and Study 05, full analysis sets)

	Number (%) of patients			
	Study 04		Study 05	
	Anifrolumab 300 mg (N = 180)	Placebo (N = 182)	Anifrolumab 300 mg (N = 180)	Placebo (N = 184)
SRI(4) responder	100 (55.6)	68 (37.4)	88 (48.9)	79 (42.9)
SRI(4) nonresponder[a]	80 (44.4)	114 (62.6)	92 (51.1)	105 (57.1)
Withdrew from study prior to Week 52	18 (10.0)	37 (20.3)	27 (15.0)	27 (14.7)
Completed Week 52 and met all clinical criteria	23 (12.8)	31 (17.0)	21 (11.7)	25 (13.6)
Discontinuation of IP only	2 (1.1)	4 (2.2)	1 (0.6)	1 (0.5)
Use of restricted medication only	20 (11.1)	22 (12.1)	17 (9.4)	22 (12.0)
Discontinued IP and used restricted medication	1 (0.6)	5 (2.7)	3 (1.7)	2 (1.1)
Completed Week 52 and failed at least one clinical criteria[b]	39 (21.7)	46 (25.3)	44 (24.4)	53 (28.8)
Reduction in SLEDAI-2K < 4 points	35 (19.4)	37 (20.3)	34 (18.9)	43 (23.4)
Worsening of BILAG-2004	3 (1.7)	7 (3.8)	8 (4.4)	8 (4.3)
Worsening of PGA	1 (0.6)	2 (1.1)	2 (1.1)	2 (1.1)

[a] Reasons for nonresponse were determined sequentially in the order shown.
[b] May include patients who have also discontinued IP or used restricted medications.
SRI(4) response is defined as a reduction from baseline of ≥ 4 points in the SLEDAI-2K, no new BILAG-2004 organ systems affected (defined as ≥ 1 new A item or ≥ 2 new B items compared to baseline) and no increase ≥ 0.30 points from baseline on a 0-3-point PGA VAS. Results are based on the study 04 rules for restricted medications. Patients who discontinued IP were considered nonresponders after the last effective visit. Patients who used restricted medications were considered nonresponders right after the initiation of the medication.
Clinical criteria: BILAG-2004, SLEDAI-2K, PGA.
BILAG-2004, British Isles Lupus Assessment Group 2004; IP, Investigational product; PGA, Physician's Global Assessment; N, Number of patients in treatment group; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000.

Overall, the primary factors contributing to SRI(4) non-response across both studies and treatment groups (listed in order of magnitude) were:

- SLEDAI-2K reduction < 4 points
- Study withdrawal
- Restricted medication use

In study 04, study withdrawal resulted in the largest difference in the proportion of non-responders, with 20.3% of patients in the placebo group withdrawing from the study prior to Week 52 compared with 10.0% of patients in the anifrolumab 300 mg group. The reasons for study withdrawal are the same as that discussed above for the BICLA endpoint.

In study 05, the largest difference in the proportion of non-responders was due to clinical criteria not being met, with 28.8% of patients in the placebo group vs 24.4% of patients in the anifrolumab 300 mg group. Proportions of non-responders due to study withdrawal or IP discontinuation/restricted medication use were similar between the treatment groups.

Treatment Policy Estimand

Sensitivity analyses excluding the use of restricted medication and discontinuation of IP components, also referred to as the treatment policy estimand, are presented for key endpoints of studies 04 and study 05. These modified endpoints used the 3 clinical disease activity components only, and patients with missing data (e.g., due to study withdrawal, lost to follow-up, or death) were considered non-responders.

The results of the treatment policy estimand for the key efficacy data are presented in Table 26.

Table 26 Treatment Policy Estimand: Study 04 and 05 endpoints, excluding IP discontinuation and restricted medication use (full analysis sets)

	Study 04		Study 05	
	Anifrolumab 300 mg (N = 180)	Placebo (N = 182)	Anifrolumab 300 mg (N = 180)	Placebo (N = 184)
BICLA response at Week 52				
n	180	182	180	184
Number (%) responders	98 (54.5)	79 (43.6)	93 (51.7)	70 (38.4)
Difference (%)[a]	10.9		13.3	
95% CI	0.7, 21.1		3.2, 23.4	
Nominal p-value	0.037		0.010	
SRI(4) response at Week 52				
n	180	182	180	184
Number (%) responders	120 (66.5)	96 (52.5)	100 (55.8)	101 (54.9)
Difference (%)[a]	14.0		0.9	
95% CI	4.0, 24.0		-9.3, 11.0	
Nominal p-value	0.006		0.867	
Maintained OCS reduction at Week 52 in subjects with OCS >=10 mg/day at baseline				
n	87	83	103	102
Number (%) responders	51 (58.4)	30 (36.3)	62 (60.5)	37 (36.0)
Difference (%)[a]	22.1		24.5	
95% CI	7.4, 36.7		11.4, 37.7	
Nominal p-value	0.003		< 0.001	
Reduction in CLASI activity score at Week 12 among subjects with baseline CLASI activity score >=10				
n	49	40	58	54
Number (%) responders	25 (51.0)	13 (32.5)	26 (45.3)	13 (23.3)
Difference (%)[a]	18.5		21.9	
95% CI	-1.8, 38.8		4.7, 39.2	
Nominal p-value	0.074		0.013	
Joint 50% reduction at Week 52 among subjects with at least 6 swollen and 6 tender joints at baseline				
n	71	90	93	100
Number (%) responders	36 (50.4)	46 (50.4)	54 (59.4)	55 (53.3)
Difference (%)[a]	0.0		6.1	
95% CI	-15.4, 15.4		-7.8, 19.9	
Nominal p-value	0.998		0.391	

[a] Difference between anifrolumab 300 mg and placebo/

CLASI, Cutaneous Lupus Erythematosus Disease Activity and Severity Index; CI, Confidence interval; IP, Investigational product; n, Number of patients in analysis; N, Number of patients in treatment group; OCS, Oral corticosteroid.

Completers Analyses

A sensitivity analysis for patients who completed Week 52 without prematurely discontinuing IP, referred to as a completers analysis, was performed for studies 04 and 05. This analysis removes the impact of IP discontinuation and premature study withdrawal while retaining the impact of restricted medication use (Table 27).

Table 27 BICLA response rates at Week 52 (Completers analysis; full analysis set)

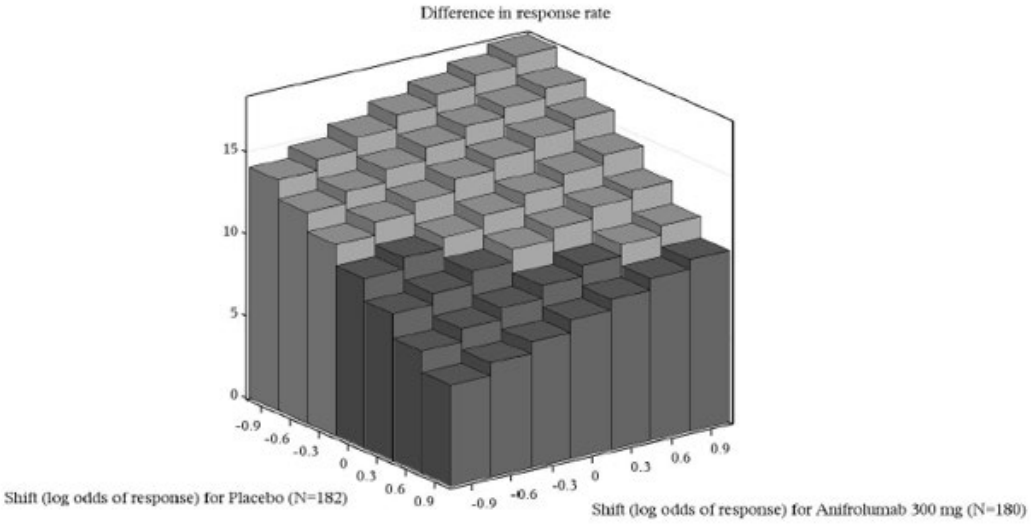
	Treatment	n	Responders (n, %)	95% CI	Difference in response rates (Anifrolumab – Placebo)	(95% CI) for difference	Nominal p-value
Study 04	Anifrolumab 300mg (N = 180)	153	86 (56.4)	48.5, 64.2	11.4	(-0.1, 23.0)	0.052
	Placebo (N = 182)	130	57 (44.9)	36.4, 53.4			
Study 05	Anifrolumab 300mg (N = 180)	145	85 (58.7)	50.5, 66.7	21.1	(10.0, 32.3)	< 0.001
	Placebo (N = 184)	146	55 (37.5)	29.8, 45.2			

Responder rates, and the difference in estimates and associated 95% CI, are calculated using a stratified CMH approach, with stratification factors SLEDAI-2K score at screening, Day 1 OCS dose, and type I IFN gene signature test result at screening.
BICLA, British Isles Lupus Assessment Group-based Composite Lupus Assessment; CI, Confidence interval; CMH, Cochran-Mantel-Haenszel; N, Number of patients in treatment group

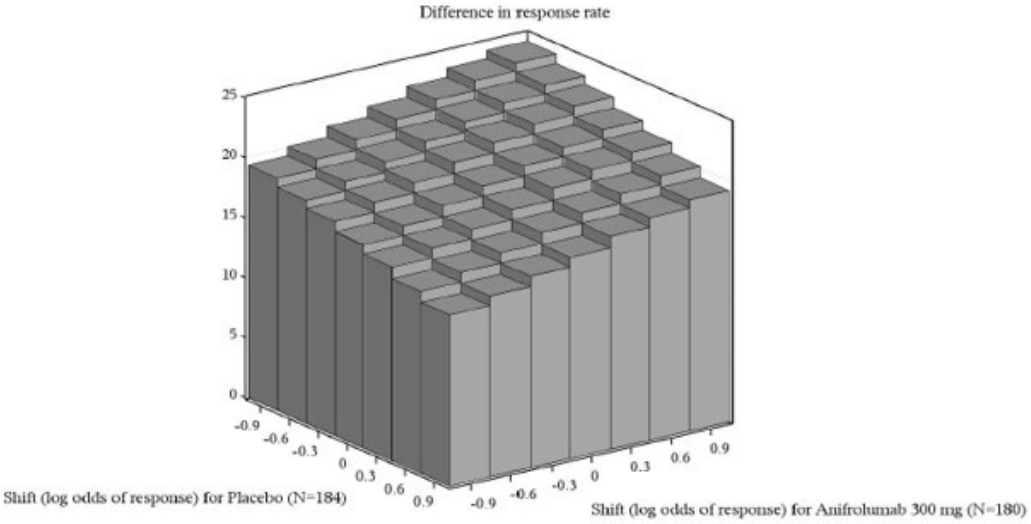
Tipping point analyses

The tipping point analyses using multiple imputation assuming MNAR are presented in Figure 12 for BICLA response and Figure 13 for SRI(4) response. In the analyses, the probabilities of response within each treatment group are shifted by fixed amounts, where the "log odds shift" translate as adjustments to the chances that the outcome is imputed as a 1 (i.e., response). This is the factor by which the MAR predicted odds of a response is getting modified by the MNAR assumption – for example, if a patient had a 20% probability of response assuming MAR, a shift -0.6 in the log odds results in a probability of response of approximately 12%. The estimand that most closely mirrors the primary estimand is the one where the log odds shift is 0 for both anifrolumab and placebo. For BICLA, this corresponds to a treatment difference of 12.6% and 19.6%, for Studies 04 and 05, respectively. The tipping point analyses are largely consistent with the primary estimand tipping point analyses in that the BICLA response for both study 04 and 05 retain nominal significance for most combinations of favourable and unfavourable responses. Similarly, the analysis for SRI(4) is consistent with the primary estimands in both studies in that SRI(4) is nominally significant for nearly all combinations of responses in study 04 and does not achieve nominal significance for any combination of favourable and unfavourable responses in Study 05.

Study: D3461C00004



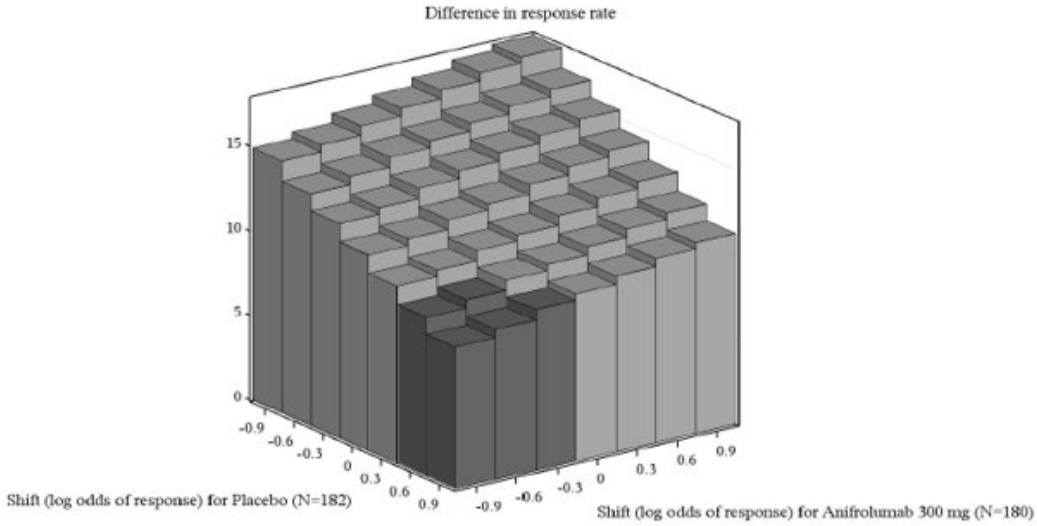
Study: D3461C00005



BICLA British Isles Lupus Assessment Group-based Composite Lupus Assessment. N Number of subjects in treatment group.
Bars where the p-value is <=0.05 are shaded in light grey. Bars where the p-value is >0.05 are shaded in dark grey.

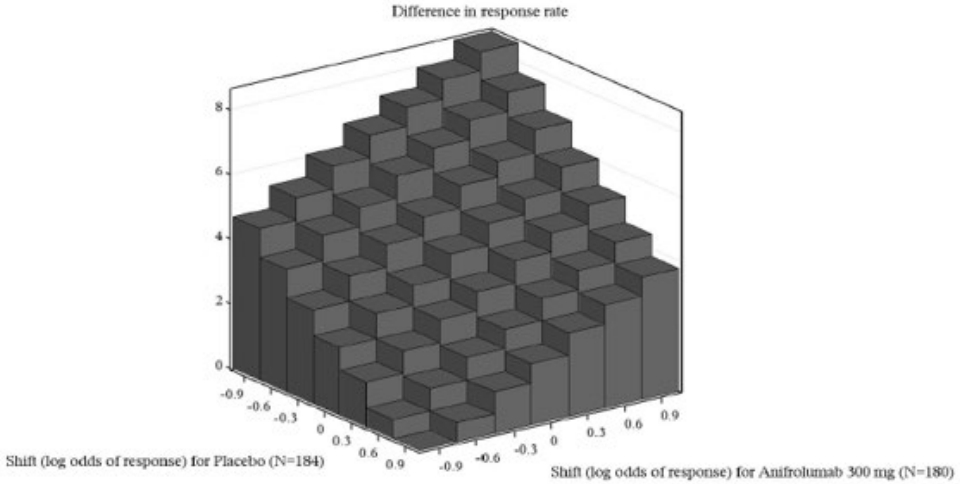
Figure 12 BICLA response at Week 52 Tipping Point analysis using on drug data and ignoring use of restricted medication (Mixed effects model, MNAR) – Study 04 and Study 05 (full analysis set)

Study: D3461C00004



SRI Systemic Lupus Erythematosus Responder Index. N Number of subjects in treatment group.
Bars where the p-value is <=0.05 are shaded in light grey. Bars where the p-value is >0.05 are shaded in dark grey.

Study: D3461C00005



SRI Systemic Lupus Erythematosus Responder Index. N Number of subjects in treatment group.
Bars where the p-value is <=0.05 are shaded in light grey. Bars where the p-value is >0.05 are shaded in dark grey. The difference in response rate is -0.3 for the Placebo shift of 0.9 and Anifrolumab shift of -0.9

Figure 13 SRI(4) response at Week 52 Tipping Point analysis using on drug data and ignoring use of restricted medication (Mixed effects model, MNAR) – Study 04 and Study 05 (full analysis set)

To further assess the impact of IP discontinuation on treatment response, the applicant undertook a detailed review of all patients discontinuing IP without prior restricted medication use. As seen in Table 28, there were 41 placebo patients and 26 anifrolumab 300 mg patients prematurely discontinuing IP without evidence of restricted medication use prior to IP discontinuation in Study 04, and 31 such patients in each treatment arm in Study 05.

Table 28 Patients who discontinued IP: Study 04 and Study 05

	Number (%) of patients			
	Study 04		Study 05	
	Anifrolumab 300 mg N=180	Placebo N=182	Anifrolumab 300 mg N=180	Placebo N=184
Patients who discontinued IP	27 (15.0)	52 (28.6)	35 (19.4)	38 (20.7)
Restricted medication use prior to IP discontinuation	1 (3.7)	11 (21.2)	4 (11.4)	7 (18.4)
No restricted medication use prior to IP discontinuation	26 (96.3)	41 (78.8)	31 (88.6)	31 (81.6)

IP, Investigational product; N, Number of patients in treatment group

The applicant then analysed the reasons for discontinuing IP in patients without prior restricted medication use using information recorded on the eCRF as the reason for IP discontinuation. The worsening components of the BICLA and SRI endpoints at the last assessment on or before IP discontinuation were also summarised to provide an objective measure of lack of efficacy in this subset of patients which show that 64.5% to 73.1% of patients had worsening of at least one clinical criterion when IP was discontinued (Table 29). In addition, a blinded review of patient profiles for all patients who discontinued IP for reasons other than reported as "lack of efficacy" or "worsening of disease" was performed by an internal applicant physician using a structured approach with predefined criteria. The reason for IP discontinuation was classified as "lack of efficacy related" only if objective measures of persistent or increased disease activity at time of IP discontinuation compared with baseline activity was evident upon review of SLEDAI-2K, BILAG-2004, and PGA scores. IP discontinuations were considered not to be efficacy related if a patient discontinued IP due to lost to follow-up, noncompliance with study procedures, pregnancy/wished to become pregnant or if the reason was reported as "other" without any further details reported in the eCRFs. Patients who discontinued due to an AE were only considered to have discontinued for efficacy reason if the reported AE term clearly indicated SLE worsening/flare.

Based on the physician's blinded review, patients treated with placebo were more likely to discontinue IP due to efficacy-related reasons than anifrolumab-treated patients (46.3% vs 15.4% for Study 04 and 71.0% vs 25.8% in study 05) (Table 29). According to the applicant, these results indicate that among patients who prematurely discontinued IP during the studies, more patients in the placebo group compared with the anifrolumab group used restricted medications prior to IP discontinuation and, among those without prior use of restricted medications, more placebo-treated patients discontinued IP with evidence of lack of efficacy compared with anifrolumab, suggesting that the imbalance in IP discontinuations in study 04 was related to a treatment effect and not a random occurrence.

Table 29 Reasons for IP discontinuation and relation to efficacy, for patients who discontinued IP without prior restricted medication use (Study 04 and Study 05; full analysis set)

	Number (%) of patients			
	Study 04		Study 05	
	Anifrolumab 300 mg N=180	Placebo N=182	Anifrolumab 300 mg N=180	Placebo N=184
Number of patients who discontinued IP without prior restricted medication use	26	41	31	31
Reasons for discontinuation of IP (eCRF)				
Adverse event	5 (19.2)	12 (29.3)	13 (41.9)	6 (19.4)
Condition under investigation worsened	2 (7.7)	3 (7.3)	1 (3.2)	3 (9.7)
Lack of efficacy	2 (7.7)	9 (22.0)	2 (6.5)	8 (25.8)
Lost to follow-up	2 (7.7)	2 (4.9)	0	2 (6.5)
Severe non-compliance to protocol	0	1 (2.4)	0	0
Withdrawal by patient	6 (23.1)	13 (31.7)	12 (38.7)	12 (38.7)
Other	9 (34.6)	1 (2.4)	3 (9.7)	0
Clinical components[a] at the last assessment prior to IP discontinuation				
No worsening in any of the clinical criteria	7 (26.9)	12 (29.3)	10 (32.3)	11 (35.5)
At least one worsening in any of the clinical criteria	19 (73.1)	29 (70.7)	21 (67.7)	20 (64.5)
BILAG worsening[b]	17 (65.4)	24 (58.5)	17 (54.8)	16 (51.6)
SLEDAI-2K worsening[c]	2 (7.7)	7 (17.1)	6 (19.4)	5 (16.1)
PGA worsening[d]	0	4 (9.8)	0	1 (3.2)
Physician's view of data related to IP discontinuation				
Efficacy related	4 (15.4)	19 (46.3)	8 (25.8)	22 (71.0)
Non-efficacy related	22 (84.6)	22 (53.7)	23 (74.2)	9 (29.0)

[a] Last assessment prior to (≤) IP discontinuation. The same patient may have more than one criterion met.
[b] BILAG worsening defined as one or more new BILAG-2004 A or 2 or more new BILAG-2004 B items compared to baseline.
[c] SLEDAI-2K worsening defined as an increase from baseline of > 0 points in SLEDAI-2K.
[d] PGA worsening defined as an increase ≥ 0.30 points on a 3-point PGA VAS.
BILAG, British Isles Lupus Assessment Group; eCRF, Electronic Case Report Form; N, Number of patients in each treatment group; IP, Investigational product; PGA, Physician's Global Assessment; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000; VAS, Visual Analogue Scale

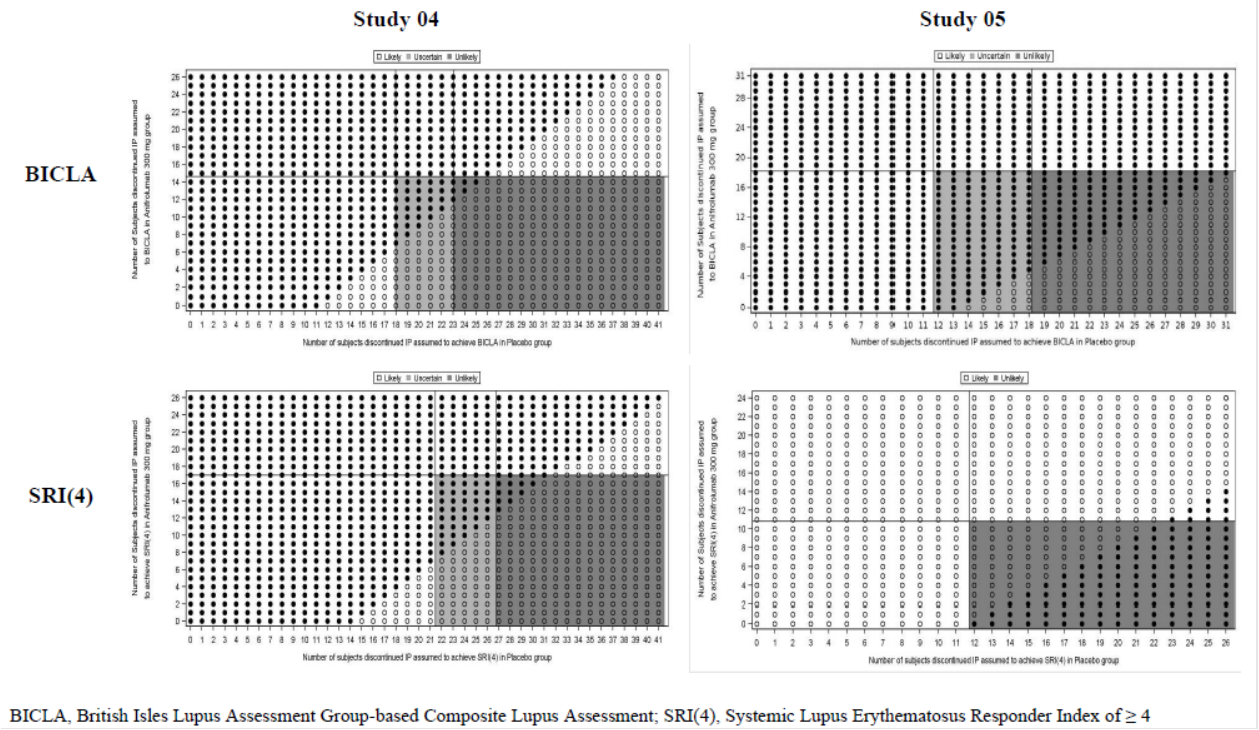
Tipping point analyses for BICLA and SRI(4), detailing all possible combinations of imputed response/nonresponse for IP discontinuation by treatment arm, are illustrated in Figure 14. These tipping point analyses were performed for the composite estimand where patients with prior restricted medication use or documented evidence that IP discontinuation was related to lack of efficacy were imputed as non-responders, and patients who prematurely discontinued IP without documented evidence of lack of efficacy or prior restricted medication use were evaluated using all possible combinations of responders/non-responders. As outlined above, in Study 04, 41 placebo patients and 26 anifrolumab 300 mg patients prematurely discontinued IP without evidence of restricted medication use prior to IP discontinuation. For BICLA, the nominal p-values tipped from < 0.05 to ≥ 0.05 when a net gain of 12 or more placebo-treated patients were imputed as BICLA responders relative to anifrolumab-treated patients, which corresponds to a treatment difference around 10%. Specifically, when the number of responders imputed for premature IP discontinuations for placebo (y) is greater than or equal to the number of responders imputed for anifrolumab (x) plus 12, then the nominal p-value is ≥ 0.05 (e.g., $y \geq x + 12$). In Study 05, 31 patients in each treatment arm prematurely discontinued IP without evidence of restricted medication use prior to IP discontinuation; the tipping point occurs for BICLA when there is a net gain of 13 more responders imputed for placebo than for anifrolumab (e.g., $y \geq x + 13$) and corresponds to a treatment difference around 10%. Additionally for Study 05, the treatment difference is always > 0 and once the imputation reaches ≥ 19 anifrolumab-treated patients imputed as responders, all values of responders imputed for placebo result in a nominal p-value < 0.05.

For SRI(4) in study 04, the tipping point is reached when 15 or more placebo-treated patients are imputed as SRI(4) responders relative to anifrolumab-treated patients. In Study 05 which did not achieve statistical significance with the SRI(4) primary estimand, the SRI(4) response tips to a nominal p-value

< 0.05 when there is a net gain of 8 anifrolumab-treated patients imputed as responders relative to placebo.

In study 04, the baseline scenario (anifrolumab 0 additional responders, placebo 0 additional responders; i.e., no changes in assumed status) yields a delta of 16.5%, with an associated p value of 0.001. To illustrate the substantial effect of various assumptions on the estimated treatment difference, a few alternative scenarios are provided below. The numbers refer to patients who discontinued IP and are assumed BICLA responders:

- Anifrolumab: 0 responders, placebo 10 responders -> delta 11.0%, p-value 0.035
- Anifrolumab: 0 responders, placebo 12 responders -> delta 9.9%, p-value 0.058
- Anifrolumab: 2 responders, placebo 12 responders -> delta 11.0%, p-value 0.035
- Anifrolumab: 2 responders, placebo 15 responders -> delta 9.3%, p-value 0.074



BICLA, British Isles Lupus Assessment Group-based Composite Lupus Assessment; SRI(4), Systemic Lupus Erythematosus Responder Index of ≥ 4

Figure 14 BICLA and SRI(4) response rate sensitivity analyses, treatment comparison at Week 52, tipping point analyses, Study 04 and Study 05 (full analysis sets)

Solid dots represent combinations which result in a nominally significant (p <0.05) treatment effect for anifrolumab compared with placebo. The open dots represent combinations which are not nominally significant (p ⩾0.05).

The applicant highlighted other specific scenarios that can be considered in the tipping point analyses. In Table 30, the first row shows the primary estimand which assumes that all IP discontinuations are non-responders. For the second and third rows, response rates were assigned to the subgroup of patients who were considered to discontinue IP for a reason that was not related to lack of efficacy (see bottom row of Table 29). Thus, the second row assumes all such IP discontinuations are responders, and the third row applies the BICLA response rate by treatment group from the completers analysis. The treatment differences for all 3 analyses range from 16.3 % to 17.6 % (nominal p-values ≤ 0.002) for Study 04 and range from 17.0 % to 25.2 % (nominal p-values < 0.001) for Study 05.

Table 30 BICLA response rates at Week 52 and sensitivity analyses for all combinations of responder/non-responder for patients who prematurely discontinued IP not due to lack of efficacy- Study 04 and Study 05 (full analysis sets)

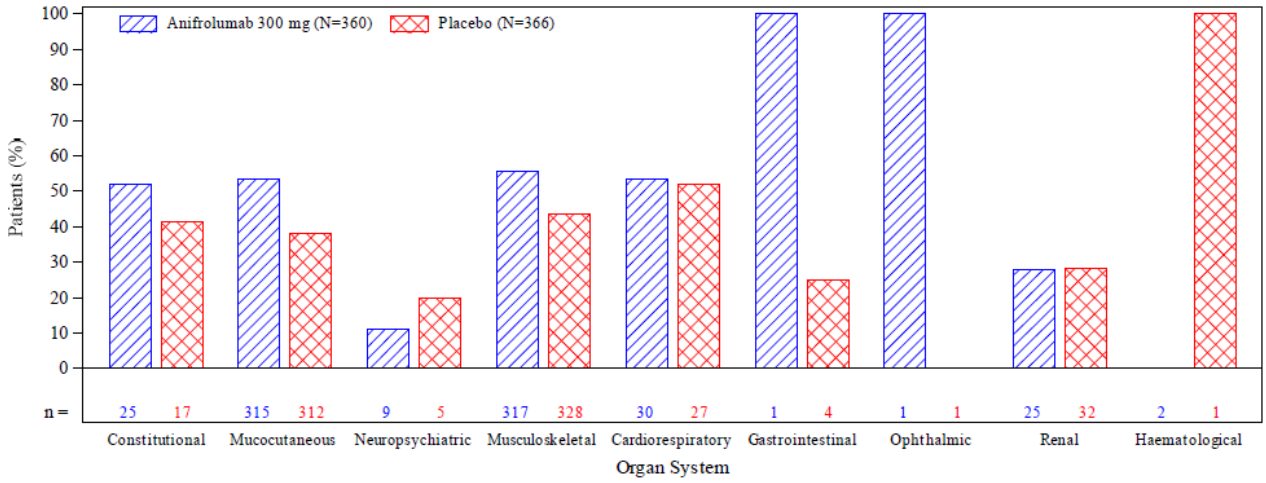
BICLA at Week 52	Study 04				Study 05			
	Anifrolumab 300 mg (N = 180)	Placebo (N = 182)	Difference in response rates	p-value	Anifrolumab 300 mg (N = 180)	Placebo (N = 184)	Difference in response rates	p-value
Primary estimand[a] (IPD/RM/WD = NR)	86 (47.8)	57 (31.5)	16.3	p=0.001	85 (47.1)	55 (30.2)	17.0	p <0.001
Prematurely discontinued IP not related to lack of efficacy	**n=22**	**n=22**			**n=23**	**n=9**		
All deemed Responders	n=22 108 (60.0)	n=22 79 (43.4)	16.6	p=0.002	n=23 108 (60.0)	n=9 64 (34.8)	25.2	p<0.001
Responders based on %Response among BICLA Completers	n=12 98 (54.4)	n=10 67 (36.8)	17.6	P<0.001	n=14 99 (55.0	n=4 59 (32.1)	22.9	p<0.001

[a] Patients treated with restricted medication beyond protocol-allowed threshold, discontinue investigational product, or withdraw from study are regarded as non-responders.
BICLA, British Isles Lupus Assessment Group-based Composite Lupus Assessment; CI, Confidence interval; IP, Investigational product; IPD, Discontinuation of investigational product; N, number of patients in treatment group; n, Number of patients in analysis; NR, Non-response; RM, Restricted medication; WD, Study withdrawal

Individual BILAG-2004 and SLEDAI-2K domains

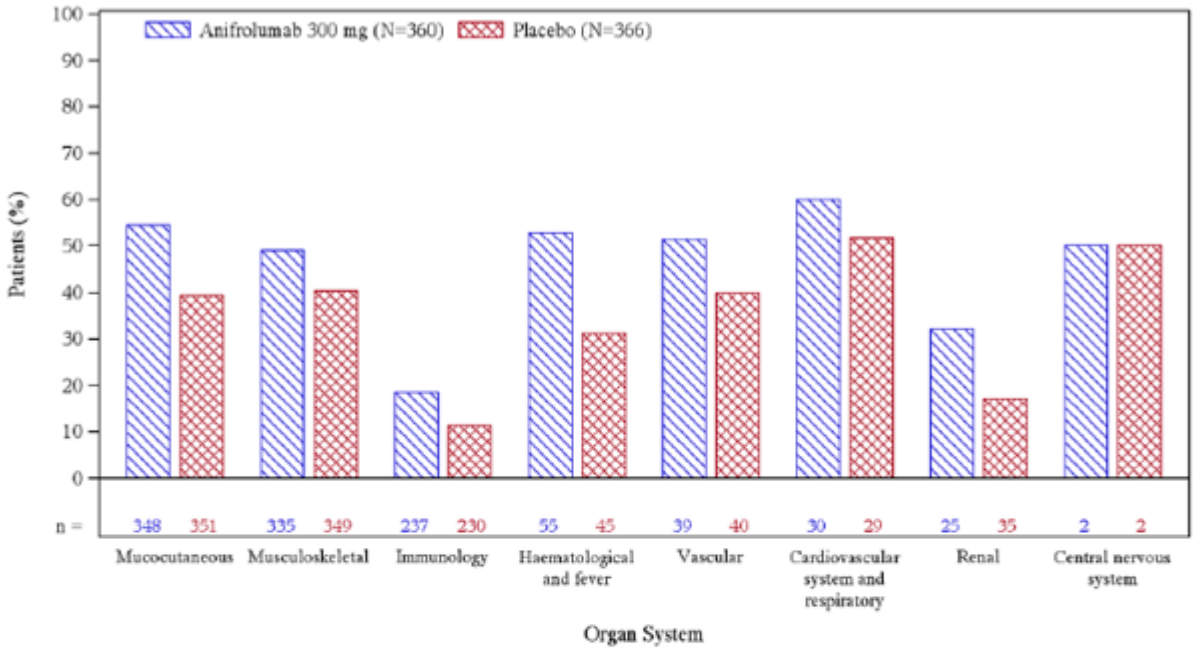
BILAG-2004 or SLEDAI-2K improvement responses were pre-specified secondary endpoints in studies 04, 05, and 1013. A BILAG-2004 improvement response is defined as the transitioning from BILAG-2004 A or B at baseline to a lower score at Week 52. A SLEDAI-2K improvement response is defined as an organ system score at Week 52 that is less than the corresponding score at baseline.

Patients treated with restricted medication beyond protocol-allowed threshold, and those who discontinued investigational product, were regarded as non-responders. For both BILAG-2004 and SLEDAI-2K most patients had moderate or severe activity in the musculoskeletal and/or mucocutaneous organ domains at baseline, with lesser involvement in other organ domains (for SLEDAI-2K, the immunology domain was also well represented); there were similar distributions of baseline organ involvement across the 3 studies. Improvement on individual BILAG-2004 domains in the Phase III studies is displayed in Figure 15, and improvement on SLEDAI-2K domains is displayed in Figure 16.



Source: Figure 2.3.1.7.2, Appendix 2.7.3.6.2 in Module 5.3.5.3.
Percentages are based upon all patients in the full analysis set within the respective treatment group with involvement of the corresponding organ system at baseline.
Phase III pool includes study 04 and study 05 (excluding the 150 mg group from study 05).
The results are based on the study 04 rules for restricted medications. For additional information, see Section 1.2.1.7.
Response in BILAG-2004 improvement is defined as the transitioning from BILAG A or B at baseline to a lower score at Week 52. Patients treated with restricted medication beyond protocol-allowed threshold, and those who discontinued investigational product, are regarded as non-responders.
BILAG-2004 British Isles Lupus Assessment Group-2004; n Number of patients in analysis; N Number of patients in treatment group.

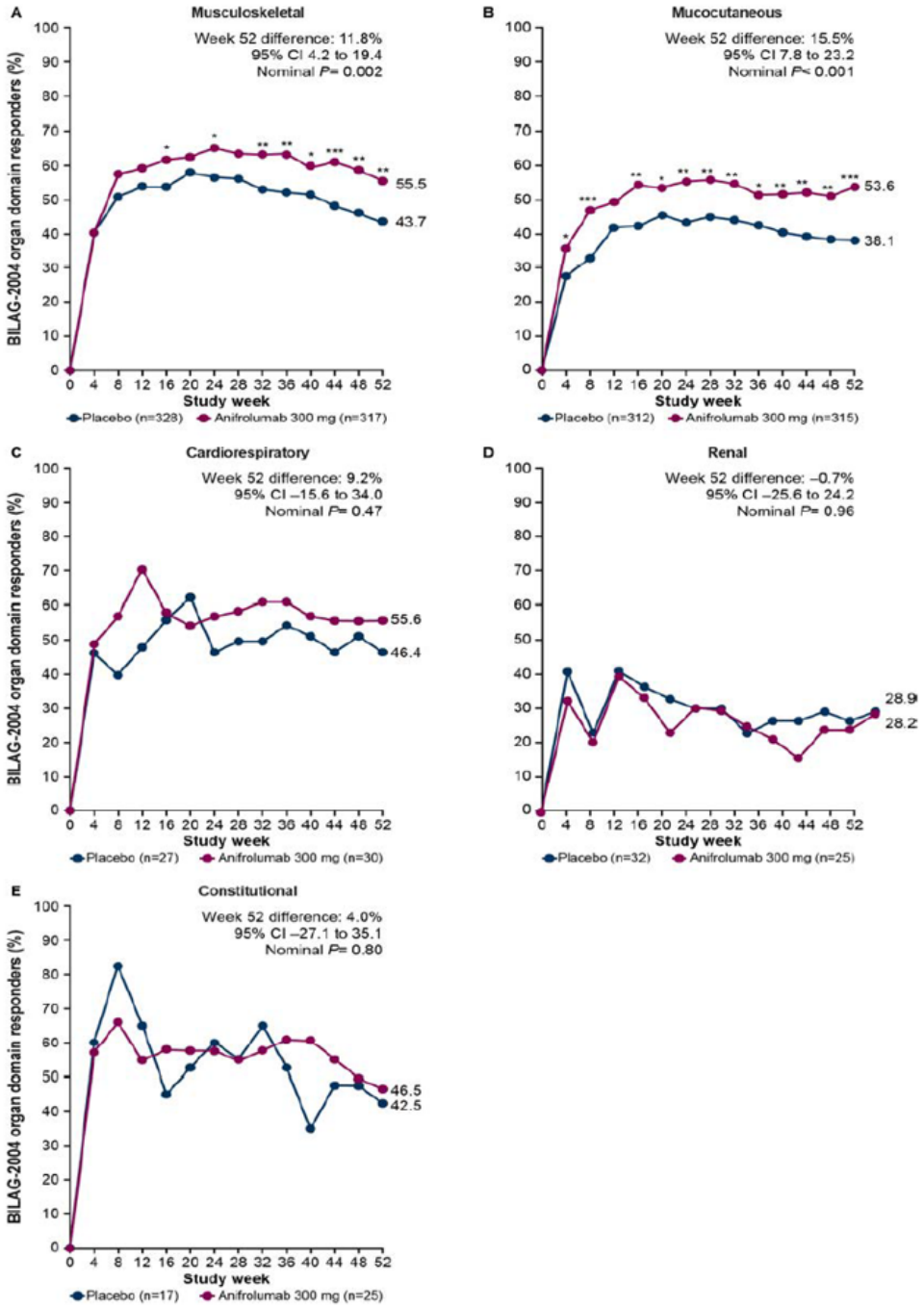
Figure 15 BILAG-2004 organ improvement response at Week 52 by organ system—phase III pool (full analysis set)



The SLEDAI-2K consists of 9 domains ('CNS'; 'vascular'; 'renal'; 'musculoskeletal'; 'serosal'; 'mucocutaneous'; 'immunologic'; 'constitutional'; and 'hematologic'). For the purposes of comparison with BILAG-2004 organ domains, 'serosal' is relabeled 'cardiovascular system and respiratory', and 'constitutional' is combined with 'hematologic' and relabeled 'hematological and fever' in this figure.
Percentages are based upon all patients in the full analysis set within the respective treatment group with involvement of the corresponding organ system at baseline.
Phase III pool includes studies 04 and 05 (excluding the 150 mg group from study 05).
The results are based on the study 04 rules for restricted medications.
Baseline is defined as the last measurement prior to randomization and IP dose administration on Day 1.
Involvement is a SLEDAI-2K organ system score greater than 0. Improvement is a SLEDAI-2K organ system score less than the corresponding score at baseline.
Patients treated with restricted medication beyond protocol-allowed threshold, and those who discontinued IP, are regarded as nonresponders with respect to improvement in SLEDAI-2K organ systems.
BILAG-2004, British Isles Lupus Assessment Group-2004; CNS, Central nervous system; IP, Investigational product; N, Number of patients within respective treatment group; n, Number of patients in analysis; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000.

