EU RMP	
Drug Substance	Anifrolumab
EMA version number	6
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EUROPEAN UNION RISK MANAGEMENT PLAN (EU RMP) for SAPHNELO ™ (Anifrolumab)

The content of this EU RMP has been reviewed and approved by the Marketing Authorisation Holder's QPPV or deputy QPPV, as delegated by the QPPV in the EU.

Administrative Information

Rationale for submitting an updated RMP*:*

- Removal of additional pharmacovigilance activity for study D3461C00009 following completion.
- Inclusion of final data from study D3461C00009 (study 09).
- Updated information for study D3461R00028 with the changes agreed by Pharmacovigilance Risk Assessment Committee (PRAC).

Summary of significant changes in this RMP

RMP Part	Description of change
Part I	Updated ATC code as per WHO ATC Index.
Part II	Sections II.3, II.4.3, and II.7 were updated to include final data from study D3461C00009. Global post-marketing patient exposure (Section II.5) to SAPHNELO™ was added.
Part III	Updated information (title, objectives, study design, study population, and milestones) for study D3461R00028 with the changes agreed by Pharmacovigilance Risk Assessment Committee (PRAC). Study D3461C00009 was removed from additional pharmacovigilance activity following completion.
Part V	The summary table of risk minimisation measures has been updated to reflect the changes made in the pharmacovigilance plan.
Part VI	Updated the description of D3461R00028 and D3461R00046 studies in Section VI.2.3 Post-authorisation development plan.
Part VII	• Annex 2: study D3461R00028 title, objective, and milestone dates have been updated. A Completed Studies table was added to list study D3461C00009 following its completion. • Annex 3: study D3461C00009 was removed. • Annex 8 has been updated to summarise changes since the previous version.

Other RMP versions under evaluation

Not applicable.

Details of currently approved RMP

Version number:	EMA version 4 AstraZeneca version 4, succession 2
Approved with procedure:	EMEA/H/C/004975/IB/0005
Date of approval:	14 September 2023

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation/Special term	Definition/Explanation
ADA	anti-drug antibody
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
CI	confidence interval
CIS	carcinoma in situ
EAIR	exposure-adjusted incidence rate
EEA	European Economic Area
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
HPV	human papillomavirus
IFN	interferon
IFNAR1	subunit 1 of the type I interferon receptor
IFNAR2	type I IFN receptor alpha 2
IgG1	immunoglobulin G1
IP	investigational product
IV	intravenous
mAb	monoclonal antibody
mCM	minor Congenital Malformation
MCM	Major Congenital Malformation
NOAEL	no-observed-adverse-effect level
PASS	post-authorisation safety study
PK	pharmacokinetic(s)
RMP	Risk Management Plan
Q4W	every 4 weeks
SC	subcutaneous
SGA	small for gestational age
SIR	standardised incidence ratio
SLE	systemic lupus erythematosus
SmPC	Summary of Product Characteristics (EU)
SOC	standard of care

Abbreviation/Special term	Definition/Explanation
TB	tuberculosis
UK	United Kingdom
WHO	World Health Organization

1 PART I: PRODUCT OVERVIEW

Table 1-1 Product Overview

Active substance	Anifrolumab
Pharmacotherapeuticgroup(s) (ATC Code)	L04AG11
Marketing authorisation applicant	AstraZeneca AB
Medicinal products to which this RMP refers	Anifrolumab
Invented name in the EEA	SAPHNELO
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: Anifrolumab is a human immunoglobulin G1 kappa mAb directed against IFNAR1. It is composed of 2 identical light chains and 2 identical heavy chains, with an overall molecular weight of approximately 148 kDa.
	Summary of mode of action: Anifrolumab binds to IFNAR1 with high specificity and affinity. This binding inhibits type I IFN signalling and blocks the biologic activity of type I IFNs. There is growing evidence that type I IFNs play a central role in the pathogenesis of autoimmune diseases such as SLE. Type I IFN or IFN-inducible gene expression levels have been associated with SLE disease activity, severity, and clinical manifestations. Therefore, targeting type I IFN signalling is expected to provide a therapeutic benefit for patients with SLE

Table 1-1 Product Overview

	Important information about its composition: Anifrolumab lacks any agonist activity and was specifically engineered to be devoid of complement activating activity via C1q protein complex, which is multivalent for attachment to the complement fixation sites of immunoglobulin, for complement- dependent cytotoxicity. Anifrolumab is also engineered to be lacking in the binding activity via Fc gamma receptor I/IIA/IIB/IIIA (FcγRI, FcγRIIA, FcγRIIB, and FcγRIIIA, respectively). Therefore, it does not mediate antibody-dependent cell-mediated cytotoxicity. Despite its Fc modification, anifrolumab retains its binding activity to the FcRn similar to a wild-type IgG1 and, thus, maintains its physiological recycling by vascular endothelial cells.
Hyperlink to the Product Information	Anifrolumab, Summary of Product Characteristics
Indication in the EEA	Current: Anifrolumab 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.
Dosage in the EEA	Current: The recommended dose of anifrolumab is 300 mg, administered as an IV infusion over a 30-minute period, every 4 weeks
Pharmaceutical form(s) and strengths	The Drug Product is supplied as a single-dose vial of concentrate for solution for infusion (sterile concentrate). One vial of 2.0 mL of concentrate contains 300 mg of anifrolumab.
Is/will the product be subject to additional monitoring in the EU?	Yes

ATC Anatomical Therapeutic Chemical; C1q Complement component 1q (protein complex); EEA European Economic Area; EU European Union; Fc Fragment crystallisable; FcRn Fc gamma neonatal receptor; IFN Interferon; IFNAR1 subunit 1 of the type I interferon receptor; IgG1 Immunoglobulin G1; IgG1κ Immunoglobulin G1 kappa; IV Intravenous, mAb Monoclonal antibody; RMP Risk management plan; SLE Systemic lupus erythematosus.