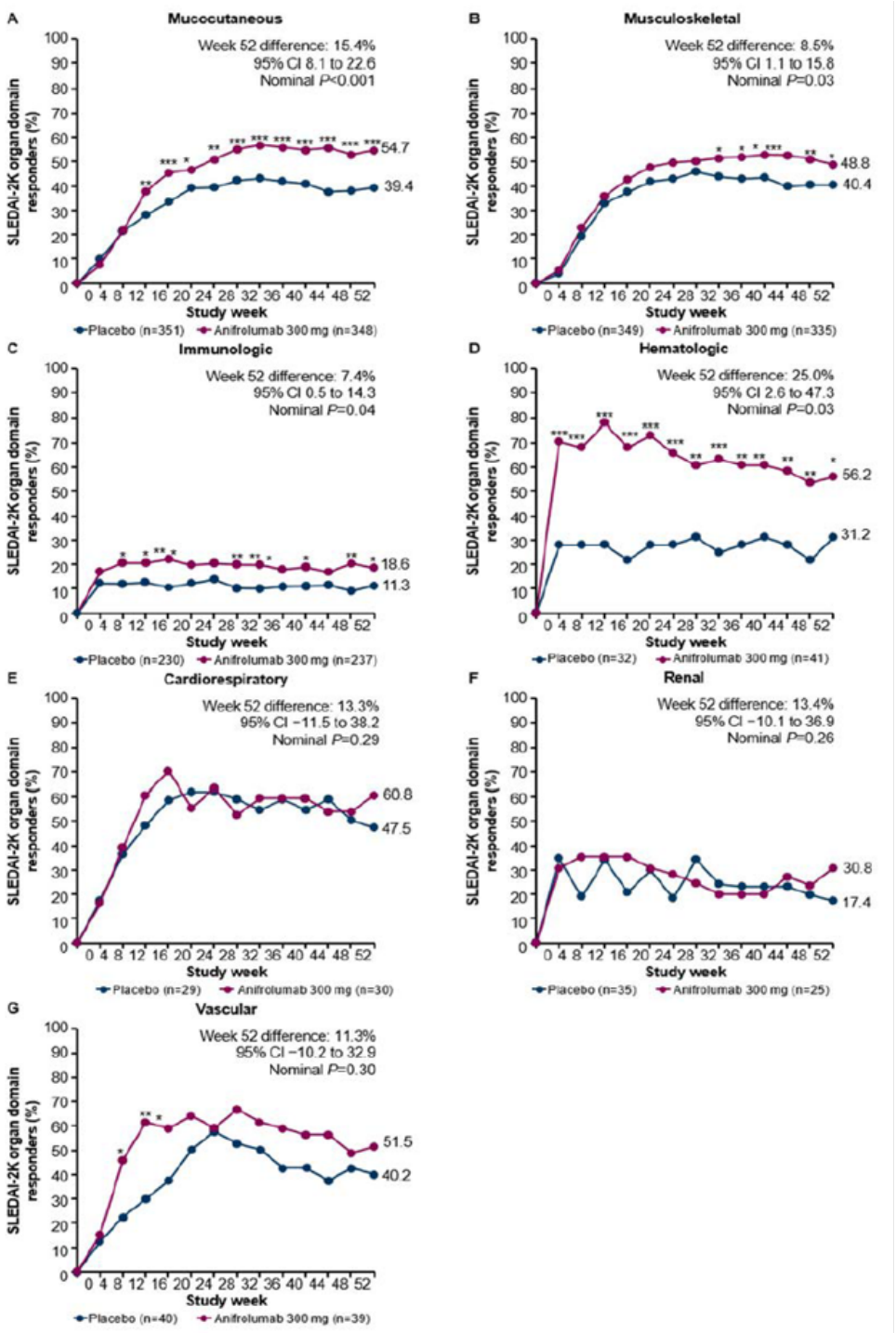
Figure 16 SLEDAI-2K organ improvement response at Week 52 by organ system—phase III pool (full analysis set)

Response rates within individual BILAG-2004 and SLEDAI-2K organ domains over time are displayed for the pooled Phase III data in *Figure 17* and Figure 18.



BILAG-2004 organ domain responder is defined as a reduction in baseline A or B score at Week 52.
BILAG-2004 neuropsychiatric, gastrointestinal, hematologic, and ophthalmic domains are not plotted because there were too few patients in each treatment group. Points are estimates. Estimates are calculated using a stratified Cochran–Mantel–Haenszel approach, with stratification factors as listed in the Methods section.
*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$ (based on Cochran–Mantel–Haenszel approach for the comparison of anifrolumab vs placebo).
BILAG-2004, British Isles Lupus Assessment Group 2004.

Figure 17 Individual BILAG-2004 organ domains: responders over time (Phase III pool)

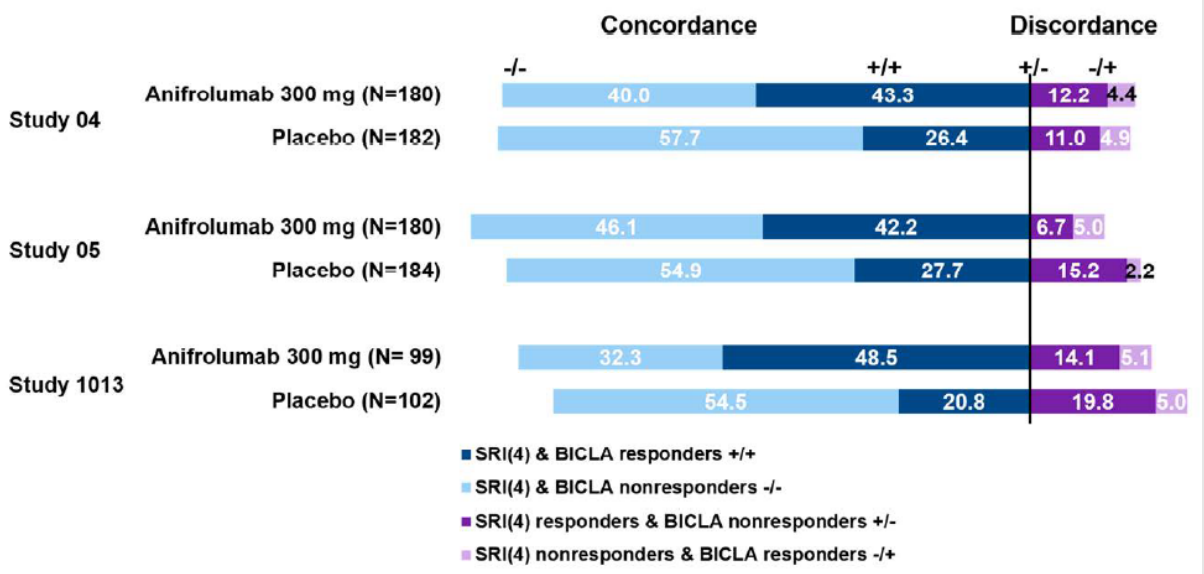


SLEDAI-2K organ domain responder is defined as a reduction in baseline SLEDAI-2K organ domain score. SLEDAI-2K central nervous system domain is not plotted because there were too few patients in each treatment group. Points are estimates. Estimates are calculated using a stratified Cochran–Mantel–Haenszel approach, with stratification factors as listed in the Methods section. $*P < 0.05$; $**P < 0.01$; $***P < 0.001$ (based on Cochran-Mantel–Haenszel approach for the comparison of anifrolumab vs placebo).
SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000.

Figure 18 Individual SLEDAI-2K organ domains: responders over time (Phase III pool)

Correlation of BICLA and SRI(4) response

The applicant conducted additional analyses to evaluate the correlation of BICLA response and SRI(4) response on an individual patient level. The outcomes on BICLA and SRI(4) response at Week 52 in each patient in studies 04, 05, and 1013 are summarised in Figure 19.



BICLA, British Isles Lupus Assessment Group-based Composite Lupus Assessment; SRI(4), Systemic Lupus Erythematosus Responder Index of ≥ 4.
Sources: Table 0000.260.6 and Table 0001.260.3, Appendix A.

Figure 19 Patient responder status for SRI[4] and BICLA in Study 04, Study 05, and Study 1013 (%)

The degree of agreement between each outcome was assessed as the proportion of patients with concordant results (calculated as the number of patients with agreement of response divided by the total number of patients). Cohen's Kappa coefficient was used to evaluate the degree of concordance or reliability between the 2 endpoints. The majority of patients in all 3 studies (approximately 75% to 85%) had concordant outcomes on SRI(4) and BICLA (i.e., responders on both, or non-responders on both). The Cohen's Kappa analysis suggested a moderate to substantial agreement (0.6 to 0.7) between the outcomes (nominal p-value: < 0.001). The proportion of patients who had both a BICLA response and a SRI[4] response at Week 52 was higher in the anifrolumab 300 mg group compared with the placebo group, with treatment differences ranging from 14.3% and 28.6% across the studies (Table 31).

Table 31 BICLA and SRI(4) dual-responders at Week 52: Study 04, Study 05, and Study 1013

BICLA and SRI(4) response at Week 52[a]	Study 04		Study 05		Study 1013	
	Anifrolumab 300 mg (N = 180)	Placebo (N = 182)	Anifrolumab 300 mg (N = 180)	Placebo (N = 184)	Anifrolumab 300 mg (N = 99)	Placebo (N = 102)
n	180	182	180	184	99	102
Number (%) of responders	78 (43.4)	48 (26.4)	76 (42.2)	51 (27.9)	48 (48.5)	21 (19.9)
Difference (%)[b]	16.9		14.3		28.6	
95% CI	7.2, 26.7		4.6, 24.0		15.7, 41.5	
Nominal p-value	< 0.001		0.004		< 0.001	

[a] Post hoc analyses.
[b] Difference between anifrolumab 300 mg and placebo.
BICLA, British Isles Lupus Assessment Group-2004-based Combined Lupus Assessment; CI, Confidence interval; n, Number of patients in analysis; N, Number of patients in treatment group; SRI(4), Systemic Lupus Erythematosus Responder Index of ≥ 4.

According to the applicant, the discordant results could be explained by a subset of SRI[4] responder/BICLA non-responder patients in study 05 (n=28 vs. n=12), with the treatment difference within this subset contributing a net of -8.5% percentage points to the overall SRI(4) treatment effect (6.7% - 15.2% = -8.5%; Figure 19; burgundy). In study 04, the number of patients in each treatment group in the SRI(4) responder/BICLA nonresponder subset was similar in both treatment groups (22 patients on anifrolumab vs. 20 patients on placebo), with the treatment difference contributing only a net +1.2 percentage points to the overall SRI(4) treatment difference in the study.

A summary of reasons for being a SRI(4) responder/BICLA non-responder is presented in Table 32.
In the SRI(4) responder/BICLA non-responder subset in study 05, a high proportion of patients in the placebo group achieved resolution of arthritis, which alone meets the 4-point reduction in SLEDAI-2K required for a SRI(4) response. In the anifrolumab 300 mg group in this subset, the reasons were more varied. In Study 04, a similar pattern was not seen. In both studies, the most frequent combination of a SRI(4) response/BICLA nonresponse discordance in this subgroup was SRI response due to arthritis/BICLA nonresponse due to rash. It should furthermore be noted that in this subgroup overall, the most common reason for BICLA nonresponse in both studies and both treatment groups was nonresponse due to rash / skin eruption (ranging from 60% to 86%).

Table 32 Overview of reasons for a SRI response and BICLA non-response at Week 52 (SRI[4] responder/BICLA non-responder subset in Study 05 and Study 04)

	SRI(4) responders/BICLA nonresponders in study 05	
	Anifrolumab 300 mg (N = 12)	Placebo (N = 28)
SRI Response/BICLA Nonresponse, n (%)		
SRI response due to Arthritis/BICLA nonresponse due to rash	5 (41.7)	20 (71.4)
SRI response not due to Arthritis/BICLA nonresponse due to rash	3 (25.0)	4 (14.3)
SRI response due to Any reason/BICLA nonresponse on arthritis	2 (16.7)	2 (7.1)
SRI response due to Any reason/Other[a] BICLA nonresponse	2 (16.7)	2 (7.1)

[a] Nonresponse due to a clinical manifestation other than rash or arthritis.
BICLA, British Isles Lupus Assessment Group-based Composite Lupus Assessment; n, Number of patients in analysis; N, Number of patients in treatment group; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000; SRI(4), Systemic Lupus Erythematosus Responder Index of ≥ 4.
Source: Table 0005.321.1, Appendix A.

	SRI(4) responders/BICLA nonresponders in Study 04	
	Anifrolumab 300 mg (N = 22)	Placebo (N = 20)
BICLA Nonresponse/SRI Response, n %	22 (100)	20 (100)
Skin eruption nonresponse on BICLA/SRI response due to arthritis	15 (68.2)	10 (50.0)
Skin eruption nonresponse on BICLA/SRI response not due to arthritis	3 (13.6)	2 (10.0)
Arthritis nonresponse on BICLA/SRI response due to any reason	2 (9.1)	6 (30.0)
Other[a] BICLA nonresponse/SRI response due to Any reason	2 (9.1)	2 (10.0)

[a] Nonresponse on BICLA not due to skin eruption or arthritis
Anti-dsDNA, Anti-double stranded DNA; BICLA, British Isles Lupus Assessment Group-based Composite Lupus Assessment; n, Number of patients in analysis; N, Number of patients in treatment group, SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000; SRI(4), Systemic Lupus Erythematosus Responder Index of ≥ 4

When comparing the baseline characteristics between the studies, some potential differences could be seen, with an overall slightly lesser joint involvement in study 04; the pattern of OCS use and tapering was also slightly different between the studies. However, no definitive underlying reason for the unique discordance pattern in study 05 could be identified.

Maintained OCS tapering

The proportion of patients who could reduce their OCS dose to a target of ≤ 7.5 mg/day prednisone or equivalent by Week 40 and maintain it to Week 52 was analysed as a key secondary endpoint in studies

04 and 05. This was analysed within the subgroup of patients with baseline OCS use ≥ 10 mg/day. The results are displayed in Table 33. A statistically significant difference between the treatment groups was seen in Study 04 (difference 21.2 percentage points (95% CI% 6.8, 35.7), p=0.004; in studies 05 and 1013, the differences between anifrolumab 300 mg and placebo were 16.6 and 29.1 percentage points, respectively.

Table 33 Proportion of patients who maintained OCS reduction at Week 52 in patients with OCS ≥ 10 mg/day at baseline—study 04, study 05, and study 1013 (full analysis sets)

	Study 04		Study 05			Study 1013	
Summary statistics	Anifrolumab 300 mg (N = 87)	Placebo (N = 83)	Anifrolumab 150 mg (N = 48)	Anifrolumab 300 mg (N = 103)	Placebo (N = 102)	Anifrolumab 300 mg (N = 55)	Placebo (N = 64)
n	87	83	48	103	102	55	64
Number (%) responders	45 (51.5)	25 (30.2)	25 (51.6)	51 (49.7)	34 (33.1)	31 (56.4)	17 (27.3)
Comparison with placebo							
Difference in response rate	21.2			16.6		29.1	
95% CI of difference in response rate	6.8, 35.7			3.4, 29.8		12.0, 46.2	
Nominal p-value [a]	0.004			0.014		< 0.001	

Derived from: Table 2.2.2.1, Appendix 2.7.3.6.1 in Module 5.3.5.3; Table 0001.138.3, Appendix 2.7.3.6.8 in Module 5.3.5.3; Table 14.2.1.3.1.1, study 1013 CSR in Module 5.3.5.1.

[a] The p-value for study 04 can be interpreted, this is a statistically significant result within the multiplicity testing. In study 05, since the primary endpoint failed to meet statistical significance, the analysis is exploratory. The p-value for study 1013 is based on the pre-specified logistic regression model for comparison of anifrolumab 300 mg versus placebo, adjusted for randomization stratification factors.

Percentages are based upon all patients in the full analysis set with baseline OCS ≥ 10 mg/day within the respective study and treatment group.

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

Study 04 and study 05 results are based on the study 04 rules for restricted medications. For additional information, see Section 1.2.1.7. Study 1013 results are based on the study 1013 rules for restricted medications.

OCS are described as 'Prednisone or equivalent'. OCS administered PRN are not considered in the calculation of the daily dose.

Maintained OCS reduction is defined as an OCS dose ≤ 7.5 mg/day by Week 40 without a dose increase between Week 40 and Week 52. Subjects treated with restricted medication beyond protocol-allowed thresholds, and those who discontinued investigational product, are regarded as non-responders.

The responder/non-responder rates, the difference in estimates, and associated 95% CI are calculated using a stratified CMH approach, with stratification factors SLEDAI-2K score and type I IFN gene signature test result at screening. The nominal p-values presented are based on this CMH model.

CI Confidence interval; CMH Cochran-Mantel-Haenszel; IFN Interferon; n Number of patients in analysis; N Number of patients in treatment group; NA Not available; OCS Oral corticosteroids; PRN Pro re nata (when necessary); SLEDAI-2K Systemic Lupus Erythematosus Disease Activity Index 2000.

As seen in Table 34, the majority of OCS reduction responders were also BICLA responders.

Table 34 BICLA response by maintained OCS reduction at Week 52—study 04 and study 05 (full analysis sets)

BICLA response	Maintained OCS reduction response	Number of patients			
		Study 04		Study 05	
		Anifrolumab 300 mg (N = 180)	Placebo (N = 182)	Anifrolumab 300 mg (N = 180)	Placebo (N = 184)
Responder	Responder	77	49	77	48
	Non-responder	9	8	8	7
Non-responder	Responder	34	30	29	37
	Non-responder	60	95	66	92

Source: Table 11.2.1.5 and Table 11.2.1.6, Appendix 2.7.3.6.3 in Module 5.3.5.3.

OCS are described as 'Prednisone or equivalent'.

BICLA responder is defined in Section 1.2.1.7.

Study 04 and study 05 results are based on the study 04 rules for restricted medications. For additional information, see Section 1.2.1.7.

Maintained OCS reduction responder is defined in Sections 1.2.1.7 and 3.2.2. For patients with baseline OCS < 10 mg/day, a responder needs to have an OCS dose at Week 40 that is less than or equal to his/her OCS dose at baseline, and no increase in OCS dose between Week 40 and Week 52. The patient also needs to meet the criteria of no permanent discontinuation of IP and no use of restricted medications.

BICLA British Isles Lupus Assessment Group-based Composite Lupus Assessment; N Number of patients in treatment group; OCS Oral corticosteroids.

CLASI Score

The CLASI score was used to evaluate the effect of anifrolumab on inflammatory cutaneous SLE lesions. A CLASI responder was defined as ≥ 50% reduction in CLASI activity score at Week 12 among patients with at least moderately active skin disease (CLASI ≥ 10) at baseline. The results are displayed in Table 35.

A statistically significant difference between the treatment groups was seen in Study 04 (difference 24.0 percentage points (95% CI% 4.3, 43.6), p=0.017; in studies 05 and 1013, the differences between anifrolumab 300 mg and placebo were 18.7 and 32.8 percentage points, respectively. An early numerical separation of the anifrolumab 300 mg group compared with the placebo group in the observed CLASI activity response was maintained through the entire 52-week treatment period in all 3 studies.

Table 35 CLASI response at Week 12 in patients with a CLASI activity score ≥ 10 at baseline—study 04, study 05, and study 1013 (full analysis sets)

	Study 04		Study 05			Study 1013	
CLASI response at Week 12	**Anifrolumab 300 mg (N = 49)**	**Placebo (N = 40)**	**Anifrolumab 150 mg (N = 30)**	**Anifrolumab 300 mg (N = 58)**	**Placebo (N = 54)**	**Anifrolumab 300 mg (N = 27)**	**Placebo (N = 26)**
n	49	40	30	58	54	27	26
Number (%) responders	24 (49.0)	10 (25.0)	15 (50.0)	25 (43.6)	14 (24.9)	13 (48.1)	4 (15.4)
Comparison with placebo							
Difference in response rate	24.0			18.7		32.8	
95% CI of difference in response rate	4.3, 43.6			1.4, 36.0		8.4, 57.1	
Nominal p-value[a]	0.017			0.034		0.013	

Derived from: Table 2.2.3.1, Appendix 2.7.3.6.1 in Module 5.3.5.3; Table 0001.138.3, Appendix 2.7.3.6.8 in Module 5.3.5.3; Table 14.2.2.8.6, study 1013 CSR in Module 5.3.5.1.

[a] The p-value for study 04 can be interpreted, this is a statistically significant result within the multiplicity testing. In study 05, since the primary endpoint failed to meet statistical significance, the analysis is exploratory. The p-value for study 1013 is based on the pre-specified logistic regression model for comparison of anifrolumab 300 mg versus placebo, adjusted for randomization stratification factors.

Percentages are based upon all patients in the full analysis set with a baseline CLASI activity score ≥ 10 within the respective study and treatment group.

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

CLASI response is defined in Sections 1.2.1.7 and 3.2.3.1.

Study 04 and study 05 results are based on the study 04 rules for restricted medications. For additional information, see Section 1.2.1.7. Study 1013 results are based on the study 1013 rules for restricted medications.

The responder/non-responder rates (percentages), the difference in estimates, and associated 95% CI are calculated using a stratified CMH approach, with stratification factors SLEDAI-2K score at screening, Day 1 OCS dose, and type I IFN gene signature test result at screening. The nominal p-values presented are based on this CMH model.

CI Confidence interval; CLASI Cutaneous Lupus Erythematosus Disease Area and Severity Index; CMH Cochran-Mantel-Haenszel; IFN Interferon; n Number of patients in analysis; N Number of patients in treatment group; NA Not available; OCS Oral corticosteroids; SLEDAI-2K Systemic Lupus Erythematosus Disease Activity Index 2000

Joint symptoms

A joint endpoint was included as a secondary endpoint in Study 05 and escalated as a multiplicity-controlled key secondary endpoint into Study 04 based on encouraging findings in Study 05. For Study 04, a responder was defined as a patient with moderate to severe disease (≥ 6 swollen and ≥ 6 tender joints) at baseline who achieved ≥ 50% reduction from baseline in swollen and tender joint counts at Week 52.Whereas a 19% difference between anifrolumab 300 mg and placebo had been observed on a corresponding joint response in Study 05, there was no difference between anifrolumab 300 mg and placebo in joint response in Study 04 (difference 4.7%, 95% CI -10.6, 20.0).

Disease flares

Numerical trends favouring anifrolumab 300 mg over placebo were seen on annual flare rates (Table 36). However, none of the differences were statistically significant, with Study 04 failing due to the multiplicity-controlled testing strategy.

Table 36 Flare rate through Week 52, negative binomial regression model (full analysis sets)

Summary statistics	Study 04		Study 05		Study 1013	
	Anifrolumab 300 mg (N = 180)	Placebo (N = 182)	Anifrolumab 300 mg (N = 180)	Placebo (N = 184)	Anifrolumab 300 mg (N = 99)	Placebo (N = 102)
Total number of flares	86	122	109	133	50	61
Total follow-up time (years)	170.2	164.6	166.7	170.8	93.8	85.1
Annualized rate (estimate)	0.43	0.64	0.57	0.68	0.42	0.58
Rate ratio, comparison with placebo						
Estimate	0.67		0.83		0.73	
95% CI of rate ratio	0.48, 0.94		0.61, 1.15		0.44, 1.20	
Nominal p-value	0.020		0.270		0.2149[a]	

Derived from: Table 2.2.5.1, Appendix 2.7.3.6.1 in Module 5.3.5.3; Table 14.2.2.4.8.1.1, study 1013 CSR in Module 5.3.5.1. Table 0001.138.3, Appendix 2.7.3.6.8 in Module 5.3.5.3; Table 0001.190.1, Appendix 2.7.3.6.8 in Module 5.3.5.3.

[a] p-value is based on the negative binomial regression model for comparison of anifrolumab 300 mg versus placebo adjusted for randomization stratification factors

A flare is defined as either one or more new BILAG-2004 A or 2 or more new BILAG-2004 B items compared with the previous visit (ie, a worsening from an E, D, or C score to a B score in at least 2 organ systems or a worsening from an E, D, C, or B score to an A score in any one organ system compared with the previous visit).

The response variable in the model is the number of flares up to Week 52/early discontinuation visit. The model includes covariates of treatment group, and the stratification factors (SLEDAI-2K score at screening, Day 1 OCS dose, and type I IFN gene signature test result at screening). The logarithm (to base e) of the follow-up time is used as an offset variable in the model to adjust for patients having different exposure times.

Note that for study 05, there are some slight differences between the results in this table and the corresponding results in the study 05 CSR. This is because of slight differences in the final-lock database and the Week 52-lock database used for the CSR. These differences did not impact the conclusion from study 05.

BILAG-2004 British Isles Lupus Assessment Group-2004; CI Confidence interval; IFN Interferon; N Number of patients in treatment group; NA Not available; OCS Oral corticosteroids; SLEDAI-2K Systemic Lupus Erythematosus Disease Activity Index 2000.

Higher SRI thresholds

In addition to SRI(4), higher level reductions in SLEDAI-2K thresholds (SLEDAI-2K ≥ 5 through ≥ 8) were calculated for the SRI responder analysis at Week 52 and analysed as secondary endpoints. Results for SRI(6), SRI(7) and SRI(8) in studies 04 and 05 are displayed in Table 37.

Table 37 SRI(6), SRI(7) and SRI(8) response rates at Week 52, studies 04, 05 and Phase III pool (full analysis set)

Variable[a]: SRI(6)

	Study 04		Study 05			Phase III pool	
	Anifrolumab 300 mg (N=180)	Placebo (N=182)	Anifrolumab 150 mg (N=93)	Anifrolumab 300 mg (N=180)	Placebo (N=184)	Anifrolumab 300 mg (N=360)	Placebo (N=366)
n	180	181	93	180	184	360	365
Number (%) responders	79 (44.0)	48 (26.4)	37 (39.8)	71 (39.6)	58 (31.8)	150 (41.8)	106 (29.1)
Number (%) non-responders	101 (56.0)	133 (73.6)	56 (60.2)	109 (60.4)	126 (68.2)	210 (58.2)	259 (70.9)
95% CI response rate	36.8, 51.2	19.9, 33.0	29.9, 49.7	32.5, 46.8	25.1, 38.5	36.7, 46.9	24.4, 33.8
Comparison with placebo							
Difference in response rate	17.6			7.9		12.7	
95% CI of difference in response rate	7.8, 27.3			-2.0, 17.7		5.8, 19.6	
Nominal p-value	<0.001			0.116		<0.001	

Variable[a]: SRI(7)

	Study 04		Study 05			Phase III pool	
	Anifrolumab 300 mg (N=180)	Placebo (N=182)	Anifrolumab 150 mg (N=93)	Anifrolumab 300 mg (N=180)	Placebo (N=184)	Anifrolumab 300 mg (N=360)	Placebo (N=366)
n	167	169	85	173	176	340	345
Number (%) responders	56 (33.6)	34 (20.0)	30 (35.2)	52 (30.1)	31 (17.6)	108 (31.8)	65 (18.7)
Number (%) non-responders	111 (66.4)	135 (80.0)	55 (64.8)	121 (69.9)	145 (82.4)	232 (68.2)	280 (81.3)
95% CI response rate	26.4, 40.7	13.6, 26.3	24.9, 45.4	23.2, 37.1	11.6, 23.6	26.8, 36.8	14.4, 23.1
Comparison with placebo							
Difference in response rate	13.6			12.6		13.1	
95% CI of difference in response rate	4.0, 23.2			3.4, 21.7		6.4, 19.7	
Nominal p-value	0.005			0.007		<0.001	

Variable[a]: SRI(8)

	Study 04		Study 05			Phase III pool	
	Anifrolumab 300 mg (N=180)	Placebo (N=182)	Anifrolumab 150 mg (N=93)	Anifrolumab 300 mg (N=180)	Placebo (N=184)	Anifrolumab 300 mg (N=360)	Placebo (N=366)
n	166	167	85	173	174	339	341
Number (%) responders	50 (30.2)	33 (19.6)	28 (32.8)	51 (29.6)	29 (16.5)	101 (29.9)	62 (18.0)
Number (%) non-responders	116 (69.8)	134 (80.4)	57 (67.2)	122 (70.4)	145 (83.5)	238 (70.1)	279 (82.0)
95% CI response rate	23.2, 37.3	13.2, 25.9	22.7, 43.0	22.7, 36.5	10.6, 22.4	25.0, 34.8	13.7, 22.3
Comparison with placebo							
Difference in response rate	10.7			13.0		11.9	
95% CI of difference in response rate	1.2, 20.2			4.0, 22.1		5.3, 18.4	
Nominal p-value	0.028			0.005		<0.001	

[a] SRI(5), SRI(6), SRI(7), and SRI(8) response at Week 52 will be evaluated only for patients with baseline SLEDAI 2K >=5 points, >=6 points, >=7 points, and >=8 points, respectively.
Percentages are based upon all patients in the full analysis set within the respective treatment group with baseline SLEDAI-2K >=X points for SRI(X).
Baseline is defined as the last measurement prior to randomization and investigational product dose administration on Day 1.
Phase III pool includes study 04 and study 05 (excluding the 150 mg group from study 05).
SRI(X) response is defined in section 7.1.3 of statistical analysis plan. Results are based on the study 04 rules for restricted medications.
The responder/non-responder rates, the difference in estimates and associated 95% CI are calculated using a stratified CMH approach, with stratification factors SLEDAI-2K score at screening, Day 1 OCS dose, type I IFN gene signature test result at screening and study (study 04 vs study 05).
BILAG-2004 British Isles Lupus Assessment Group-2004; CI Confidence Interval; CMH Cochran-Mantel-Haenszel; IFN Interferon; n Number of patients in analysis; N Number of patients in treatment group; OCS Oral corticosteroids; PGA Physician's Global Assessment; SLEDAI-2K Systemic Lupus Erythematosus Disease Activity Index 2000; SRI Systemic Lupus Erythematosus Responder Index.

Patient-reported outcomes

FACIT-fatigue was used to evaluate the effect of anifrolumab on fatigue, which is often a very prominent and disabling manifestation of SLE. On average, patients had severe fatigue at baseline, with mean FACIT-F scores between 24.5 and 27.0 out of a maximum scale score of 52 points across the studies and treatment groups. As seen in Table 38, small numerical trends favouring anifrolumab were observed in studies 04 and 05.

Table 38 FACIT-fatigue response at Week 52—study 04, study 05, and phase III pool (full analysis set)

BICLA response at Week 52	FACIT-Fatigue response at Week 52	Study 04		Study 05		Phase III pool	
		Anifrolumab 300 mg (N = 180)	Placebo (N = 182)	Anifrolumab 300 mg (N = 180)	Placebo (N = 184)	Anifrolumab 300 mg (N = 360)	Placebo (N = 366)
All patients	n	180	182	180	184	360	366
	Number (%) responders	60 (33.2)	45 (24.7)	64 (35.4)	52 (28.4)	124 (34.3)	97 (26.5)
	Number (%) non-responders	120 (66.8)	137 (75.3)	116 (64.6)	132 (71.6)	236 (65.7)	269 (73.5)
	95% CI responder rate	26.2, 40.1	18.3, 31.1	28.4, 42.5	21.7, 35.0	29.4, 39.2	21.9, 31.1
	Comparison with placebo						
	Difference in response rate	8.5		7.1		7.8	
	95% CI of difference in response rate	-0.9, 17.9		-2.6, 16.7		1.0, 14.5	
BICLA responder	FACIT-fatigue responder	47 (26.1)	29 (15.9)	50 (27.8)	29 (15.8)	97 (26.9)	58 (15.8)
	FACIT-fatigue non-responder	36 (20.0)	24 (13.2)	34 (18.9)	22 (12.0)	70 (19.4)	46 (12.6)
BICLA non-responder	FACIT-fatigue responder	13 (7.2)	16 (8.8)	14 (7.8)	23 (12.5)	27 (7.5)	39 (10.7)
	FACIT-fatigue non-responder	57 (31.7)	71 (39.0)	48 (26.7)	71 (38.6)	105 (29.2)	142 (38.8)

Derived from: Table 2.3.3.3 and Table 2.3.3.4, Appendix 2.7.3.6.1 in Module 5.3.5.3.

Percentages are based upon all patients in the full analysis set within the respective treatment group.

Phase III pool includes study 04 and study 05 (excluding the 150 mg group from study 05).

A response in FACIT-fatigue is defined as an improvement from baseline to Week 52 of > 3 points (ie, change from baseline < -3). Patients treated with restricted medication beyond protocol-allowed threshold, and those who discontinued investigational product, are regarded as non-responders.

Results are based on the study 04 rules for restricted medications. For additional information see Section 1.2.1.7.

The FACIT-fatigue responder/non-responder rates, the difference in estimates and associated 95% CI are calculated using a stratified CMH approach, with stratification factors SLEDAI-2K score at screening, Day 1 OCS dose, type I IFN gene signature test result at screening, and study (study 04 vs study 05).

BICLA response is defined in Section 1.2.1.7.

BICLA British Isles Lupus Assessment Group-based Composite Lupus Assessment; BILAG-2004 British Isles Lupus Assessment Group-2004; CI Confidence interval; CMH Cochran-Mantel-Haenszel; CSR Clinical study report; FACIT-fatigue Functional Assessment of Chronic Illness Therapy-fatigue; IFN Interferon; n Number of patients in analysis; N Number of patient in treatment group; OCS Oral corticosteroids; PGA Physician Global Assessment; SLEDAI-2K Systemic Lupus Erythematosus Disease Activity Index 2000; VAS Visual analog scale.

Results on Short Form-36 (SF-36), a widely used PRO instrument for measuring general health status, showed small numerical differences favouring anifrolumab 300 mg over placebo in the pooled Phase III dataset.

Immunology/Serology (anti-dsDNA; C3; C4)

Anti-dsDNA positivity was detected in 44.4% of patients in the phase III pool. At baseline, median levels of anti-dsDNA were 50.1 U/mL and 53.0 U/mL, in the anifrolumab 300 mg and placebo groups, respectively.

Among patients with positive anti-dsDNA at baseline in the phase III pool, median change from baseline to Week 52 in anti-dsDNA antibody levels was -14.82 U/mL in the anifrolumab 300 mg group and -5.37 U/mL in the placebo group. In patients with anti-dsDNA antibodies at baseline, 7.8% of patients treated with anifrolumab 300 mg and 5.8% of patients receiving placebo had converted to anti-dsDNA negative by Week 52 in the phase III pool.

In the phase III pool, 36.8% of patients had low/abnormal complement C3 levels at baseline. At baseline, mean levels of C3 were 0.691 g/L in the anifrolumab 300 mg group and 0.701 g/L. For patients with an abnormal C3 level at baseline, mean change from baseline to Week 52 in C3 levels was 0.13 g/L in the anifrolumab 300 mg group and 0.04 g/L in the placebo group in the phase III pool. Among patients with low/abnormal complement levels at baseline, normalisation of C3 was observed at Week 52 in 16.2% of patients receiving anifrolumab and in 9.5% of patients receiving placebo in the phase III pool.

In addition, 23.3% of patients in the phase III pool had low/abnormal C4 levels at baseline. At baseline, mean levels of C4 were 0.073 g/L in the anifrolumab 300 mg group and 0.072 g/L in the placebo group. For patients with an abnormal C4 level at baseline, similar small increases were observed over the 52 weeks in both treatment groups (mean change from baseline of 0.02 g/L for anifrolumab vs. 0.02 g/L for placebo at Week 52 in the phase III pool). In patients with low/abnormal complement levels at

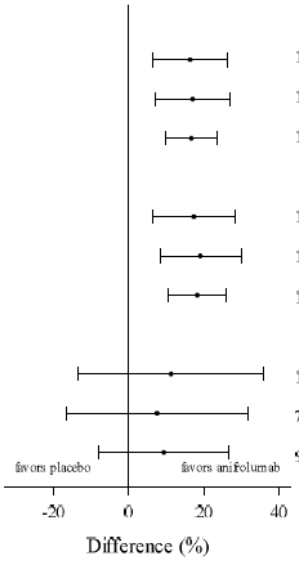
baseline, normalisation of C4 was observed at Week 52 in 22.6% of patients receiving anifrolumab and in 7.1% of patients receiving placebo in the phase III pool.

Ancillary analyses

Analysis of BICLA response by IFN gene signature

To evaluate the role of the IFN gene signature as a potential predictor of treatment response, the BICLA response at Week 52 was analysed in the respective subgroups on pooled Phase III data; response in the IFN gene signature - high subgroup was designated a key secondary endpoint in Study 04 and evaluated as an exploratory endpoint in studies 05 and 1013. The results are outlined in Figure 20. As the responder rates for anifrolumab 300 mg were similar across all patients (the smaller treatment difference in test-low patients being due to a higher placebo response rate), the applicant considers that the totality of data in the Phase III pool supports that type I IFN gene signature test-low patients may also benefit from anifrolumab treatment. Consequently, the test is not included as part of the applicant's proposed indication in the SmPC.

	Anifrolumab 300mg n/N (response rate)[a]	Placebo n/N (response rate)[a]	Difference[95%CI][a]	Nominal p-value
In all patients				
BICLA at Week 52, study 04	86 /180 (47.8%)	57 /182 (31.5%)	16.3 (6.3%, 26.3%)	0.001
BICLA at Week 52, study 05	85 /180 (47.1%)	55 /184 (30.2%)	17.0 (7.2%, 26.8%)	<0.001
BICLA at Week 52, phase III pool	171 /360 (47.5%)	112 /366 (30.8%)	16.6 (9.7%, 23.6%)	<0.001
In IFN gene signature test high patients				
BICLA at Week 52, study 04	72 /150 (48.0%)	46 /151 (30.7%)	17.3 (6.5%, 28.2%)	0.002
BICLA at Week 52, study 05	70 /148 (47.2%)	42 /151 (28.2%)	19.0 (8.3%, 29.8%)	<0.001
BICLA at Week 52, phase III pool	142 /298 (47.6%)	88 /302 (29.4%)	18.2 (10.5%, 25.8%)	<0.001
In IFN gene signature test low patients				
BICLA at Week 52, study 04	14 /30 (46.7%)	11 /31 (35.5%)	11.2 (-13.5%, 35.8%)	0.374
BICLA at Week 52, study 05	15 /32 (46.9%)	13 /33 (39.4%)	7.5 (-16.6%, 31.6%)	0.543
BICLA at Week 52, phase III pool	29 /62 (46.8%)	24 /64 (37.5%)	9.3 (-8.0%, 26.5%)	0.291



Source: Figure 2.2.1.4, Appendix 2.7.3.6.2 in Module 5.3.5.3.

[a] The responder/non-responder rates, the difference in estimates and associated 95% CI, are calculated using a stratified CMH approach with stratification factors. In the pooled analysis, an additional stratification factor is added for study (study 04 vs study 05)

Phase III pool includes study 04 and study 05 (excluding the 150 mg group from study 05).

Results are based on the study 04 rules for restricted medications. For additional information, see Section 1.2.1.7.

BICLA response is defined in Section 1.2.1.7.

BICLA British Isles Lupus Assessment Group-based Composite Lupus Assessment; BMI Body mass index; CI Confidence interval; CMH Cochran-Mantel-Haenszel; IFN Interferon; n Number of patients in analysis; N Number of patients in treatment group.

Figure 20 BICLA response at Week 52 by type I IFN gene signature test (full analysis set)

Other subgroup analyses

A forest plot of BICLA response at Week 52 in pooled Phase III data across subgroups based on demographic and baseline disease characteristics is displayed in Figure 21. A corresponding standardised effects plot for subgroups of interest is displayed in Figure 22.

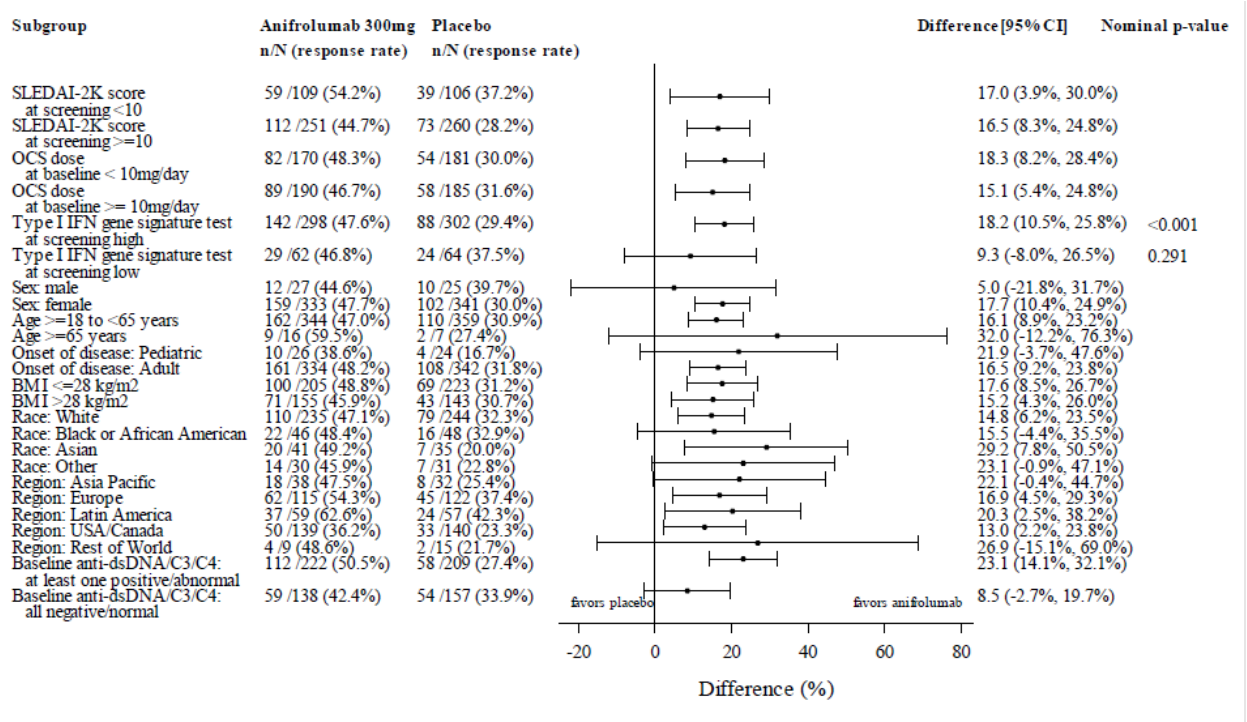


Figure 21 BICLA response rate at Week 52, by subgroup, forest plot of estimated difference (%) and CI, stratified Cochran-Mantel-Haenszel approach (full analysis set: phase III pool)

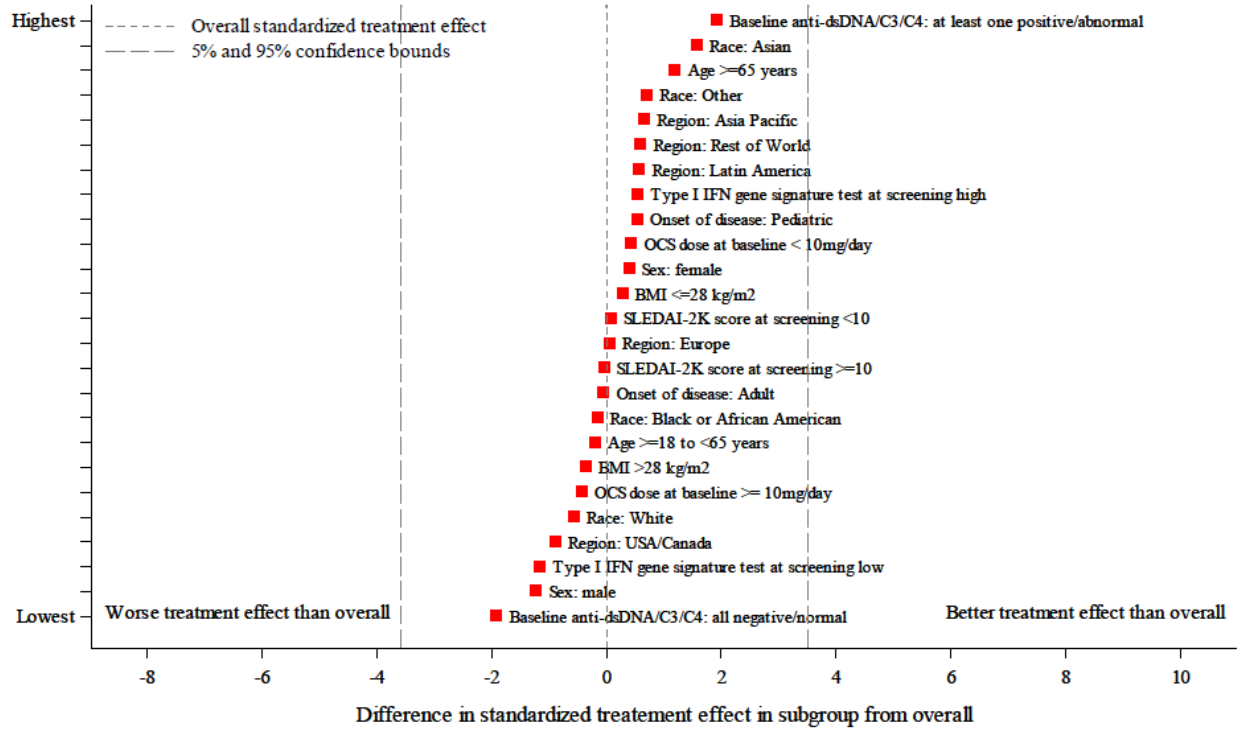
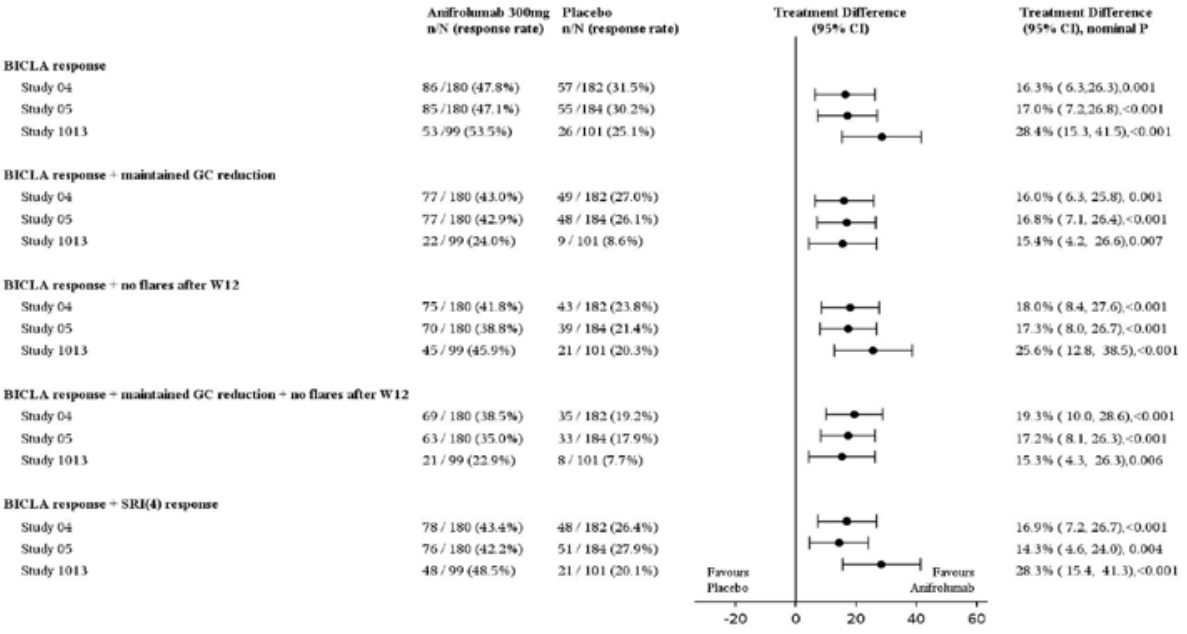


Figure 22 BICLA response rate at Week 52, by subgroup, stratified Cochran-Mantel-Haenszel approach - standardised effects plot (full analysis set: phase III pool)

Combined outcomes

The applicant conducted a post hoc analysis to evaluate attainment of BICLA response combined with another outcome of interest. Results are displayed in Figure 23.



Maintained OCS reduction - Patients receiving ≥ 10 mg/day OCS at baseline: Week 40 OCS dose ≤ 7.5 mg/day and maintained through Week 52.
Low OCS maintenance - Patients receiving < 10 mg/day OCS at baseline: Week 40 OCS dose ≤ baseline dose and ≤ 7.5 mg/day, and maintained through Week 52.
Maintained OCS reduction and low OCS maintenance - Patients treated with restricted medication beyond protocol-allowed threshold, and those who discontinued investigational product, are regarded as nonresponders.
A flare was defined as either 1 or more new BILAG-2004 A items or 2 or more new BILAG-2004 B items compared with the previous visit (ie, a worsening from an E, D, or C score to a B score in at least 2 organ systems or a worsening from an E, D, C, or B score to an A score in any 1 organ system compared with the previous visit).
BICLA, British Isles Lupus Assessment Group-based Composite Lupus Assessment; CI, Confidence interval; GC, Glucocorticoids; SRI(4), Systemic Lupus Erythematosus Responder Index of ≥ 4; W, Week

Figure 23 Summary of the effect of Anifrolumab 300 mg on BICLA response at Week 52 (Study 04, Study 05, and Study 1013)

Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 39 Summary of efficacy in the proposed indication: study 04

Overall design			
Title	A Multicentre, Randomised, Double-blind, Placebo-controlled, Phase 3 Study Evaluating the Efficacy and Safety of Anifrolumab in Adult Subjects with Active Systemic Lupus Erythematosus		
Study identifier	D3461C00004, 2014-004632-19		
Design	A phase III, multicentre, multinational, randomised, double-blind, placebo-controlled study to evaluate the efficacy and safety of an IV treatment regimen of anifrolumab 300 mg versus placebo in adult patients (18 to 70 years of age) with moderate to severe, autoantibody positive SLE while receiving standard of care treatment.		
	Duration of main phase: Duration of run-in phase: Duration of extension phase:	52 weeks NA NA	
Hypothesis	Superiority		
Treatment groups	Anifrolumab 300 mg	A total of 180 patients were randomised to receive anifrolumab 300 mg Q4W for a total of 13 doses (Week 0 to Week 48).	
	Placebo	A total of 182 patients were randomised to receive placebo Q4W for a total of 13 doses (Week 0 to Week 48).	
Endpoints and definitions to assess the efficacy of anifrolumab for the proposed indication			
Overall disease activity	BICLA response at Week 52	The proportion of patients with a BICLA response at Week 52	Primary endpoint
	BICLA response at Week 52 for the subgroup of type 1 IFNGS test high patients	The proportion of patients with a BICLA response at Week 52 in the type I IFNGS test high subgroup	Key secondary endpoint (adjusted for multiplicity control)
	SRI(4) response at Week 52	The proportion of patients with a SRI(4) response at Week 52	Secondary endpoint (predefined in protocol, not adjusted for multiplicity)
OCS use	Maintained OCS tapering at Week 52	The proportion of patients who achieved an OCS dose ≤ 7.5 mg/day at Week 40, which was maintained through Week 52 in the subgroup of patients with baseline OCS ≥ 10 mg/day	Key secondary endpoint (adjusted for multiplicity control)
Cutaneous SLE activity	CLASI response at Week 12	The proportion of patients with a ≥ 50% reduction in CLASI activity score at Week 12 in the subgroup of patients with baseline CLASI activity score ≥ 10	Key secondary endpoint (adjusted for multiplicity control)

Table 39 Summary of efficacy in the proposed indication: study 04

Joints	Joints at Week 52	The proportion of patients with ≥ 50% reduction in joint counts at Week 52 in the subgroup of patients with ≥ 6 swollen and ≥ 6 tender joints at baseline	Key secondary endpoint (adjusted for multiplicity control)
Flares	Annualised flare rate	The annualised flare rate through 52 weeks	Key secondary endpoint (adjusted for multiplicity control)
Database lock	19 August 2019		
Results: the efficacy of anifrolumab for the proposed indication			
Analysis population	The full analysis set, defined as patients who were randomised and received at least 1 dose of IP, was used as the primary population; patients were analysed according to randomised treatment (mITT).		

Descriptive statistics:	**Overall disease activity**	**BICLA response at Week 52**	Anifrolumab 300 mg (N = 180)	Placebo (N = 182)
		n	180	182
		Number (%) responders	86 (47.8)	57 (31.5)
		SRI(4) response at Week 52	Anifrolumab 300 mg (N = 180)	Placebo (N = 182)
		n	180	182
		Number (%) responders	100 (55.5)	68 (37.3)
Effect estimates:	**Overall disease activity**	**BICLA response at Week 52**		**Comparison with placebo**
		Difference in response rate		16.3
		95% CI of difference in response rate		6.3, 26.3
		P-value		0.001
		SRI(4) response at Week 52		**Comparison with placebo**
		Difference in response rate		18.2
		95% CI of difference in response rate		8.1, 28.3
		Nominal p-value		< 0.001[a]
Notes				

Table 39 Summary of efficacy in the proposed indication: study 04

Patient disposition	Fewer patients in the anifrolumab 300 mg group prematurely discontinued IP compared with the placebo group (15.0% vs 28.6%). The main reasons for discontinuation of IP was "withdrawal of patient" and "AEs". Fewer patients in the anifrolumab 300 mg group prematurely discontinued IP due to "lack of efficacy" compared with the placebo group (1.1% vs 6.6%). Similarly, fewer patients in the anifrolumab 300 mg group prematurely discontinued IP due to "condition under investigation worsened" compared with the placebo group (1.1% vs 2.2%).

[a] Not part of the multiplicity controlled testing strategy ie, not adjusted for multiplicity and not assessed in terms of statistical significance.

BICLA, British Isles Lupus Assessment Group-based Composite Lupus Assessment; CI, confidence interval; CLASI, Cutaneous Lupus Erythematosus Disease Area and Severity Index; IFNGS, interferon gene signature; IP, investigational product; mITT, modified intention-to-treat; N, number of patients in treatment group; n, number of patients in analysis; NA, not applicable; OCS, oral corticosteroids; SLE, systemic lupus erythematosus; SRI, Systemic Lupus Erythematosus Responder Index; Q4W, every 4 weeks.

Table 40 Summary of efficacy in the proposed indication: study 05

Overall design			
Title	A Multicentre, Randomised, Double-blind, Placebo-controlled, Phase 3 Study Evaluating the Efficacy and Safety of Two Doses of Anifrolumab in Adult Subjects with Active Systemic Lupus Erythematosus		
Study identifier	D3461C00005, 2014-004632-96		
Design	A phase III, multicentre, multinational, randomised, double-blind, placebo-controlled study to evaluate the efficacy and safety of an IV treatment regimen of 300 mg anifrolumab versus placebo in adult patients (18 to 70 years of age) with moderate to severe, autoantibody positive SLE while receiving standard of care treatment		
	Duration of main phase: Duration of run-in phase: Duration of extension phase:	52 weeks NA NA	
Hypothesis	Superiority		
Treatment groups	Anifrolumab 300 mg	A total of 180 patients were randomised to receive anifrolumab 300 mg Q4W for a total of 13 doses (Week 0 to Week 48).	
	Placebo	A total of 184 patients were randomised to receive placebo Q4W for a total of 13 doses (Week 0 to Week 48).	
Endpoints and definitions to assess the efficacy of anifrolumab for the proposed indication			
Overall disease activity	BICLA response at Week 52	The proportion of patients with a BICLA response at Week 52	Secondary endpoint (predefined in protocol, not adjusted for multiplicity)

Table 40 Summary of efficacy in the proposed indication: study 05

	BICLA response at Week 52 for the subgroup of type 1 IFNGS test high patients	The proportion of patients with a BICLA response at Week 52 in the type I IFNGS test high subgroup	Exploratory endpoint (not predefined in the study protocol)
	SRI(4) response at Week 52	The proportion of patients with a SRI(4) response at Week 52	Primary endpoint
OCS use	Maintained OCS tapering at Week 52	The proportion of patients who achieved an OCS dose ≤ 7.5 mg/day at Week 40, which was maintained through Week 52 in the subgroup of patients with baseline OCS ≥ 10 mg/day	Key secondary endpoint (adjusted for multiplicity control)
Cutaneous SLE activity	CLASI response at Week 12	The proportion of patients with a ≥ 50% reduction in CLASI activity score at Week 12 in the subgroup of patients with baseline CLASI activity score ≥ 10	Key secondary endpoint (adjusted for multiplicity control)
Joints	Joints at Week 52	The proportion of patients with ≥ 50% reduction in joint counts at Week 52 in the subgroup of patients with ≥ 6 swollen and ≥ 6 tender joints at baseline	Secondary endpoint (predefined in protocol, not adjusted for multiplicity)
Flares	Annualised flare rate	The annualised flare rate through 52 weeks	Key secondary endpoint (adjusted for multiplicity control)
Other endpoints	SRI(4) response at Week 52 for the subgroup of type 1 IFNGS test high patients	The proportion of patients with an SRI(4) response at Week 52 in the type I IFNGS test high subgroup	Key secondary endpoint (adjusted for multiplicity control)
	SRI(4) response at Week 24	The proportion of patients with an SRI(4) response at Week 24	Key secondary endpoint (adjusted for multiplicity control)
Database lock	23 August 2018 for the 52-week treatment period, 04 March 2019 for follow-up data at last patient last visit		
Results[a]: the efficacy of anifrolumab for the proposed indication			
Analysis population	The full analysis set, defined as patients who were randomised and received at least 1 dose of IP, was used as the primary population; patients were analysed according to randomised treatment (mITT).		
Descriptive statistics:	**Overall disease activity**	**BICLA response at Week 52[a]**	Anifrolumab 300 mg (N = 180)	Placebo (N = 184)

Table 40 Summary of efficacy in the proposed indication: study 05

		n	180	184
		Number (%) responders	85 (47.1)	55 (30.2)
		SRI(4) response at Week 52[a]	Anifrolumab 300 mg (N = 180)	Placebo (N = 184)
		n	180	184
		Number (%) responders	88 (49.0)	79 (43.0)
Effect estimates:	**Overall disease activity**	**BICLA response at Week 52[a]**		**Comparison with placebo**
		Difference in response rate		17.0
		95% CI of difference in response rate		7.2, 26.8
		Nominal p-value		< 0.001[b]
		SRI(4) response at Week 52[a]		**Comparison with placebo**
		Difference in response rate		6.0
		95% CI of difference in response rate		-4.2, 16.2
		P-value		0.248
Notes				
Patient disposition	Similar proportions of patients across the treatment groups discontinued IP prematurely (20.0% in the anifrolumab 300 mg group, and 20.7% in the placebo group). The main reasons for discontinuation was "withdrawal of patient" and "AEs". Fewer patients in the anifrolumab 300 mg group prematurely discontinued IP due to "lack of efficacy" compared with the placebo group (1.7% vs 4.9%). Similarly, fewer patients in the anifrolumab 300 mg group prematurely discontinued IP due to "condition under investigation worsened" compared with the placebo group (0.6% vs 2.2 %).			

[b] Based on the study 04 restricted medication rules (post-hoc analyses).

Not part of the multiplicity controlled testing strategy ie, not adjusted for multiplicity and not assessed in terms of statistical significance.

BICLA, British Isles Lupus Assessment Group-based Composite Lupus Assessment; CI, confidence interval; CLASI, Cutaneous Lupus Erythematosus Disease Area and Severity Index; IFNGS, interferon gene signature; IP, investigational product; mITT, modified intention-to-treat; N, number of patients in treatment group; n, number of patients in analysis; NA, not applicable; OCS, oral corticosteroids; SLE, systemic lupus erythematosus; SRI, Systemic Lupus Erythematosus Responder Index; Q4W, every 4 weeks.

Table 41 Summary of efficacy in the proposed indication: study 1013

Overall design			
Title	A Phase 2, Randomized Study to Evaluate the Efficacy and Safety of MEDI-546 in Subjects with Systemic Lupus Erythematosus		
Study identifier	CD-IA-MEDI-546-1013		
Design	A phase II, multinational, multicentre, randomised, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of 2 intravenous treatment regimens in adult subjects with chronic, moderately-to-severely active SLE with an inadequate response to standard of care treatment for SLE		
	Duration of main phase: Duration of run-in phase: Duration of extension phase:	52 weeks NA NA	
Hypothesis	Superiority		
Treatment groups	Anifrolumab 300 mg	A total of 100 patients were randomised to receive anifrolumab 300 mg Q4W for a total of 13 doses (Week 0 to Week 48).	
	Placebo	A total of 103 patients were randomised to receive placebo Q4W for a total of 13 doses (Week 0 to Week 48).	
Endpoints and definitions to assess the efficacy of anifrolumab for the proposed indication			
Overall disease activity[a]	BICLA response at Week 52	The proportion of patients with a BICLA response at Week 52	Secondary endpoint (predefined in protocol, not adjusted for multiplicity)
	BICLA response at Week 52 for the subgroup of type 1 IFNGS test high patients	The proportion of patients with a BICLA response at Week 52 in the type I IFNGS test high subgroup	Exploratory endpoint (not predefined in protocol)
	SRI(4) response at Week 52	The proportion of patients with a SRI(4) response at Week 52	Secondary endpoint (predefined in protocol, not adjusted for multiplicity)
OCS use	Maintained OCS tapering at Week 52	The proportion of patients on OCS ≥ 10 mg/day prednisone or equivalent at Day 1 who were able to taper to ≤ 7.5 mg/day at Day 365	Exploratory endpoint (predefined in protocol, not adjusted for multiplicity)

Table 41 Summary of efficacy in the proposed indication: study 1013

Cutaneous SLE activity	CLASI response at Week 12	The proportion of patients with a ≥ 50% reduction in CLASI activity score at Week 12 in the subgroup of patients with baseline CLASI activity score ≥ 10	Secondary endpoint (predefined in protocol, not adjusted for multiplicity)
Joints	Joints at Week 52	The proportion of patients with ≥ 50% reduction in joint counts at Week 52 in the subgroup of patients with ≥ 6 swollen and ≥ 6 tender joints at baseline	Exploratory endpoint (not predefined in protocol, not adjusted for multiplicity)
Flares	Annualised flare rate	The annualised flare rate through 52 weeks	Exploratory endpoint (not predefined in protocol, not adjusted for multiplicity)
Other endpoints	SRI(4) response + OCS tapering at Week 24	The proportion patients with an SRI(4) response with OCS tapering at Week 24	Primary endpoint (predefined in protocol, statistical significance assessed at an alpha 0.1 level)
	SRI(4) response + OCS tapering at Week 24 for type I IFNGS test high patients	The proportion of type I IFNGS test high patients with an SRI(4) response with OCS tapering at Week 24	Primary endpoint (predefined in protocol, statistical significance assessed at an alpha 0.1 level)
Database lock	10 October 2014 for Stage I (Week 24) and 02 April 2015 for Stage II (Week 52)		
Results: the efficacy of anifrolumab for the proposed indication			
Analysis population	Efficacy analyses were based on the mITT population defined as all randomised subjects who received any IP and had a baseline primary efficacy measurement. Treatment arm was assigned according to the randomised treatment group.		
Descriptive statistics:	**Overall disease activity**	**BICLA response at Week 52[b]**	Anifrolumab 300 mg (N = 99) / Placebo (N = 102)
		n	99 / 101
		Number (%) responders	53 (53.3) / 26 (25.1)
		SRI(4) response at Week 52[b]	Anifrolumab 300 mg (N = 99) / Placebo (N = 102)
		n	99 / 102
		Number (%) responders	62 (62.8) / 41 (38.8)

Table 41 Summary of efficacy in the proposed indication: study 1013

Effect estimates:	**Overall disease activity**	**BICLA response at Week 52**	**Comparison with placebo**
		Difference in response rate[b]	28.4
		95% CI of difference in response rate[b]	15.3, 41.5
		Nominal p-value[c]	< 0.001
		SRI(4) response at Week 52	**Comparison with placebo**
		Difference in response rate[b]	24.0
		95% CI of difference in response rate[b]	10.9, 37.2
		Nominal p-value[c]	< 0.001
Notes			
Patient disposition	Fewer patients in the anifrolumab 300 mg group prematurely discontinued IP compared with the placebo group (16.0% vs 25.2%). Reasons for discontinuation of IP were recorded but not summarised in this study.		

[c] Note that the primary endpoint in study 1013 was SRI(4) response with OCS tapering at Week 24. In order to assess the effect of anifrolumab on overall disease activity out to Week 52 in this application, and to align with the endpoints used to assess this in studies 04 and 05, data on BICLA and SRI(4) response at Week 52 are presented for study 1013.

[d] Analyzed using the Cochran-Mantel-Haenszel approach.

[e] Based on the pre-specified logistic regression model for comparison of anifrolumab 300 mg versus placebo, adjusted for randomisation stratification factors.

BICLA, British Isles Lupus Assessment Group-based Composite Lupus Assessment; CI, confidence interval; CLASI, Cutaneous Lupus Erythematosus Disease Area and Severity Index; IFNGS, interferon gene signature; IP, investigational product; mITT, modified intention-to-treat; N, number of patients in treatment group; n, number of patients in analysis; OCS, oral corticosteroids; SLE, systemic lupus erythematosus; SRI, Systemic Lupus Erythematosus Responder Index; Q4W, every 4 weeks.

2.5.5.3. Clinical studies in special populations

No dedicated studies in special populations have been conducted. The age group distribution among patients participating in the Phase III studies (studies 04 and 05) is seen in Table 42 which also summarises main results by age group.

Table 42 Efficacy endpoints by age group (full analysis set: Phase III pool)

	Number (%) of patients							
	Anifrolumab 300 mg (N = 360)				Placebo (N = 366)			
Age, years	18 to 64 (N = 344)	65 to 74 (N = 16)	75 to 84 (N = 0)	≥ 85 (N = 0)	18 to 64 (N = 359)	65 to 74 (N = 7)	75 to 84 (N = 0)	≥ 85 (N = 0)
BICLA response at Week 52 [a], n/N (%)	162/344 (47.1)	9/16 (56.3)	0	0	110/359 (30.6)	2/7 (28.6)	0	0
SRI(4) response at Week 52 [a], n/N (%)	180/344 (52.3)	8/16 (50.0)	0	0	144/359 (40.1)	3/7 (42.9)	0	0
Maintained OCS reduction at Week 52 in patients with OCS ≥ 10 mg/day at baseline [a], n/N (%)	95/185 (51.4)	1/5 (20.0)	0	0	57/181 (31.5)	2/4 (50.0)	0	0
CLASI response at Week 52 in patients with baseline CLASI activity score ≥ 10 [a], n/N (%)	65/103 (63.1)	3/4 (75.0)	0	0	40/92 (43.5)	2/2 (100.0)	0	0
Joint reduction rate at Week 52 in patients with at least 6 swollen and 6 tender joints at baseline [a], n/N (%)	77/158 (48.7)	4/6 (66.7)	0	0	68/184 (37.0)	3/6 (50.0)	0	0
Flare rate through Week 52 [b]								
Total number of flares	190	5	0	0	247	8	0	0
Total follow-up time, years	322.8	14.0	0	0	329.3	6.1	0	0
Annualized rate estimate	0.51	0.25	0	0	0.65	1.10	0	0

[a] For efficacy endpoint definitions and details of the analysis used, consult the relevant sections in the statistical analysis plan.
[b] For flare rate definitions and details of the analysis used, consult the relevant sections in the statistical analysis plan.
Baseline is defined as the last measurement prior to randomization and investigational product dose administration on Day 1.
Phase III pool includes studies 04 and 05 (excluding the 150 mg group from study 05).
BICLA, British Isles Lupus Assessment Group-based Composite Lupus Assessment; CLASI, Cutaneous Lupus Erythematosus Disease Area and Severity Index; n, Number of patients in analysis; N, Number of patients in treatment group; OCS, Oral corticosteroids; SRI, Systemic Lupus Erythematosus Responder Index.

2.5.6. Discussion on clinical efficacy

Design and conduct of clinical studies

The applicant has sought a marketing authorisation for anifrolumab 300 mg Q4W IV as "*add on therapy for the treatment of adult patients with moderate to severe systemic lupus erythematosus, despite standard therapy*".

The goal of SLE treatment is to achieve a clinically meaningful reduction of overall disease activity and the rate of disease flares, while at the same time reducing steroid use in order to avoid additional long-term organ damage.

The key studies within the clinical development programme for anifrolumab comprise two Phase III studies and a large Phase II study. All three studies had a 52-week double-blind placebo-controlled treatment period and were generally similar in design. The CHMP Guideline on clinical investigation of medicinal products for the treatment of systemic lupus erythematosus and lupus nephritis (EMA/CHMP/51230/2013 corr) states that the duration of a trial aimed for the control of disease activity should be at least 12 months; within the application, 12 month efficacy data is provided for the three key studies. The ongoing Study 09 will assess efficacy over a 3 year double blind treatment period.

The primary objective in all 3 studies was to evaluate the effect of anifrolumab compared to placebo on overall disease activity. Secondary objectives were chosen to further characterise the reduction in overall disease activity, in particular the ability to reduce OCS use, the effect on organ-specific endpoints (cutaneous SLE activity and joints), and flare rates.

Contrary to CHMP advice, the applicant selected to enroll paediatric-onset SLE patients in studies 04 and 05. In its response to the D120 LoQ, the applicant described the measures to mitigate risks from enrolling a significantly diverging subpopulation into the studies. The CHMP agreed that the small subgroup with paediatric-onset disease does not appear to strikingly differ from the adult-onset subgroup in terms of baseline characteristics. The small sample size limits the robustness of the subgroup analysis for

treatment response, but whereas the absolute response rates for both anifrolumab and placebo are lower among paediatric-onset patients, the differences between treatment groups appear to be similar among paediatric-onset and adult-onset patients. Specific restrictions regarding the use of anifrolumab in paediatric-onset SLE patients are not deemed necessary by the CHMP.

Similar eligibility criteria were applied across the three studies. The minimum SLEDAI-2K and BILAG criteria are overall appropriate to select a population with active disease of at least moderate severity. The 1997 ACR classification criteria for diagnosis of SLE were used in the studies. This is reflected in the Section 5.1 of the SmPC. The applicant also confirmed that patients who were positive for anti-phospholipid antibodies were included in the Phase III studies. In the pooled population, 18% (131/726) of patients were positive for anti-phospholipid antibodies with similar proportions observed between treatment groups, ranging from 12.6% to 25.0% of patients. It was also confirmed that over 98% of patients participating in the studies also met the 2019 EULAR/ACR classification criteria for SLE, with very high concordance demonstrated between the two classification systems.

Exclusion criteria reflect the main potential safety concerns related to the mechanism of action of the drug and this is acceptable. Patients with severe neuropsychiatric or renal manifestations of SLE were excluded from the programme; this exclusion is adequately reflected in Section 4.4 of the SmPC.

Rules were established for restricted medications so that overall standard of care treatment remained stable throughout all 3 studies (04, 05, 1013), except for OCS that were tapered according to specific instructions (mandated in studies 04 and 05 as recommended in the CHMP Guideline and encouraged in study 1013) in view of the fact that an important clinical (efficacy and safety) achievement in SLE patients is obtaining and maintaining a lower disease activity and steroid tapering (low doses/without). The wash out period required for prohibited medications before study drug was started is acceptable. Concomitant use of other biological therapies for SLE (such as belimumab) was prohibited. A corresponding warning has been added in Section 4.4 of the SmPC at the CHMP's request.

The dose proposed for labelling, 300 mg Q4W, was included in all three studies and is the focus of the current assessment.

The heterogeneity and complexity of SLE makes it difficult to evaluate the efficacy of experimental drugs for SLE treatment, and composite endpoints are often used to evaluate disease activity across multiple organ systems. The selected primary and secondary endpoints are in accordance with the "Guideline on clinical investigation of medicinal products for the treatment of systemic lupus erythematosus and lupus nephritis (EMA/CHMP/51230/2015)". According to the Guideline, the selection of the primary endpoint in SLE trials depends on the objective of the clinical study and should be generally aimed at the control of disease activity and/or prevention of long-term damage. Given the heterogeneity of SLE manifestations, supportive evidence derived from secondary endpoints is of particular interest in this clinical setting to fully characterise the treatment effect.

Both BICLA and SRI(4) are endorsed as potential primary endpoints in the CHMP Guideline for SLE. At face value, many elements within both BICLA and SRI(4) response refer to "no worsening" rather than definite "improvement". BILAG classifies the severity of each organ system as A (severe), B (moderate), C (mild), or D (inactive) semi-quantitatively and detects changes in severity of clinical manifestations reflecting disease activity over the last 4 weeks. The BILAG system is comprehensive but complicated. The weakness of BILAG is that does not contain serological evaluation (K. Ohmura. Modern Rheumatology, 2021). On the other hand, SRI(4) captures treatment benefit across SLEDAI-2K defined organ systems, where assessment of symptoms within a given system is dichotomous (present/absent) and differential weighting assigned to different organ systems. SLEDAI-2K assessment can be translated to a numeric score ranging from 0 to 105, with SRI(4) response requiring a 4 point improvement from baseline in total score. It is noteworthy that while the scale in principle ranges from 0 to 105, individual scores above 20 are rare. Of note, a clinically meaningful improvement i.e. reduction in SLEDAI-2K of 4

points (Gladman 2000) is only recorded on complete resolution of a disease manifestation and it cannot evaluate improvement. This represents a weak point of SLEDAI score (K. Ohmura. Modern Rheumatology, 2021).

The addition of key secondary endpoints which are meant to assess organ specific disease activity on some common SLE features i.e. skin and joint are of importance for gaining information about clinical efficacy that is not otherwise properly captured by some composite/more general endpoint. Inclusion of flares is of importance since it correlates with long term damage, affecting in turn survival and health-related QoL.

While both BICLA and SRI(4) are considered acceptable endpoints according to the Guideline, no single measure has yet been validated as the gold standard. The limitations of currently available efficacy measures are also recognised in current scientific literature and have been implicated as a potential reason for the numerous failures in therapeutic trials in SLE (Arora et al, Arth Care Res 2020; 72 No. S10: 27–46).

The applicant initially chose SRI(4) as the primary endpoint for the anifrolumab programme based on its previous use in the belimumab programme as well as favourable data in Study 1013. However, the first Phase III study (Study 05) did not meet this primary endpoint. Based on efficacy being observed on BICLA in Study 05, the applicant subsequently changed the primary endpoint for Study 04 from SRI(4) to BICLA while that study was still blinded.

Whereas a data-driven change in primary endpoint during a clinical programme can be considered suboptimal from the perspective of GCP principles and statistical inference, the change process has been described in detail within the application. The measures taken by the applicant during the process to protect the integrity of data collected in Study 04 were generally considered procedurally adequate by the CHMP. As end-of-study notifications for Study 04 had already been submitted in the EU; hence, the applicant could not notify health authorities in the EU of the endpoint change. However, based on the submitted documentation, no significant concern regarding potential breach of data integrity can be identified. One study site was closed due to sustained protocol non-compliance.

In principle, two consistent pivotal studies would be strongly preferred from a regulatory perspective to allow an adequate assessment of efficacy in an indication like SLE and this was also the original intention of this development programme. With the submission being formally based on one positive Phase II study, one negative Phase III study and one Phase III study in which the testing strategy, including the primary endpoint, was fully changed as a result of the failed study, the overall statistical approach cannot be considered to provide confirmatory evidence of efficacy based on conventional standards.

Among the secondary endpoints assessed, decrease in steroid use and prevention of flares are recognised concepts within the CHMP Guideline; furthermore, the assessment of effects on cutaneous symptoms was endorsed in the CHMP SA process. The OCS tapering target (to $\leq$ 7.5 mg/day prednisone equivalent for any patient with $\geq$ 10 mg/day at baseline) sets the minimum threshold of a successful taper slightly lower than in the Guideline example, in which a taper from 15 mg/day to $\leq$ 7.5 mg/day is provided. However, the target dose of $\leq$ 7.5 mg/day is in itself consistent with EULAR recommendations.

The assessment of joint symptoms in SLE is less well established, and it is noted that responder definitions were adjusted during the programme and joint assessments were escalated in the statistical analysis hierarchy for Study 04 after data from studies 1013 and 05 was available. As such, this endpoint can overall be only considered as exploratory in nature.

The studies included 180 patients in the active arms. The applicant states that the number of patients in the study is based on adequate size of the safety database. For the primary endpoint, the study is considered to have >80% power.

When the primary endpoint for Study 04 was changed, the applicant conducted a power calculation for the new primary endpoint and confirmed there was adequate powered based on the effect size seen in Study 05. The number of patients in the study was not changed.

The plans to control Type 1 error are methodologically adequate as such. However, due to the changes implemented when Study 04 was ongoing and differences between the two studies, the CHMP assessment has been focused on the totality of evidence rather than confirmatory testing.

Study 1013 was conducted between January 2012 and April 2015. First patient for Study 05 was enrolled on 09 June 2015, and last subject last visit took place on 17 July 2018. First patient for Study 04 was enrolled on 09 July 2015, and last subject last visit took place on 06 December 2018.

A total of 1124 patients received investigational product in the three key studies; 459 patients received anifrolumab at the 300 mg Q4W dosage. Some 80% of patients in all studies completed 52 weeks of treatment.

In Study 05, the proportions of patients completing treatment with investigational product and placebo were very similar, about 80% across the three treatment groups. The most common reasons for not completing treatment were patient decision (8.3% for anifrolumab 300 mg, 5.4% for anifrolumab 150 mg, 7.1% for placebo), adverse events (7.2% for anifrolumab 300 mg, 6.5% for anifrolumab 150 mg, 4.3% for placebo), and lack of efficacy (1.7% for anifrolumab 300 mg, 3.2% for anifrolumab 150 mg, 4.9% for placebo).

In contrast, in studies 04 and 1013, the proportion of patients completing treatment was higher with anifrolumab than placebo (Study 04: 85% for anifrolumab vs. 71% for placebo; Study 1013: 84% for anifrolumab 300 mg, 82% for anifrolumab 1000 mg, 75% for placebo).

In Study 04, the most common reasons for withdrawal were patient decision (3.9% for anifrolumab, 8.8% for placebo), adverse events (2.8% for anifrolumab, 7.7% for placebo), and lack of efficacy (1.1% for anifrolumab, 6.6% for placebo). The imbalance between treatment groups in study withdrawals carries particular relevance for the efficacy analysis, as all of the withdrawals are interpreted as non-responders in the applicant's primary analysis (see below).

In Study 1013, the reasons for non-completion were categorised in a slightly different manner. The reason for non-completion was withdrawal of consent in 7.2% of patients (3.0% for anifrolumab 300 mg, 7.7% for anifrolumab 1000 mg, 10.7% for placebo); other reasons were reported for 9.8% of patients (11.0% for anifrolumab 300 mg, 7.7% for anifrolumab 1000 mg, 10.7% for placebo). According to the applicant, discontinuation due to lack of efficacy was not recorded separately. An adverse event was reported as the reason for discontinuation in 1 patient in each of the anifrolumab groups and 2 patients on placebo.