2 PART II: SAFETY SPECIFICATION

2.1 MODULE SI: EPIDEMIOLOGY OF THE INDICATION AND TARGET POPULATION

Incidence

Globally, the incidence of SLE ranges from 0.3 to 23.7 cases per 100,000 person-years (Pons-Estel et al 2017). In Europe, the incidence of SLE is estimated at 3.3 to 5.0 per 100,000 person-years of the general population (Danchenko et al 2006). In the UK, the incidence was estimated to be 4.91 per 100,000 person-years (Rees et al 2016).

Prevalence:

Globally, the prevalence of SLE in the general population is estimated between 6.5 and 178 cases per 100,000 persons (Pons-Estel et al 2017). In Europe, the prevalence of SLE is estimated at 25.4 to 91.0 per 100,000 persons (Danchenko et al 2006). In the UK, prevalence is estimated 97.04 per 100,000 persons. The prevalence of SLE has been increasing in the UK in recent years (Rees et al 2016).

Demographics of the population in the indication – age, sex, and racial and/or ethnic origin and risk factors for the disease:

Systemic lupus erythematosus affects more females than males, with the female:male ratio of 8 to 15:1 (Pons-Estel et al 2017). Onset of SLE can occur at any age. Among adult-onset cohorts, incidence is highest from 24 to 32 years of age (Pons-Estel et al 2017), while maximal prevalence of SLE is between 45 to 64 years of age for females and between 40 to 89 years of age for males (Rees et al 2017). Incidence and prevalence rates in people of African or Asian descent are 2 to 3 times higher than in Caucasian populations (Pons-Estel et al 2010). 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 (Pons-Estel et al 2017, Pons-Estel et al 2010).

Systemic lupus erythematosus is a complex, heterogeneous disease with no known aetiology, but some genetic and familial connections have been identified in regional analyses and case studies (Michel et al 2001, Chebbi et al 2020, Demirkaya et al 2020).

Lifestyle risk factors may also contribute to disease susceptibility. A 2004 meta-analysis examining the risk of cigarette smoking, demonstrated an increased risk of SLE in current smokers (Costenbader et al 2004, Jiang et al 2015). Active smokers with SLE have also been shown to have increased disease activity, severity, and organ involvement (Ghaussy et al 2003, Rubin et al 2005, Ho et al 2005, Mont et al 1997).

Environmental and occupational risk factors such as exposure to metals, pesticides, particulates, such as silica, and other chemical agents have also been associated with increased risk of SLE (Miller et al 2012, Kamen 2014).

The main existing treatment options:

Given the individual variability in SLE manifestations, there is no single treatment paradigm, and a tailored, multidisciplinary strategy is required that adjusts to patients' individual clinical manifestations. The 2019 update of the European League Against Rheumatism recommendations for the management of SLE advises that treatment goals

include long-term survival, prevention of organ damage, and optimisation of health-related quality of life (Fanouriakis et al 2019). Healthcare providers may start with the lowest dose of the least toxic medicine to treat the highest concern manifestation. For mild disease, first line treatments include antimalarials (eg, hydroxychloroquine) and oral corticosteroids (e.g., prednisone).
Treatment options for moderate to severe disease and refractory disease (in addition to antimalarials and oral corticosteroids) include immunosuppressants (methotrexate, azathioprine, and mycophenolate mofetil), biologics (belimumab), calcineurin inhibitors, and chemotherapy (cyclophosphamide). Rituximab is considered in severe, organ-threatening refractory cases (Fanouriakis et al 2019).

Most current therapies are non-specific and inhibit broad inflammatory pathways that are not always relevant to SLE pathogenesis, leading to significant toxicity and organ damage (Lichtman et al 2012). Long-term use of hydroxychloroquine can cause retinopathy and poor adherence to treatment remains an issue with this drug (Fanouriakis et al 2019). Steroids are powerful immunosuppressant and anti-inflammatory agents that remain a mainstay of treatment for mild to severe disease (Apostolopoulos and Morand 2017). Although steroids provide benefits in SLE, over time, organ damage from steroid use increases. Chronic steroid use is a contributing factor in long-term morbidity and early cardiovascular mortality (Petri 2001, Ruiz-Arruza et al 2014, Al Sawah et al 2015) and the risk of irreversible organ damage increases with steroid dose (Petri et al 2012, Thamer et al 2009). The use of immunosuppressants is associated with an increased risk of infection, malignancy, cardiovascular disease, and bone marrow suppression. In addition, immunosuppressants are not effective in all patients for all manifestations of SLE.

In the EU, belimumab (Benlysta™) is the only medicine approved for SLE in the last 60 years. Belimumab, a neutralising anti-B-lymphocyte stimulator mAb, was approved by the EMA in 2011, for the treatment of adult patients with active, autoantibody-positive SLE with a high degree of disease activity (eg, positive anti-dsDNA and low complement) despite standard therapy (Benlysta SmPC). It targets one pathway, while patients are likely to have different underlying immunopathological pathways driving their SLE disease manifestations (Dörner and Furie 2019). As such, it is not effective in all patients.

Natural history of the indicated condition in the <untreated> population, including mortality and morbidity:

Systemic lupus erythematosus is a chronic inflammatory connective tissue disease that affects multiple organs such as the joints, kidney, skin, mucous membranes, and blood vessel walls (Ruiz-Irastorza et al 2001). 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') (Györi et al 2017). Uncontrolled, ongoing disease activity over time has been associated with poorer outcomes such as organ damage and coronary artery disease in SLE (Ibañez et al 2003, Ibañez et al 2005). Systemic lupus erythematosus is associated with significant morbidity, which impacts quality of life (Holloway et al 2014) and life expectancy (Moss et al 2002, Bernatsky et al 2006) and imposes a significant economic burden (Drenkard et al 2014, Holloway et al 2014).