Within each of the three studies, demographic characteristics between the treatment groups were balanced. Across the studies, mean age was about 40 years and over 90% patients were female. When comparing the three studies, the higher proportion of European patients in Study 05, the higher proportion of Asian patients in Study 04 (this was the only study including patients from Japan), as well as the substantial mestizo/mestiza population in Study 1013 were noted by the CHMP.

About 70% of patients in studies 04 and 05, and 60% of patients in Study 1013 had a baseline SLEDAI-2K score of 10 or above, consistent with high disease activity. Disease activity based on SLEDAI-2K was balanced between treatment arms. On the BILAG-2004 index, about 45-50% of patients across the three studies had at least one BILAG A, indicating severe disease in at least one organ system. In Study 04, a slight imbalance is noted (45% anifrolumab and 52% placebo) meaning higher activity in the placebo arm; in Study 05, at least one BILAG A was reported in 52% of patients on anifrolumab 300 mg and 46% of patients on placebo. Median time from first diagnosis to randomisation ranged from 65 to 94

months. About 93% of patients enrolled into the Phase III studies had adult-onset SLE. Baseline disease characteristics were generally well balanced between treatment groups.

The 4-gene type I IFN gene signature high was detected in the great majority of enrolled patients across studies (more than 80% in studies 04 and 05), making it difficult to discriminate potential differences in the efficacy of anifrolumab between patients with high and low type I IFN gene signature. A comparison of baseline data between patients with high and low type I IFN gene signature pointed to generally higher disease activity (based e.g. on serological markers and skin symptomatology) among patients with a high gene signature, the main difference being greater serological abnormalities in type I IFN gene signature high patients: positive anti-dsDNA antibodies (47.8% versus 27.8%), and abnormal complement C3 (41.5% versus 14.3%) or C4 (27.0% versus 5.6%). The exception to this general finding was greater joint involvement among patients with low type I IFN gene signature.

Based on the BILAG-2004 index, the most frequently affected organ systems were mucocutaneous and musculoskeletal; these were also the only organ systems with substantial numbers of BILAG A severity. These finding are consistent with the majority of patients having dermatological involvement, based on a median CLASI score of 5 to 6 and 20-30% of patients having a CLASI score of 10 or higher. Most patients also had active joint involvement, with median active joint counts ranging from 4 to 6 in the phase III studies. Neuropsychiatric, gastrointestinal, ophthalmic and haematological symptomatology was infrequent. Autoantibody (ANA, Anti-dsDNA or anti-Sm) positivity, an eligibility requirement, was most commonly in relation to ANA. Therefore, a moderate to severe disease activity according to BILAG for organ specific involvement denotes a SLE population with moderate to severe disease activity that is rather restricted to a few clinical manifestations (musculoskeletal and mucocutaneous) only. The reason for not including patients with active nephritis or CNS involvement in the Phase III trials seems justified as these patients require a different treatment for the control of disease activity; however, restriction makes difficult to draw conclusions on the effect of anifrolumab on key target organs, although it can be agreed that a dominance of mucocutaneous and musculoskeletal organ domains is also present in the wider general population of patients with moderate to severe SLE despite SOC.

Some 80% of patients across the three studies were on OCS at baseline. Among these patients, the proportion of patients with a daily dose $\geq$ 10 mg was 46 to 48% in Study 04, 55 to 57% in Study 05 and 56 to 63% in Study 1013. Anti-malarials were used by 66 to 77% of patients, and in studies 04 and 05, 57 to 63% were taking anti-malarials together with OCS and/or immunosuppressants. Immunosuppressants were used by 45 to 52% of patients across the three studies. In Study 04, the proportion of patients who were only receiving an OCS at baseline was slightly higher in the anifrolumab 300 mg group than the placebo group (31 patients (17.2%) in the anifrolumab 300 mg group vs. 17 patients (9.3%) in the placebo group). Regarding the claimed indication, the applicant has clarified its position and provided efficacy and safety data supporting the view that no detrimental effect seems to be seen in biologic experienced patients compared to biologic naive ones. However, since concomitant use of other biologicals was prohibited, a warning was included at the CHMP's request in Section 4.4 of the SmPC to inform prescribers that anifrolumab has not been studied in combination with other biologic therapies, including B-cell-targeted therapies. Therefore, treatment with anifrolumab is not recommended in combination with biologic therapies.

Efficacy data and additional analyses

A difference in response rates based on the BICLA composite was consistently observed across the three key studies. Between studies 04 and 05, the observed response rates for anifrolumab 300 mg and placebo (Study 04: 47.8% vs. 31.5%; Study 05: 47.1% vs. 30.2%) as well as the differences in response rates between groups (Study 04, 16.3 percentage points; Study 05, 17.0 percentage points), using the applicant's primary composite estimand, were very consistent. For Study 05, it should be noted that as

the study failed on the primary endpoint of SRI(4) response, p values for key secondary endpoints cannot be formally interpreted due to the analysis hierarchy. A larger treatment effect (28.4% difference in response rates between treatment groups) was seen in the Phase II study 1013.

In study 04, a numerical separation of the BICLA response rates in favour of anifrolumab was seen early (starting at week 8) and was sustained until week 52; this behavior is similar across studies. Moreover, a numerically higher percentage of anifrolumab-treated patients achieved a sustained BICLA response at week 52 (the visit of first BICLA response that is sustained up to, and including, Week 52: HR 1.55 (95% CI 1.1-2.18)). Comparison across studies shows higher HRs of 1.94 (95% CI 1.38-2.73) and 2.51 (95% CI 1.56-4.16) for 05 and 1013 study, respectively. From a clinical perspective, achievement of a sustained BICLA response rate is of value and a numerical trend in favour of anifrolumab gives reassurance. At the CHMP's request, the applicant conducted additional analyses regarding sustained responses which demonstrated a higher response rate with anifrolumab that remained stable over different periods of time; as an example, among Week 52 responders, a response that was sustained for at least 6 months was achieved by 24.4% of patients on anifrolumab vs. 12.6% of patients on placebo in study 04, and by 30.0% of patients on anifrolumab vs. 17.4% of patients on placebo in study 05.

The lower bound of the 95% confidence interval (CI) was only 6% and 7%, in study 04 and 05 respectively, and increases to almost 10% (CI 9.7-23.6) in the pooled analysis, indicating limited efficacy (with <10% being considered not clinically meaningful, as stated by the applicant). At the CHMP's request, the applicant also provided additional analyses on study 04: using the treatment policy estimand, the difference is 10.9% (95% CI 0.7, 21.1), and in the completers analysis, the difference is 11.4% (95% CI -0.1, 23.0). Lastly, the proportions of patients failing to improve on BILAG-2004 are 32.2% on anifrolumab and 34.6% on placebo (i.e., a difference of 2.4 percentage points).

The study 05 failed on the primary endpoint of SRI(4) response. Discordant numeric results between the Phase III studies are observed on this endpoint which was initially envisaged as the primary endpoint for the programme. Indeed, the SRI(4) response at Week 52, anifrolumab 300 mg vs. placebo was 55.5% vs. 37.3%; difference 18.2% (95% CI 8.1, 28.3) in Study 04 (secondary endpoint), 49.0% vs. 43.0%; difference 6.0% (95% CI -4.2, 16.2) in Study 05 (primary endpoint) and 62.8% vs. 38.8%; difference 24.0% (95% CI 10.9, 37.2) in Study 1013 (secondary endpoint).

For a better understanding of the relationship of the two endpoints, the applicant was requested to provide a summary of how the BICLA and SRI(4) responses correlate on an individual patient level within each key study. The analysis demonstrated concordant outcomes on BICLA and SRI(4) in the large majority (75-85%) of cases, which is in itself reassuring and confirms that the two endpoints do not measure clearly different aspects of the same condition. The proportionally largest discordant category was BICLA non-response / SRI(4) response, and whereas BICLA response / SRI(4) non-response discordance was observed at relatively constant frequencies in both treatment groups across all studies, and the same is true for BICLA non-response / SRI(4) response discordance in studies 04 and 1013, an imbalance between treatment groups was seen for BICLA non-response / SRI(4) response in study 05, with fewer patients in the anifrolumab group than the placebo group in this subset. A definitive reason for failure of the pre-defined primary endpoint (SRI(4) response) in Study 05 could not be identified.

The proportion of patients who could taper and maintain a reduced dose of OCS was consistently greater in the anifrolumab group than the placebo group across the three studies. In Study 04, the difference was statistically significant based on a multiplicity-corrected analysis. Overall data in respect of OCS tapering at week 52 supports a steroid-sparing effect of anifrolumab across the 3 studies. Most, but not all patients who were BICLA responders were also responders on the OCS reduction endpoint; among BICLA non-responders, the correlation was less clear. The use of a "corticosteroid burst" was permitted during the first 12 weeks of treatment but was used by a very limited number of patients.

Numerical trends favouring anifrolumab were seen on flare rates, but none of the differences were statistically significant. According to the applicant, flares will be assessed as safety events throughout the LTE study (study 09). For this purpose, a modified SELENA flare index, using SLEDAI 2K instead of the SELENA SLEDAI, is used, and flare assessments are completed once every 3 months during the first year of the LTE study and once every 6 months during the second and third years.

The proportion of patients with a CLASI response was consistently higher in the anifrolumab 300 mg group than the placebo group across the three studies. In Study 04, the difference was statistically significant based on a multiplicity-corrected analysis. However, it should be borne in mind that CLASI response was only assessed in a limited subgroup of patients with a CLASI score ≥ 10 points at baseline. Moreover, excluding subjects who had a burst and taper of steroids in the first 12 weeks as per an exploratory analysis, the results were weaker with a minor difference from placebo and a wide CI with a lower bound below/near to 0. A further weakness is that CLASI response by time point throughout the period (week 52) showed only for some time-periods a separation of CI i.e. week 12-16, and week 36-52 and CI overlapping in the remaining period. Of reassurance on the anifrolumab effect on SLE skin manifestations is the numerical trend seen in anifrolumab-treated patients as compared to placebo when a higher threshold for response (CLASI≥ 75% or ≥ 90% reductions) is applied and when looking at the SLEDAI-2K and BILAG-2004 mucocutaneous domains. This provides overall support on the beneficial effect of anifrolumab on muco-cutaneous manifestations of SLE.

There are no widely validated musculoskeletal endpoints in SLE although joint disease is a common feature of SLE impairing physical function and reducing QoL. Moreover, assessing efficacy in joints is difficult because of the clinical heterogeneity of these manifestations and the degree of inter-observer variability. The majority of patients had active joint manifestations at baseline, with 88.9% to 92.4% of patients having swollen joints (median joint counts of 5.0 to 7.0), and 93.3% to 100% of patients having tender joints (median joint counts of 7.0 to 11.0), across the studies. 30% and more than 50% of subjects had severe (BILAG A) or moderate (BILAG B) involvement. A joint endpoint was included as a secondary endpoint in Study 05 and escalated as a multiplicity-controlled key secondary endpoint into Study 04 based on encouraging findings in Study 05. Whereas a 19% difference between anifrolumab 300 mg and placebo was observed on joint response in Study 05, there was no difference between anifrolumab 300 mg and placebo in joint response in Study 04. In light of the sequence of events, the effect of anifrolumab on joint symptoms cannot be considered to have been reliably demonstrated.

Small numerical trends favouring anifrolumab were seen on patient-reported outcomes.

Given the failure of one of the key studies on its original primary endpoint as well as the uncertainties regarding the clinical relevance of the observed treatment effect, the results were discussed within an Ad Hoc Expert Group (AHEG) comprising methodological and clinical experts on SLE. While the experts considered the failure of Study 05 on its original primary endpoint a notable weakness, they still considered that the total weight of evidence based on BICLA and SRI(4) responses, as well as other effects including steroid sparing, is supportive of beneficial treatment effects, and that the failure of Study 05 on SRI(4) would not prevent an overall conclusion that efficacy was demonstrated in the programme (see full report below). This position was followed by the CHMP.

Results on OCS tapering and flare rate (although not statistically robust) have been included in the Section 5.1 of the SmPC as they are reflecting important overarching treatment goals in SLE. However, the inclusion of other subdomain analyses (CLASI, joint activity) in this section has not been endorsed by the CHMP.

Three intercurrent events were incorporated into the composite endpoints in studies 04 and 05: IP discontinuation, restricted medication use, and study withdrawal. Patients who experiences an intercurrent event were counted as non-responders. Additional sensitivity analyses conducted by the applicant revealed that a large proportion of non-responders stem from intercurrent events, which

decreases the robustness of the results. Notably, in study 04, there was no difference in the proportion of true, clinical non-responders between the groups. The impact of intercurrent events was notably large in this study where there is a large, unexplained imbalance in study withdrawals between the arms. The most common reason was "withdrawal by patient". At the CHMP's request, the potential impact of these patients on the magnitude of the treatment effect was explored through the tipping point analyses. Based on those analyses, there are realistic scenarios where difference between the treatment arms could be in the range of 10-11%. This was also discussed with the AHEG. The Experts considered that, despite the notable effect of intercurrent events on the point estimate of treatment effect and differences in the behaviour of the placebo groups, even a treatment difference that based on some scenarios could be in the range of 10-11%, can be considered clinically meaningful (see full report below). This position was followed by the CHMP.

With respect to specific organ involvement, it is of note that almost all subjects (more than 90%) belong to BILAG C, D or E for renal, neuropsychiatric or haematological manifestations therefore having a mild (C), inactive but previous affected (D) or inactive and not previous affected (E) disease activity; a severe (A) or moderate (B) disease activity was only represented by musculoskeletal involvement (as A in 30% and as B in 50%, of subjects, percentages balanced across arms) and mucocutaneous symptoms (A 17% B 68.9% C 13%, percentages slightly higher in anifrolumab arm as compared to placebo). Therefore, a moderate to severe disease activity according to BILAG for organ specific involvement denotes a SLE population with moderate to severe disease activity that is quite restricted to a few clinical manifestations (musculoskeletal and mucocutaneous). The reason for not including patients with active nephritis or CNS involvement in the Phase 3 trials is justified as these patients require a different treatment for the control of disease activity; however, this restriction makes difficult to draw conclusions on anifrolumab effect on key target organs and to extrapolate to the general population with moderate to severe SLE despite SOC. The CHMP agreed that the patient population enrolled into the anifrolumab studies, with predominantly mucocutaneous and musculoskeletal symptomatology, seems representative of the wider population of SLE patients. Moreover, the dynamic nature of disease manifestations across different organ systems and the fluctuating nature of the disease was also acknowledged.

Serological markers, such as low serum complement levels and the presence of anti-dsDNA antibodies, are often indicative of active disease in SLE. Therefore, anti-dsDNA antibodies and serum levels of complement components (C3 and C4) were measured as potential markers of inflammation/disease activity. Subgroup analyses demonstrated some heterogeneity in treatment response. The impact of anifrolumab treatment on serological endpoints was overall minor: a greater numerical reduction in anti-dsDNA antibody levels through 52 weeks was seen in the anifrolumab arm, but only a minority of patients with anti-dsDNA antibodies at baseline were negative by Week 52 in the phase III pool (7.8% anifrolumab vs. 5.8% placebo, difference of 2%). Negligible effect was seen on complement levels. Nevertheless, a larger treatment effect was observed in patients with high disease activity based on serological markers. In Study 04, the difference between anifrolumab 300 mg and placebo in BICLA response at Week 52 was 9.2% (95% CI -7.5, 25.8) in patients with normal C3 and C4 and no anti-dsDNA antibodies at baseline, compared with 21.3% (95% CI 8.8, 33.9) in patients with at least one of the following: low C3, low C4 or positive anti-dsDNA. In Study 05, the corresponding values were 7.9% (95% CI –7.2, 22.9) in patients with normal C3 and C4 levels and no anti-dsDNA antibodies at baseline, compared with 25.0% (95% CI 12.0, 37.9) in patients with at least one low/positive value.

Initially, the selection of 21 type I IFN-inducible genes for development into a PD marker assay applicable in clinical studies was described in detail in Yao et al 2009. In the phase I scleroderma clinical trial MI-CP180, a 5-gene type I IFN PD signature comprised of a subset of the 21 type I IFN-inducible genes (IFI27, IFI44, IFI44L, RSAD2, and IFI6) was shown to correlate with the 21-gene signature. A type I IFN gene signature test based on over-expression of 4 type I IFN inducible genes was used to divide the patient population in two subgroups as either "type I IFN gene signature test high" or "type I IFN gene

signature test low". The test measures the expression of the genes IFI27, IFI44, IFI44L, and RSAD2 relative to 3 housekeeping genes, the expression of which are not modulated (reference genes 18S, ACTB, and GAPDH) by type I IFN. Based on results in Study 1013, it was considered that the subpopulation "type I IFN gene signature test high" of SLE patients would be more likely to benefit from treatment with anifrolumab. The 21-gene signature test was used throughout the clinical studies. In subgroup analyses based on pooled efficacy for the Phase III studies, a difference between treatment groups favouring anifrolumab was seen in BICLA response rates regardless of the IFN gene signature subtype; however, the difference in the low subgroup was considerably smaller and not statistically significant in Study 04. Intriguingly, the smaller treatment effect seems to be due to a higher placebo response rate in the low subgroup, whereas response rates with anifrolumab are very similar between the high and low subgroups.

A treatment effect of similar magnitude was observed between patients with high and moderate disease activity at baseline (SLEDAI-2K score of <10 vs. ≥10).

A very small treatment effect was also seen among male patients; however, baseline imbalances or other factors that could potentially explain the apparent lack of a treatment effect among male patients were not identified, and the small sample size and wide confidence intervals are acknowledged.

Based on the studies' results and at the CHMP's request, the applicant accepted to modify the wording of the indication as follows to include a proper characterisation of the target population and the level of disease activity.

"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."

Considering that subgroup analyses demonstrated some heterogeneity in treatment response (i.e. larger treatment effect was observed in patients with high disease activity based on serological markers), the applicant is recommended to continue, through additional analyses or new studies, attempts to identify subpopulations that could be considered the best treatment candidates with anifrolumab.

Additional expert consultation

The CHMP consulted experts in SLE and statistics to provide input regarding the clinical relevance of the effects observed. Upon request from the CHMP, an ad hoc expert group meeting was convened on 07 December 2021.

1. **Given the study results of the 04 and the 05 study, can an effect be considered as established in the studied population? Please elaborate with reference to the data. In particular;**

    a. **Can both the BILAG-2004 and the SLEDAI-2K indices provide a clinically meaningful characterisation of change in disease activity?**

There was a consensus amongst the experts and the patient representatives that both BILAG-2004 and SLEDAI-2K provide a clinically meaningful characterisation of change in disease activity.

The experts agreed that none of the endpoints were ideal and recognised the challenges related to their use in clinical trials. The SLEDAI-2K was more adequate to assess disease activity. It is frequently used in clinical practice; however, it is quite insensitive to change. The BILAG-2004 would better evaluate the organ involvement and is considered more granular by the experts; however, it very time consuming and therefore rarely used in clinical practice.

The experts and the patient representatives agreed that, although the indices were mostly concordant, there could be discordant results. They considered that a demonstration of effect only on the BILAG-2004 could still be considered clinically meaningful.

b. What is your view on the importance of the fact that one of the key studies (Study 05) failed on its originally designated primary endpoint, demonstrating no benefit on SRI(4)?

The clinical experts and the patients' representatives agreed that Study 05 failed on its primary endpoint. In addition, changing the primary endpoint in Study 04 after having seen the study results from Study 05 was considered suboptimal. However, they recognised that the effect demonstrated by anifrolumab on BICLA was clinically relevant.

The statistical experts considered that there was a fundamental statistical issue with the prospective change of the primary endpoint midway after having seen the results in Study 05. They were of the view that the efficacy analysis was not robust and there were concerns that it would lower the statistical thresholds for medicine registration. Study 04 was considered non-conclusive enough by one statistical expert (in particular, with regard to the tipping point analyses). However, given the clinical considerations, the statistical experts could agree with a potentially beneficial effect of the treatment.

Despite this recognised limitation, taking into account overall the results, the effect and the high unmet medical need the clinical experts recognised a beneficial effect.

The experts also formulated the following recommendations:

- They were of the view that anifrolumab, if registered, would not be equally effective in all patients. Hence, they recommended further subdomain analyses to better define the target population. Some experts indicated that anifrolumab could be more effective on musculoskeletal and mucosal (skin) manifestations.

- They considered that the high placebo effect observed in the studies has not been adequately characterised by the applicant and would recommend that the applicant further investigates this point including possible reasons for high placebo effect in Study 05.

- In the view of the experts, there are not enough data on detail of corticosteroid tapering. For example, how tapering would be effective in patients on high or low dose corticosteroids at baseline. Yet, the possibility of corticosteroid tapering in patients on anifrolumab is a clinically meaningful strength of administering anifrolumab.

2. **Please discuss what would be a minimal treatment difference that could be considered clinically meaningful in light of the endpoints studied in this programme and considering also the variability in the magnitude of the treatment effect estimate for anifrolumab. If you consider that an effect has been established based on the presented development programme (question 1), can it be concluded that this effect is of such magnitude that it would translate into a clinically meaningful effect in patients with moderate to severe, active autoantibody-positive SLE?**

By consensus, the experts and the patients' representatives agreed that clinically meaningful effects were demonstrated and comparable in magnitude to other approved treatment in SLE. The primary endpoint was met in Study 04. It was also mentioned that responders had received several treatments before and still had a positive response which was seen as advantageous. Some important secondary endpoints were also met and were considered clinically relevant and meaningful: possibility of corticosteroid tapering, reduction of flares, patients reported outcomes (quality of life improvements).

Considering the immense unmet need in this disease, the experts agreed that the effect observed translates into a clinically meaningful effect in patients with moderate to severe, active autoantibody-positive SLE.

As it is anticipated that not all SLE patients will respond to the treatment, the expert recommended that, if anifrolumab is registered, the applicant should better characterise the patients who would benefit from the treatment (e.g. need to identify biomarkers).

2.5.7. Conclusions on clinical efficacy

Within the three key studies, anifrolumab demonstrated signs of efficacy across a range of endpoints studied. While the failure of Study 05 on its original primary endpoint (SRI(4) response) remains a notable weakness of the overall programme, the CHMP concluded following recommendations from the AHEG that the totality of evidence is supportive of beneficial treatment effects of anifrolumab. Based on the composite estimand, the treatment difference on BICLA response was 16% in Study 04 and 17% in Study 05, although the point estimate is associated with some uncertainty particularly in Study 04, where differential treatment attrition complicates interpretation of the results and the difference in some scenarios is closer to 10-11%. Nevertheless, this difference, albeit modest, is considered clinically meaningful in the following indication:

"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."

2.5.8. Clinical safety

A tabular summary of safety treatment comparisons and studies contributing in the data are summarised in Table 43.

Table 43 Integrated summary of safety treatment comparisons and studies contributing data

	Phase III studies contributing data							Phase II studies contributing data			
	Study 05			Study 04		Study 09		Study 1013			Study 1145
Treatments compared Pool/comparison	Ani 150 mg	Ani 300 mg	Placebo	Ani 300 mg	Placebo	Ani 300 mg	Placebo	Ani 300 mg	Ani 1000 mg	Placebo	Ani 300/1000 mg
300 mg vs placebo											
Primary pool		X	X	X	X						
Supportive pool		X	X	X	X			X		X	
Phase III LT safety		X	X	X	X	X	X				
150 mg vs placebo											
150 mg vs placebo	X		X								
1000 mg vs placebo											
1000 mg vs placebo									X	X	
All anifrolumab vs placebo											
All anifrolumab pool	X	X	X	X	X	X	X	X	X	X	X

Safety analysis population Safety data in the integrated safety analyses were summarised using the safety analysis set, including all randomised patients who received at least one dose of IP.

Safety variables Safety assessments in the anifrolumab clinical development programme were based on AEs (including AEs, SAEs, DAEs, and AESIs), clinical laboratory evaluations, vital signs measurements, 12-lead ECGs, physical examinations and, for the 52-week phase III studies, disease flares using a modified SELENA flare index, the C-SSRS, and PHQ-8.

The primary safety pool (study 04 and study 05) was used to evaluate AEs, SAEs, DAEs, AESIs, clinical laboratory data, vital signs, ECGs, and the C-SSRS results over 52 weeks of treatment and to perform subgroup analyses.

The supportive safety pool was also used to evaluate the AE profile for anifrolumab IV 300 mg over 52 weeks (AEs, SAEs, DAEs, and AESIs). Only data from the anifrolumab 300 mg treatment groups and the placebo treatment groups in studies 04, 05, and 1013 were included in the supportive safety pool.

The phase III long-term safety data were used to evaluate AEs, SAEs, DAEs, AESIs, and clinical laboratory data up to 4 years of treatment.

The all anifrolumab safety pool (studies 04, 05, 09, 1013, and 1145) included multiple anifrolumab IV treatment groups (150, 300, and 1000 mg) across 5 studies (studies 05, 04, 09, 1013, and 1145). This pool was designed to capture all AEs and SAEs in patients who received any anifrolumab dose in those studies.

Treatments In Study 04, patients received anifrolumab at a dose of 300 mg or matching placebo. In Study 05, patients received anifrolumab at doses of 150 mg or 300 mg, or matching placebo. In Study 1013, patients received anifrolumab at doses of 300 mg or 1000 mg, or matching placebo. In all studies, dosing was at 4-week intervals, with the last dose administered at Week 48.

2.5.8.1. Patient exposure

The design of the studies, including demographic and patient characteristics, treatments and patient disposition can be found in the Efficacy section.

Size of the safety database

In total, 1029 subjects have been exposed to any dose of anifrolumab (IV or SC) for periods of up to 4 years in the clinical development programme. Of those 1029 subjects, at least 837 patients with SLE were exposed to IV anifrolumab (doses ≥ 150 mg), including 688 patients for ≥ 52 weeks, 497 patients for ≥ 104 weeks, 263 patients for ≥156 weeks, and 108 patients for ≥ 208 weeks.

Although the total subject number (1029 subjects) is less than the ICH target (1500), the total patient-years of exposure to IV anifrolumab 150, 300, or 1000 mg in SLE patients (1888.2 PY) was, according to the applicant, adequate to evaluate the safety profile of anifrolumab in patients with SLE, a chronic disease with an estimated global prevalence of 6.5 to 178.0 cases per 100000 persons (Pons-Estel et al 2017). Importantly, the number of patients treated with anifrolumab in the programme exceeds the ICH E1 recommendations for > 6 months of exposure (300 to 600 patients) and > 1 year of exposure (100 patients). Duration of exposure is shown in Table 44.

Table 44 Duration of exposure – Phase III long-term safety (safety analysis set)

Exposure		Phase III long-term safety	
		Anifrolumab 300 mg (N = 360)	Placebo (N = 365)
Duration of exposure (days) [a]	n	360	365
	Mean (SD)	760.8 (381.44)	487.2 (328.85)
	Median	853.0	365.0
	Min, max	3, 1459	21, 1437
	Total PY of exposure	749.9	486.8
Cumulative exposure over time, n (%)	≥ 1 day	360 (100.0)	365 (100.0)
	≥ 12 weeks	346 (96.1)	351 (96.2)
	≥ 24 weeks	326 (90.6)	326 (89.3)
	≥ 36 weeks	311 (86.4)	300 (82.2)
	≥ 48 weeks	300 (83.3)	280 (76.7)
	≥ 52 weeks	294 (81.7)	242 (66.3)
	≥ 76 weeks	248 (68.9)	102 (27.9)
	≥ 104 weeks	223 (61.9)	86 (23.6)
	≥ 128 weeks	161 (44.7)	57 (15.6)
	≥ 156 weeks	76 (21.1)	31 (8.5)
	≥ 180 weeks	21 (5.8)	10 (2.7)
	≥ 208 weeks	1 (0.3)	0
Total follow-up time [b]	n	360	365
	Mean (SD)	794.6 (355.23)	527.3 (317.98)
	Median	881.0	373.0
	Min, max	3, 1459	21, 1459

Source: Table 3.1.1, Appendix 2.7.4.7.1 in Module 5.3.5.3.
[a] Duration of exposure (days) = min ((last dosing date + 28 days), end of study date, death date) – first dosing date + 1, or = min ((last dosing date + 28 days), end of study date, death date, data cut-off date) – first dosing date + 1 for study 09.
[b] Total follow-up time (days) = end of study date – first dosing date + 1, or = min (end of study date, data cut-off date) – first dosing date + 1 for study 09.
The definition of each pool and details of treatment groups within each pool are described in SAP Section 2.2.1.
If not stated otherwise, percentages are based upon all patients in the safety analysis set within the respective pool and treatment group.
max Maximum; Min Minimum; n Number of patients included in analysis; N Number of patients in treatment group;
PY Patient-years; SAP Statistical analysis plan; SD Standard deviation.

Overall extent of exposure: Other treatment comparisons

In the *all anifrolumab pool*, 837 patients received at least one dose of anifrolumab (150, 300 or 1000 mg). Total exposure was 1888.2 PY in the all anifrolumab group. A total of 766 (91.5%) patients were exposed to anifrolumab (150, 300, or 1000 mg) for ≥ 24 weeks, 688 (82.2%) were exposed for ≥ 52 weeks, 497 (59.4%) were exposed for ≥ 104 weeks, and 263 (31.4%) were exposed for ≥ 156 weeks. As of 01 August 2019, 108 patients (12.9%) had completed 208 weeks (~ 4 years) of treatment. The mean duration of exposure was 824.0 days in the all anifrolumab group and 499.0 days in the placebo group.

Anifrolumab 150 mg vs placebo

In study 05, 93 patients were randomised to receive anifrolumab IV 150 mg Q4W and received at least one dose of IP. There were 184 patients in the placebo group in study 05. The mean (SD) duration of IP exposure was 326.3 days (87.00) in the anifrolumab 150 mg group and 326.9 days (87.67) in the placebo group. Most patients had a cumulative exposure of ≥ 48 weeks: 81.7% and 80.4% in the anifrolumab 150 mg group and placebo group, respectively.

Anifrolumab 1000 mg vs placebo

In study 1013, 105 patients received at least one dose of anifrolumab IV 1000 mg. There were 101 patients in the placebo group. The mean (SD) duration of IP exposure was 321.4 days (91.45) in the anifrolumab 1000 mg group and 304.3 days (106.61) in the placebo group. Most patients had a cumulative exposure of ≥ 48 weeks: 74.3% and 70.3% in the anifrolumab 1000 mg group and placebo group, respectively.

2.5.8.2. Adverse events

Overview of adverse events

Primary and supportive safety pools

In the primary safety pool, the incidence of any AE during treatment was, according to the applicant greater in the anifrolumab 300 mg group (88.3%) than in the placebo group (80.8%) (Table 45). Most AEs experienced by patients treated with anifrolumab 300 mg were mild or moderate in intensity. Patients in the anifrolumab 300 mg group had a lower incidence of any SAE during treatment than the placebo group (11.1% vs 16.4%). The proportion of patients with any Discontinuations due to AEs was low and similar between the treatment groups.

Two deaths occurred during treatment in the primary safety pool. Both deaths were in the anifrolumab 300 mg group (EAIR: 0.6/100 PY).

In the primary safety pool, the proportion of patients with AEs of herpes zoster and the corresponding event rates were higher in the anifrolumab 300 mg group compared with the placebo group through 52 weeks. For all other AESIs, the incidence rates were similar between anifrolumab 300 mg and placebo groups through 52 weeks. There was no case of active TB in either treatment group.

Overall, most patients had AEs considered by the investigator to be unrelated to IP. A higher proportion of patients in the anifrolumab group had AEs considered by the investigator to be related to IP compared with placebo (36.9% vs 26.0%).

The overall AE profile in the supportive safety pool was similar to the overall AE profile in the primary safety pool (see Table 46).

Table 45 Adverse events during treatment in any category – Primary safety pool (safety analysis set)

AE category	Anifrolumab 300 mg (N = 360)			Placebo (N = 365)			Risk difference c (95% CI)
	n (%) patients	Exposure years	EAIR (per 100 PY)	n (%) patients	Exposure years	EAIR (per 100 PY)	
Patients with any AE	318 (88.3)	102.3	310.9	295 (80.8)	127.3	231.7	NC
Any AE with outcome of death	2 (0.6)	326.0	0.6	0	318.8	0	0.6 (-0.6, 2.2)
SAE (including events with outcome of **eath)"**	40 (11.1)	310.8	12.9	60 (16.4)	297.5	20.2	-7.3 (-13.3, -1.4)
Any DAE	17 (4.7)	325.0	5.2	18 (4.9)	317.5	5.7	-0.4 (-4.1, 3.2)
Any AE related to IP (investigator)	133 (36.9)	239.5	55.5	95 (26.0)	259.5	36.6	NC

Any AE by maximum reported intensity:							
Mild	141 (39.2)	132.9	106.1	140 (38.4)	153.8	91.1	NC
Moderate	150 (41.7)	228.1	65.8	128 (35.1)	242.8	52.7	NC
Severe	27 (7.5)	317.2	8.5	27 (7.4)	309.5	8.7	NC
Any AESI	46 (12.8)	306.0	15.0	36 (9.9)	305.3	11.8	3.2 (-2.2, 8.7)
Non-opportunistic serious infections	16 (4.4)	320.6	5.0	22 (6.0)	310.5	7.1	-2.1 (-6.0, 1.7)
Opportunistic infections	1 (0.3)	325.9	0.3	0	318.8	0	0.3 (-0.9, 1.7)
Anaphylaxis	0	326.0	0	0	318.8	0	0
Malignancy	3 (0.8)	324.3	0.9	3 (0.8)	318.7	0.9	-0.0 (-1.9, 1.9)
Herpes zoster	23 (6.4)	314.9	7.3	5 (1.4)	316.0	1.6	5.7 (2.7, 9.3)
Tuberculosis (including latent TB) a	2 (0.6)	325.1	0.6	1 (0.3)	318.8	0.3	0.3 (-1.2, 1.9)
Tuberculosis b	0	326.0	0	0	318.8	0	0
Influenza	6 (1.7)	324.3	1.9	8 (2.2)	314.9	2.5	-0.7 (-3.3, 1.8)
Vasculitis (non SLE)	0	326.0	0	0	318.8	0	0
MACE	1 (0.3)	325.1	0.3	0	318.8	0	0.3 (-0.9, 1.7)

Derived from: Table 3.2.1.1.1, Appendix 2.7.4.7.1 in Module 5.3.5.3. a Includes the PTs “Latent tuberculosis”" and “Mycobacterium tuberculosis complex test positive”. b Includes the PT “Tuberculosis”. c Risk difference is the difference between the EAIRs per 100 PY (anifrolumab 300 mg group – placebo group). Influenza and herpes zoster categories include serious and non-serious events. Patients with events classified in multiple AESI categories are counted once in each category. The definition of each pool and details of treatment groups within each pool are described in SAP Section 2.2.1.If not stated otherwise, percentages are based upon all patients in the safety analysis set within the respective pool and treatment group. An AE during treatment is defined as an AE with a date of onset ≥ day of first ever dose of IP and ≤ minimum ((last dosing date + 28 days), end of study date, death date). Adverse events are coded using MedDRA version 22.1. Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories. Any AE by intensity was counted once by maximum reported intensity. The patient’s duration of exposure by intensity is the time from first dose of IP up to the start of the event with maximum reported intensity, and this duration of exposure is applied across all of the intensity categories. The EAIR per 100 PY is defined as the number of patients with the specific event divided by the total exposure time in years and then multiplied by 100. The exposure time is defined as from the date of first administration of IP to the date of first event, death, end of treatment + 28 days, or end of study, whichever comes first. AE Adverse event; AESI Adverse event of special interest; CI Confidence interval; DAE Adverse event leading to discontinuation of IP; EAIR Exposure-adjusted incidence rate; IP Investigational product; MACE Major adverse cardiovascular events; n Number of patients with an event; N Number of patients in treatment group; NC Not calculated; PT Preferred term; PY Patient-years; SAE Serious adverse events; SAP Statistical analysis plan; SLE Systemic lupus erythematosus; TB Tuberculosis.

Table 46 Adverse events during treatment in any category – Supportive safety pool (safety analysis set)

AE category	**Anifrolumab 300 mg (N = 459)**			**Placebo (N = 466)**			**Risk difference c (95% CI)**
	n (%) patients	**Exposure years**	**EAIR (per 100 PY)**	**n (%) patients**	**Exposure years**	**EAIR (per 100 PY)**	
Patients with any AE	399 (86.9)	137.5	290.1	370 (79.4)	164.3	225.2	NC
Any AE with outcome of death	2 (0.4)	419.4	0.5	0	403.0	0	0.5 (-0.5, 1.7)
Any SAE (including events with outcome of death)	54 (11.8)	397.9	13.6	78 (16.7)	376.0	20.7	-7.2 (-12.5, -1.9)
Any DAE	19 (4.1)	418.1	4.5	24 (5.2)	401.3	6.0	-1.4 (-4.7, 1.7)
Any AE related to IP (investigator)	154 (33.6)	319.5	48.2	119 (25.5)	330.3	36.0	NC

Any AE by maximum reported intensity:							
Mild	168 (36.6)	176.1	95.4	179 (38.4)	195.1	91.8	NC
Moderate	189 (41.2)	289.5	65.3	154 (33.0)	309.7	49.7	NC
Severe	42 (9.2)	401.7	10.5	37 (7.9)	388.9	9.5	NC
Any AESI	61 (13.3)	392.6	15.5	47 (10.1)	385.5	12.2	3.3 (-1.5, 8.2)
Non-opportunistic serious infections	22 (4.8)	411.2	5.4	26 (5.6)	393.2	6.6	-1.3 (-4.7, 2.1)
Opportunistic infections	1 (0.2)	419.3	0.2	1 (0.2)	402.6	0.2	-0.0 (-1.2, 1.1)
Anaphylaxis	0	419.4	0	0	403.0	0	0
Malignancy	3 (0.7)	417.6	0.7	3 (0.6)	402.9	0.7	-0.0 (-1.5, 1.4)
Herpes zoster	28 (6.1)	406.9	6.9	6 (1.3)	399.5	1.5	5.4 (2.8, 8.4)
Tuberculosis (including latent TB) a	4 (0.9)	418.3	1.0	1 (0.2)	403.0	0.2	0.7 (-0.5, 2.2)
Tuberculosis b	0	419.4	0	0	403.0	0	0
Influenza	12 (2.6)	414.0	2.9	9 (1.9)	398.6	2.3	0.6 (-1.7, 3.0)
Vasculitis (non SLE)	0	419.4	0	2 (0.4)	403.0	0.5	-0.5 (-1.8, 0.4)
MACE	1 (0.2)	418.5	0.2	3 (0.6)	401.1	0.7	-0.5 (-2.0, 0.7)

a Includes the PTs “Latent tuberculosis” and “Mycobacterium tuberculosis complex test positive”. b Includes the PT “Tuberculosis”. c Risk difference is the difference between the EAIRs per 100 PY (anifrolumab 300 mg group – placebo group). Influenza and herpes zoster categories include serious and non-serious events. Patients with events classified in multiple AESI categories are counted once in each category. The definition of each pool and details of treatment groups within each pool are described in SAP Section 2.2.1. If not stated otherwise, percentages are based upon all patients in the safety analysis set within the respective pool and treatment group. An AE during treatment is defined as an AE with a date of onset ≥ day of first ever dose of IP and ≤ minimum ((last dosing date + 28 days), end of study date, death date). Adverse events are coded using MedDRA version 22.1. Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories. Any AE by intensity was counted once by maximum reported intensity. The patient’s duration of exposure by intensity is the time from first dose of IP up to the start of the event with maximum reported intensity, and this duration of exposure is applied across all of the intensity categories. The EAIR per 100 PY is defined as the number of patients with the specific event divided by the total exposure time in years and then multiplied by 100. The exposure time is defined as from the date of first administration of IP to the date of first event, death, end of treatment + 28 days, or end of study, whichever comes first. AE Adverse event; AESI Adverse event of special interest; CI Confidence interval; DAE Adverse event leading to discontinuation of IP; EAIR Exposure-adjusted incidence rate; IP Investigational product; MACE Major adverse cardiovascular events; n Number of patients with an event; N Number of patients in treatment group; NC Not calculated; PT Preferred term; PY Patient-years; SAE Serious adverse events; SAP Statistical analysis plan;

Phase III long-term safety data

Based on an evaluation of AEs by category in the phase III long-term data, long-term treatment with anifrolumab 300 mg (> 1 year) resulted in a safety profile consistent with what was observed in the primary safety pool (Table 47).

In the phase III long-term data, the EAIR of any SAE (including deaths) was lower in the anifrolumab 300 mg group than in the placebo group.

The EAIRs of individual AESIs in the phase III long-term data were generally similar to the primary safety pool.

Table 47 Adverse events during treatment in any category – Phase III long-term safety (safety analysis set)

AE category	Anifrolumab 300 mg (N = 360)			Placebo (N = 365)			Risk difference d (95% CI)
	n (%) patients	Exposure years	EAIR (per 100 PY)	n (%) patients	Exposure years	EAIR (per 100 PY)	
Patients with any AE	334 (92.8)	138.3	241.4	314 (86.0)	149.7	209.7	
Any AE with outcome of death	2 (0.6)	749.9	0.3	0	486.8	0	0.3 (-0.5, 1.0)
Any SAE (including events with outcome of death)	73 (20.3)	675.0	10.8	80 (21.9)	440.0	18.2	-7.4 (-11.8, -3.2)
Any DAE	23 (6.4)	748.4	3.1	21 (5.8)	484.0	4.3	-1.3 (-3.7, 0.8)
Any AE related to IP (investigator)	160 (44.4)	495.5	32.3	99 (27.1)	379.8	26.1	
Any AE by maximum reported intensity:							
Mild	115 (31.9)	253.4	45.4	135 (37.0)	208.7	64.7	
Moderate	170 (47.2)	445.0	38.2	145 (39.7)	337.9	42.9	
Severe	49 (13.6)	704.5	7.0	34 (9.3)	469.9	7.2	
Any AESI	88 (24.4)	653.7	13.5	51 (14.0)	450.0	11.3	2.1 (-1.9, 6.0)
Non-opportunistic serious infections	32 (8.9)	719.8	4.4	29 (7.9)	468.5	6.2	-1.7 (-4.6, 0.8)
Opportunistic infections	2 (0.6)	749.2	0.3	1 (0.3)	485.8	0.2	0.1 (-0.9, 0.8)
Anaphylaxis	0	749.9	0	0	486.8	0	0
Malignancy	4 (1.1)	744.5	0.5	4 (1.1)	486.7	0.8	-0.3 (-1.6, 0.7)
Herpes zoster	39 (10.8)	706.7	5.5	8 (2.2)	476.4	1.7	3.8 (1.7, 6.0)
Tuberculosis (including latent TB) a	16 (4.4)	735.3	2.2	3 (0.8)	484.3	0.6	1.6 (0.2, 3.0)
Tuberculosis b	0	749.9	0	0	486.8	0	0
Influenza	15 (4.2)	732.5	2.0	9 (2.5)	479.8	1.9	0.2 (-1.7, 1.8)
Vasculitis (non-SLE)	0	749.9	0	1 (0.3)	486.7	0.2	-0.2 (-1.2, 0.3)
MACE c	1 (0.3)	747.5	0.1	0	486.8	0	0.1 (-0.7, 0.8)

a Includes the PTs "Latent tuberculosis" and "Mycobacterium tuberculosis complex test positive".
b Includes the PT "Tuberculosis".
c Includes only data from the completed 52-week studies (studies 04 and 05). The CV-EAC adjudication of events in study 09 will not be entered into the clinical database until the end of the study and are not included.
d Risk difference is the difference between the EAIRs per 100 PY (anifrolumab 300 mg group – placebo group). Influenza and herpes zoster categories include serious and non-serious events. Patients with events classified in multiple AESI categories are counted once in each category. The definition of each pool and details of treatment groups within each pool are described in SAP Section 2.2.1.
If not stated otherwise, percentages are based upon all patients in the safety analysis set within the respective pool and treatment group.
An AE during treatment is defined as an AE with a date of onset ≥ day of first ever dose of IP and ≤ minimum ((last dosing date + 28 days), end of study date, death date).
Adverse events are coded using MedDRA version 22.1.
Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories. Any AE by intensity was counted once by maximum reported intensity. The patient's duration of exposure by intensity is the time from first dose of IP up to the start of the event with maximum reported intensity, and this duration of exposure is applied across all of the intensity categories.
The EAIR per 100 PY is defined as the number of patients with the specific event divided by the total exposure time in years and then multiplied by 100. The exposure time is defined as from the date of first administration of IP to the date of first event, death, end of treatment + 28 days, or end of study, whichever comes first.
AE Adverse event; AESI Adverse event of special interest; CI Confidence interval; CV-EAC Cardiovascular Event Adjudication Committee; DAE Adverse event leading to discontinuation of IP; EAIR Exposure-adjusted incidence rate;

IP Investigational product; MACE Major adverse cardiovascular events; n Number of patients with an event; N Number of patients in treatment group; PT Preferred term; PY Patient-years; SAE Serious adverse events; SAP Statistical analysis plan; SLE Systemic lupus erythematosus; TB Tuberculosis.

Common adverse events

Primary safety pool

In the primary safety pool, the most common AEs (reported in > 2% of patients in either treatment group) are listed by decreasing frequency in the anifrolumab 300 mg group in Table 48. In the anifrolumab 300 mg group, the highest frequency AEs (reported in ≥ 5% of patients) by PT were nasopharyngitis, upper respiratory tract infection, urinary tract infection, infusion-related reaction, bronchitis, headache, herpes zoster, back pain, cough, arthralgia, sinusitis, and vomiting.

Adverse events that were more common (≥ 5% difference or at least 5% incidence and twice the frequency) in the anifrolumab 300 mg group than the placebo group were: nasopharyngitis (17.8% vs 11.2%), upper respiratory tract infection (16.9% vs 9.9%), bronchitis (10.6% vs 4.7%), herpes zoster (6.4% vs 1.4%), and arthralgia (5.6% vs 2.2%). Those 5 AEs are summarised by intensity in Table 49.

The SOC with the greatest frequency of AEs in the anifrolumab 300 mg group during the treatment period was Infections and infestations (71.7% vs 57.8% in the placebo group).

Table 48 Adverse events reported in > 2% of patients during treatment, by PT – Primary safety pool (safety analysis set)

Preferred Term	Anifrolumab 300 mg			Placebo (N = 365)		
	n (%) Patients	Exposure years	EAIR per 100 PY	N (%) Patients	Exposure years	EAIR per 100 PY
Patients with any AE above reporting threshold of 2%	275 (76.4)	NC	NC	240 (65.8)	NC	NC
Nasopharyngitis	64 (17.8)	289.7	22.1	41 (11.2)	296.9	13.8
Upper respiratory tract infection	61 (16.9)	293.2	20.8	36 (9.9)	297.8	12.1
Urinary tract infection	42 (11.7)	304.3	13.8	52 (14.2)	291.8	17.8
Infusion related reaction	41 (11.4)	294.2	13.9	27 (7.4)	296.9	9.1
Bronchitis	38 (10.6)	307.2	12.4	17 (4.7)	312.2	5.4
Headache	26 (7.2)	310.9	8.4	32 (8.8)	302.5	10.6
Herpes zoster	23 (6.4)	314.9	7.3	5 (1.4)	316.0	1.6
Back pain	21 (5.8)	315.4	6.7	16 (4.4)	310.0	5.2
Cough	21 (5.8)	312.5	6.7	13 (3.6)	312.6	4.2
Arthralgia	20 (5.6)	312.9	6.4	8 (2.2)	315.6	2.5
Sinusitis	20 (5.6)	314.9	6.4	21 (5.8)	311.2	6.7
Vomiting	18 (5.0)	317.6	5.7	10 (2.7)	313.3	3.2
Nausea	16 (4.4)	317.6	5.0	22 (6.0)	307.4	7.2
Oral herpes	15 (4.2)	316.9	4.7	10 (2.7)	312.7	3.2
Pharyngitis	14 (3.9)	319.0	4.4	16 (4.4)	310.3	5.2
Hypersensitivity	13 (3.6)	317.1	4.1	3 (0.8)	317.4	0.9
Pneumonia	13 (3.6)	321.2	4.0	12 (3.3)	316.2	3.8

Respiratory tract infection	13 (3.6)	318.4	4.1	2 (0.5)	317.4	0.6
Diarrhoea	11 (3.1)	319.8	3.4	21 (5.8)	309.4	6.8
Gastroenteritis viral	11 (3.1)	318.9	3.4	5 (1.4)	316.9	1.6
Depression	10 (2.8)	320.7	3.1	8 (2.2)	314.7	2.5
Anxiety	9 (2.5)	321.4	2.8	7 (1.9)	315.0	2.2
Gastroenteritis	9 (2.5)	321.4	2.8	10 (2.7)	314.2	3.2
Pain in extremity	9 (2.5)	322.3	2.8	2 (0.5)	318.6	0.6
Arthropod bite	8 (2.2)	322.2	2.5	4 (1.1)	316.7	1.3
Gastrooesophageal reflux disease	8 (2.2)	322.1	2.5	11 (3.0)	313.0	3.5
Iron deficiency anaemia	8 (2.2)	323.5	2.5	6 (1.6)	316.0	1.9
Oedema peripheral	8 (2.2)	321.1	2.5	4 (1.1)	317.0	1.3
Abdominal pain upper	7 (1.9)	320.4	2.2	11 (3.0)	313.5	3.5
Dizziness	7 (1.9)	321.7	2.2	10 (2.7)	312.4	3.2
Pyrexia	7 (1.9)	322.8	2.2	8 (2.2)	316.4	2.5
Influenza	6 (1.7)	324.3	1.9	8 (2.2)	314.9	2.5
Insomnia	6 (1.7)	323.7	1.9	16 (4.4)	311.1	5.1
Non-cardiac chest pain	6 (1.7)	322.6	1.9	9 (2.5)	314.9	2.9
Systemic lupus erythematosus	6 (1.7)	323.7	1.9	9 (2.5)	316.2	2.8
Abdominal pain	5 (1.4)	322.5	1.6	8 (2.2)	315.8	2.5
Cystitis	4 (1.1)	324.0	1.2	8 (2.2)	314.6	2.5
Hypertension	4 (1.1)	323.5	1.2	11 (3.0)	314.0	3.5
Gastritis	3 (0.8)	324.9	0.9	9 (2.5)	315.3	2.9
Anaemia	2 (0.6)	325.0	0.6	9 (2.5)	315.4	2.9

The definition of the pool and details of treatment groups within the pool are described in SAP Section 2.2.1. If not stated otherwise, percentages are based upon all patients in the safety analysis set within the respective pool and treatment group. An AE during treatment is defined as an AE with a date of onset ≥ day of first ever dose of IP and ≤ minimum ((last dosing date + 28 days), end of study date, death date). Adverse events are coded using MedDRA version 22.1. Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories. AEs are sorted by descending frequency of PT in the anifrolumab 300 mg group. The EAIR per 100 PY is defined as the number of patients with the specific event divided by the total exposure time in years and then multiplied by 100. The exposure time is defined as from the date of first administration of IP to the date of first event, death, end of treatment + 28 days, or end of study, whichever comes first. AEs that are present in > 2% of patients in any treatment group are reported. AE Adverse event; EAIR Exposure-adjusted incidence rate; IP Investigational product; n Number of patients with an event; N Number of patients in treatment group; NC Not calculated; PT Preferred term; PY Patient-years; SAP Statistical analysis plan.

Table 49 Adverse events by PT and intensity reported more commonly (≥ 5% difference or ≥ 5% incidence and twice the frequency) during treatment in the anifrolumab 300 mg group than the placebo group (safety analysis set)

Preferred Term Max reported intensity	Primary safety pool Anifrolumab 300 mg (N = 360) n (%) patients	Placebo (N = 365) n (%) patients
Nasopharyngitis	**64 (17.8)**	**41 (11.2)**
Max reported intensity		
Mild	48 (13.3)	33 (9.0)
Moderate	16 (4.4)	8 (2.2)
Severe	0	0
Upper respiratory tract infection	**61 (16.9)**	**36 (9.9)**
Max reported intensity		
Mild	44 (12.2)	31 (8.5)
Moderate	17 (4.7)	5 (1.4)
Severe	0	0
Bronchitis	**38 (10.6)**	**17 (4.7)**
Max reported intensity		
Mild	19 (5.3)	7 (1.9)
Moderate	17 (4.7)	8 (2.2)
Severe	2 (0.6)	2 (0.5)
Herpes zoster	**23 (6.4)**	**5 (1.4)**
Max reported intensity		
Mild	8 (2.2)	0
Moderate	14 (3.9)	5 (1.4)
Severe	1 (0.3)	0
Arthralgia	**20 (5.6)**	**8 (2.2)**
Max reported intensity		
Mild	15 (4.2)	5 (1.4)
Moderate	5 (1.4)	2 (0.5)
Severe	0	1 (0.3)

The definition of each pool and details of treatment groups within each pool are described in SAP Section 2.2.1. If not stated otherwise, percentages are based upon all patients in the safety analysis set within the respective pool and treatment group. An AE during treatment is defined as an AE with a date of onset ≥ day of first ever dose of IP and ≤ minimum ((last dosing date + 28 days), end of study date, death date). Adverse events are coded using MedDRA version 22.1. Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories. Patients with multiple events are counted only once as related if at least one AE is related, and as not related if all occurrences are not related. Any AE by intensity was counted once at the highest intensity level. AEs are sorted by descending frequency of PT in the anifrolumab 300 mg group. AE Adverse event; IP Investigational product; n Number of patients with an event; N Number of patients in treatment group and subgroup; SAP Statistical analysis plan.

Supportive safety pool

The most common AE data in the supportive safety pool were similar to the data in the primary safety pool. In the anifrolumab 300 mg group (N = 459), the highest frequency AEs (reported in ≥ 5% of patients) by PT were nasopharyngitis (16.3%), upper respiratory tract infection (15.5%), urinary tract infection (12.0%), bronchitis (9.8%), infusion-related reaction (9.4%), headache (8.1%), herpes zoster (6.1%), back pain (5.2%), sinusitis (5.2%), and cough (5.0%).

In the supportive safety pool, AEs that were more common (≥ 5% difference or at least 5% incidence in the anifrolumab group and twice the frequency as the placebo group) in the anifrolumab 300 mg group

(N = 459) than the placebo group (N = 466) were nasopharyngitis (16.3% vs 9.4%), upper respiratory tract infection (15.5% vs 9.7%), bronchitis (9.8% vs 4.3%), and herpes zoster (6.1% vs 1.3%).

Phase III long-term safety data

In the phase III long-term safety data, the most common AEs by PT were similar to those observed in the primary safety pool. During up to 4 years of treatment, in the anifrolumab 300 mg group (N = 360), the highest frequency AEs (reported in ≥ 5% of patients) by PT were nasopharyngitis (25.0%), upper respiratory tract infection (24.4%), urinary tract infection (18.6%), bronchitis (17.2%), infusion-related reaction (13.9%), headache (11.4%), herpes zoster (10.3%), arthralgia (9.2%), cough (8.6%), back pain (8.6%), sinusitis (8.6%), vomiting (6.9%), nausea (6.7%), oral herpes (6.7%), diarrhea (6.4%), pharyngitis (6.1%), and pneumonia (5.0%).

On request, the applicant provided tables of AEs by relatedness to IP, intensity, and seriousness, for the primary and supportive safety pools and for the Phase III long-term safety data. The majority of AEs in each pool were unrelated to IP in both anifrolumab 300 mg and placebo group. Related AEs were more common in the anifrolumab 300 mg groups than in placebo groups, as expected, and the majority were mild or moderate in intensity. A lower rate of related SAEs was observed in anifrolumab 300 mg groups compared to placebo groups (EAIR per 100 PY: Primary safety group: 2.8 vs 5.5; Supportive safety pool: 2.9 vs 5.3; Long-term safety data: 2 vs 3.8). In addition, the applicant provided information on most common AEs by relatedness.

2.5.8.3. Serious adverse events and deaths

Serious Adverse Events

Primary safety pool

In the primary safety pool, fewer patients in the anifrolumab 300 mg group had any SAE during treatment than patients in the placebo group (11.1% vs 16.4%); the EAIR risk difference was -7.3 (95% CI: -13.3, -1.4) (Table 50). Among patients with SAEs during treatment, in both treatment groups, the most common SAEs by PT were pneumonia and systemic lupus erythematosus. There were no other trends by PT; no other SAEs were reported in > 2 patients in either treatment group.

There were 6 patients (1.7%) in the anifrolumab group and 8 patients (2.2%) in the placebo group who had a SAE of pneumonia. Among the 6 SAEs of pneumonia in the anifrolumab 300 mg group, 2 were fatal.

As a safety variable, the PT of systemic lupus erythematosus included SLE flares and increases in disease activity involving new or worsening clinical signs and symptoms. There were 4 patients (1.1%) in the anifrolumab group and 9 patients (2.5%) in the placebo group who had a SAE of systemic lupus erythematosus. During the 52-week treatment period, there was no trend in the timing of these events in either treatment group. For an analysis of disease flares as an efficacy variable, refer to the Clinical Efficacy Section 2.5.5.

Table 50 Serious adverse events during treatment by PT in ≥ 2 patients in the anifrolumab 300 mg group – Primary safety pool (safety analysis set)

Preferred Term	Anifrolumab 300 mg (N = 360)			Placebo (N = 365)			Risk difference [a] (95% CI)
	n (%) patients	Exposure years	EAIR (per 100 PY)	n (%) patients	Exposure years	EAIR (per 100 PY)	
Patients with any SAE	**40 (11.1)**	**310.8**	**12.9**	**60 (16.4)**	**297.5**	**20.2**	**-7.3 (-13.3, -1.4)**
Pneumonia	6 (1.7)	324.6	1.8	8 (2.2)	317.2	2.5	-0.7 (-3.3, 1.8)
Systemic lupus erythematosus	4 (1.1)	325.1	1.2	9 (2.5)	316.2	2.8	-1.6 (-4.2, 0.6)
Angioedema	2 (0.6)	325.2	0.6	0	318.8	0	0.6 (-0.6, 2.2)
Appendicitis	2 (0.6)	325.5	0.6	0	318.8	0	0.6 (-0.6, 2.2)
Asthma	2 (0.6)	325.4	0.6	1 (0.3)	318.8	0.3	0.3 (-1.2, 1.9)
Chest pain	2 (0.6)	325.4	0.6	0	318.8	0	0.6 (-0.6, 2.2)
Gastroenteritis viral	2 (0.6)	325.1	0.6	0	318.8	0	0.6 (-0.6, 2.2)

Derived from: Table 3.4.1.1.1, Appendix 2.7.4.7.1 in Module 5.3.5.3.

[a] Risk difference is the difference between the EAIRs per 100 PY (anifrolumab 300 mg group– placebo group).

The definition of each pool and details of treatment groups within each pool are described in SAP Section 2.2.1.

If not stated otherwise, percentages are based upon all patients in the safety analysis set within the respective pool and treatment group.

An AE during treatment is defined as an AE with a date of onset ≥ day of first ever dose of IP and ≤ minimum ((last dosing date + 28 days), end of study date, death date).

Adverse events are coded using MedDRA version 22.1.

Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.

AEs are sorted by descending frequency of PT in the anifrolumab 300 mg group.

The EAIR per 100 PY is defined as the number of patients with the specific event divided by the total exposure time in years and then multiplied by 100. The exposure time is defined as from the date of first administration of IP to the date of first event, death, end of treatment + 28 days, or end of study, whichever comes first.

AE Adverse event; CI Confidence interval; EAIR Exposure-adjusted incidence rate; IP Investigational product; n Number of patients with an event; N Number of patients in treatment group; PT Preferred term; PY Patient-years; SAE Serious adverse event; SAP Statistical analysis plan.

Supportive safety pool

The SAEs in the supportive safety pool were similar to the SAEs in the primary safety pool. In the supportive safety pool, the proportions of patients with one or more SAEs were 11.8% and 16.7% in the anifrolumab 300 mg and placebo groups, respectively; the EAIR risk difference was -7.2 per 100 PY (95% CI: -12.5, -1.9).

Phase III long-term safety data

As observed during the 52-week treatment period, SAE EAIRs in the phase III long-term safety data were lower in the anifrolumab 300 mg group than the placebo group: 10.8/100 PY vs 18.2/100 PY; risk difference of -7.4 (95% CI: -11.8, -3.2). Also consistent with the primary safety pool, the most common SAEs in both treatment groups in the phase III long-term safety data were pneumonia and systemic lupus erythematosus (Table 51). During up to 4 years of treatment, the EAIR of systemic lupus erythematosus SAEs was lower in the anifrolumab 300 mg group than the placebo group.

The evaluation of SAEs by yearly intervals did not suggest any change in overall SAE incidence over the course of long-term treatment (Table 52). Evaluation of the most common SAEs in the anifrolumab 300 mg group by yearly intervals showed similar event rates over time (Table 52).

Table 51 Serious adverse events during treatment by PT in ≥ 2 patients in the anifrolumab 300 mg group – Phase III long-term safety (safety analysis set)

Preferred Term	Anifrolumab 300 mg			Placebo (N = 365)			Risk difference a
	n (%)	Exposure	EAIR (per 100	n (%)	Exposure	EAIR (per 100	(95% CI)
Patients with any SAE	**73 (20.3)**	**675.0**	**10.8**	**80 (21.9)**	**440.0**	**18.2**	**-7.4 (-11.8, -3.2)**
Pneumonia	8 (2.2)	743.5	1.1	9 (2.5)	481.1	1.9	-0.8 (-2.5, 0.6)
Systemic lupus erythematosus	6 (1.7)	745.7	0.8	15 (4.1)	480.4	3.1	-2.3 (-4.3, -0.8)
Herpes zoster	5 (1.4)	745.8	0.7	0	486.8	0	0.7 (-0.1, 1.6)
Non-cardiac chest pain	3 (0.8)	746.0	0.4	1 (0.3)	486.8	0.2	0.2 (-0.8, 1.0)
Pyelonephritis	3 (0.8)	746.5	0.4	0	486.8	0	0.4 (-0.4, 1.2)
Acute kidney injury	2 (0.6)	749.3	0.3	1 (0.3)	486.4	0.2	0.1 (-0.9, 0.8)
Acute respiratory failure	2 (0.6)	749.6	0.3	0	486.8	0	0.3 (-0.5, 1.0)
Angioedema	2 (0.6)	748.0	0.3	0	486.8	0	0.3 (-0.5, 1.0)
Appendicitis	2 (0.6)	747.9	0.3	0	486.8	0	0.3 (-0.5, 1.0)
Asthma	2 (0.6)	745.4	0.3	1 (0.3)	486.8	0.2	0.1 (-0.9, 0.8)
Chest pain	2 (0.6)	749.3	0.3	0	486.8	0	0.3 (-0.5, 1.0)
Coronary artery disease	2 (0.6)	747.3	0.3	0	486.8	0	0.3 (-0.5, 1.0)
Gastroenteritis	2 (0.6)	745.5	0.3	2 (0.5)	485.1	0.4	-0.1 (-1.2, 0.6)
Gastroenteritis viral	2 (0.6)	746.9	0.3	0	486.8	0	0.3 (-0.5, 1.0)
Influenza	2 (0.6)	749.3	0.3	1 (0.3)	486.1	0.2	0.1 (-0.9, 0.8)
Post herpetic neuralgia	2 (0.6)	749.8	0.3	0	486.8	0	0.3 (-0.5, 1.0)
Urinary tract infection	2 (0.6)	748.5	0.3	2 (0.5)	486.0	0.4	-0.1 (-1.2, 0.6)

a Risk difference is the difference between the EAIRs per 100 PY (anifrolumab 300 mg group– placebo group). The definition of each pool and details of treatment groups within each pool are described in SAP Section 2.2.1. If not stated otherwise, percentages are based upon all patients in the safety analysis set within the respective pool and treatment group. An AE during treatment is defined as an AE with a date of onset ≥ day of first ever dose of IP and ≤ minimum ((last dosing date + 28 days), end of study date, death date). Adverse events are coded using MedDRA version 22.1. Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories. AEs are sorted by descending frequency of PT in the anifrolumab 300 mg group. The EAIR per 100 PY is defined as the number of patients with the specific event divided by the total exposure time in years and then multiplied by 100. The exposure time is defined as from the date of first administration of IP to the date of first event, death, end of treatment + 28 days, or end of study, whichever comes first. AE Adverse event; CI Confidence interval; EAIR Exposure-adjusted incidence rate; IP Investigational product; n Number of patients with an event; N Number of patients in treatment group; PT Preferred term; PY Patient-years; SAE Serious adverse event; SAP Statistical analysis plan.

Table 52 Serious adverse events during treatment, by PT and time interval – Phase III long-term safety (safety analysis set)

Preferred Term	Time interval	Anifrolumab 300 mg			Placebo (N = 365)		
		n/N' (%)	Exposure	EAIR (per 100 PY)	n/N' (%)	Exposure	EAIR (per 100 PY)
Patients with any SAE	Total	73/360 (20.3)	675.0	10.8	80/365 (21.9)	440.0	18.2
	Year 1	40/360 (11.1)	310.3	12.9	60/365 (16.4)	296.6	20.2
	Year 2	29/277 (10.5)	233.7	12.4	15/174 (8.6)	96.6	15.5
	Year 3	17/222 (7.7)	146.0	11.6	10/85 (11.8)	53.1	18.8
	Year 4+	0/73	26.5	0	1/29 (3.4)	10.6	9.4

The definition of each pool and details of treatment groups within each pool are described in SAP Section 2.2.1. If not stated otherwise, percentages are based upon all patients in the safety analysis set within the respective pool and treatment group. An AE during treatment is defined as an AE with a date of onset ≥ day of first ever dose of IP and ≤ minimum ((last dosing date + 28 days), end of study date, death date). Adverse events are coded using MedDRA version 22.1. Patients with multiple events in the same category are counted only once in that category. Patients with events

in more than one category are counted once in each of those categories. AEs in the same category onset in different time intervals are summarised in each of the time intervals. The Total row may contain events that occurred after 52 weeks. N' is the number of patients staying in on-treatment period at the beginning of the interval. The EAIR per 100 PY is defined as the number of patients with the specific event in each time interval divided by the total exposure time in years and then multiplied by 100. The exposure time in an interval is defined as from the start date of the interval to the date of first event, death, end of treatment + 28 days, end of the interval, or end of study, whichever comes first. n Number of patients with an event; PT Preferred term; SAE Serious adverse event; SAP Statistical analysis plan.

SAEs EAIR seem not to increase over time.

Deaths

Overall, there were 9 deaths during the anifrolumab clinical studies in the anifrolumab development programme (across studies MI-CP180, 02, 04, 05, 06, 08, 09, 1013, and 1145). Key patient data for patients with fatal AEs are listed in Table 53.

Table 53 Adverse events with outcome of death, key patient information (safety analysis set)

Study	IP received	IP at AE or last IP before AE (days [b])	Preferred term name/ verbatim text	First dose to AE (days [c])/last dose to AE (days [d])	First dose to death (days [e])/last dose to death (days [f])	Causally related to IP [g]
Study 1013	Ani 1000 mg	Ani 1000 mg (27)	Colitis/Colitis*	27/27	34/34	Unrelated
Study 1145	Placebo/ Ani 1000 mg/ Ani 300 mg	Ani 300 mg (430)	Pneumonia/Community-acquired pneumonia*	1368/20	1368/20	Related
Study 04	Ani 300 mg	Ani 300 mg (219)	Pneumonia/Pneumonia*	219/24	221/26	Related
Study 05	Placebo	Placebo (259)	Encephalitis/Acute meningoencephalitis	259/36	259/36	Unrelated
Study 05	Ani 300 mg	Ani 300 mg (50)	Pneumonia/Nosocomial pneumonia*	50/22	64/36	Unrelated
Study 09			Pulmonary hypertension/Severe pulmonary hypertension	730/128	792/190	Unrelated
Study 09			Myocardial infarction/ Possible heart attack	1100/37	1100/37	Unrelated

[a] Age at study entry. [b] Days is calculated as the AE onset date – the first dose date of the IP patient received at AE (or last IP patient had prior to death if discontinued the treatment). [c] Days is calculated as the AE onset date – the first dose date of IP (any) patient received. [d] Days is calculated as the AE onset date – the last dose date of IP (any) patient received. [e] Days is calculated as the death date – the first dose date of IP (any) patient received. [f] Days is calculated as the death date – the last dose date of IP (any) patient received. [g] As judged by the investigator. * AE during treatment. Adverse events are coded using MedDRA version 22.1. anifrolumab; B Black or African American; F Female; IP Investigational product; O Other; W White.

Two (2) additional deaths occurred in study 09 from 02 August 2019 to 19 March 2020, both in the anifrolumab 300 mg group. The fatal outcome event was pneumonia in one case and myocarditis in the other one. Both have been considered as unrelated to IP by the investigator.

Adverse Events of Special Interest

Infections

Infections were identified as a topic of interest in the anifrolumab programme due to the immunomodulatory mechanism of action of anifrolumab. Serious non-opportunistic infections, opportunistic infections, herpes zoster, TB (including latent TB), and influenza were analyzed as individual AESI categories. Overall infections were not a category of AESI, but are discussed here as an additional supportive analysis.

Primary and supportive safety pools

In the primary safety pool, infections overall during treatment, as assessed by the SOC Infections and infestations, were reported in a greater proportion of patients in the anifrolumab 300 mg group than the placebo group (71.7% vs 57.8%) (Table 54). Most infections in both treatment groups were mild or moderate in intensity, were not considered serious, and did not result in discontinuation from treatment. The difference between the overall rates of infection in the 300 mg anifrolumab group versus placebo group was driven by differences in the incidence rates of mild and moderate infections involving the respiratory tract, excluding pneumonia (comparable in both treatment groups), and separately, herpes zoster.

The incidence of serious infections was similar between the treatment groups: 16 patients (4.4%) in the anifrolumab 300 mg group and 22 patients (6.0%) in the placebo group had one or more SAE in the SOC Infections and infestations. Rates of non-opportunistic serious infections and opportunistic infections were also both similar between the treatment groups.

Table 54 Infections and infestations during treatment, overall and by intensity – Primary safety pool (safety analysis set)

	Maximum reported intensity	Anifrolumab 300 mg (N = 360)			Placebo (N = 365)		
		n (%) Patients	Exposure years	EAIR (per 100 PY)	n (%) Patients	Exposure years	EAIR (per 100 PY)
Infections and infestations	All	258 (71.7)	170.0	151.8	211 (57.8)	200.2	105.4
	Mild	148 (41.1)	186.4	79.4	125 (34.2)	205.3	60.9
	Moderate	98 (27.2)	273.9	35.8	78 (21.4)	274.6	28.4
	Severe	12 (3.3)	322.8	3.7	8 (2.2)	315.7	2.5

The definition of the pool and details of treatment groups within the pool are described in SAP Section 2.2.1. If not stated otherwise, percentages are based upon all patients in the safety analysis set within the respective pool and treatment group. An AE during treatment is defined as an AE with a date of onset ≥ day of first ever dose of IP and ≤ minimum ((last dosing date + 28 days), end of study date, death date). Adverse events are coded using MedDRA version 22.1. Patients with multiple events in the same category are counted only once in the category. Patients with events in more than one category are counted once in each of those categories. The EAIR per 100 PY is defined as the number of patients with the specific event divided by the total exposure time in years and then multiplied by 100. The exposure time is defined as from the date of first administration of IP to the date of first event, death, end of treatment + 28 days, or end of study, whichever comes first. IP Investigational product; n Number of patients with an event; Number of patients in treatment group and subgroup; PY Patient-years; SAP Statistical analysis plan.

In the supportive safety pool, the incidence of infections during treatment (any AE in the SOC Infections and infestations) was greater in the anifrolumab 300 mg group (69.7%; EAIR: 141.8/100 PY) than the placebo group (55.4%; EAIR: 99.9/100 PY). Similar to the primary safety pool, this difference was driven by differences in the incidence rates of mild and moderate infections involving the respiratory tract, excluding pneumonia (comparable in both treatment groups), and, separately, herpes zoster.

Phase III long-term safety data

In the phase III long-term safety study, the EAIRs of overall infections (AEs in the SOC Infections and infestations) were similar to the 52-week primary safety pool data. In the primary safety pool, the EAIRs were 151.8/100 PY and 105.4/100 PY in the anifrolumab 300 mg and placebo groups, respectively, and both decreased in the long-term safety data to 112.9/100 PY and 93.2/100 PY, respectively.

Serious infections

Primary and supportive safety pools

In the primary safety pool, patients in the anifrolumab 300 mg group had a similar rate of non-opportunistic serious infections compared with patients in the placebo group (Table 55). The most

common non-opportunistic serious infection by PT was pneumonia and similar proportions of patients experienced a serious pneumonia event in the anifrolumab 300 group (1.7%) and in the placebo group (2.2%). No other non-opportunistic infection SAE, by PT, was reported in > 2 patients in either treatment group.

There were few non-opportunistic serious infections during treatment that resulted in discontinuation of IP (2 DAEs in each treatment group). One patient in the anifrolumab 300 mg group had diverticulitis leading to discontinuation of IP, and the other 3 patients (1 in the anifrolumab 300 mg group and 2 in the placebo group) had pneumonia events leading to discontinuation of IP.

In the supportive safety pool, the proportions of patients with a non-opportunistic serious infection were similar to the primary safety pool: 4.8% (22/459) in the anifrolumab 300 mg group and 5.6% (26/466) in the placebo group. In the anifrolumab 300 mg group, events reported in > 2 patients by PT were pneumonia (1.7%, 8/459) and appendicitis (0.7%, 3/459). In the placebo group, events reported in > 2 patients by PT were pneumonia (1.9%, 9/466) and gastroenteritis (0.6%, 3/466).

Table 55 Summary of non-opportunistic serious infections during treatment – Primary safety pool (safety analysis set)

AESI AE category	Anifrolumab 300 mg (N = 360)			Placebo (N = 365)			Risk Difference [a] (95% CI)
	n (%) patients	Exposure years	EAIR (per 100 PY)	n (%) patients	Exposure years	EAIR (per 100 PY)	
Non-opportunistic serious infections							
Any SAE (including fatal events)	16 (4.4)	320.6	5.0	22 (6.0)	310.5	7.1	-2.1 (-6.0, 1.7)
Any DAE	2 (0.6)	326.0	0.6	2 (0.5)	318.7	0.6	-0.0 (-1.7, 1.6)
Any AE by maximum reported intensity:							
Mild	1 (0.3)	320.6	0.3	0	310.5	0	NC
Moderate	8 (2.2)	321.4	2.5	15 (4.1)	310.5	4.8	NC
Severe	7 (1.9)	324.5	2.2	7 (1.9)	315.7	2.2	NC

[a] Risk difference is the difference between the EAIRs per 100 PY (anifrolumab 300 mg group– placebo group). The definition of each pool and details of treatment groups within each pool are described in SAP Section 2.2.1. If not stated otherwise, percentages are based upon all patients in the safety analysis set within the respective pool and treatment group. An AE during treatment is defined as an AE with a date of onset ≥ day of first ever dose of IP and ≤ minimum ((last dosing date + 28 days), end of study date, death date). Adverse events are coded using MedDRA version 22.1. Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories. The patient's duration of exposure by intensity is the time from first dose of IP up to the start of the event with maximum reported intensity, and this duration of exposure is applied across all of the intensity categories. The EAIR per 100 PY is defined as the number of patients with the specific event divided by the total exposure time in years and then multiplied by 100. The exposure time is defined as from the date of first administration of IP to the date of first event, death, end of treatment + 28 days, or end of study, whichever comes first. AE Adverse event; AESI Adverse event of special interest; CI Confidence interval; DAE Adverse event leading to discontinuation of IP; EAIR Exposure-adjusted incidence rate; IP Investigational product; n Number of patients with an of patients in treatment group; NC Not calculated; PY Patient-years; SAE Serious adverse events; SAP al analysis plan.

Phase III long-term safety data

Consistent with the 52-week data, the phase III long-term safety data demonstrated that patients in the anifrolumab 300 mg group had a similar risk for non-opportunistic serious infections compared with patients in the placebo group. In the phase III long-term safety data, the most common non-opportunistic serious infection by PT was pneumonia and similar proportions of patients experienced a serious pneumonia event in the anifrolumab 300 group (2.2%) and the placebo group (2.5%). In the anifrolumab 300 mg group, other non-opportunistic serious infections reported in > 2 patients were:

herpes zoster (1.4%, 5 patients) and pyelonephritis (0.8%, 3 patients). No other non-opportunistic SAE, by PT, was reported in > 2 patients in either treatment group. In the long-term safety data, non-opportunistic serious infections were reported at rates of 4.4/100 PY in the anifrolumab 300 mg and 6.2/100 PY in the placebo group, with no trend in either treatment group by yearly intervals (Table 56).

Table 56 Non-opportunistic serious infections during treatment by time interval – Phase III long-term safety (safety analysis set)

AESI Category Year	Anifrolumab 300 mg (N = 360)			Placebo (N = 365)		
	n/N' (%) patients	Exposure years	EAIR (per 100 PY)	n/N' (%) patients	Exposure years	EAIR (per 100 PY)
Non-opportunistic serious infections, Total	32/360 (8.9)	719.8	4.4	29/365 (7.9)	468.5	6.2
Year 1	16/360 (4.4)	320.0	5.0	22/365	309.5	7.1
Year 2	10/277 (3.6)	242.1	4.1	5/174	100.0	5.0
Year 3	7/222 (3.2)	149.0	4.7	3/85 (3.5)	55.2	5.4
Year 4+	0/73	26.5	0	0/29	11.2	0

The definition of each pool and details of treatment groups in each pool are described in SAP Section 2.2.1. If not stated otherwise, percentages are based upon all patients in the safety analysis set within the respective pool and treatment group. An AE during treatment is defined as an AE with a date of onset ≥ day of first ever dose of IP and ≤ minimum ((last dosing date). AEs are coded using MedDRA version 22.1. Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories. AEs in the same category onset in different time intervals are summarised in each of the time intervals. The Total row may contain events that occurred after 52 weeks. N' is the number of patients staying in on-treatment period at the beginning of the interval. The EAIR per 100 PY is defined as the number of patients with the specific event in each time interval divided by the total exposure time in years and then multiplied by 100. The exposure time in an interval is defined as from the start date of the interval to the date of first event, death, end of treatment + 28 days, end of the interval, or end of study, whichever comes first. AE Adverse event; AESI Adverse event of special interest; EAIR Exposure-adjusted incidence rate; n Number of patients with an event; N Number of patients in treatment group; PY Patient-years; SAP Statistical analysis plan.

Opportunistic infections

There was 1 opportunistic infection reported in the primary safety pool during the 52-week treatment period: 1 patient in the anifrolumab 300 mg group had a non-serious AE with PT mycobacterium avium complex infection that led to discontinuation of IP.

In the supportive safety pool, 2 additional opportunistic infections were reported; both in the placebo group. One patient had a non-serious AE during treatment (PT oropharyngeal candidiasis). One patient had a SAE (PT meningitis cryptococcal) with an onset date 32 days after the prior dose of IP.

In the phase III long-term safety data, in addition to the mycobacterium avium complex infection in the 52-week treatment period, there were opportunistic infections reported in 1 patient in the anifrolumab 300 mg group (ophthalmic herpes simplex; non-serious) and 1 patient in the placebo group (respiratory moniliasis; non-serious).

Herpes zoster

Primary and supportive safety pools

During treatment in the primary safety pool, patients in the anifrolumab 300 mg group had an increased risk for cutaneous herpes zoster through 52 weeks compared with patients in the placebo group: 23 patients (6.4%) had a herpes zoster event in the anifrolumab 300 mg group and 5 patients (1.4%) had a herpes zoster event in the placebo group (Table 57).

Of the 23 patients in the anifrolumab 300 mg group with a herpes zoster event during treatment, 22 patients had cases that were mild or moderate in intensity. In the anifrolumab 300 mg group, one patient had a SAE of herpes zoster and 2 patients discontinued IP due to a herpes zoster AE. In the placebo group, none of the 5 herpes zoster events were serious or resulted in discontinuation of IP. All herpes zoster cases in both treatment groups resolved; in the anifrolumab 300 mg group 9 cases resolved with sequelae and in the placebo group 1 case resolved with sequelae. Most patients received antiviral treatment: all patients in the anifrolumab 300 mg group and 3 of the 5 patients in the placebo group.