Important co-morbidities:

Patients with SLE are at increased risk of developing cardiovascular disease (Ward 1999, Fischer et al 2004, Bernatsky et al 2006), stroke (Mok et al 2009), osteoporosis (Ramsey-Goldman et al 1999, Yee et al 2005, Almehed et al 2007), infection (Gladman et al 2002, Bosch et al 2006, Goldblatt et al 2009, Mosca et al 2010), malignancies (Choi et al 2017, Tessier-Cloutier et al 2014), and other comorbidities.

Prospective cohort studies in patients with SLE have identified increased standardised incidence rates for several malignancies compared with the general population (Apor et al 2014, Goobie et al 2015). Bernatsky et al 2013 reported a SIR for all malignancies in patients with SLE of 1.14 (95% CI: 1.05, 1.23); for haematologic malignancies, SIR of 3.02 (95% CI:2.48, 3.63) (Bernatsky et al 2013).

Lupus nephritis is a frequent cause of SLE-associated morbidity and mortality. Renal involvement occurs in 40% to 70% of patients, and 10% to 20% progress to end-stage renal disease (Bernatsky et al 2006, Kasitanon et al 2006, Ward 2009, Hanly et al 2011). End-stage renal failure can be a consequence of lupus nephritis (Hui et al 2013).

Mortality rates from lupus have improved with earlier diagnosis and better treatment; however, patients with SLE still experience disease flares that are interspersed with periods of reduced disease activity (Urowitz et al 2008, Chambers et al 2009, Bertsias et al 2010, Ceccarelli et al 2015). The rate and severity of flares may contribute to disease outcomes and organ damage. About half of all patients with SLE will have some form of organ damage within 5 years of SLE diagnosis (Gladman et al 2013, Leuchten et al 2014).

2.2 MODULE SII: NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Key safety findings from non-clinical studies and relevance to human usage

2.2.1 Summary of key findings from non-clinical data

Toxicity

Cynomolgus monkey was selected as the pharmacologically relevant species for non-clinical safety assessment based on anifrolumab binding and neutralisation activity in monkey cells. Anifrolumab cross-reacts with cynomolgus monkey IFNAR1 on peripheral blood mononuclear cells with a similar binding affinity compared to human IFNAR1. In addition, anifrolumab has shown comparable ability to neutralise the biological activity of available recombinant cynomolgus monkey IFN-α subtypes on monkey cells expressing monkey IFNAR1 compared to the same human IFN-α subtypes on human cells expressing human IFNAR1. Anifrolumab does not bind to murine IFNAR1 and does not inhibit the biological activity of murine IFN-α. Based on these data, the rodent was not considered a pharmacologically relevant species. The species specificity of anifrolumab precluded direct evaluation of carcinogenicity in rodents.

Key issues identified from acute or repeat-dose toxicity studies

No adverse anifrolumab findings were seen following single IV administration of up to 100 mg/kg or single SC administration of 5 mg/kg in cynomolgus monkeys, which are considered toxicologically relevant dose levels.

In a single-/repeated-dose toxicity study (study 7140-123), one animal of a cohort of 3 animals that received a repeated (Days 1, 37, and 50) 5 mg/kg IV dose exhibited signs consistent with a hypersensitivity response that worsened with each dose but were relieved by administration of IV antihistamine. Investigative and exploratory analyses (cytokine analyses [serum] and isotyping, and specificity characterisation of the ADA response) conducted in an effort to identify the underlying mechanism of the apparent hypersensitivity response did not reveal any conclusive information beyond the association with the development of ADA response.
This isolated case of hypersensitivity-like reaction was not reproducible in the subsequent 4-week or 39-week repeated-dose studies (study SNBL.263.01 and study 7140-129, respectively).

In study 7140-129, following weekly IV infusion (5 or 50 mg/kg/week) or SC injection (15 or 60 mg/kg/week) for 39 weeks, focal arteritis was observed in small- and medium-sized arteries of several organs in 5 of the 24 anifrolumab-dosed male animals. No arteritis was evident in male control animals or in female animals regardless of treatment group. Findings were less pronounced and generally less widespread in animals in the recovery phase, following a 13-week dose-free period. The NOAEL for anifrolumab in females is considered to be 50 mg/kg/week IV and 60 mg/kg/week SC, approximately 4-fold higher than the highest dose administered in clinical trials. For males, it is the same if the observed arteritis is not factored into the NOAEL determination. If the observed arteritis is factored into the NOAEL determination, the NOAEL for males is less than 5 mg/kg/week IV and 15

mg/kg/week SC; in that case, there is no safety margin for males. Given the known immunogenicity of anifrolumab in non-human primates, a possible explanation is that the vascular findings are the result of a species-specific, chronic immune-mediated reaction in the animals against a foreign human protein possibly related to formation of immune complexes and, as a result, its relevance to human safety is unknown. This explanation is supported by recent literature abstracts describing similar vascular lesions in monkeys dosed with human mAbs without previously identified vascular targets. In those cases, the findings were considered likely due to deposits of ADA/drug complexes (Bussiere and Johnson 2010, Todd 2010). The arteritis findings in the anifrolumab study may likewise be a consequence of species-specific immunogenicity. However, a possibility of other factors than production of antibodies to anifrolumab cannot be ruled out.

Reproductive/developmental toxicity

There is a wealth of information on the harmful effects of increased level of IFNs during pregnancy. The literature suggests that elevated type I IFNs could negatively impact pregnancy, maternal-fetal tolerance, and development (Yockey et al 2018, De Jesus et al 2015, Andrade et al 2015). However, there is little published evidence about the adverse effects of blockade of IFN signalling on the establishment, maintenance, and induction of maternal-fetal tolerance. The reported literature notes a lack of developmental defects in mice deficient for type I IFN receptor (Muller et al 1994, Hwang et al 1995). Similarly, deficiency in IFN-β (IFNB) in mice does not result in any impact to growth and development, though the mice are unable to mount an antiviral defence (Takaoka et al 2000, Deonarain et al 2000). Alpha/beta IFN and gamma IFN exert widely overlapping biological effects. Mice have been generated with a combined receptor defect (IFNAR -/-, IFN gamma receptor -/-; [AG129 mice]; Van den Broek et al 1995). As with mice with the individual mutations, AG129 mice had no apparent anomalies. These double-knockout mice (AG129) were healthy by 12 months of age and showed no gross abnormalities in hematological status, in the major lymphocyte subsets, or in constitutive major histocompatibility complex expression. The ability of deficient mice in these studies to reproduce suggests that type I IFN is not required for successful pregnancy.

Reproductive toxicity in cynomolgus monkeys: Fertility parameters were evaluated in sexually mature cynomolgus monkeys in the 39-week IV and SC repeat-dose toxicity study (study 7140-129). No adverse anifrolumab-related effects on menses or semen analyses or testicular staging parameters were observed. Reproductive organ weights, and histopathology of reproductive tissues were not impacted by anifrolumab administration. Fertility parameters were not adversely impacted following repeated administration of anifrolumab for 9 months at doses up to 50 mg/kg/week IV and 60 mg/kg/week SC. These findings suggest that the reproductive risks associated with anifrolumab administration are low.

Developmental toxicity in cynomolgus monkeys: No adverse effects of anifrolumab on pregnant, neonatal, or infant cynomolgus monkeys were observed in an enhanced peri- and post-natal developmental toxicology study in cynomolgus monkeys with IV anifrolumab (study SNBL.263.11). There was no effect on offspring growth and no structural or functional abnormalities were detected in offspring. Embryo-fetal losses (including abortion [on or before GD135] and in utero embryo-fetal death) in the anifrolumab enhanced pre- and post-natal development study occurred in 1/16 (6.3%), 5/17 (29.4%), and 3/16 (18.8%) females in the control, 30 mg/kg (low), and 60 mg/kg (high) groups, respectively. However, these values were within the testing facility's historical control range (14.2 ±10.2%, historical control range minimum to maximum range 0.0 to 33.3%) and did not attain statistical significance. Eight of the 9 fetal losses occurred before GD50, the period where the incidence of spontaneous embryo-fetal loss is the highest (Fujimoto et al 1983) and the timeframe when anifrolumab exposure to the fetus is anticipated to be the lowest. It cannot be concluded that the apparent increases in abortion resulted from treatment with anifrolumab. Given the spontaneous occurrence of these events, this model is insensitive to reveal minor or moderate effects on fetal survival. The number of surviving infants (ie, after removing all embryo-fetal losses, stillbirths, and post-birth infant deaths) was 11/16 in the control group, 10/17 in the 30 mg/kg group, and 8/16 in the 60 mg/kg group in this study. These survival numbers were within the anticipated distribution of live infant numbers based on Monte Carlo simulation analysis (Jarvis et al 2010). Finally, based on the available data, the potential effect of anifrolumab on conception and implantation cannot be excluded.

In the offspring, growth and development of the infants were not affected by anifrolumab exposure during pregnancy and no immunotoxicity was observed. The NOAEL was considered 60 mg/kg/dose IV, the highest dose tested. These findings suggest that the developmental toxicity risks associated with anifrolumab administration are low.

Genotoxicity

Anifrolumab is a mAb composed entirely of naturally occurring amino acids and contains no inorganic or synthetic organic linkers or other non-protein portions. Thus, it is highly unlikely that anifrolumab would react directly with DNA or other chromosomal material, and since anifrolumab is a large protein molecule, it is not expected to cross the nuclear or mitochondrial membranes. Based on consideration of the product attributes and pharmaceutical class to which anifrolumab belongs, genotoxic risks associated with anifrolumab administration are low.

Carcinogenicity

In the cynomolgus monkey toxicology studies, no evidence was observed of proliferative or pre-neoplastic changes, following repeated weekly administration of anifrolumab at doses up to 50 mg/kg IV and 60 mg/kg SC for 39 weeks. Anifrolumab does not bind to murine IFNAR1 and does not inhibit the biological activity of murine IFN-α, thus precluding a direct evaluation of anifrolumab carcinogenic risk in a 2-year rodent bioassay.

Alternative non-clinical models to evaluate carcinogenic risk for anifrolumab were considered; however, none of these models could assess carcinogenic risk associated with anifrolumab administration; at best they could identify a potential risk. This potential risk had already been identified based on the existing type I IFN non-clinical literature, including studies with IFNAR1- and IFNAR2-deficient mice and mice administered IFN-α/β and anti-IFN-α/β antibodies, that included the MAR1-5A3 antibody (representing the available alternative models to the Sponsor for carcinogenicity risk assessment) to characterise carcinogenic potential of IFNAR blockade in rodents. Due to the limited species specificity of anifrolumab, none of the alternative models could evaluate the quantitative or dose-dependent risk of carcinogenicity associated with anifrolumab administration.

The direct carcinogenic risks associated with anifrolumab administration are not known. Published non-clinical literature identifies a potential risk. Administration of murine IFN-α/β enhanced anti-tumour effects in mice that contained transplanted tumours. In IFNAR1- and IFNAR2-deficient mice or mice treated with analogous murine anti-IFNAR1 or IFN-α/β antibodies, decreased host defence to tumours was observed. The relevance of these experimental findings in mouse models for malignancy risk in humans is unknown.

2.2.2 Safety pharmacology

No standalone studies were conducted. Safety pharmacology endpoints were included in repeat-dose toxicity studies. There were no anifrolumab-related adverse findings in any of the safety pharmacologic parameters assessed in any non-clinical safety study.

2.3 MODULE SIII: CLINICAL TRIAL EXPOSURE

Exposure to anifrolumab IV (150, 300, and/or 1000 mg) in patients with moderate to severe SLE is summarised by duration (Table 2-1), by age group and sex (Table 2-2), by dose (Table 2-3), and by race and ethnic origin (Table 2-4). In each table, the exposure data are presented by the pools used to evaluate the safety of anifrolumab IV in patients with SLE: the primary safety pool, supportive safety pool, Phase III long-term safety and the all anifrolumab pool. Unless stated otherwise, exposure data and safety evaluations are based on data up to and including 31 December 2023.