In the anifrolumab 300 mg group, approximately half (12/23) events had an onset during the first 12 weeks of treatment (Table 58). There was no pattern in the duration of events during the 52-week treatment period and no differences between the anifrolumab 300 mg group and placebo group in event duration.

Subgroup analyses did not demonstrate any clear trends in herpes zoster cases by demographics, baseline disease characteristics, or SLE-related medication use in the primary safety pool.

Table 57 Herpes zoster events during treatment – Primary safety pool (safety analysis set)

Herpes zoster AEs	Anifrolumab 300 mg (N = 360)			Placebo (N = 365)			Risk difference [d] (95% CI)
	n (%) patients	Exposure years	EAIR per 100 PY	n (%) patients	Exposure years	EAIR per 100 PY	
Any AE	23 (6.4)	314.9	7.3	5 (1.4)	316.0	1.6	NC
Any AE with outcome of death	0	326.0	0	0	318.8	0	0
Any SAE (including events with outcome of death)	1 (0.3)	325.2	0.3	0	318.8	0	0.3 (-0.9, 1.7)
Any DAE	2 (0.6)	325.9	0.6	0	318.8	0	0.6 (-0.6, 2.2)
Any AE by maximum reported intensity							
Mild	8 (2.2)	314.9	2.5	0	316.0	0	NC
Moderate	14 (3.9)	318.9	4.4	5 (1.4)	316.0	1.6	NC
Severe	1 (0.3)	326.0	0.3	0	318.8	0	NC
Any cutaneous (localised) herpes zoster [a, e]	18 (5.0)	316.6	5.7	5 (1.4)	316.0	1.6	NC
Any cutaneous disseminated herpes zoster [b, e]	2 (0.6)	324.7	0.6	0	318.8	0	NC
Any visceral disseminated herpes zoster [c, e]	0	326.0	0	0	318.8	0	NC

Table 58 Herpes zoster events during treatment by time interval – Primary safety pool (safety analysis set)

AESI Category	Time interval	Anifrolumab 300 mg (N = 360) n/N' (%) patients	Placebo (N = 365) n/N' (%) patients
Herpes zoster	Total	23/360 (6.4)	5/365 (1.4)
	≤ Week 12	12/360 (3.3)	1/365(0.3)
	Weeks 12-24	2/346 (0.6)	2/349 (0.6)
	Weeks 24-36	5/325 (1.5)	1/325 (0.3)
	Weeks 36-48	3/311 (1.0)	1/299 (0.3)
	Weeks 48-52	1/298 (0.3)	0/279

In the supportive safety pool, incidence of herpes zoster was similar to the primary safety pool: 28 patients (6.1%) and 6 patients (1.3%) had any AE of herpes zoster in the anifrolumab 300 mg and placebo groups, respectively. In study 1013, there was 1 patient in the anifrolumab 300 mg group with reported SAEs of herpes zoster as well as myelitis transverse.

Phase III long-term safety data

The increased risk for herpes zoster infections in anifrolumab-treated patients was also observed in the phase III long-term safety data. Over up to 4 years of treatment, AEs of herpes zoster were reported in 39 patients (10.8%; EAIR: 5.5/100 PY) in the anifrolumab 300 mg group and 8 patients (2.2%; EAIR: 1.7/100 PY) in the placebo group. The EAIR of herpes zoster AEs in the anifrolumab 300 mg group was highest in the first 52 weeks of treatment (7.3/100 PY) and decreased slightly during Year 2 and Year 3 (4.1 and 4.7/100 PY), with no events observed during Year 4. Similar to the primary safety pool, there was no difference noted between the treatment groups in the length of events (onset to resolution) in the phase III long-term safety data.

Most herpes zoster events in the phase III long-term safety data were mild or moderate in intensity (34 of 39 events). Over up to 4 years of treatment, there were 7 patients (1.9%; EAIR: 0.9/100 PY) in the anifrolumab 300 mg group with an SAE of herpes zoster. Two of the patients with herpes zoster SAEs additionally experienced SAEs of post-herpetic neuralgia, leading to discontinuation of IP.

Tuberculosis (including latent TB)

To be eligible for the controlled phase II and III studies (studies 1013, 04, and 05), patients were to have no evidence of active TB or latent TB, unless the latent TB was documented to have been appropriately treated or active treatment had been initiated. All patients in the controlled phase II and III studies underwent TB testing at screening and at Week 52.

In the anifrolumab clinical programme, there were no cases of active TB reported during any study.

Primary and supportive safety pools

In the primary safety pool, there were 6 patients with AEs with the PT latent tuberculosis during the study: 4 patients (1.1%; EAIR 1.1/100 PY) in the anifrolumab 300 mg group and 2 patients (0.5%; EAIR: 0.6/100 PY) in the placebo group.

In the supportive safety pool, the numbers of AEs reported as latent TB during study were similar to the primary safety pool. There were 6 patients (1.3%; EAIR: 1.3/100 PY) and 3 patients (0.6%; EAIR: 0.7/100 PY) with an AE recorded as latent TB in the anifrolumab 300 mg group and the placebo group, respectively.

Phase III long-term safety data

Over up to 4 years of treatment with anifrolumab 300 mg, there were no active TB cases. In the phase III long-term data, patients in the anifrolumab 300 mg group were more likely to have an AE reported as latent TB. The exposure-adjusted incidence of latent TB was 2.2/100 PY in the anifrolumab 300 mg group and 0.8/100 PY in the placebo group, a risk difference of 1.6 (95% CI: 0.2, 3.0).

In the anifrolumab 300 mg group, the exposure-adjusted incidence of latent TB AEs reported during treatment trended upward, as measured by yearly intervals.

Influenza

Primary and supportive safety pools

In the primary safety pool, the incidence of influenza during treatment was similar in both treatment groups: 6 patients (1.7%; EAIR: 1.9/100 PY) in the anifrolumab 300 mg group and 8 patients (2.2%; EAIR: 2.5/100 PY) in the placebo group had AEs with the PT influenza.

The event rates for influenza in the supportive pool were generally similar to the primary safety pool: 12 patients (2.6%; EAIR: 2.9/100 PY) in the anifrolumab 300 mg group and 9 patients (1.9%; EAIR: 2.3/100 PY) in the placebo group had AEs with the PT influenza.

Phase III long-term safety data

Consistent with the 52-week data, in the phase III long-term safety data, patients in the anifrolumab 300 mg group and placebo group had similar EAIRs of influenza: 2.0/100 PY and 1.9/100 PY, respectively.

Anaphylaxis, hypersensitivity, and infusion-related reactions

Anaphylaxis was considered an AESI. As anifrolumab is a protein-based infusion therapy, hypersensitivity and infusion-related reactions were also topics of interest.

In the placebo-controlled phase II and III studies (studies 1013, 04, and 05), patients did not receive premedication unless they had a prior infusion-related reaction to anifrolumab. If a prior infusion-related reaction was documented, the investigator could elect to administer prophylactically an antihistamine and/or acetaminophen/paracetamol for the comfort and safety of the patient prior to subsequent infusions. Prophylactic use of glucocorticosteroids prior to subsequent infusions was not permitted.

Anaphylaxis

In study 05, one patient in the anifrolumab 150 mg group had an anaphylactic reaction. There were no other anaphylaxis events reported in the anifrolumab development programme.

Hypersensitivity

Primary and supportive safety pools

In the primary safety pool, there were numerically more AEs categorised as hypersensitivity reactions in the anifrolumab 300 mg group than the placebo group: 12 patients (3.3%) and 3 patients (0.8%), respectively. In the primary safety pool, all hypersensitivity AEs were mild or moderate in intensity, and all events in the anifrolumab 300 mg group resolved spontaneously or with symptomatic treatment (Table 59). One patient in the anifrolumab 300 mg group had a hypersensitivity SAE, was treated, and continued with the IP dosing schedule with prophylaxis given for subsequent infusions. One patient in the placebo group had a hypersensitivity AE that led to discontinuation of IP. During the 52-week treatment period, all hypersensitivity AEs occurred the first 24 weeks of treatment.

The incidence of hypersensitivity events in the supportive safety pool were similar to the incidence in the primary safety pool.

Table 59 Hypersensitivity events during treatment. Primary safety pool (safety analysis set)

AE category	Anifrolumab 300 mg			Placebo (N = 365)			Risk difference b (95% CI)
	n (%) patients	Exposure years	EAIR per 100 PY	n (%) patients	Exposure years	EAIR per 100 PY	
Hypersensitivity [a]							
Patients with any AE	12 (3.3)	317.1	3.8	3 (0.8)	317.4	0.9	NC
Any AE with outcome of death	0	326.0	0	0	318.8	0	0
Any SAE (including events with outcome of death)	1 (0.3)	325.0	0.3	0	318.8	0	0.3 (-0.9, 1.7)
Any DAE	0	326.0	0	1 (0.3)	318.8	0.3	-0.3 (-1.8, 0.9)
Any AE by maximum reported intensity:							
Mild	8 (2.2)	317.1	2.5	2 (0.5)	317.4	0.6	NC
Moderate	4 (1.1)	324.0	1.2	1 (0.3)	318.2	0.3	NC
Severe	0 (0.0)	326.0	0	0 (0.0)	318.8	0	NC

[a]Hypersensitivity excludes those events meeting anaphylaxis criteria. b Risk difference is the difference between the EAIRs per 100 PY (anifrolumab 300 mg group– placebo group). The definition of each pool and details of treatment groups within each pool are described in SAP Section 2.2.1. If not stated otherwise, percentages are based upon all patients in the safety analysis set within the respective pool and treatment group. An AE during treatment is defined as an AE with a date of onset ≥ day of first ever dose of IP and ≤ minimum ((last dosing date + 28 days), end of study date, death date). Adverse events are coded using MedDRA version 22.1. Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories. Any AE by intensity was counted once by maximum reported intensity. The patient's duration of exposure by intensity is the time from first dose of investigational product up to the start of the event with maximum reported intensity, and this duration of exposure is applied across all of the intensity categories. The EAIR per 100 PY is defined as the number of patients with the specific event divided by the total exposure time in years and then multiplied by 100. The exposure time is defined as from the date of first administration of IP to the date of first event, death, end of treatment + 28 days, or end of study, whichever comes first. AE Adverse event; CI Confidence interval; DAE Adverse event leading to discontinuation of IP; EAIR Exposure-adjusted n event; N Number of patients in treatment group; ars; SAE Serious adverse events; SAP Statistical analysis plan.

Infusion-related reactions

In the primary safety pool, patients in the anifrolumab 300 mg group had a numerically greater incidence of infusion-related reactions through 52 weeks compared with patients in the placebo group (11.4% vs 7.4%; Table 60). All infusion-related reactions were mild or moderate in intensity and there were no serious infusion-related reactions. One patient in the placebo group had an infusion-related reaction that led to discontinuation of IP; no patient in the anifrolumab 300 mg group discontinued IP due to an infusion-related reaction. During the 52-week treatment period, most AEs with the PT infusion-related reaction occurred in the first 24 weeks of treatment (Table 61)

In the primary safety pool, in the anifrolumab 300 mg group, there were 79 infusion-related reaction events in 39 patients. Among the events, the most common symptoms (reported in ≥ 5% of events) in the anifrolumab 300 mg group were headache (45.6% of events), nausea (22.8% of events), vomiting (7.6% of events), and fatigue (5.1% of events).

In the supportive safety pool, at least one infusion-related reaction was reported for 43 patients (9.4%) in the anifrolumab 300 mg group and 33 patients (7.1%) in the placebo group. All of the infusion-related reactions in the supportive safety pool were mild or moderate in intensity and, similar to the primary safety pool, most events occurred in the first 24 weeks of treatment.

The most common symptoms related to infusion-related reactions (reported in ≥ 5% of events) in the anifrolumab 300 mg group were headache (45.6%), nausea (22.8%), vomiting (7.6%), and fatigue (5.1%).

Table 60 Infusion-related reactions during treatment – Primary safety pool (safety analysis set)

AE category	Anifrolumab 300 mg			Placebo (N = 365)			Risk difference a (95% CI)
	n (%) patients	Exposure years	EAIR per 100 PY	n (%) patients	Exposure years	EAIR per 100 PY	
Infusion-related reaction							
Patients with any AE	41 (11.4)	294.2	13.9	27 (7.4)	296.9	9.1	NC
Any AE with outcome of death	0	326.0	0	0	318.8	0	0
Any SAE (including events with outcome of death)	0	326.0	0	0	318.8	0	0
Any DAE	0	326.0	0	1 (0.3)	318.8	0.3	-0.3 (-1.8, 0.9)
Any AE by maximum reported intensity:							
Mild	29 (8.1)	294.5	9.8	23 (6.3)	297.0	7.7	NC
Moderate	12 (3.3)	317.5	3.8	4 (1.1)	315.4	1.3	NC
Severe	0 (0.0)	326.0	0	0 (0.0)	318.8	0	NC

a Risk difference is the difference between the EAIRs per 100 PY (anifrolumab 300 mg group– placebo group). Infusion-related reactions are as reported by the investigators. The definition of each pool and details of treatment groups within each pool are described in SAP Section 2.2.1.
If not stated otherwise, percentages are based upon all patients in the safety analysis set within the respective pool and treatment group. An AE during treatment is defined as an AE with a date of onset ≥ day of first ever dose of IP and ≤ minimum ((last dosing date + 28 days), end of study date, death date). Adverse events are coded using MedDRA version 22.1. Patients with multiple events in the same category are counted only once in that category. Any AE by intensity was counted once by maximum reported intensity. The patient's duration of exposure by intensity is the time from first dose of investigational product up to the start of the event with maximum reported intensity, and this duration of exposure is applied across all of the intensity categories. The EAIR per 100 PY is defined as the number of patients with the specific event divided by the total exposure time in years and then multiplied by 100. The exposure time is defined as from the date of first administration of IP to the date of first event, death, end of treatment + 28 days, or end of study, whichever comes first. AE Adverse event; CI Confidence interval; DAE Adverse event leading to discontinuation of IP; EAIR Exposure-adjusted incidence rate; IP Investigational product; n Number of patients with an event; N Number of patients in treatment group; NC Not calculated; PY Patient-years; SAE Serious adverse events; SAP Statistical analysis plan.

Table 61 Infusion-related reactions during treatment by time interval – Primary safety pool (safety analysis set)

Preferred term Time interval	Anifrolumab 300 mg (N = 360)	Placebo (N = 365) n/N' (%) patients
Infusion-related reaction, Total	41/360 (11.4)	27/365 (7.4)
≤ 12 weeks	30/360 (8.3)	22/365 (6.0)
12 - 24 weeks	13/346 (3.8)	10/349 (2.9)
24 - 36 weeks	6/325 (1.8)	3/325 (0.9)
36 - 48 weeks	3/311 (1.0)	2/299 (0.7)
48 - 52 weeks	0/298	1/279 (0.4)

An AE during treatment is defined as an AE with a date of onset ≥ day of first ever dose of IP and ≤ minimum ((last dosing date + 28 days), end of study date, death date). Adverse events are coded using MedDRA version 22.1. Patients with multiple events in the same category are counted only once in that category. AEs in the same category onset in different time intervals are summarised in each of the time intervals. The Total row may contain events that occurred after 52 weeks. N' is the number of patients staying in on-treatment period at the beginning of the interval. AE Adverse event; IP Investigational product; n Number of patients with an event; N Number of patients in treatment group.

Malignancies

Across the phase II and III SLE controlled and uncontrolled studies of IV anifrolumab (studies 02, 04, 05, 09, 1013, and 1145), there were 14 malignancies reported in patients who received any dose of anifrolumab. Only non-melanoma skin cancers (n = 7) and breast cancers (n = 3) were reported in more than 1 patient.

Among 6 total malignancies reported in anifrolumab-treated patients in the 52-week phase III studies (study 04 and 05), there were 4 malignancies reported within 180 days of the first exposure to anifrolumab, which were likely pre-existing: 2 cases of squamous cell carcinoma in the anifrolumab 300 mg group (31 days and 51 days after the patient's first dose, respectively), an invasive breast carcinoma in the anifrolumab 150 mg group (113 days after the first dose), and a B-cell lymphoma in the anifrolumab 300 mg group (12 days after the first dose).

Table 62 Summary of malignancy by type, during study – Primary safety pool (safety analysis set)

Type of malignancy Preferred term	Anifrolumab 300 mg (N = 360)			Placebo (N = 365)			Risk difference [a] (95% CI)
	n (%) patients	Exposure years	EAIR per 100 PY	n (%) patients	Exposure years	EAIR per 100 PY	
Any malignancy	**5 (1.4)**	**347.6**	**1.4**	**3 (0.8)**	**347.0**	**0.9**	**0.6 (-1.2, 2.6)**
Non-haematological malignant tumours							
Invasive ductal breast carcinoma	1 (0.3)	350.1	0.3	0	348.7	0	0.3 (-0.8, 1.6)
Lip squamous cell carcinoma	1 (0.3)	350.0	0.3	0	348.7	0	0.3 (-0.8, 1.6)
Squamous cell carcinoma	1 (0.3)	349.2	0.3	0	348.7	0	0.3 (-0.8, 1.6)
Carcinoid tumour	0	350.1	0	1 (0.3)	348.1	0.3	-0.3 (-1.6, 0.8)
Squamous cell carcinoma of the cervix	0	350.1	0	1 (0.3)	348.4	0.3	-0.3 (-1.6, 0.8)
Uterine cancer	0	350.1	0	1 (0.3)	347.8	0.3	-0.3 (-1.6, 0.8)
Malignant lymphomas							
B-cell lymphoma	1 (0.3)	349.8	0.3	0	348.7	0	0.3 (-0.8, 1.6)
Skin malignant tumours							
Squamous cell carcinoma of skin	1 (0.3)	349.1	0.3	0	348.7	0	0.3 (-0.8, 1.6)

In the supportive safety pool, in addition to the events in the primary pool, there was one additional case of invasive ductal breast carcinoma in a patient in the anifrolumab 300 mg group in study 1013. In total, in the supportive pool, there were 6 patients (1.3%) and 3 patients (0.6%) with any malignancy in the anifrolumab 300 mg group and placebo group, respectively. Similar to the primary safety pool, in the supportive pool, the risk difference in EAIRs between the anifrolumab 300 mg group (EAIR: 1.3/100 PY) and placebo group (EAIR: 0.7/100 PY) was 0.6 (95% CI: -0.8, 2.2).

Phase III long-term safety data

Overall, in the phase III long-term safety data, 6 patients (1.7%) and 4 patients (1.1%) had a malignancy in the anifrolumab 300 mg group and placebo group, respectively. In addition to the events reported in the primary safety pool, there was one patient in the anifrolumab 300 mg group with a basal cell carcinoma and one patient in the placebo group with a squamous cell carcinoma.

The phase III long-term safety data did not suggest any change in the rate of malignancies with long-term exposure to anifrolumab, with no temporal patterns observed by yearly intervals of malignancies during treatment (Table 63).

Table 63 Malignancies and EAIRs during treatment by time interval – Phase III long-term safety (safety analysis set)

AESI Category Year	Anifrolumab 300 mg (N = 360)			Placebo (N = 365)		
	n/N' (%) patients	Exposure years	EAIR (per 100 PY)	n/N' (%) patients	Exposure years	EAIR (per 100 PY)
Malignancy, Total	4/360 (1.1)	744.5	0.5	4/365 (1.1)	486.7	0.8
Year 1	3/360 (0.8)	323.5	0.9	3/365 (0.8)	317.6	0.9
Year 2	1/277 (0.4)	245.2	0.4	1/174 (0.6)	101.7	1.0
Year 3	0/222	152.4	0	0/85	56.1	0
Year 4+	0/73	26.5	0	0/29	11.2	0

Mace

In the primary safety pool, there were no trends in the patients' histories of cardiovascular risk factors. Only one MACE event was reported in the primary safety pool: one patient (0.3%) in the anifrolumab 300 mg group had an AE of acute coronary syndrome; the EAIR was 0.3/100 PY. In the supportive safety pool, in addition to the acute coronary syndrome event, there were 3 patients with MACE events, all in the placebo group in study 1013. Two of the patients had an ischemic stroke and one patient had a cerebral infarction.

Vasculitis (non-SLE)

Vasculitis has been evaluated because of the findings of focal arteritis in a non-clinical study. However, non-SLE vasculitis was not observed in any anifrolumab-treated patient in the primary safety pool, supportive safety pool, or the phase III long-term data.

Analysis of adverse events: Other treatment comparisons and other phase I and II studies not included in the ISS analyses

As the proposed dosage of anifrolumab is IV 300 mg Q4W, the analyses focused on a comparison of patients who received anifrolumab IV 300 mg versus patients who received placebo in the SLE phase II and III controlled clinical studies. As supportive analyses, other treatment comparisons were also performed: all anifrolumab (150, 300, and 1000 mg) vs placebo, anifrolumab 150 mg vs placebo, and anifrolumab 1000 mg vs placebo.

<u>All anifrolumab (150, 300, and 1000 mg) pool</u>

The overall safety profile of the all anifrolumab pool was consistent with the primary safety pool, supportive safety pool, and phase III long-term safety data (Table 64). Similar to the anifrolumab 300 mg vs placebo analyses, in the all anifrolumab pool most AEs in both treatment groups were mild or moderate in intensity and the exposure-adjusted incidence of SAEs was lower in the all anifrolumab group than the placebo group (EAIR/100 PY: 10.9 vs 21.4). In contrast to the primary safety pool, the exposure-adjusted event rate of patients with any AE was lower in the all anifrolumab group (EAIR: 178.2/100 PY) than in the placebo group (EAIR: 212.2/100 PY). The most common AEs among patients who received any dose of anifrolumab in the all anifrolumab pool were similar to the most common AEs identified in the anifrolumab 300 mg vs placebo.

In the all anifrolumab pool, 4 patients in the all anifrolumab group had a fatal AE during treatment.

The overall profile of AESIs in the all anifrolumab pool was also consistent with the anifrolumab 300 mg vs placebo analyses: there were more AEs of herpes zoster and latent TB in the all anifrolumab group than the placebo group but the EAIRs of other AESIs was similar between the all anifrolumab and placebo groups. There were no cases of active TB.

Also, of note were uncommon events that were not reported in the primary, supportive, or long-term data, but were reported in the all anifrolumab group: 1 patient with an anaphylaxis AE (anifrolumab 150 mg group in study 05) and 3 patients with vasculitis AEs. The 3 vasculitis AEs in the all anifrolumab group were all non-serious, resolved prior to the next scheduled dose of IP, and were not considered by investigators to be related to IP. For 2 of the vasculitis AEs, causes were identified by the investigator: infection and SLE, respectively.

Table 64 Adverse events and EAIR during treatment in any category – All anifrolumab pool (safety analysis set)

AE category	All anifrolumab (N = 837)			Placebo (N = 286)			Risk difference [a] (95% CI)
	n (%) patients	Exposure years	EAIR (per 100 PY)	n (%) patients	Exposure years	EAIR (per 100 PY)	
Patients with any AE	741 (88.5)	415.9	178.2	244 (85.3)	114.8	212.6	NC
Any AE with outcome of death	4 (0.5)	1888.1	0.2	0	390.7	0	0.2 (-0.8, 0.5)
Any SAE (including events with outcome of death)	182 (21.7)	1664.2	10.9	75 (26.2)	349.7	21.4	-10.5 (-15.3, -6.2)
Any DAE	56 (6.7)	1881.7	3.0	27 (9.4)	387.6	7.0	-4.0 (-7.0, -1.7)
Any AE related to IP (investigator)	314 (37.5)	1370.8	22.9	81 (28.3)	302.5	26.8	NC
Any AE by maximum reported intensity:							
Mild	219 (26.2)	665.5	32.9	97 (33.9)	167.2	58.0	NC
Moderate	381 (45.5)	1066.1	35.7	115 (40.2)	266.3	43.2	NC
Severe	141 (16.8)	1689.9	8.3	32 (11.2)	375.0	8.5	NC
Any AESI	212 (25.3)	1598.6	13.3	47 (16.4)	358.5	13.1	0.1 (-4.0, 3.7)
Non-opportunistic serious infections	82 (9.8)	1781.9	4.6	26 (9.1)	375.1	6.9	-2.3 (-5.5, 0.1)
Opportunistic infections	4 (0.5)	1886.5	0.2	1 (0.3)	389.7	0.3	-0.0 (-1.2, 0.4)
Anaphylaxis	1 (0.1)	1888.2	< 0.1	0	390.7	0	0.1 (-0.9, 0.3)
Malignancy	8 (1.0)	1879.8	0.4	4 (1.4)	390.6	1.0	-0.6 (-2.2, 0.1)
Herpes zoster	88 (10.5)	1778.9	4.9	6 (2.1)	381.7	1.6	3.4 (1.4, 4.8)
Tuberculosis (including latent TB) [a]	28 (3.3)	1858.4	1.5	3 (1.0)	388.2	0.8	0.7 (-0.8, 1.6)
Tuberculosis [b]	0	1888.2	0	0	390.7	0	0
Influenza	48 (5.7)	1807.6	2.7	5 (1.7)	385.8	1.3	1.4 (-0.4, 2.5)
Vasculitis (non SLE)	3 (0.4)	1883.3	0.2	3 (1.0)	390.5	0.8	-0.6 (-2.1, -0.0)
MACE	3 (0.4)	1885.7	0.2	2 (0.7)	389.8	0.5	-0.4 (-1.7, 0.1)

Anifrolumab 150 mg vs placebo

The proportion of patients who experienced one or more AE during treatment was higher in the anifrolumab 150 mg group (84.9%, 79/93) than the placebo group (77.7%, 143/184). The majority of

AEs were non-serious, mild or moderate in intensity, and did not lead to discontinuation of IP. In the anifrolumab 150 mg group, the most common AEs by PT (≥ 5% of patients) were upper respiratory tract infection (17.2%), nasopharyngitis (15.1%), urinary tract infection (9.7%), bronchitis (7.5%), pharyngitis (6.5%), gastroenteritis, herpes zoster, pneumonia, and sinusitis (5.4% each).

In the anifrolumab 150 mg group, 10.8% of patients experienced at least one SAE during treatment, compared with 16.3% of patients in the placebo group; the risk difference was -6.8 (95% CI: -16.0, 3.7). Among the SAEs reported during treatment, the most common by SOC was Infections and infestations (3 patients [3.2%] in the anifrolumab 150 mg group and 10 patients [5.4%] in the placebo group) and the most common SAE by PT (≥ 2%) was systemic lupus erythematosus (2 patients [2.2%] in the anifrolumab 150 mg group and 3 patients [1.6%] in the placebo group). The proportions of patients with a DAE were 6.5% in the anifrolumab 150 mg group and 2.7% in the placebo group.

During treatment in study 05, there were no deaths in the anifrolumab 150 mg group or the placebo group. There was one death (placebo group, PT encephalitis) during follow-up.

The proportion of patients with AEs of herpes zoster were numerically higher in the anifrolumab 150 mg group compared with the placebo group: 5 patients (5.4%) vs 3 patients (1.6%), respectively. For all other AEs of special interest, the incidence rate was similar between the anifrolumab 150 mg group and placebo group.

In study 05, there was one case of anaphylaxis observed in a patient in the anifrolumab 150 mg group. In this patient, AEs of rash and pruritus were associated with the first dose of IP, and the second dose was associated with AEs of wheezing, flushing, dyspnea, and recurrence of dermatological symptoms. The patient received treatment for the event and was considered recovered one day later. The patient withdrew from the study due to this SAE of anaphylactic reaction. There was one malignancy in the anifrolumab 150 mg group (PT invasive breast carcinoma) and one malignancy in the placebo group (PT squamous cell carcinoma of the cervix).

Anifrolumab 1000 mg vs placebo

The proportion of patients who experienced one or more AEs during treatment was higher in the anifrolumab 1000 mg group (87/105, 82.9%) than the placebo group (75/101, 74.3%). The majority of AEs were non-serious, mild or moderate in intensity, and did not lead to discontinuation of IP. In the anifrolumab 1000 mg group, the most common AEs by PT (≥ 5% of patients) were nasopharyngitis (11.4%), headache (11.4%), upper respiratory tract infection (9.5%), herpes zoster (8.6%), influenza (7.6%), cough (7.6%), diarrhea (6.7%), and bronchitis (6.7%).

In the anifrolumab 1000 mg group, 14.3% of patients experienced at least one SAE during treatment, compared with 17.8% of patients in the placebo group; the EAIR risk difference was -5.9 (95% CI: -18.4, 6.3).

Among the SAEs reported during treatment, the most common by PT (≥ 2% in the anifrolumab 1000 mg group) was systemic lupus erythematosus (3 patients [2.9%] in the anifrolumab 1000 mg group and 5 patients [5.0%] in the placebo group) and the most common by SOC was Infections and infestations (5 patients [4.8%] in the anifrolumab 1000 mg group and 4 patients [4.0%] in the placebo group). The proportion of patients with a DAE was numerically greater in the anifrolumab 1000 mg treatment group (8.6%) than in the placebo group (5.9%). During treatment in study 1013, there was one death in the anifrolumab 1000 mg group (PT: colitis) and no deaths in the placebo group.

For most of the AESIs, the incidence rate was similar between the anifrolumab 1000 mg and placebo groups. However, the proportions of patients with AEs with the PTs herpes zoster and influenza were higher in the anifrolumab 1000 mg group compared with the placebo group. There were 9 patients (8.6%) in the anifrolumab 1000 mg group with a herpes zoster AE, compared with 1 patient (1.0%) in

the placebo group. There were 8 patients (7.6%) in the anifrolumab 1000 mg group who had an AE reported by the investigator as influenza during treatment, compared with 1 patient (1.0%) in the placebo group.

2.5.8.4. Laboratory findings

Hematology

Primary safety pool

The mean hematology values were generally similar between the anifrolumab 300 mg 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 hematology variables at 52 weeks.

Phase III long-term safety data

The mean changes in hematology variables in the phase III long-term treatment pool did not demonstrate any clinically meaningful trends with long-term treatment of anifrolumab 300 mg Q4W. There were few clinically important treatment-emergent changes in individual patients treated with anifrolumab 300 mg in the phase III long-term safety data.

Clinical chemistry

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

Primary safety pool

In the primary safety pool, no differences in mean clinical chemistry values were noted between anifrolumab 300 mg and placebo and no clinically meaningful trends in change from baseline values over time were detected. Renal function as assessed by serum creatinine remained stable from baseline to Week 52.

There was also no difference noted between the treatment groups in the frequency and pattern of potentially clinically significant changes or categorical shifts from baseline in clinical chemistry variables at 52 weeks.

Phase III long-term safety data

The mean changes in clinical chemistry variables in the phase III long-term treatment pool did not demonstrate any clinically meaningful trends with long-term treatment of anifrolumab 300 mg Q4W (up to 4 years). Renal function also remained stable in the phase III long-term safety data as assessed by serum creatinine.

There were also generally no differences noted between the treatment groups in the frequency and pattern of potentially clinically significant changes in clinical chemistry variables over up to 4 years of treatment. However, in comparison to the 52-week treatment period, there were numerically more patients in the anifrolumab 300 group in the phase III long-term data with glucose values ≥ 7.0 mmol/L (4.9% in the primary pool vs 7.4% in the phase III long-term data). This trend was not observed in the placebo group and few patients in either treatment group had glucose values ≥ 11.1 mmol/L in the phase III long-term data.

Urinalysis and renal laboratory results

Primary safety pool

In the primary safety pool, the change from baseline to Week 52 in mean specific gravity was similar in the anifrolumab 300 mg and placebo groups. Urine protein/creatinine ratio values remained stable from baseline to Week 52.

There was also no difference noted between the treatment groups in the frequency and pattern of potentially clinically significant changes in UPCR over 52 weeks of treatment.

Phase III long-term safety data

In the phase III long-term safety data, the change from baseline to the end of treatment in mean specific gravity was similar in the anifrolumab 300 mg and placebo groups. From baseline to end of treatment, the change in median UPCR values was -0.23 and 0.64 mg/mmol in the anifrolumab 300 mg and placebo groups, respectively. In the phase III long-term safety data, 2.2% and 2.5% of patients had a UPCR value categorised as a potentially meaningful change in the anifrolumab 300 mg group and placebo group, respectively.

Vital signs, physical findings, and other observations related to safety

In the primary safety pool, no clinically significant differences were reported in *mean blood pressure* values, *heart rate* or shifts in *ECG* parameters from normal to abnormal.

In studies 04 and 05, there were no clinically important differences among treatment groups in mean changes from baseline in *body weight* to Week 52.

In both studies, the proportions of patients with *Cushingoid features* at baseline were similar among the treatment groups. In general, fewer patients had Cushingoid features at Week 52 compared with baseline across all treatment groups.

Renal-related effects

Patients with serum creatinine > 2.0 mg/dL (or > 181 µmol/L) or UPCR > 2.0 mg/mg (or > 226.30 mg/mmol) were excluded from the phase II and III SLE studies. Patients with active lupus nephritis were excluded from these studies. The efficacy and safety of anifrolumab in lupus nephritis is being evaluated in a separate study.

Renal-related laboratory assessments (SAEs and DAEs)

In the primary safety pool, frequency of renal-related SAEs was low and balanced between the anifrolumab 300 mg and placebo groups. There were 2 patients (0.6%) in the anifrolumab 300 mg group and 5 patients (1.4%) in the placebo group with SAEs in the SOC Renal and urinary disorders. Similarly, the proportion of patients with renal-related DAEs was low and balanced between the anifrolumab 300 mg group (1 patient, PT nephritis) and placebo group (1 patient, PT lupus nephritis).

Suicidality and depression

There was no evidence in the primary safety pool of an increased risk in suicidal ideation or behavior in patients receiving anifrolumab compared with placebo, as assessed by the C-SSRS. Similarly, no patients in the anifrolumab 300 mg group and 2 patients in the placebo group had related AEs (PTs: suicide attempt and suicidal ideation). PHQ-8 scores were also similar across all treatment groups at baseline and no clinically meaningful changes from baseline to Week 52 were observed for any treatment group and as assessed by the MedDRA SMQ depression (excluding suicide and self-injury), there were few AEs related to depression and the proportion of patients with those events was balanced between the treatment groups.

2.5.8.5. Safety in special populations

Table 65 Elderly Age-related AEs During Treatment by Age Categories (Years) - Anifrolumab 300 mg vs Placebo (Safety Analysis Set, Primary Safety Pool)

Adverse events	Anifrolumab 300 mg (N = 360) n (%) patients				Placebo (N = 365) n (%) patients			
	Age: ≥ 18 to < 65 (N = 344)	Age: ≥ 65 to < 75 (N = 16)	Age: ≥ 75 to < 85 (N = 0)	Age: ≥ 85 (N = 0)	Age: ≥ 18 to < 65 (N = 358)	Age: ≥ 65 to < 75 (N = 7)	Age: ≥ 75 to < 85 (N = 0)	Age: ≥ 85 (N = 0)
Any AEs	304 (88.4)	14 (87.5)	0	0	288 (80.4)	7 (100)	0	0
Any SAEs, seriousness criteria:	36 (10.5)	4 (25.0)	0	0	57 (15.9)	3 (42.9)	0	0
Fatal	1 (0.3)	1 (6.3)	0	0	0	0	0	0
Hospitalisation/prolongation of existing hospitalisation	32 (9.3)	4 (25.0)	0	0	53 (14.8)	3 (42.9)	0	0
Life-threatening	1 (0.3)	0	0	0	4 (1.1)	0	0	0
Persistent or significant disability/incapacity	2 (0.6)	0	0	0	3 (0.8)	0	0	0
Important medical event	14 (4.1)	2 (12.5)	0	0	18 (5.0)	0	0	0
Any DAE	15 (4.4)	2 (12.5)	0	0	18 (5.0)	0	0	0
AEs by MedDRA levels								
Psychiatric disorders[a]	25 (7.3)	1 (6.3)	0	0	35 (9.8)	1 (14.3)	0	0
Nervous system disorder[a]	67 (19.5)	2 (12.5)	0	0	53 (14.8)	1 (14.3)	0	0
Cardiac disorders[a]	4 (1.2)	0	0	0	11 (3.1)	2 (28.6)	0	0
Vascular disorders[a]	9 (2.6)	1 (6.3)	0	0	17 (4.7)	0	0	0
Infections and infestations[a]	244 (70.9)	14 (87.5)	0	0	206 (57.5)	5 (71.4)	0	0
Cerebrovascular disorders[b]	0	0	0	0	0	0	0	0
Accidents and injuries[c]	10 (2.9)	0	0	0	9 (2.5)	0	0	0
Sum[d] of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	26 (7.6)	0	0	0	30 (8.4)	2 (28.6)	0	0
Anticholinergic syndrome[e]	0	0	0	0	0	0	0	0
Quality of life decreased[e]	0	0	0	0	0	0	0	0

[f] System Organ Class (SOC) level; included all PTs in the SOC.

High Level Term (HLT) level; included Preferred Term (PTs) "Cerebral infarction", "Cerebrovascular accident", "Cerebrovascular disorder", "Haemorrhagic cerebral infarction" in the HLTs Central nervous system vascular disorders NEC and Central nervous system haemorrhages and cerebrovascular accidents.

Preferred Term level; PT "Accident" and PTs with the word "injury" in the SOC Injury, poisoning and procedural complications.

Total = PT level "Postural hypotension" + PT "Fall" + PT "Loss of consciousness" (for AE 'black outs') + PT "Syncope" + PT "Dizziness" + PT "Ataxia" + PTs with the word "fracture" in HLTs Limb fractures and dislocations, Fractures and dislocations NEC, Skull fractures, facial bone fractures and dislocations, Spinal fractures and dislocations, Pelvic fractures and dislocations, and Thoracic cage fractures and dislocations.

Preferred Term level.

The definition of primary safety pool (including studies D3461C00004 and D3461C00005) and details of treatment groups within the pool are described in ISS SAP Section 2.2.1.

Percentages are based upon all patients in the safety analysis set within the primary safety pool, treatment group, and subgroup.

Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.
AE, adverse event; DAE, adverse event leading to discontinuation of investigational product; ISS, integrated summary of safety; MedDRA, Medical Dictionary for Regulatory Activities; n, number of patients with an event; N, number of patients in treatment group; NEC, not elsewhere classified; PT, preferred term; SAE, serious adverse events; SAP, statistical analysis plan; SLE, systemic lupus erythematosus; SOC, system organ class.

Intrinsic factors

Effect of sex, age, race and body mass index

As the vast majority of patients with SLE are female, approximately 92.8% of patients in the primary safety pool were females. Although based on a relatively small sample size of males, the safety profile of anifrolumab is generally similar between men and women for up to 52 weeks of treatment.

The proportion of patients in the programme ≥ 65 years of age was small (3.2%). Based on the limited data, the safety profile of anifrolumab appears to be similar in patients ≥ 65 years compared with those < 65 years of age for up to 52 weeks of treatment.

Anifrolumab has not been studied in pediatric patients < 18 years of age.

Although the primary safety pool study population was predominantly white (65.9% of patients), the AE profile of anifrolumab was generally similar across racial groups for up to 52 weeks of treatment.

The safety profile of anifrolumab is generally similar in patients with BMI ≥ 28 kg/m2 compared with those < 28 kg/m2 for up to 52 weeks of treatment.

Effect of renal function and hepatic function

The 52-week phase III studies enrolled patients with mild and moderate renal impairment, but did not include patients with severe impairment.

As measured by eGFR at baseline, most patients in the primary safety pool had normal kidney function (≥ 90 mL/min/1.73 m^2): 65.8% and 67.9% in the anifrolumab 300 mg group and placebo group, respectively. About a third of patients (29.7% in the anifrolumab 300 group and 28.2% in the placebo group) had eGRF values categorised as mild disease (60 to 89 mL/min/1.73 m^2). Few patients (4.4% and 3.8%) had eGRF values categorised as moderate disease (30 to 59 mL/min/1.73 m^2) and none as severe disease (≤ 29 mL/min/1.73 m^2).

Subgroups based on disease-related factors at baseline

In the primary safety pool, 71.6% of patients had baseline SLEDAI-2K ≥ 10 points. The safety profile of anifrolumab is generally similar in patients with SLEDAI-2K ≥ 10 points compared with those < 10 points for up to 52 weeks of treatment.