- Primary and supportive safety pools (anifrolumab 300 mg): The safety evaluation of

anifrolumab IV 300 mg Q4W over 52 weeks was based on a primary safety pool (Phase III placebo-controlled studies D3461C00004 [study 04] and D3461C00005 [study 05]) and a supportive safety pool (study 04, study 05, and a Phase II placebo-controlled study, CD-IA-MEDI-546-1013 [study 1013]). Patients randomised to receive other doses of anifrolumab (150 mg in study 05 or 1000 mg in study 1013) were not included in the primary or supportive safety pools.

- Phase III long-term safety (anifrolumab 300 mg): The evaluation of the long-term safety profile of anifrolumab IV 300 mg Q4W was based on the Phase III long-term safety data: studies 04, 05, and 09. Study 09 is an extension study that enrolled patients who completed study 04 or study 05. Patients randomised to anifrolumab 150 mg in study 05 were not included in the Phase III long-term data.
- All anifrolumab pool (anifrolumab 150, 300, and 1000 mg): The all anifrolumab safety pool included patients who received any dose of anifrolumab in studies 04, 05, 09, 1013, and CD-IA-MEDI-546-1145 study [study 1145]. Study 1145 was an extension study for patients who completed study 1013. The exposure data includes data up to 19 March 2020.

Table 2-1 Duration of exposure (pooled clinical study data)

Pool	Duration of exposure	Patients n(%)	Person time (patient-years)
SLE primary safety pool	≥ 1 day	360 (100.0)	326.0
	≥ 12 weeks	346 (96.1)	324.2
	≥ 24 weeks	326 (90.6)	317.5
	≥ 36 weeks	311 (86.4)	309.2
	≥ 48 weeks	299 (83.1)	299.4
	≥ 52 weeks	238 (66.1)	239.5
	Total person time	NA	326.0
SLE supportive safety pool	≥ 1 day	459 (100.0)	419.4
	≥ 12 weeks	441 (96.1)	417.1
	≥ 24 weeks	420 (91.5)	410.1
	≥ 36 weeks	403 (87.8)	400.8
	≥ 48 weeks	387 (84.3)	387.9
	≥ 52 weeks	315 (68.6)	317.2
	Total person time	NA	419.4
SLE Phase III long-term safety data	≥ 1 day	435 (100.0)	1528.4
	≥ 24 weeks	435 (100.0)	1528.4
	≥ 52 weeks	435 (100.0)	1528.4

Table 2-1 Duration of exposure (pooled clinical study data)

Pool	Duration of exposure	Patients n(%)	Person time (patient-years)
	≥ 76 weeks	413 (94.9)	1501.1
	≥ 104 weeks	388 (89.2)	1458.9
	≥ 128 weeks	366 (84.1)	1409.9
	≥ 156 weeks	334 (76.8)	1322.1
	≥ 180 weeks	317 (72.9)	1266.7
	≥ 208 weeks	244 (56.1)	984.4
	Total person time	NA	1528.4
SLE all anifrolumab safety pool	≥ 1 day	837 (100.0)	2091.9
	≥ 24 weeks	766 (91.5)	2074.0
	≥ 52 weeks	694 (82.9)	2023.3
	≥ 76 weeks	606 (72.4)	1926.8
	≥ 104 weeks	548 (65.5)	1827.5
	≥ 128 weeks	487 (58.2)	1690.9
	≥ 156 weeks	375 (44.8)	1385.1
	≥ 180 weeks	237 (28.3)	949.3
	≥ 208 weeks	147 (17.6)	614.4
	Total person time	NA	2091.9

NA Not applicable; SLE Systemic lupus erythematosus.

The all anifrolumab safety pool include data from study 09 up to 19 March 2020

Table 2-2 Exposure by age group and sex (pooled clinical study data)

Pool	Age group	Patients n (%)			Person Time (patient-years)		
		M	F	All	M	F	All
SLE primary safety pool	Paediatric (< 18 years)	0	0	0	0	0	0
	Adults (18-64 years)	27 (100.0)	317 (95.2)	344 (95.6)	25.1	287.4	312.5
	Elderly people (≥ 65 years)	0	16 (4.8)	16 (4.4)	0	13.5	13.5
	Total	27 (100.0)	333 (100.0)	360 (100.0)	25.1	300.9	326.0
SLE supportive safety pool	Paediatric (< 18 years)	0	0	0	0	0	0
	Adults (18-64 years)	33 (100.0)	409 (96.0)	442 (96.3)	31.2	373.7	404.9
	Elderly people (≥ 65 years)	0	17 (4.0)	17 (3.7)	0	14.5	14.5
	Total	33 (100.0)	426 (100.0)	459 (100.0)	31.2	388.2	419.4
SLE Phase III long-term safety data	Paediatric (< 18 years)	0	0	0	0	0	0
	Adults (18-64 years)	33 (100.0)	386 (96.0)	419 (96.3)	117.3	1352.6	1469.9

Table 2-2 Exposure by age group and sex (pooled clinical study data)

Pool	Age group	Patients n (%)			Person Time (patient-years)		
		M	F	All	M	F	All
	Elderly people (≥ 65 years)	0	16 (4.0)	16 (3.7)	0	58.6	58.6
	Total	33 (100.0)	402 (100.0)	435 (100.0)	117.3	1411.2	1528.4
SLE all anifrolumab safety pool	Paediatric (< 18 years)	0	0	0	0	0	0
	Adults (18-64 years)	61 (100.0)	750 (96.6)	811 (96.9)	153.4	1873.2	2026.6
	Elderly people (≥ 65 years)	0	26 (3.4)	26 (3.1)	0	65.3	65.3
	Total	61 (100.0)	776 (100.0)	837 (100.0)	153.4	1938.5	2091.9

F Female; M Male; SLE Systemic lupus erythematosus.

The all anifrolumab safety pool include data from study 09 up to 19 March 2020.

Table 2-3 Exposure by dose (pooled clinical study data)

Pool	Dose of Exposure	Patients n (%)	Person time (patient-years)
SLE primary safety pool	300 mg Q4W	360 (100.0)	326.0
	Total	360 (100.0)	326.0
SLE supportive safety pool	300 mg Q4W	459 (100.0)	419.4
	Total	459 (100.0)	419.4
SLE Phase III long-term safety data	300 mg Q4W	435 (100.0)	1528.4
	Total	435 (100.0)	1528.4
SLE all anifrolumab safety pool	150 mg Q4W	24 (2.9)	14.4
	300 mg Q4W	563 (67.3)	1335.4
	1000 mg Q4W	250 (29.9)	742.1
	Total	837 (100.0)	2091.9

The all anifrolumab safety pool include data from study 09 up to 19 March 2020.

Patients who received 2 different doses of anifrolumab are counted in the dose category of the highest dose received. Q4W Every 4 weeks; SLE Systemic lupus erythematosus.

Table 2-4 Exposure by race (pooled clinical study data)

Pool	Race	Patients n (%)	Person time (patient-years)
SLE primary safety pool	White	235 (65.3)	214.4
	Black or African American	46 (12.8)	39.3
	Asian	41 (11.4)	38.5

Table 2-4 Exposure by race (pooled clinical study data)

Pool	Race	Patients n (%)	Person time (patient-years)
	Native Hawaiian or Other Pacific Islander	0	0
	American Indian or Alaska Native	4 (1.1)	3.6
	Other	26 (7.2)	23.9
	Missing	8 (2.2)	6.4
	Total	360 (100.0)	326.0
SLE supportive safety pool	White	270 (58.8)	246.5
	Black or African American	65 (14.2)	57.4
	Asian	44 (9.6)	41.5
	Native Hawaiian or Other Pacific Islander	0	0
	American Indian or Alaska Native	8 (1.7)	7.3
	Other	64 (13.9)	60.4
	Missing	8 (1.7)	6.4
	Total	459 (100.0)	419.4
SLE Phase III long-term safety data	White	288 (66.2)	1018.2
	Black or African American	55 (12.6)	186.4
	Asian	51 (11.7)	180.0
	Native Hawaiian or Other Pacific Islander	0	0
	American Indian or Alaska Native	3 (0.7)	9.4
	Other	31 (7.1)	112.3
	Missing	7 (1.6)	22.2
	Total	435 (100.0)	1528.4
SLE all anifrolumab safety pool	White	485 (57.9)	1202.1
	Black or African American	113 (13.5)	272.7
	Asian	75 (9.0)	190.9
	Native Hawaiian or Other Pacific Islander	0	0
	American Indian or Alaska Native	9 (1.1)	17.3
	Other	145 (17.3)	388.7
	Missing	10 (1.2)	20.2
	Total	837 (100.0)	2091.9

The race category Other includes Latin American patients in study 1013 who did not identify with the race definitions provided.

The anifrolumab safety pool include data from study 09 up to 19 March 2020.

SLE Systemic lupus erythematosus.

2.4 MODULE SIV: Populations not studied in clinical trials

2.4.1 Exclusion Criteria in pivotal clinical studies within the development programme

Pregnant or lactating females

Reason for exclusion:

For ethical reasons, this potentially vulnerable population was excluded from all anifrolumab clinical studies. For the same reason, any patient who became pregnant during a study was discontinued from treatment with IP. Therefore, there are no data of patients taking anifrolumab throughout the entirety of their pregnancy, and there is no data on the effect of anifrolumab on patients who are breastfeeding or their offspring.

Is it considered to be included as missing information: Yes

Paediatric patients aged less than 18 years

Reason for exclusion:

Patients aged less than 18 years were excluded from the anifrolumab clinical programme since it was not considered appropriate to expose paediatric patients to anifrolumab until after the benefit-risk profile was established for the intended adult population.

Is it considered to be included as missing information: No

Rationale:

Use of anifrolumab in paediatric patients is not part of the indication, therefore this population is not relevant for missing information.

Elderly patients aged greater than 70 years

Reason for exclusion:

Anifrolumab has not been specifically studied in elderly patients (> 70 years of age). Comorbid conditions in elderly patients may confound assessment of safety. Thus, this population was excluded in all anifrolumab clinical studies.

Is it considered to be included as missing information: No

Rationale:

Based on a population PK analysis that included 20 patients (3%) ≥ 65 years of age, age did not impact the clearance of anifrolumab (age range: 18 to 69 years). Additionally, no overall differences in safety or effectiveness were observed between older and younger patients who received anifrolumab in clinical trials.

Therefore, there is no clinical evidence to suggest a different safety profile for anifrolumab in elderly patients > 70 years of age than in younger patients. Therefore, this population is not considered missing information.

Patients with hepatic impairment

Reason for exclusion:

These patients were excluded in order to protect potentially vulnerable patients and to avoid factors that may confound a complete understanding of the safety data.

Is it considered to be included as missing information: No

Rationale:

Anifrolumab is eliminated by a target-mediated non-linear pathway through binding to IFNAR1 as well as a non-specific linear pathway in the reticuloendothelial system. Generally, clearance of monoclonal antibodies by the liver is considered to be a minor pathway; physiologically-based pharmacokinetic modelling estimates have found the liver's contribution to eliminating endogenous IgG to be around 16% (Keizer et al 2010).

There is no scientific rationale to suspect that the safety profile of patients with moderate to severe hepatic impairment may differ significantly to that characterised so far for the general target population. Therefore, this population is not relevant for missing information.

Patients with severe renal impairment

Reason for exclusion:

These patients were excluded in order to protect potentially vulnerable patients and to avoid factors that may confound a complete understanding of the safety data.

Is it considered to be included as missing information: No

Rationale:

There is no scientific rationale, based on anifrolumab's clearance mechanisms, to suspect the safety profile of anifrolumab in patients with severe renal impairment (due to lupus nephritis or any other cause) may differ from the general target population. Anifrolumab is eliminated by a target-mediated non-linear pathway through binding to IFNAR1 as well as a non-specific linear pathway in the reticuloendothelial system.