HZ events were more common (only for anifrolumab 300 mg arm) in the SLEDAI-2K ≥ 10 group (8%) than in the < 10 group (2.8%).

Approximately 82.6% of patients in the primary safety pool were IFN gene signature high at screening. The safety profile of anifrolumab was generally similar in patients with IFN gene signature high compared with low for up to 52 weeks of treatment.

Extrinsic factors

Geographic region

The safety profile of anifrolumab is generally similar in patients across geographic regions for up to 52 weeks of treatment. No clinically meaningful differences were observed in the frequency or pattern of AEs.

Subgroups based on concomitant medication use at baseline

In the primary safety pool, 51.7% of patients were taking ≥ 10 mg/day OCS at baseline. The safety profile of anifrolumab was generally similar in patients across baseline OCS dose baseline (< 10 mg/day versus ≥ 10 mg/day prednisone or equivalent) up to 52 weeks of treatment.

In the primary safety pool, 48.1% of patients were on immunosuppressant therapy at baseline. The safety profile of anifrolumab is generally similar in patients taking or not taking immunosuppressant therapy for up to 52 weeks of treatment.

In patients taking immunosuppressant therapy (for up to 52 weeks of treatment) compared to patients not taking immunosuppressant was observed a higher incidence of non-opportunistic serious infections (5.2% vs 3.7%) and of HZ (9.8% vs 3.2%).

Safety related to drug-drug interactions and other interactions

There have been no formal drug-drug interaction studies conducted with anifrolumab.

Immunisations

No vaccine studies in anifrolumab have been performed.

Pregnancy

Women with SLE have greater risks during pregnancy and delivery than women without SLE (Mehta et al 2019). Although outcomes have improved in recent years, pregnant SLE patients experience higher rates of preeclampsia or eclampsia during delivery (Mehta et al 2019).

In the anifrolumab clinical programme, females of childbearing potential were counseled to use 2 effective methods of avoiding pregnancy during study participation, and had a negative serum pregnancy test during screening and negative urine pregnancy test during the study prior to receiving any IP.

Pregnancy: non-clinical and clinical experience

In animal studies of anifrolumab increased amount of embryo-foetal losses and dead fetuses were seen (see non-clinical section).

No clinical study has been conducted in pregnant or lactating women and there is a limited amount of data from the use of anifrolumab in pregnant women. The data on pregnancy exposure from the clinical studies are insufficient to inform on drug-associated risk.

Overall, in the anifrolumab SLE clinical programme there were 31 patients with one or more pregnancy as of 01 August 2019. Of those 31 patients, 20 patients were randomised to receive anifrolumab. Among the patients who received anifrolumab and reported a pregnancy, no congenital anomalies associated with IP or no drug-associated AEs were observed.

However, among these 31 pregnancies, there were 18 live births[1] (14 in an anifrolumab group, 4 in a placebo group), 9 elective abortions (7 in an anifrolumab group, 2 in a placebo group), and 4

[1] The count of "live births" includes outcomes of live birth, premature birth, full term, and "not available" or "not reported" where additional source documents indicate a live baby was born.

spontaneous abortions (4 in an anifrolumab group and 0 in a placebo group). One spontaneous abortion was assessed by the investigator as related to methotrexate. The applicant further clarified and discussed the possible reasons for the spontaneous abortions seen in the anifrolumab SLE clinical programme. Narratives were also provided for the four reported cases.

2.5.8.6. Immunological events

Description of bioanalytical methods

An MSD electrochemiluminescent, solution-phase, bridging immunoassay is used for the detection, confirmation, and titration of anti-anifrolumab antibodies in human serum. Diluted samples were incubated overnight in solution with a mixture of biotinylated anifrolumab and ruthenium (sulfo-TAG)-labelled anifrolumab. Bridged biotin drug:ADA:sulfo-TAG drug complexes were subsequently captured onto streptavidin-coated plates (MSD) and measured on the MSD Sector Imager.

Method validations followed the guidelines in FDA's May 2001 Guidance for Industry on Bioanalytical Method Validation and/or FDA's December 2009 Draft Guidance for Industry on Assay Development for Immunogenicity Testing of Therapeutic Proteins.

A plate-specific cut points were determined as recommended by Shankar et al., 2008. No significant differences were observed between NHS, scleroderma and SLE matrixes. During the validation several samples were confirmed positive without exposure to the drug. The applicant explains this with false positive results by possible matrix interference and potential aggregation of the ruthenylated reagents.

Anti-drug antibody incidence and prevalence

Immunogenicity was investigated both in the primary safety pool from the two phase III studies (in total 359 patients in the anifrolumab 300 mg group and 365 patients in the placebo group) and in the phase III long-term pool (N=372, of which 259 in the anifrolumab arm).

In the primary safety pool, ADA positivity at any visit was seen in 7.0% [25/359 patients] in the anifrolumab and 9.6% [35/365 patients] in the placebo group. Unexpectedly, ADA were already present at baseline in 3.7 % of subjects in the anifrolumab group and 1.1 % in the placebo group. The incidence of ADA, defined as ADA positive post baseline or boosted pre-existing baseline titres, was low in both treatment groups but unexpectedly higher in the placebo group: 1.7% [6/352] and 4.8% [17/357] for anifrolumab and placebo groups, respectively. Oddly, the incidence of nAb was also higher in the placebo group even though overall very low: 1/359 patients in the anifrolumab group and 6/365 in the placebo group.

The phase III long-term ADA data (N=372, of which 259 in the anifrolumab arm) were the primary source of long-term immunogenicity assessment. In the anifrolumab 300 mg group, 18/259 (6.9%) patients were ADA positive compared with 11/113 (9.7%) patients in the placebo group. One subject in the placebo group developed transient nAb and none in the anifrolumab group developed nAb.

Similar to the primary safety pool, the observed incidence of ADA was overall smaller in the anifrolumab arm vs. placebo arm in the long-term ADA pool (Figure 24).

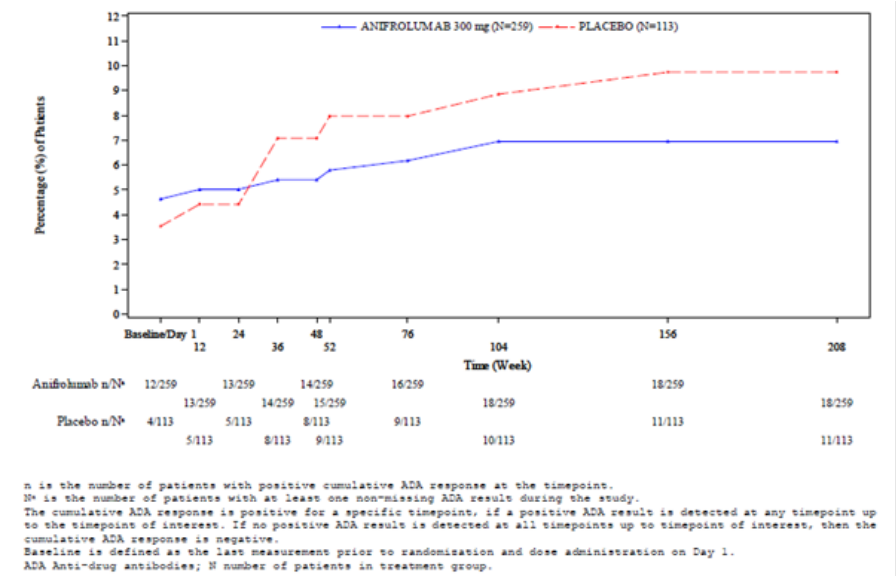


Figure 24 Cumulative percentage of patients with positive ADA results by timepoint - phase III long-term ADA pool (full analysis set)

The applicant was requested to discuss the reasons for presence of ADA in subjects not exposed to anifrolumab and higher incidence of ADA in the placebo group than active group. During scientific advice in 2018, the CHMP recommended measures to quantify the contribution of potential matrix effect caused by rheumatoid factor on ADA results. The applicant clarified that, after the scientific advice, appropriate changes were made to the assay to mitigate the observed high false-positive rate. A possible reason for false positive results was identified to be potential aggregation in the ruthenylated reagent. With the improved ADA assay, incidence of false positive results is lower, although false positive results are still obtained. The applicant informed that one patient had a reduction in the inhibitory effect of anifrolumab on type I IFN PD signature proportional to the ADA titre.

ADA and PK

No comparison of PK for ADA-positive and ADA-negative subjects was prespecified in the statistical analysis plans for the Phase 3 trials due to the expected low number of ADA-positive subjects. However, the potential impact of ADA on PK was reviewed in individual phase 1, 2 and 3 studies and in the primary safety pool (of phase 3 studies) and long-term ADA pool. The PK profiles were similar in ADA positive and negative subject both in the primary safety pool with 25/332 ADA-positive among subjects who received anifrolumab and in the long-term ADA pool with 18/241 ADA-positive subjects in the anifrolumab group (data not shown for brevity). The estimated CL in ADA positive and ADA negative patients was found to be similar regardless of ADA status also in population PK analyses (data not shown for brevity).

ADA and PD

Expression of the type I IFN PD signature was measured during the clinical development programme and analysed to determine if ADAs cause any inhibition on binding of anifrolumab to IFNAR1 and hence neutralization of its activity.

In the primary safety pool, of the 25 ADA-positive patients in the anifrolumab group, 19 ADA-positive patients were positive already at baseline and 6/25 had treatment-emergent ADA. Persistent ADA were ween in 4 subjects in the anifrolumab group and 5 in the placebo group. In the 4 persistently ADA-positive patients given anifrolumab, the median PD effect (as measured by percent neutralization of the type I IFN PD signature compared with baseline) was less than that observed in ADA negative patients.

However, this was interpreted to be due to early discontinuation in 2 patients and lack of elevated expression in type I IFN PD signature at baseline in the remaining 2 patients, and not related to ADA.

In the long-term ADA pool, the median PD effect was comparable in ADA-positive and ADA-negative subjects in the anifrolumab 300 mg group.

ADA and efficacy

In the primary safety pool, the proportion of patients with a BICLA response at Week 52 in ADA-positive patients compared with ADA-negative patients was 36.2% (9/25) vs 48.4% (162/334) in the anifrolumab group and 17.9% (6/35) vs 32.6% (106/330) in the placebo group. The proportion of patients with an SRI(4) response at Week 52 in ADA-positive patients compared with ADA-negative patients was 48.3% (12/25) vs 52.6% (176/334) in the anifrolumab 300 mg group and 27.8% (9/35) vs 41.9% (138/330) in the placebo group. Consequently, the proportion of subjects achieving BICLA and SRI(4) response was slightly higher in ADA negative subjects than ADA positive subjects in both anifrolumab and placebo groups. Due to the small number of ADA positive subjects, no firm conclusions on any potential association between presence of ADA and treatment response can be drawn.

ADA and safety

In the primary safety pool, the incidence of any adverse event (AE) during treatment was greater in the anifrolumab 300 mg group (88.3%) than in the placebo group (80.8%). The incidence of AE was similar in ADA-positive and ADA-negative subjects: 88.0% vs 89.2% in the anifrolumab 300 mg group and 82.9% vs 81.8% in the placebo group. In the anifrolumab group, 4.0 % of ADA-positive vs. 12.6 % of ADA-negative subjects reported SAE. The corresponding proportions of subjects reporting SAE were 37.1 % and 17.0 % of ADA-positive and ADA-negative subjects in the placebo group. All deaths (2 in the anifrolumab 300 mg group and 1 in the placebo group) occurred in ADA-negative subjects.

In the anifrolumab 300 mg group, 12.0% (3/25) ADA-positive patients versus 4.5% (15/334) ADA-negative patients had at least one AE leading to discontinuation of drug (DAE), whereas in the placebo group, 14.3% (5/35) versus 5.2% (17/330), respectively, had at least one DAE. No pattern was seen between ADA status and incidence of AESI.

There was no apparent trend or pattern suggesting a correlation between the presence of anifrolumab ADA and occurrence of hypersensitivity or anaphylaxis events in the Phase III studies (data not shown for brevity).

In the phase III long-term ADA pool, the proportion of ADA-positive patients with any AE was lower compared with ADA-negative patients in the anifrolumab 300 mg group (83.3% vs 95.0%) but was comparable between ADA categories in the placebo group (90.9% vs 93.1% for ADA-positive and ADA-negative patients, respectively). The incidence of SAEs in ADA-positive patients compared with ADA-negative patients was 33.3% (6/18 patients) versus 19.9% (48/241) in the anifrolumab 300 mg group and 36.4% (4/11) versus 28.4% (29/102) in the placebo group. In the anifrolumab 300 mg group, no ADA-positive patients versus 3.7% (9/241) ADA-negative patients had at least one DAE, and 9.1% (1/11) versus 3.9% [4/102], respectively, in the placebo group had at least one DAE.

The incidence of hypersensitivity and infusion reactions overall were consistently more numerous in the anifrolumab 300 mg treatment group than in the placebo group, although no severe cases were seen and with a low incidence of SAEs (0.3%). One patient with an anaphylactic reaction in the anifrolumab 150 mg group (study 5) was reported in the anifrolumab development programme. Upon request, the applicant provided further data on the timing of hypersensitivity events, including infusion-related reactions. In the supportive safety pool, all hypersensitivity reactions in the anifrolumab 300 mg group did indeed occur only during the first 6 treatment courses that is between infusion 1 and infusion 6, and majority of these during the first 2 infusions. The mean time to the onset of the first hypersensitivity

reaction was shorter in the anifrolumab 300 mg group, 46.4 days (SD: 50.64) in comparison to that in the placebo group, 93.0 days (SD: 60.53).

In both the anifrolumab 300 mg group and the placebo group, more patients experienced infusion-related reactions with the initial infusions (Infusions 1 and 2) and the incidence of infusion-related reactions decreased with subsequent infusions, acknowledging the overall small number of events in the placebo treatment group.

Any possible association of ADAs and safety issues cannot be assessed reliably as the ADA results are compromised by unspecific binding to matrix proteins and potential aggregation of the ruthenylated reagents.

2.5.8.7. Discontinuation due to adverse events

Primary and supportive safety pools

The proportion of patients with DAEs was low and balanced between the anifrolumab 300 mg group (4.7%) and placebo group (4.9%) in the primary safety pool with no PT or SOC predominating (Table 66).

In the primary safety pool, the most commonly reported DAEs by SOC were in the Infections and infestations category with no PT predominating. The incidence of DAEs in the supportive safety pool was similar to the primary safety pool.

Table 66 Adverse events leading to discontinuation of IP during treatment, by SOC and PT – Primary safety pool (safety analysis set)

System Organ Class Preferred Term	Anifrolumab 300 mg (N = 360)			Placebo (N = 365)			Risk difference [a] (95% CI)
	n (%) patients	Exposure years	EAIR per 100 PY	n (%) patients	Exposure years	EAIR per 100 PY	
Patients with any DAE	**17 (4.7)**	**325.0**	**5.2**	**18 (4.9)**	**317.5**	**5.7**	**-0.4 (-4.1, 3.2)**
Infections and infestations	**7 (1.9)**	**325.7**	**2.1**	**3 (0.8)**	**318.6**	**0.9**	**1.2 (-0.8, 3.5)**
Herpes zoster	2 (0.6)	325.9	0.6	0	318.8	0	0.6 (-0.6, 2.2)
Acute sinusitis	1 (0.3)	326.0	0.3	0	318.8	0	0.3 (-0.9, 1.7)
Bronchitis	1 (0.3)	326.0	0.3	0	318.8	0	0.3 (-0.9, 1.7)
Diverticulitis	1 (0.3)	326.0	0.3	0	318.8	0	0.3 (-0.9, 1.7)
Mycobacterium avium complex infection	1 (0.3)	325.9	0.3	0	318.8	0	0.3 (-0.9, 1.7)
Pneumonia	1 (0.3)	326.0	0.3	2 (0.5)	318.7	0.6	-0.3 (-2.0, 1.1)
Upper respiratory tract infection	1 (0.3)	326.0	0.3	0	318.8	0	0.3 (-0.9, 1.7)
Gastroenteritis	0	326.0	0	1 (0.3)	318.7	0.3	-0.3 (-1.8, 0.9)
Nervous system disorders	**4 (1.1)**	**325.9**	**1.2**	**0**	**318.8**	**0**	**1.2 (0.0, 3.1)**
Headache	1 (0.3)	326.0	0.3	0	318.8	0	0.3 (-0.9, 1.7)
Migraine	1 (0.3)	326.0	0.3	0	318.8	0	0.3 (-0.9, 1.7)
Myasthenia gravis	1 (0.3)	326.0	0.3	0	318.8	0	0.3 (-0.9, 1.7)
Syncope	1 (0.3)	326.0	0.3	0	318.8	0	0.3 (-0.9, 1.7)
Skin and subcutaneous tissue disorders	**2 (0.6)**	**326.0**	**0.6**	**0**	**318.8**	**0**	**0.6 (-0.6, 2.2)**
Angioedema	1 (0.3)	326.0	0.3	0	318.8	0	0.3 (-0.9, 1.7)
Ecchymosis	1 (0.3)	326.0	0.3	0	318.8	0	0.3 (-0.9, 1.7)

System Organ Class Preferred Term	Anifrolumab 300 mg (N = 360)			Placebo (N = 365)			Risk difference [a] (95% CI)
	n (%) patients	Exposure years	EAIR per 100 PY	n (%) patients	Exposure years	EAIR per 100 PY	
General disorders and administration site conditions	**1 (0.3)**	**325.9**	**0.3**	**2 (0.5)**	**318.7**	**0.6**	**-0.3 (-2.0, 1.1)**
Face oedema	1 (0.3)	325.9	0.3	0	318.8	0	0.3 (-0.9, 1.7)
Influenza like illness	0	326.0	0	2 (0.5)	318.7	0.6	-0.6 (-2.3, 0.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**1 (0.3)**	**326.0**	**0.3**	**1 (0.3)**	**318.8**	**0.3**	**-0.0 (-1.5, 1.4)**
B-cell lymphoma	1 (0.3)	326.0	0.3	0	318.8	0	0.3 (-0.9, 1.7)
Uterine cancer	0	326.0	0	1 (0.3)	318.8	0.3	-0.3 (-1.8, 0.9)
Renal and urinary disorders	**1 (0.3)**	**325.9**	**0.3**	**1 (0.3)**	**318.8**	**0.3**	**-0.0 (-1.5, 1.4)**
Nephritis	1 (0.3)	325.9	0.3	0	318.8	0	0.3 (-0.9, 1.7)
Lupus nephritis	0	326.0	0	1 (0.3)	318.8	0.3	-0.3 (-1.8, 0.9)
Reproductive system and breast disorders	**1 (0.3)**	**326.0**	**0.3**	**3 (0.8)**	**318.5**	**0.9**	**-0.6 (-2.5, 0.9)**
Cervical dysplasia	1 (0.3)	326.0	0.3	2 (0.5)	318.6	0.6	-0.3 (-2.0, 1.1)
Adnexa uteri cyst	0	326.0	0	1 (0.3)	318.7	0.3	-0.3 (-1.8, 0.9)
Cardiac disorders	**0**	**326.0**	**0**	**1 (0.3)**	**318.8**	**0.3**	**-0.3 (-1.8, 0.9)**
Atrial fibrillation	0	326.0	0	1 (0.3)	318.8	0.3	-0.3 (-1.8, 0.9)
Immune system disorders	**0**	**326.0**	**0**	**1 (0.3)**	**318.8**	**0.3**	**-0.3 (-1.8, 0.9)**
Hypersensitivity	0	326.0	0	1 (0.3)	318.8	0.3	-0.3 (-1.8, 0.9)
Injury, poisoning and procedural complications	**0**	**326.0**	**0**	**1 (0.3)**	**318.8**	**0.3**	**-0.3 (-1.8, 0.9)**
Infusion related reaction	0	326.0	0	1 (0.3)	318.8	0.3	-0.3 (-1.8, 0.9)
Musculoskeletal and connective tissue disorders	**0**	**326.0**	**0**	**4 (1.1)**	**318.6**	**1.3**	**-1.3 (-3.2, -0.1)**
Systemic lupus erythematosus	0	326.0	0	4 (1.1)	318.6	1.3	-1.3 (-3.2, -0.1)
Respiratory, thoracic and mediastinal disorders	**0**	**326.0**	**0**	**1 (0.3)**	**318.8**	**0.3**	**-0.3 (-1.8, 0.9)**
Pulmonary alveolar haemorrhage	0	326.0	0	1 (0.3)	318.8	0.3	-0.3 (-1.8, 0.9)

[a] Risk difference is the difference between the EAIRs per 100 PY (anifrolumab 300 mg group– placebo group). The definition of each pool and details of treatment groups within each pool are described in SAP Section 2.2.1. If not stated otherwise, percentages are based upon all patients in the safety analysis set within the respective pool and treatment group. An AE during treatment is defined as an AE with a date of onset ≥ day of first ever dose of IP and ≤ minimum ((last dosing date + 28 days), end of study date, death date). Adverse events are coded using MedDRA version 22.1. Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories. AEs are sorted by descending frequency of SOC and PT in the anifrolumab group. The EAIR per 100 PY is defined as the number of patients with the specific event divided by the total exposure time in years and then multiplied by 100. The exposure time is defined as from the date of first administration of IP to the date of first event, death, end of treatment + 28 days, or end of study, whichever comes first. AE Adverse event; CI Confidence interval; DAE Adverse event leading to discontinuation of IP; EAIR Exposure-adjusted incidence rate; IP Investigational product; n Number of patients with an event; N Number of patients in treatment group; PT rs; SAP Statistical analysis plan; SOC System organ class.

Phase III long-term safety data

There was no evidence for an increase in rate of discontinuations over time in the phase III long-term safety data. As observed during the 52-week treatment period, rates of DAEs in the phase III long-term safety data were low and similar between the anifrolumab 300 mg group (3.1/100 PY) and placebo group (4.3/100 PY).

2.5.8.8. Post marketing experience

As of the date of submission of the application, anifrolumab has not been marketed anywhere in the world; therefore, no post marketing data are available for anifrolumab.

2.5.9. Discussion on clinical safety

The primary safety pool includes the two phase 3 studies, and the supportive safety pool in addition the phase 2 study.

The safety evaluation of anifrolumab IV 300 mg Q4W over 52 weeks was based on a primary safety pool and a supportive safety pool. The primary safety pool included two phase III studies (study 04 and study 05). The supportive safety pool included study 04, study 05, and a phase II placebo-controlled study (study 1013).

The evaluation of the long-term safety profile of anifrolumab IV 300 mg Q4W over up to 4 years of treatment was based on the phase III long-term safety data. The phase III long-term safety data included studies 04 and 05 plus interim data from study D3461C00009 (study 09). Study 09 was a phase III extension study that enrolled patients who completed study 04 or study 05. Study IA-MEDI-546-1145 (study 1145) was an open-label extension study for patients who completed study 1013.

Study 09 is ongoing and the applicant provided, upon CHMP's request, updated safety data (data cut-off date of 19 March 2020) from this study 9. In addition, the Risk Management Plan (RMP) includes the most recent patient exposure data from this study with a data-lock date in March 2020. For this study 09, a clinical study report (CSR) has not yet been prepared since this is interim data only. The submission of the final study report for the long-term extension study 09 is Q2 2022 (see RMP Section 2.6).

Overall, the exposure to anifrolumab can be considered acceptable, as the numbers exceed the ICH E1 recommendations for > 6 months of exposure (300 to 600 patients) and > 1 year of exposure (100 patients). This exposure would appear adequate to evaluate the safety profile of anifrolumab in patients with SLE, a chronic disease with an estimated global prevalence of 6.5 to 178.0 cases per 100000 persons).

Overall, demographic characteristics and baseline disease characteristics are generally balanced between the primary and supportive safety pool and also between the two treatment arms. The majority of patients were white female with a mean age of about 41 years old, which is in line with the mean age of onset of SLE disease and subjects ≥ 65 years are underrepresented. Most patients had more severe disease (SLEDAI 2K score of ≥ 10) and were classified as type I IFN gene signature test high at screening (82.6%). Ninety point one per cent (90.1%) were anti-nuclear antibody positive, but less than half of patients at baseline (44.4% and 40.2%) were anti-dsDNA positive and had abnormal C3 levels (36.8% and 23.3%) in primary and supportive safety pool, respectively, suggesting a prevalence of patients with less active disease at baseline. Regarding SLE treatment at baseline, in the primary safety pool, 81.9% of patients were treated with OCS at a mean dose of 11.54 mg/day and approximately 69.0% were in combination with immunosuppressants and/or anti-malarials, which is not unexpected in a moderate/severe disease.

Potential safety concerns related to the mechanism of action of anifrolumab include those associated with immunomodulation, for example serious/opportunistic infection, viral infection (including reactivation), and malignancy. Potential concerns associated with protein-based infusion therapies include anaphylaxis, hypersensitivity reactions, and infusion-related reactions.

In the primary safety pool, the overall incidence of any AE during treatment was somewhat higher in the anifrolumab 300 mg group (88.3%) than in the placebo group (80.8%). Most AEs were mild, 141 AEs

(in 39.2% of patients) vs 140 (38.4%) or moderate 150 (41.7%) vs 128 (35.1%) in intensity, with similar incidences also of severe cases, 27 (7.5%) vs 27 (7.4%), in the anifrolumab vs placebo groups, respectively.

The SOC with the greatest frequency of AEs in the anifrolumab group was Infections and infestations, 71.7% vs 57.8% in the anifrolumab and placebo groups, respectively.

The most common AEs by PT (≥ 5% difference or at least 5% incidence and twice the frequency) in the anifrolumab 300 mg group vs. the placebo group were: nasopharyngitis (17.8% vs 11.2%), upper respiratory tract infection (16.9% vs 9.9%), bronchitis (10.6% vs 4.7%), herpes zoster (6.4% vs 1.4%), and arthralgia (5.6% vs 2.2%). The most commonly reported adverse reactions during anifrolumab treatment (studies 4, 5 and 1013 pooled) were upper respiratory tract infection (34%), bronchitis (11%), infusion-related reaction (9.4%) and herpes zoster (6.1%). The AEs reported and assessed as related more commonly than unrelated to IP by investigators in anifrolumab 300 mg group for each safety pool were, in terms of EAIR: infusion related reactions (in the phase III long term safety pool: EAIR related 5.7/100 PY vs unrelated 1/100 PY), herpes zoster (in the phase III long term safety pool: EAIR related 3/100 PY vs unrelated 1.8/100 PY) and hypersensitivity (in the phase III long term safety pool: EAIR related 1.5/100 PY vs unrelated 0.4/100 PY). Other AEs most commonly reported as related to IP by investigators were: upper respiratory tract infection, nasopharyngitis and bronchitis. These AEs are adequately reported in the SmPC.

In the supportive safety pool and consistently also in long-term safety data (up to 4 years of treatment), the overall anifrolumab safety profile was comparable to that of the primary safety pool. In the by study comparisons (studies 04, 05, and 1013), the most common AEs by PT in the anifrolumab and placebo treatment groups were generally similar. If discrepancies were seen, no plausible reason was clearly evident.

Overall, there were 9 deaths during the anifrolumab clinical studies in the anifrolumab development programme. Four deaths in the anifrolumab (three pneumonia and one colitis) and three (MI, pulmonary hypertension and encephalitis) in the control group, were reported with the initial MAA. Two (2) additional deaths occurred in study 09 from 02 August 2019 to 19 March 2020, both in the anifrolumab 300 mg group. The fatal outcome event was pneumonia in one case and myocarditis in the other one. Both have been considered as unrelated to IP by the investigator. Only two of the deaths from pneumonia were considered related to the study drug. One death from macrophage activation syndrome (MAS), colitis and portal vein thrombosis was reported in a patient, who received a single dose of 1000mg anifrolumab (study 1013). The death was judged to not be related to the study treatment. MAS has been reported in most rheumatic diseases, including SLE and rather than being a consequence of a specific mechanism in these conditions, concomitant immunosuppression and infections are thought to be likely triggering factors. The applicant discussed the biology/pathophysiology behind this syndrome with reference to anifrolumab and re-evaluated the possible causes of this death from MAS and colitis, with special reference to immunosuppression and possible infections. On the basis of the currently available data, it appears unlikely that anifrolumab treatment would increase the existing risk of MAS in patients with SLE and, thus, the CHMP considered that MAS appears not to be a current safety concern for anifrolumab.

Deaths in anifrolumab groups are often associated with infections, mainly pneumonia. Hence, at the CHMP's request, the Section 4.4 of the SmPC has been updated to specify that serious and sometimes fatal infections have occurred in patients receiving anifrolumab.

Overall, in the primary and supportive safety pools and the phase 3 long-term data, fewer SAEs were reported in the anifrolumab 300 mg group than the placebo groups quite consistently. Most common SAEs in the anifrolumab group were infections and in the control placebo group SLE. Pneumonia was most common, but the rate was lower than in placebo. HZ was the most common with a rate higher than in the placebo group. The SAE pattern appeared to be similar in short and long-term safety data. Analysis

of long-term phase 3 data by PT and time interval (from year 1 to 4) did not appear to indicate any change in the overall SAE incidence over time up to 4 years. In the long-term pneumonia and SLE are confirmed to be the most frequent SAEs, followed by herpes zoster. Even if with a slightly lower rate compared to placebo, pneumonia were the most frequent SAEs by PT in anifrolumab group and were also fatal in three patients (of which two were considered related to IP), suggesting a possible more severe course in anifrolumab treated patients. The applicant provided a list of all patients in the supportive pool who had a pneumonia SAE during treatment, along with patient characteristics and potential risk factors for pneumonia. Overall, no important differences in patient's characteristics and risk factors were noted between patients with pneumonia SAEs in the anifrolumab group and in the placebo group.

In the primary safety pool, the incidence of discontinuations from anifrolumab due to AEs (DAE) was low for this type of studies, and similar across treatment groups, 17 (4.7%) and 18 (4.9%), in the anifrolumab and placebo treatment groups, respectively. The most commonly reported DAEs by SOC were in the Infections and infestations category: 7 (1.9%) vs. 3 (0.8%) in the anifrolumab and placebo treatment groups, respectively. At PT level, two discontinuations were ascribed to herpes zoster infections, while the remaining discontinuations were single occurrences. There was no evidence for an increase in rate of discontinuations over time in the phase III long-term safety data. The incidence of DAEs in the supportive safety pool was similar to that of the primary safety pool.

Based on the mode of action of anifrolumab and the provided safety data, infections are a safety concern for anifrolumab treatment, also in long-term. More than half of patients in the primary safety pool experienced infections, with a higher frequency in the anifrolumab 300 mg (71.7%) compared to placebo (57.8%) group. The majority of infections were mild or moderate in intensity. The EAIRs of infections seems to decrease in the long-term. In the primary safety pool, serious infections (non-opportunistic) were less frequent in anifrolumab 300 mg (4.4%) than in placebo (6%) group and this was confirmed in the long-term safety pool where it remained constant by yearly intervals. Discontinuations due to SAE were rare, with only single occurrences in each treatment group. Opportunistic infections were also rare. In the anifrolumab 300 mg group pneumonia was the most frequent event followed by herpes zoster and pyelonephritis (0.8%, 3 patients). The events of serious pyelonephritis was further characterised by the applicant, but due to the presence of concomitant confounding factors, a clear association of anifrolumab with the events of pyelonephritis cannot be drawn. This issue was not further pursued by the CHMP.

Although no cases of active TB were reported during any of the clinical studies, exposure-adjusted incidence of latent TB AEs reported during anifrolumab treatment showed an increasing trend with time, measured at yearly intervals. According to exclusion criteria of the phase III studies, a warning on TB was added in section 4.4 of the SmPC with appropriate precautions to be taken before starting anifrolumab treatment.

In the primary safety pool, there was an increased incidence of herpes zoster infections in patients in the anifrolumab treatment arm: 23 (6.4%), compared to 5 (1.4%) the placebo arm. Most occurrences were cutaneous, mild or moderate in severity, not serious and did not lead to discontinuation. This finding was quite consistent throughout the safety data. In addition, two cases of cutaneous disseminated herpes zoster were also reported. All responded to treatment and generally resolved without sequelae. Approximately half (12/23) events had an early onset, during the first 12 weeks of treatment; however, herpes zoster events were reported up to 52 weeks. This finding was quite consistent throughout the anifrolumab safety database.

In the supportive safety pool two patients were PCR positive for HZV in the cerebrospinal fluid although in the absence of cutaneous lesions suggestive of herpes zoster. In the first case, the investigator assessed the event of herpes zoster SAE and the myelitis transverse SAE as unrelated to anifrolumab,

while the second case of HZ meningitis was judged as moderate in intensity and related to IP by the investigator. Even if the applicant does not consider that there is a certain causal relationship between anifrolumab and the event of myelitis transverse, it is considered to be very likely by the CHMP and cannot be ruled out.

In the long term EAIR of herpes zoster AEs was highest in the first 52 weeks of treatment (7.3/100 PY) and decreased slightly during Year 2 and Year 3 (4.1 and 4.7/100 PY), with no events observed during Year 4. The majority were mild or moderate, but 7 patients experienced a SAE of herpes zoster.

Overall, increase in herpes zoster-infections could be seen as an indicator of potential for reactivation of pre-existing chronic viral infections by anifrolumab. Whether anifrolumab treatment could activate other types of chronic viral infections, such as chronic hepatitis or the John Cunningham (JC)-virus, remains currently unknown. During the AHEG, the experts indicated that the long-term safety profile would need to be carefully monitored and recommended to further look into recommendations for vaccination against herpes zoster. In addition, considering the mechanism of action of anifrolumab (interferon I blocker), the experts recommended to follow-up in the long term on the possible increase of, mainly atypical, mycobacterial infections. The risk of herpes zoster in anifrolumab treated patients (including disseminated herpes zoster events) is adequately described in the SmPC. Indeed, it was considered of importance that physicians are aware of the possible occurrence of a herpes zoster infection showing neurological symptoms also in absence of cutaneous lesions.

There was some uncertainty on the possible effect of concomitant treatment, namely corticosteroids, on the incidence of infections. A protocol based secondary endpoint of the controlled phase 2 and 3 studies was the ability of anifrolumab to reduce corticosteroid use, thus tapering was integral to the study design. The safety data on infections was re-analysed and appeared not to be confounded by corticosteroid use.

In conclusion, the risk of infections is adequately described in the Sections 4.4 and 4.8 of the SmPC. Serious infection is included as an important potential risk in the RMP and adequate post authorisation studies are planned to better assess this risk (see Section 2.6).

The incidence of AEs of influenza were similar between anifrolumab 300 mg and placebo group and among different safety pools. Two (2) patients in anifrolumab 300 mg compared to 1 in placebo group had a SAE of influenza both. The event rates for influenza in the supportive safety pool were similar in the anifrolumab 300 mg group [12 patients (2.6%; EAIR: 2.9/100 PY)] and in the placebo group [9 patients (1.9%; EAIR: 2.3/100 PY)]. Moreover, 2 patients in anifrolumab 300 mg compared to 1 in placebo group had a SAE of influenza. Apparently, these data suggest a similar risk of influenza in the two groups. However, data reported by the applicant show that a higher rate of patients in the anifrolumab 300 mg group [37 patients (8.1%)] than in the placebo group [23 patients (4.9%)] received seasonal influenza vaccines during the study, maybe preventing from further events of influenza and/or reducing the seriousness of the events. However, considering that a general warning on immunisations is included in Section 4.4 of the SmPC, this was considered acceptable to the CHMP.

Concerning other AEs of special interest, the applicant performed analyses of hypersensitivity, anaphylaxis and infusion-related reactions. In the primary safety pool, there were more AEs categorised as hypersensitivity reactions in the anifrolumab 300 mg group than the placebo group: 12 patients (3.3%) and 3 patients (0.8%), respectively. All hypersensitivity AEs were mild or moderate in intensity, and resolved spontaneously or with symptomatic treatment. One patient in the anifrolumab group had a hypersensitivity SAE, which was treated. The patient continued the study treatment, with prophylaxis given for subsequent infusions. One patient in the placebo group had a hypersensitivity AE that led to discontinuation of treatment. During the 52-week treatment period, all hypersensitivity AEs occurred in the first 24 weeks of treatment. The incidence of hypersensitivity events in the supportive safety pool were similar to that of the primary safety pool. As hypersensitivity reactions are usually more common early on in treatment, usually within few days or weeks of treatment, the applicant was requested to

present hypersensitivity reactions also by treatment course and provide the mean times to onset of symptoms. In the supportive safety pool, all hypersensitivity reactions in the anifrolumab 300 mg group did indeed occur only during the first 6 treatment courses, that is between infusion 1 and infusion 6. The mean time to the onset of the first hypersensitivity reaction was shorter in the anifrolumab 300 mg group, 46.4 days (SD: 50.64) in comparison to that in the placebo group, 93.0 days (SD: 60.53).

In the primary safety pool, incidence of infusion-related reactions through 52 weeks was higher in patients on anifrolumab 300 mg compared to those treated with placebo group (11.4% vs 7.4%), all being mild or moderate in intensity, with no serious reactions. One patient in the placebo group and none in the anifrolumab group discontinued. During the 52-week treatment period, most reactions occurred in the first 24 weeks of treatment. The most common symptoms related to infusion-related reactions (reported in ≥ 5% of events) in the anifrolumab 300 mg group were headache (45.6%), nausea (22.8%), vomiting (7.6%), and fatigue (5.1%). In the supportive safety pool, at least one infusion-related reaction was reported for 43 patients (9.4%) in the anifrolumab 300 mg group and for 33 patients (7.1%) in the placebo group. The majority of infusion-related reactions occurred during the first 2 infusions with the incidence of these reactions decreasing with subsequent infusions in both the active and the placebo groups. All of the infusion-related reactions in the supportive safety pool were also mild or moderate in intensity.

Overall, the data indicate quite consistently that the incidence of hypersensitivity and infusion-reactions was higher in the anifrolumab treatment group than in the placebo group. Although with no severe cases seen and SAEs were reported with a low incidence of 0.3%. one anaphylactic reaction was reported in study 05 in a patient on anifrolumab 150 mg treatment. The reactions occurred mainly in the first 24-weeks, with a decline in incidence over time. On this background, the applicant has included adequate warning on hypersensitivity and infusion-related reactions in the Section 4.4 of the SmPC.

Malignancies are reported with a higher incidence in patients in the anifrolumab 300 mg arm than in placebo arm both in primary (1.4% vs 0.8%) and supportive safety pool (1.3% vs 0.6%), which is of concern, even if 4 malignancies reported within 180 days of the first exposure to anifrolumab, were considered by the applicant as likely pre-existing. The rate of malignancies seems to not increase over time in the long term (1.7% vs 1.1%). Malignancies are included in the RMP as important potential risk (see Section 2.6) and a warning has been included in the 4.4 section of the SmPC. Due to the higher incidence of malignancies observed in the 52-week studies and the plausibility of anifrolumab mechanism of action in the loss of IFN tumour surveillance, a careful post-marketing surveillance is of importance and a post authorisation safety study will be conducted.

Concerning laboratory findings, the mean haematology, clinical chemistry, and urine analysis results were generally similar or lower between the anifrolumab 300 mg and placebo groups at baseline and at Week 52. There were no clinically meaningful differences or trends between the treatment arms. In long term, the findings were similar, except that in the 52-week time period hyperglycaemia was seen more often in the anifrolumab patients, even though at present firm conclusion on an association with anifrolumab treatment could not be drawn. Vital signs, physical examination and ECG results showed not no clinically significant changes.

In subgroup analyses (primary safety pool), the overall safety profile was consistent across all predefined subgroups. No clinically meaningful differences were observed in the frequency or pattern of AEs. The safety profile of anifrolumab was generally similar also in patients with IFN gene signature high, compared with low, for up to 52 weeks of treatment. Also, consistently higher, at least numerically, incidences for herpes zoster infections were seen in both of these subpopulations on the anifrolumab treatment.

The applicant provided at CHMP's request the most common AEs and SAEs by BMI subgroups. Overall, the frequency of AEs and SAEs in anifrolumab 300 mg group was similar in patients with BMI ≤ or > 28

kg/m2 (74.1% vs 79.4% and 9.8% vs 12.9%, respectively). Some numerical differences were noted; however, there was not a clear trend in the AEs and SAEs between the BMI subgroups, either for anifrolumab or placebo. A higher rate of pneumonia was noted in anifrolumab 300 mg treated patients with BMI > 28 kg/m2 compared to the lower BMI group, both as AE and SAE. However, this difference is reported also for placebo arm suggesting an increased susceptibility of this subgroup of patients rather than a correlation with study drug. Hypersensitivity was more common in patients with BMI > 28 kg/m2 compared to patients BMI ≤ 28 kg/m2 (6.4% vs 1.5%, respectively). However, it was reported as a SAE in only one patient. Hence, this issue was not further pursued by the CHMP.

Furthermore, at the CHMP's request the applicant provided AEs and SAEs by SLEDAI-2K subgroups (SLEDAI-2K scores < 10 and ≥ 10 points), both in the anifrolumab group and in the placebo group. Overall, AEs were similar in frequency in both subgroups and no clinically important differences or particular trends were noted for different AEs, except HZ was more common in subgroup of patients with SLEDAI-2K ≥ 10 than in those with SLEDAI-2K scores < 10 in anifrolumab 300 mg group. SAEs were more frequent in patients with SLEDAI-2K scores≥ 10 at baseline compared to patients with SLEDAI-2K score < 10, in anifrolumab 300 mg treatment group as well in placebo group, suggesting that SLE patients with a greater disease activity may be at higher risk of SAEs. At the moment, firm conclusions on a possible association of disease activity and risk of HZ, cannot be drawn. Immunosuppressant treatment is a confounding factor for the risk of HZ and the number of patients with SLEDAI-2K <10 and HZ is too limited for a clear comparison. It is stated in Section 4.4 of the SmPC that SLE patients also taking immunosuppressants may be at higher risk of herpes zoster infections. This is considered acceptable to the CHMP.

In the anifrolumab SLE clinical programme there were 31 patients with one or more pregnancy as of 01 August 2019. Of those 31 patients, 20 patients were randomised to receive anifrolumab. Among the patients who received anifrolumab and reported a pregnancy, no congenital anomalies associated with IP or no drug-associated AEs were observed. However, among these 31 pregnancies, there were 18 live births (14 in an anifrolumab group, 4 in a placebo group), 9 elective abortions (7 in an anifrolumab group, 2 in a placebo group), and 4 spontaneous abortions (4 in an anifrolumab group and 0 in a placebo group). One spontaneous abortion was assessed by the investigator as related to methotrexate. Investigator assessment is not reported in two cases. The causes of miscarriage are in general multifactorial and the exact cause of most miscarriages remains often unknown. Furthermore, multiple confounders are at play. No firm conclusion could be drawn considering the lack of known biological plausibility, the higher risk in SLE population, the presence additional risk factors of advancing age, hypothyroidism, endometriosis, and the concomitant use methotrexate which is contraindicated during pregnancy. Hence, the evidence to suggest causal association to anifrolumab treatment for the four cases of spontaneous abortions seen is scarce. However, use in pregnancy is included as a missing information in the RMP and this issue will be further followed-up post approval in a dedicated study (see Section 2.6). In addition, at the CHMP's request, the sections 4.6 and 5.3 of the SmPC were revised to adequately communicate the risk (see also Non-clinical section 2.4).

SLE patients have been reported to be at high risk of neuropsychiatric disorders. The mechanism is so far unclear, but chronic inflammation and immunomodulation have been put forward as possible causes. Thus, it has been suggested that anifrolumab, as an anti-IFNAR, could have protective effects on the neuropsychiatric symptoms of SLE. In the present clinical data, overall, there appeared to be no indication of an increased or decreased risk of depression or suicidality in the anifrolumab treated patients, as measured by AEs related to depression and by the chosen validated instruments (PHQ-8 and C-SSRS), as no relevant differences between the study treatment groups were seen in the indices currently measured. These results were not confounded by antidepressive medication. Hence, this issue was not pursued further by the CHMP.

No dedicated studies have been performed related to drug-drug interactions. No clinically relevant findings, for example interactions with concomitant medications, were evident from the available clinical trial data. Hence, this issue was not pursued further by the CHMP.

No information on MACE events are available from study 09. No AEs of stroke or myocardial infarction was reported in study 1145 (N = 218). In this study MACE was not an AESI and was not adjudicated by an independent committee. This issue was not pursued further by the CHMP.

Patients with SLE are at risk of infections and additional risk may be posed by the use of immunosuppressive agents and corticosteroids required to treat the disease. Therefore, these patients are potential candidates for vaccinations. No vaccine studies in anifrolumab have been previously performed. Thus, it is not known whether subjects receiving anifrolumab are able to mount a sufficient, clinically significant positive immune response. This risk is adequately reflected in Section 4.4 of the SmPC. Effects on responses to inactivated vaccines is listed as missing information in the RMP (section 2.6) and the applicant will conduct a post authorisation study to better understand the impact of anifrolumab on vaccination responses, including measuring antibody concentrations. The applicant is reminded that CHMP scientific advice may also be sought on these issues (preferably at the planning stage of any study).

As supportive analyses, the applicant also compared All anifrolumab (150, 300, and 1000 mg) vs placebo. The safety profile in the All anifrolumab pool was overall consistent with the anifrolumab 300 mg vs placebo analyses. There were more AEs of herpes zoster and latent TB in the all database. Uncommon events that were not reported in the primary, supportive, or long-term data, but were reported in the all anifrolumab group were 1 patient with an anaphylaxis AE (anifrolumab 150 mg group) and 3 patients with vasculitis AEs. Possible dose dependent trends were seen for herpes zoster infections and influenza, consistent with the mode of action of anifrolumab.

In the pre-clinical programme, focal arteritis has been identified as a risk beyond the findings related to the pharmacological action of anifrolumab itself. In the current clinical phase 2 and phase 3 studies no vasculitis were seen in either of the treatment groups. Of note, however, is that of the uncommon events that were not reported in the primary, supportive, or long-term data, 3 cases of vasculitis were reported in the all anifrolumab pool. They were all non-serious, resolved prior to the next scheduled dose of IP, were less frequent in the anifrolumab group (0.4%) compared to placebo group (1%) and were considered not related to IP by the investigator. The causes identified were infection, SLE and for one case it could not be specified. Moreover, 3 patients in the placebo group had AEs of vasculitis and one of these was serious. Therefore, based on the information provided, a clear association of vasculitis with anifrolumab cannot be drawn. Vasculitis (non-SLE) AE will be followed in the long-term study 9.

The proportion of ADA positive subjects did not differ in the IFNGS(+) subgroup (type I interferon gene signature test high) compared with the total study population either in the primary safety pool or the long-term immunogenicity pool. The applicant was requested to discuss the reasons for presence of ADA in subjects not exposed to anifrolumab and higher incidence of ADA in the placebo group than active group. During scientific advice in 2018, the CHMP recommended measures to quantify the contribution of potential matrix effect caused by rheumatoid factor on ADA results. The applicant clarified that after the scientific advice, appropriate changes were made to the assay to mitigate the observed high false-positive rate. A possible reason for false positive results was identified to be potential aggregation in the ruthenylated reagent. With the improved ADA assay, incidence of false positive results is lower, although false positive results are still obtained. The applicant informed that one patient had a reduction in the inhibitory effect of anifrolumab on efficacy proportional to the ADA titre, i.e. the ADAs were neutralising based on loss of type I IFN PD signature suppression, which was proportional to the ADA titre. Any possible association of ADAs and safety issues cannot be assessed reliably as the ADA results are compromised by unspecific binding to matrix proteins and potential aggregation of the ruthenylated

reagents. Therefore, at the CHMP's request, the applicant's original claim in the Section 4.8 of the SmPC of no relation of immunogenicity on efficacy was amended to a statement that the clinical relevance of the presence of anti-anifrolumab antibodies is not known.

Considering the novel mechanism of action of anifrolumab and that there is no approved treatment with this pharmacological mechanism of action, the identification of long-term risks is important and will be made via the Study 09. The provisions for long term safety monitoring, to further characterise risks discussed in safety specification are made in the RMP.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics

Additional expert consultations

The CHMP consulted experts in SLE and statistics to provide input regarding the safety profile. Upon request from the CHMP, an ad hoc expert group meeting was convened on 07 December 2021.

3. Please discuss whether the observed safety profile of anifrolumab in the population studied can be considered acceptable, and whether any particular measures should be considered for mitigation of risks.

The experts agreed by consensus that the safety profile observed in the clinical trials was acceptable.

The long-term safety profile would need to be carefully monitored.

Considering the safety data, the experts suggested to look into recommendations for vaccination against herpes zoster. In addition, considering the mechanism of action of anifrolumab (interferon I blocker), the experts recommended to follow-up in the long term on the possible increase of, mainly atypical, mycobacterial infections. They also mentioned to potentially recommend or consider screening for latent TB at treatment initiation; although it was recognised that no issue was identified in the current results.

2.5.10. Conclusions on the clinical safety

The key studies within the clinical development programme for anifrolumab comprise two Phase 3 studies and a large Phase 2 study. All three studies had a 52-week double-blind placebo-controlled treatment period and were generally similar in design. Within the application, 12-month safety data is provided for these three key studies. The primary safety pool included two phase III studies (study 04 and study 05). The supportive safety pool included study 04 and study 05, and a phase II placebo-controlled study (study 1013). Long-term data was from the ongoing long-term extension study 09 of the phase III studies.

Of the overall 1029 SLE subjects exposed to anifrolumab in the applicant development programme, at least 837 patients with SLE were exposed to IV anifrolumab, including 688 patients for ≥ 52 weeks with a total exposure to anifrolumab IV 150, 300, or 1000 mg in SLE patients (1888.2 PY). Of these 459 were exposed to the proposed dose of 300 mg for at least the 52 weeks. Up to 19 March 2020, the total exposure to anifrolumab IV 150, 300, or 1000 mg in SLE patients increased from 1888.2 PY to 2091.9 PY, including 548 patients exposed to anifrolumab for ≥ 104 weeks.

The overall exposure of anifrolumab appears adequate for the assessment of safety. The overall safety profile of anifrolumab seems to include an increased risk for infections (including herpes zoster), as well as for hypersensitivity and infusion-related events. Otherwise, anifrolumab seems to be well tolerated, with relatively similar number of AEs, SAEs and discontinuations due to AEs when compared to placebo.

Adequate warnings are included in the SmPC and those risks will be followed-up in the post-authorisation setting (See RMP section 2.6).

The long-term safety profile would need to be carefully monitored and adequate measures have been put in place (see RMP section 2.6).

This was agreed by the AHEG as the experts agreed by consensus that the safety profile observed in the clinical trials was acceptable.

In conclusion, the overall safety of anifrolumab in treatment of SLE is acceptable.

2.6. Risk Management Plan

2.6.1. Safety concerns

Important identified risks	None
Important potential risks	Malignancy Serious infection
Missing information	Use in pregnant and breastfeeding women
	Effects on responses to inactivated vaccines

2.6.2. Pharmacovigilance plan

Study Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 – Not applicable				
Category 2 – Not applicable				
Category 3 – Required additional pharmacovigilance activities				
D3461R00028 – A multiple database study of the use (and safety) of anifrolumab in women with SLE during pregnancy	To describe pregnancy outcomes (including live births and non-live births) and infant outcomes (including congenital anomalies/birth defects) in pregnancies among women with SLE exposed to anifrolumab	Use in pregnant women	Study protocol	Within 3 months from authorisation date
			Population size update	Annual basis

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Planned	anytime during pregnancy, including within 12 weeks of last menstrual period. To compare outcomes in pregnancies exposed to anifrolumab among women with SLE with the outcomes in pregnancies not exposed to anifrolumab among women with SLE. To compare outcomes in pregnancies exposed to anifrolumab among women with SLE with the outcomes in pregnancies among women without SLE.		Final report submission	Q4 2032
D3461R00046 – A non-interventional cohort study and meta-analysis on the risk of malignancy in systemic lupus erythematosus patients receiving anifrolumab. Planned	To describe the incidence of new malignancies in patients with SLE newly exposed to anifrolumab during a 5-year observation period; overall and by selected covariates and risk factors. To compare the incidence of new malignancies in patients with SLE newly exposed to anifrolumab with the incidence in comparable SLE patients exposed to other standard of care (including biologics) regimens.	Malignancy	Study protocol	Within 3 months from authorisation date
			Final report submission	Q4 2032
D3461R00050 – A non-interventional cohort study on the risk of serious	To estimate the incidence of hospitalisations due to serious infection in patients with SLE newly exposed to anifrolumab	Serious infection	Study protocol	Within 3 months from authorisation date

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
infections in systemic lupus erythematosus patients receiving anifrolumab. Planned	plus standard of care and the incidence in comparable SLE patients exposed to other standard of care regimen alone (including biologics). To estimate the incidence of hospitalisations due to serious infection in patients with SLE newly exposed to anifrolumab plus standard of care and the incidence in comparable SLE patients exposed to other standard of care regimen alone (including biologics) by serious infection type, deaths due to serious infections, and treatment with IV antimicrobials (if available in the data source).		Final report submission	Q4 2028
D3461C00023 – Nature of anifrolumab impact on vaccine-emergent immunity in patients with moderately to severely active systemic lupus erythematosus: A multi-centre open label parallel group trial: The NAÏVE study Ongoing	To compare induction of influenza immunity after receipt of a currently recommended quadrivalent flu shot in 2 groups of patients who enter the trial with moderately to severely active SLE, 10 having initiated anifrolumab at baseline in addition to standard of care, and 10 receiving only standard of care. To evaluate the safety and tolerability of influenza vaccine given with or without anifrolumab treatment	Effects on responses to inactivated vaccines	Final report submission	Q4 2022
D3461C00009 – A multicentre, randomised, double-blind, placebo-controlled Phase III extension study to characterise the long-term safety and tolerability of anifrolumab in adult subjects with active systemic lupus erythematosus Ongoing	To characterise the long-term safety and tolerability of intravenous anifrolumab	Serious infection and malignancy	Final report submission	Q2 2022

For studies D3461R00028, D3461R00046 and D3461R00050, the full study protocols should be submitted for assessment by PRAC.

2.6.3. Risk minimisation measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risks		
None	N/A	N/A
Important potential risks		
Malignancy	Routine risk minimisation measures: SmPC Section 4.4 Package leaflet Section 2	Routine pharmacovigilance activity: Targeted safety questionnaire Additional pharmacovigilance activities: D3461R00046, A non-interventional cohort study and meta-analysis on the risk of malignancy in SLE patients receiving anifrolumab D3461C00009, A multicentre, randomised, double-blind, placebo-controlled Phase III extension study to characterise the long-term safety and tolerability of anifrolumab in adult subjects with active systemic lupus erythematosus
Serious infection	Routine risk minimisation measures: SmPC Section 4.4 Package leaflet Section 2	Additional pharmacovigilance activities: D3461R00050, A non-interventional cohort study on the risk of serious infections in systemic lupus erythematosus patients receiving anifrolumab D3461C00009, A multicentre, randomised, double-blind, placebo-controlled Phase III extension study to characterise the long-term safety and tolerability of anifrolumab in adult subjects with active systemic lupus erythematosus
Missing information		
Use in pregnant and breastfeeding women	Routine risk minimisation measures: SmPC Section 4.6 Package leaflet Section 2	Additional pharmacovigilance activity: D3461R00028, A multiple database study of the use (and safety) of anifrolumab in women with SLE during pregnancy
Effects on responses to inactivated vaccines	Routine risk minimisation measures: SmPC Section 4.4 and 4.5 Package leaflet Section 2	Additional pharmacovigilance activity: D3461C00023, Nature of anifrolumab impact on vaccine-emergent immunity in patients with moderately to severely active systemic lupus erythematosus: A multi-centre open label parallel group trial: The NAÏVE study

2.6.4. Conclusion

The CHMP considers that the risk management plan version 1.4 is acceptable.

2.7. Pharmacovigilance

2.7.1. Pharmacovigilance system

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

2.7.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 30.07.2021. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.8. Product information

2.8.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant 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.*

2.8.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Saphnelo (anifrolumab) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The applicant has sought marketing authorisation for anifrolumab for the following indication:

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

3.1.2. Available therapies and unmet medical need

SLE is a chronic, multisystem, 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. 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 patient survey, severe fatigue was ranked as one of their most burdensome symptoms.

Most of the current therapies for SLE are non-specific and inhibit broad inflammatory pathways. For mild disease, first line treatments include anti-malarials (hydroxychloroquine) and oral corticosteroids (OCSs; e.g., prednisone). NSAIDs are used for temporary symptom control, but, in contrast to glucocorticoids and immunosuppressants, have no impact on disease progression. Steroids remain a mainstay of treatment for mild to severe disease. Additional treatment options for moderate to severe disease include immunosuppressants, such as methotrexate, azathioprine, and mycophenolate mofetil. Each of these classes of agents are however associated with potentially significant toxicity and are sometimes poorly tolerated.

The only targeted therapy for SLE is belimumab (Benlysta), a monoclonal antibody targeting soluble human B Lymphocyte Stimulator protein. Belimumab blocks the binding of soluble BLyS, a B cell survival factor, to its receptors on B cells and inhibits B cell survival and differentiation into immunoglobulin-producing plasma cells. Belimumab is authorised in the EU since July 2011 as an add-on therapy in adult patients with active, autoantibody-positive systemic lupus erythematosus (SLE) with a high degree of disease activity (e.g., positive anti-dsDNA and low complement) despite standard therapy. Benlysta has recently been indicated in combination with background immunosuppressive therapies for the treatment of adult patients with active lupus nephritis.

Given the substantial disease burden, the nonspecific nature of the older therapeutics, their potential for poor tolerability and substantial toxicity as well as the paucity of medicinal products specifically targeting SLE, there exists a significant unmet need in terms of new therapeutic agents for SLE.

3.1.3. Main clinical studies

The key studies for assessment of safety and efficacy within the programme comprised:

- Two completed 52-week, randomised, double-blind, placebo controlled, Phase III studies: D3461C00004 or 'Study 04' (TULIP 2; total N randomised=365), and D3461C00005 or 'Study 05' (TULIP 1; total N randomised=457)
- An ongoing 3-year, double-blind, placebo-controlled, long-term extension study containing patients rolled over from studies 04 and 05 (D3461C00009 or 'Study 09')
- One completed 52-week Phase II study: CD-IA-MEDI-546-1013 or 'Study 1013' (MUSE; total N randomised=307)
- A completed 3-year, open-label extension study containing patients rolled over from study 1013 (study CD-IA-MEDI-546-1145 or 'Study 1145')

An anifrolumab dose of 300 mg Q4W was included in all key studies and is the only proposed dose.

3.2. Favourable effects

The efficacy of anifrolumab has been evaluated across a range of endpoints. Primary efficacy was evaluated using composite endpoints designed to assess global disease activity; a systematic attempt to reduce use of oral corticosteroids was included in the protocols; the effect on disease flares was studied; and scales were included to assess effects on the most frequently affected individual body systems. Below are the most relevant results with regards to the favourable effects.

BICLA response at Week 52, anifrolumab 300 mg vs. placebo (primary analysis using applicant's composite estimand):

- 47.8% vs. 31.5%; difference 16.3% (95% CI 6.3, 26.3); p=0.0013 (primary endpoint in Study 04)
- 47.1% vs. 30.2%; difference 17.0% (95% CI 7.2, 26.8) (secondary endpoint in Study 05)
- 53.5% vs. 25.1%; difference 28.4% (95% CI 15.3, 41.5) (secondary endpoint in Study 1013)

Maintained OCS tapering at Week 52, anifrolumab 300 mg vs. placebo:

- 51.5% vs. 30.2%; difference 21.2% (95% CI 6.8, 35.7); adjusted p=0.014 (key secondary endpoint in Study 04)
- 49.7% vs. 33.1%; difference 16.6% (95% CI 3.4, 29.8) (key secondary endpoint in Study 05)
- 56.4% vs. 27.3%; difference 29.1% (95% CI 12.0, 46.2) (secondary endpoint in Study 1013)

CLASI response at Week 12, anifrolumab 300 mg vs placebo:

- 49.0% vs. 25.0%; difference 24.0% (95% CI 4.3, 43.6); adjusted p=0.039 (key secondary endpoint in Study 04)
- 43.6% vs. 24.9%; difference 18.7% (95% CI 1.4, 36.0) (key secondary endpoint in Study 05)
- 48.1% vs. 15.4%; difference 32.8% (95% CI 8.4, 57.1) (secondary endpoint in Study 1013)

3.3. Uncertainties and limitations about favourable effects

For Study 05, it should be noted that as the study failed on the primary endpoint of SRI(4) response, p values for key secondary endpoints (BICLA response at Week 52, Maintained OCS tapering at Week 52, CLASI response at Week 12) cannot be formally interpreted due to the analysis hierarchy.

Discordant numeric results between the Phase III studies are observed on several endpoints (notably SRI(4), initially envisaged as the primary endpoint for the programme) as well as among distinct subgroups; some of the inconsistencies are due to varying response rates on placebo. There are thus limitations in terms of the overall robustness of the observed results, but the limitations do not preclude overall consideration of a clinically relevant effect as discussed with the AHEG experts.

SRI(4) response at Week 52, anifrolumab 300 mg vs. placebo

- 55.5% vs. 37.3%; difference 18.2% (95% CI 8.1, 28.3); (secondary endpoint in Study 04)
- 49.0% vs. 43.0%; difference 6.0% (95% CI -4.2, 16.2) (primary endpoint in Study 05; result presented according to Study 04 rules for restricted medications)
- 62.8% vs. 38.8%; difference 24.0% (95% CI 10.9, 37.2) (secondary endpoint in Study 1013)

Annualised flare rate, anifrolumab 300 mg vs. placebo

- 0.43 vs. 0.64; rate ratio 0.67 (95% CI 0.48, 0.94); adjusted p=0.08 (key secondary endpoint in Study 04)
- 0.57 vs. 0.68; rate ratio 0.83 (95% CI 0.61, 1.15) (key secondary endpoint in Study 05)

Joint response at Week 52, anifrolumab 300 mg vs. placebo

- 42.2% vs. 37.5%; difference 4.7% (95% CI -10.6, 20.0) (key secondary endpoint in Study 04)
- 55.6% vs. 36.3%; difference 19.3% (95% CI 5.4, 33.2) (secondary endpoint in Study 05)

BICLA response at Week 52, effect of type I IFN gene signature test (Phase III pool)

- 171/360 (47.5%) vs. 112/366 (30.8%); difference 16.6% (95% CI 9.7, 23.6) in all patients
- 142/298 (47.6%) vs. 88/302 (29.4%); difference 18.2% (95% CI 10.5, 25.8) in IFN gene signature high patients
- 29/62 (46.8%) vs. 24/64 (37.5%); difference 9.3% (95% CI -8.0, 26.5) in IFN gene signature low patients

BICLA response at Week 52, effect of baseline anti-dsDNA/C3/C4 status

- 112/222 (50.5%) vs. 58/209 (27.4%); difference 23.1% (95% CI 14.1, 32.1) in patients with at least one positive/abnormal value
- 59/138 (42.4%) vs. 54/157 (33.9%); difference 8.5% (95% CI -2.7, 19.7) in patients with baseline anti-dsDNA/C3/C4 all negative/normal

There are some uncertainties in respect of the magnitude of the ”true” treatment effect. According to additional sensitivity analyses conducted by the applicant, a large proportion of non-responders stemmed from intercurrent events, and in study 04, there was no difference in the proportion of true, clinical non-responders between the groups. The impact of intercurrent events was notably large in study 04 where there was a large imbalance in study withdrawals between the arms. This is considered a weakness, as Study 04 was stronger in demonstrating benefit according to the original analysis. Nevertheless, despite the notable effect of intercurrent events on the point estimate of treatment effect and differences in the behaviour of the placebo groups, even a treatment difference that based on some scenarios which can be considered realistic is in the range of 10-11% (as opposed to 16-17% based on the applicant’s primary analyses) is considered clinically meaningful following recommendations from the AHEG.

Regarding secondary endpoints only results on OCS tapering and flare rate (although not statistically robust) have been included in the Section 5.1 of the SmPC as they are reflecting important overarching treatment goals in SLE.

Subgroup analyses demonstrated some heterogeneity in treatment response. Of potential clinical relevance, a larger treatment effect was observed in patients with high disease activity based on serological markers. In Study 04, the difference between anifrolumab 300 mg and placebo in BICLA response at Week 52 was 9.2% (95% CI -7.5, 25.8) in patients with normal C3 and C4 and no anti-dsDNA antibodies at baseline, compared with 21.3% (95% CI 8.8, 33.9) in patients with at least one of the following: low C3, low C4 or positive anti-dsDNA. In Study 05, the corresponding values were 7.9% (95% CI –7.2, 22.9) in patients with normal C3 and C4 levels and no anti-dsDNA antibodies at baseline, compared with 25.0% (95% CI 12.0, 37.9) in patients with at least one low/positive value. Considering those subgroup analyses and the modest effect size observed in the overall population, there may be clinically relevant heterogeneity with respect to treatment response in biologically and/or clinically distinct subpopulations; one such example is the larger treatment effect observed in patients with high disease activity based on serological markers. While not considered restrictive from the perspective of the therapeutic indication, the applicant is recommended to continue, through additional analyses or new

studies, attempts to identify subpopulations that could be considered the best treatment candidates with anifrolumab. Moreover, as the most appropriate time frame for evaluating treatment responsiveness has not yet been established, the applicant is recommended to investigate criteria that could be used in evaluating whether anifrolumab treatment should be continued or discontinued and considered successful or not successful in clinical practice.

3.4. Unfavourable effects

Of the overall 1029 SLE subjects exposed to anifrolumab in the company development programme, at least 837 patients with SLE were exposed to IV anifrolumab, including 688 patients for ≥ 52 weeks with a total exposure to anifrolumab IV 150, 300, or 1000 mg in SLE patients (1888.2 PY). Of these, 459 patients were exposed to the proposed dose of 300 mg for at least the 52 weeks. Some long-term safety data beyond the 52 weeks are available. Up to 19 March 2020, the total exposure to anifrolumab IV 150, 300, or 1000 mg in SLE patients increased from 1888.2 PY to 2091.9 PY, including 548 patients exposed to anifrolumab for ≥ 104 weeks.

Overall, there were 9 deaths during the anifrolumab clinical studies in the anifrolumab development programme of which four occurred in the anifrolumab arm (3 pneumonia and one colitis/MAS) and 3 in the placebo arm (encephalitis, pulmonary hypertension, and MI). Four deaths occurred during treatment in the primary safety pool, one in the 1000 mg and 3 in the in the anifrolumab 300 mg treatment group (EAIR: 0.6/100 PY). Two 2 additional deaths occurred in study 09 from 02 August 2019 to 19 March 2020, both in the anifrolumab 300 mg group. Deaths in anifrolumab groups are often associated with infections, mainly pneumonia. Hence, at the CHMP's request, the Section 4.4 of the SmPC to specify that serious and sometimes fatal infections have occurred in patients receiving anifrolumab.

The current safety data show an increased overall incidence of infections in SLE patients on anifrolumab treatment, compared to patients on placebo treatment, also in the long-term data. Especially, an increased number of herpes zoster infections were reported: 23 (6.4%) compared to 5 (1.4%) the placebo arm. Most occurrences were cutaneous, mild or moderate in severity, not serious and did not lead to discontinuation. All responded to treatment and generally resolved without sequelae. Although no cases of active TB reported during any of the clinical studies, exposure-adjusted incidence of latent TB AEs reported during anifrolumab treatment showed an increasing trend with time, as measured by yearly intervals. Serious infection is included as an important potential risk in the RMP and adequate post authorisation studies are planned to better assess this risk (see Section 2.6).

In the primary safety pool, there were numerically more AEs categorised as hypersensitivity reactions in the anifrolumab 300 mg group than the placebo group: 12 patients (3.3%) and 3 patients (0.8%), respectively. Although all were mild or moderate in intensity, and resolved spontaneously or with symptomatic treatment, also one anaphylactic reaction was reported in the anifrolumab 150mg study group (in study 5). The incidence of hypersensitivity events in the supportive safety pool were similar to that observed in the primary safety pool.

In the primary safety pool, incidence of infusion-related reactions was also higher in patients on anifrolumab 300 mg compared to those treated with placebo group (11.4% vs 7.4%, respectively), all being mild or moderate in intensity, with no serious reactions. Most reactions occurred in the first 24 weeks of treatment. The most common symptoms of infusion-related reactions in the anifrolumab 300 mg group were headache (45.6%), nausea (22.8%), vomiting (7.6%), and fatigue (5.1%).

Adequate warning on hypersensitivity and infusion-related reactions are included in the Section 4.4 of the SmPC.

Malignancies are reported with a higher incidence in patients in the anifrolumab 300 mg arm than in placebo arm both in primary (1.4% vs 0.8%) and supportive safety pool (1.3% vs 0.6%). This higher rate could be expected in view of the mechanism of the action of the drug interfering with IFN tumour surveillance. The rate of malignancies seems to not increase over time in the long term (1.7% vs 1.1%). Since careful post-marketing surveillance is of importance, malignancies are included in the RMP as important potential risk and a warning has been included in the 4.4 section of the SmPC.

In the primary safety pool, the incidence of discontinuations in anifrolumab group due to AEs (DAE) was low, and similar across treatment groups: 17 (4.7%) and 18 (4.9%), in anifrolumab and placebo groups, respectively. The most commonly reported DAEs by SOC were in the Infections and infestations category: 7 (1.9%) vs. 3 (0.8%) in the anifrolumab and placebo groups, respectively. At PT level, two discontinuations were ascribed to herpes zoster infections, while the remaining discontinuations were single occurrences. The incidence of DAEs in the supportive safety pool was similar to that in the primary safety pool in the anifrolumab and placebo arms respectively.

3.5. Uncertainties and limitations about unfavourable effects

Animal studies show no adverse effects of anifrolumab on indirect measures of fertility. However, the risk to reproduction cannot be excluded based on the available nonclinical data. Given that it is unlikely that further animal studies would provide clinically meaningful data to inform about the risk in SLE patients, a revision of the SmPC sections 4.6 and 5.3 of the SmPC was requested by the CHMP to correctly describe the nonclinical reproductive toxicity data. Saphnelo is not recommended during pregnancy and in women of childbearing potential not using contraception, unless the possible benefit justifies the potential risk.

In the anifrolumab SLE clinical programme there were 31 patients with one or more pregnancy as of 01 August 2019. Four spontaneous abortions were reported in an anifrolumab group and 0 in a placebo group. The evidence to suggest causal association to anifrolumab treatment for the four cases of spontaneous abortions is scarce. However, use in pregnancy is included as a missing information in the RMP and this issue will be further followed-up post approval in a dedicated study (see Section 2.6).

The ADA results are compromised by unspecific binding to matrix proteins and potential aggregation of the ruthenylated reagent. Therefore, the observed numbers and proportion of subjects with treatment-emergent ADA are unreliable. This is adequately reflected in the Section 4.8 of the SmPC.

Patients with SLE are at risk of infections and additional risk may be posed by the use of immunosuppressive agents and corticosteroids required to treat the disease. Therefore, these patients are potential candidates for vaccinations. No vaccine studies in anifrolumab-treated subjects have been previously performed. Thus, it is not known whether subjects receiving anifrolumab have the ability to mount a sufficient, clinically significant positive immune response. This risk is adequately reflected in Section 4.4 of the SmPC. Effects on responses to inactivated vaccines is reflected as missing information in the RMP. In addition, a post approval safety study to assess the antibody response to vaccines in individuals receiving anifrolumab is in place.

3.6. Effects Table

Table 67 Effects table for anifrolumab for the treatment of SLE [data cut-off: 01 Aug 2019 (based on cut-off for safety data from ongoing Study 09)].

Effect	Short Description	Unit	Ani 300 mg	Placebo	Uncertainties/ Strength of evidence	References
Favourable Effects						
BICLA RR	BICLA response rate at Week 52	%	47.8%	31.5%	difference 16.3% (95% CI 6.3, 26.3); p=0.0013 (escalated to primary endpoint after Study 05 results were available)	Study 04
			47.1%	30.2%	difference 17.0% (95% CI 7.2, 26.8) (secondary endpoint)	Study 05
SRI(4) RR	SRI(4) response rate at Week 52	%	55.5%	37.3%	difference 18.2% (95% CI 8.1, 28.3); (demoted to secondary endpoint after results of Study 05 were available)	Study 04
			49.0%	43.0%	difference 6.0% (95% CI -4.2, 16.2) (primary endpoint)	Study 05
OCS tapering	Patients able to maintain tapered OCS dose at Week 52	%	51.5%	30.2%	difference 21.2% (95% CI 6.8, 35.7); adjusted p=0.014 (key secondary endpoint)	Study 04
			49.7%	33.1%	difference 16.6% (95% CI 3.4, 29.8); not formally tested (key secondary endpoint)	Study 05
Flares	Annualised flare rate	events per annum	0.43	0.64	rate ratio 0.67 (95% CI 0.48, 0.94); adjusted p=0.08 (key secondary endpoint)	Study 04
			0.57	0.68	rate ratio 0.83 (95% CI 0.61, 1.15); not formally tested (key secondary endpoint)	Study 05
CLASI RR	CLASI response rate at Week 12	%	49.0%	25.0%	difference 24.0% (95% CI 4.3, 43.6); adjusted p=0.039 (key secondary endpoint)	Study 04
			43.6%	24.9%	difference 18.7% (95% CI 1.4, 36.0); not formally tested (key secondary endpoint)	Study 05
Unfavourable Effects						
Primary safety pool (phase III studies 04 and 05)						
				EAIR risk difference (95% CI)		

Effect	Short Description	Unit	Ani 300 mg	Placebo	Uncertainties/ Strength of evidence	References
Any AEs		n (%)	318 (88.3)	295 (80.8)		
Any AE related to IP	(Investigator judged)	n (%)	133 (36.9)	95 (26.0)		
Any SAE		n (%)	40 (11.1)	60 (16.4)	-7.3 (-13.3, -1.4)	
Deaths		n (%)	2 (0.6)	3		
SOC[b]	Infections and infestations	n (%)	258 (71.7)	211 (57.8)		
Nasopharyngitis[c]		n (%)	64 (17.8)	41 (11.2)		
Upper respiratory tract infection[c]		n (%)	61 (16.9)	36 (9.9)		
Urinary tract infection[c]		n (%)	42 (11.7)	52 (14.2)		
Bronchitis[c]		n (%)	38 (10.6)	17 (4.7)		
Arthralgia[c]		n (%)	20 (5.6)	8 (2.2)		
Any AESI		n (%)	46 (12.8)	36 (9.9)	3.2 (-2.2, 8.7)	
Discontinuations due to AEs		n (%)	17 (4.7)	18 (4.9)	-0.4 (-4.1, 3.2)	
Infections	All	n (%)	258 (71.7)	211 (57.8)		
SAE infections		n (%)	16 (4.4)	22 (6.0)	-2.1 (-6.0, 1.7)	
DAE Infections	By SOC	n (%)	7 (1.9)	3 (0.8)	1.2 (-0.8, 3.5)	
Severe infections		n (%)	12 (3.3)	8 (2.2)		
Herpes Zoster		n (%)	23 (6.4)	5 (1.4)	5.7 (2.7, 9.3)	
Hypersensitivity		n (%)	12 (3.3%)	3 (0.8%),		
Anaphylaxis[a]		n (%)	0	0		
Infusion related reaction		n (%)	41 (11.4)	27 (7.4)		
Malignancy		n (%)	3 (0.8)	3 (0.8)	-0.0 (-1.9, 1.9)	

Abbreviations: AE, adverse event; AESI, adverse event of special interest; ADR, Adverse drug reaction; BICLA, British Isles Composite Lupus Assessment; CI, confidence interval; CLASI, Cutaneous Lupus Erythematosus Disease Area and Severity Index; IP, investigational product; OCS, oral corticosteroids; RR, response rate; SOC, ; SRI, Systemic Lupus Erythematosus Responder Index
Notes: [a]one anaphylactic reaction was identified in the anifrolumab 150 mg treatment group. [b]SOC with greatest frequency of AEs. [c] The most common AE reported in>2% patients in both anifrolumab and placebo arms.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The efficacy of anifrolumab has been evaluated across a range of endpoints within the clinical development programme. Primary efficacy was evaluated using composite endpoints designed to assess global disease activity; a systematic attempt to reduce use of oral corticosteroids was included in the protocols; the effect on disease flares was studied; and scales were included to assess effects on the most frequently affected individual body systems. The overall approach is in line with the CHMP Guideline on SLE (EMA/CHMP/51230/2013 corr).

Compared to placebo, an increase in BICLA response rates with anifrolumab was seen in all three key studies. In addition, a higher proportion of patients were able to reduce their use of oral corticosteroids; and a skin response was detected with the CLASI score. Numerical trends favouring anifrolumab were seen on flare rates, but none of the differences were statistically significant. Whereas promising effects had been observed on the SRI(4) composite in the Phase II study 1013, Study 05 failed on SRI(4), its designated primary endpoint. Although Study 04 would have been positive on its original endpoint of SRI(4) response, that endpoint had already been demoted as a secondary endpoint outside of the confirmatory testing framework.

Considering the uncertainties, the CHMP sought an expert consultation on this application. The experts agreed that Study 05 failed on its primary endpoint. In addition, changing the primary endpoint in Study 04 after having seen the study results from Study 05 was considered suboptimal. However, the experts agreed that clinically meaningful effects were demonstrated on BICLA. Some important secondary endpoints were considered clinically relevant and meaningful though not statistically robust: possibility of corticosteroid tapering, reduction of flares, patients reported outcomes (quality of life improvements). Considering the high unmet need in this disease, the experts agreed that the effect observed with anifrolumab translates into a clinically meaningful effect in patients with moderate to severe, active, autoantibody-positive SLE. The CHMP followed the experts' recommendations.

Within treatment guidelines, corticosteroids, antimalarials and immunosuppressants have an established position in the treatment of SLE. However, they have a broad spectrum of effects and carry risks in terms of organ damage and poor tolerability. In principle, mAb-based therapies have the potential of reduced off-target effects, but the specific pharmacological profile of anifrolumab, targeting an important component of the immunological system, carries a risk of unfavourable effects directly linked to its primary pharmacology. This is reflected in the safety profile, in which an increased risk of infections has been noted.

Hypersensitivity and infusion-related events, common phenomena with protein-based therapies, have also been reported. The available clinical information on the use of anifrolumab during pregnancy will be followed-up post approval. Otherwise, anifrolumab seems to be well tolerated, with relatively similar number of AEs, SAEs and discontinuations due to AEs when compared to placebo. Adequate warnings are included in the SmPC and those risks will be followed-up in the post-authorisation setting (See RMP section 2.6).

The long-term safety profile will be carefully monitored and adequate measures have been put in place (see RMP section 2.6).

This was agreed by the AHEG as the experts agreed by consensus that the safety profile observed in the clinical trials was acceptable.

3.7.2. Balance of benefits and risks

The challenges related to the disease itself as well as the available efficacy instruments in SLE were acknowledged by the CHMP. Despite the recognised limitations of the results, taking into account overall the results, the effect and the high unmet medical need for new therapies in SLE and following recommendation from the AHEG, the CHMP concluded that the totality of evidence is supportive of a beneficial treatment effect of anifrolumab. The effect size on BICLA response, albeit modest, is considered clinically meaningful.

The safety profile observed in the clinical trials was acceptable. An increased risk of infections has been observed in line with the mechanism of action. The long-term safety profile would need to be carefully monitored and adequate measures have been put in place (see RMP section 2.6).

Based on the totality of evidence, the CHMP concluded that the benefit/risk balance of anifrolumab in the revised indication "*add-on therapy for the treatment of adult patients with moderate to severe, active autoantibody-positive systemic lupus erythematosus (SLE), despite standard therapy*" is positive. The revised indication was accepted by the applicant.

3.8. Conclusion

The overall benefit/risk balance of Saphnelo is positive.

4. Recommendations

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Saphnelo 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 granting of the marketing authorisation 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).

Other 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.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

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.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that anifrolumab is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.

5. Appendices

1. CHMP AR on New Active Substance (NAS) dated 16 December 2021