Additionally, there is no clinical evidence, based on patients with mild to moderate renal disease, to suggest that the safety profile of anifrolumab in patients with renal impairment will differ from patients with normal renal function. Although patients with severe renal disease were not included in the SLE clinical programme, patients with mild or moderate renal disease (n = 427) were enrolled. There were no differences in PK observed for patients with mild to moderate renal disease compared to patients with normal renal function. In addition to the studies in the SLE clinical programme, there is an ongoing study of anifrolumab in patients with lupus nephritis (eGFR ≥ 35 mL/min/1.73 m2 at baseline).

As there is no scientific rationale or clinical evidence to suggest the safety profile of anifrolumab will differ in patients with severe renal impairment, this population is not relevant for missing information.

History of anaphylaxis to any human gamma globulin therapy

Reason for exclusion:

Anifrolumab is a human mAb and its activity may be associated with hypersensitivity reactions, including anaphylaxis. Patients with a known allergy or reaction to any component of the drug formulation were excluded from clinical trials to ensure they were not exposed to product for which they had a documented allergy.

Is it considered to be included as missing information: No

Rationale:

Use of anifrolumab in this population is not anticipated and, therefore, it is not relevant as missing information.

History of cancer or current ongoing cancer treatment

Reason for exclusion:

Treatments that induce immune suppression may impair immune surveillance and thereby increase the risk for development of malignancies. Patients with a history of cancer (apart from successfully-treated [a] squamous or basal cell carcinoma of the skin or [b] cervical CIS) were excluded in order to avoid factors that may confound a complete understanding of the

safety data of anifrolumab and ensure interpretability of data. These patients were also excluded because they were likely taking medications that were protocol prohibited.

Is it considered to be included as missing information: No

Rationale:

Patients with a history of non-melanoma skin cancer or of high-grade squamous intraepithelial lesions (cervical intraepithelial neoplasia Grade 3, CIS) treated with curative therapy were not excluded from the clinical development programme studies based on safety, and there is no scientific rationale to suspect that the safety profile in this population of "cured" cancer is different to that of the general SLE population.

Among patients with ongoing cancer treatment, the anticipated use of anifrolumab is expected to be very low and further study of anifrolumab in those patients is not warranted. Malignancy and its treatments, including oncology drugs and radiation, add to the immunosuppressive burden experienced by patients with SLE from the disease itself (SLE) and its standard of care treatments. This burden increases the risk of infections that may be more frequent, more severe, or opportunistic. In addition, pharmacokinetic and immunologic interactions with chemotherapeutic and immunomodulating therapies are possible with potentially unpredictable and possibly harmful outcomes, making further study of anifrolumab in patients taking those medications not feasible. Therefore, further characterisation of patients with SLEundergoing cancer treatment with the addition of anifrolumab is neither warranted nor feasible and is not relevant for consideration as missing information.

History of, risk factors for, or recent diagnosis of certain clinically significant infections

Reason for exclusion:

Patients with SLE have an increased risk of infection. Patients with ongoing or recurrent clinically significant infections were excluded so as not to confound a complete understanding of the safety of anifrolumab and to ensure interpretability of the data.

Patients were excluded if they had (a) a primary immunodeficiency, splenectomy, or any underlying condition that predisposed the patient to infection (aside from SLE), (b) a positive test for human immunodeficiency virus, hepatitis B or C, or (c) history of a severe herpes infection. Patients with recent histories of other clinically significant infections were excluded depending on the infection type and the time elapsed since resolution. Patients were also required to meet TB criteria for inclusion in the studies: no history of active TB and a negative test for latent TB or appropriate treatment for latent TB prior to randomisation.

Is it considered to be included as missing information: No

Rationale:

Patients with immunosuppressive diseases being treated with immunosuppressive therapies are known to be at risk for infections. Healthcare providers will exercise medical judgement when advising patients with active infections or risk factors for clinically significant infections whether to begin or continue treatment with anifrolumab. Patients will be carefully monitored for exacerbations of underlying infections (see SmPC Section 4.4) and, in addition, herpes zoster is listed in SmPC Section 4.8. As healthcare providers are likely to treat underlying infections prior to adding immunosuppressants, use of anifrolumab in patients with clinically significant infections is expected to be low. Accordingly, utilisation of anifrolumab in patients with ongoing or recurrent infections, is not missing information.

History of, or current diagnosis of, a clinically significant non-SLE-related vasculitis syndrome

Reason for exclusion:

In a repeat-dose toxicology study in cynomolgus monkeys, new events of focal arteritis were observed in a subset of male animals after receiving anifrolumab treatment. Therefore, patients with either a history of, or current diagnosis of, a clinically significant

non-SLE-related vasculitis syndrome were excluded in order to mitigate this possible risk and to avoid factors that may confound a complete understanding of the potential association of anifrolumab and vasculitis.

Is it considered to be included as missing information: No

Rationale:

There is no clinical evidence of an association between anifrolumab and a new diagnosis of non-SLE-related vasculitis in clinical study patients. There is no scientific rationale to suspect that the safety profile of anifrolumab in patients with a history of vasculitis may differ from that characterised so far for the general target population. Therefore, this population is not considered missing information.

Diagnosis of mixed connective tissue disease, any history of overlap syndromes of SLE and systemic sclerosis, or history of uncontrolled or severe neuropsychiatric SLE

Reason for exclusion:

Patients were excluded in order to avoid factors that may confound a complete understanding of the safety data of anifrolumab and ensure interpretability of data.

Is it considered to be included as missing information: No

Rationale:

There is no scientific rationale to suspect that the safety profile of anifrolumab in patients with these diseases may differ from that characterised so far for the general target population.

History of, or current evidence of, suicidal ideation

Reason for exclusion:

Compared to the general population, patients with SLE have a higher rate of depression and suicide. Patients with history or presence of suicidal ideation were excluded from the clinical studies to help ensure patient safety during participation in the study and to ensure that unstable medical conditions or concomitant therapy for the condition did not confound the assessment of the safety of anifrolumab.

Is it considered to be included as missing information: No

Rationale:

There is no scientific rationale to suspect that the safety profile of anifrolumab in patients with a history or evidence of suicidal ideation may differ to that characterised so far for the general target population.

History of, or current diagnosis of, catastrophic or severe anti-phospholipid syndrome within one year prior to study entry

Reason for exclusion:

Patients with a history of, or current diagnosis of, catastrophic or severe anti-phospholipid syndrome within one year prior to signing the informed consent form were excluded. Patients with anti-phospholipid syndrome adequately controlled by anticoagulant therapy for at least 3 months were eligible for the Phase III studies. These exclusions were designed to help ensure patient safety during participation in the study and to ensure that unstable medical conditions or concomitant therapy for the condition did not confound the assessment of the safety of anifrolumab.

Is it considered to be included as missing information: No

Rationale:

There is no scientific rationale to suspect that the safety profile of anifrolumab in patients with catastrophic or severe anti-phospholipid syndrome may differ to that characterised so far for the general targeted population.

Use of live/attenuated vaccines

Reason for exclusion:

Patients were excluded in order to avoid factors that may confound a complete understanding of the safety data of anifrolumab and ensure interpretability of data.

Is it considered to be included as missing information: No

Rationale:

Use of anifrolumab concurrently with live/attenuated vaccines is not recommended in the SmPC; therefore, this population is not relevant for inclusion as missing information.

2.4.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect rare adverse reactions or adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

2.4.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table 2-5 Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	Not included in the development programme; however, despite the exclusion criteria, a small number of patients have reported pregnancies during the studies.
Breastfeeding women	Not included in the development programme
Patient with relevant comorbidities:	
Patients with hepatic impairment: • AST or ALT > 2.0 × ULN • Bilirubin > ULN	Not included in the development programme
Patients with mild or moderate renal impairment	427 patients who were exposed to any dose of anifrolumab had mild or moderate kidney disease at baseline (eGFR 30-89 mL/min/1.73 m^2), in the completed SLE studies (studies 04, 05, and 09).
Patients with severe renal impairment (serum creatinine > 2.0 mg/dL)	Not included in the development programme.

ALT Alanine aminotransferase; AST Aspartate aminotransferase; eGFR estimated glomerular filtration rate; SLE Systemic lupus erythematosus; ULN Upper limit of normal.

2.5 MODULE SV: POST-AUTHORISATION EXPERIENCE

2.5.1 Method used to calculate exposure

The post-marketing patient exposure data presented here is based on SAPHNELO's monthly actual ex-factory sales volume from each local marketing company. These data represent all *SAPHNELO* formulation delivered to various distribution channels (e.g., wholesalers, pharmacies, etc) worldwide.

The sales volume is provided as the number of vials distributed. The estimated post-marketing patient exposure data for the reporting period is an approximation based on the assumption that each patient received 1 vial (300mg/2 mL) of SAPHNELO IV Q4W and 13 vials in total per year (52weeks). Therefore, a patient-year worth of exposure is calculated by dividing number of vials by 13 (13 vials of 300mg/2 ml SAPHNELO per patient year [PY]).

The current methodology does not distinguish between sales that are related to initial prescriptions versus those related to repeat prescriptions. Therefore, it is not possible to estimate the number of patients exposed to SAPHNELO. More detailed patient-level data (eg, gender, ethnicity, age category, off-label use, specific populations, etc) are not available.

The estimated exposure of SAPHNELO is calculated from the number of vials that have been delivered to wholesalers worldwide, including those provided for the early access programmes.

2.5.2 Exposure

Cumulative global post-marketing patient exposure to SAPHNELO (300 mg/2 mL per vial) since launch to 31 December 2023 has been estimated to be approximately 10343.67 patient years.

2.6 MODULE SVI: ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Since anifrolumab is administered via IV infusion in a healthcare setting, the risk for misuse is low.

2.7 MODULE SVII: IDENTIFIED AND POTENTIAL RISKS

2.7.1 Identification of safety concerns in the initial RMP submission

2.7.1.1 Risk not considered important for inclusion in the list of safety concerns in the RMP

Reasons for not including an identified or potential risk in the list of safety concerns in the RMP.

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):

- Respiratory tract infection, upper respiratory tract infection, and bronchitis are identified risks. In the placebo-controlled Phase II and III SLE studies, patients in the anifrolumab 300 mg group reported more AEs in the Medical Dictionary for Regulatory Activities system organ class of infections and infestations than patients in the placebo group. The difference in the rates of infections was driven by mild and moderate infections involving the respiratory tract, excluding pneumonia (comparable in both treatment groups). These mild and moderate infections have minimal clinical impact on patients in relation to SLE.
- Infusion related reaction is an identified risk. In the placebo-controlled Phase II and III SLE studies, numerically more patients in the anifrolumab 300 mg group had AEs reported as infusion related reaction than in the placebo group. All infusion related reactions were mild or moderate in intensity and non-serious, and therefore have minimal clinical impact on patients in relation to SLE. In addition, treating physicians are familiar with these types of reactions, which are managed through routine labelling (see SmPC Section 4.4) and clinical practice.

Known risks that require no further characterisation and are followed up via routine pharmacovigilance; namely, through signal detection and adverse reaction reporting:

- Herpes zoster is an identified risk. In the placebo-controlled Phase II and III studies, herpes zoster infections were reported in more patients treated with anifrolumab 300 mg (6.1%) than in the placebo group (1.3%). Most cases were mild or moderate in intensity, non-serious, and did not result in discontinuation of IP. Treating physicians are aware there is an increased incidence of herpes zoster in patients with SLE due to the disease and its immunosuppressive treatment and are familiar with the medical management of herpes zoster in this patient population. Hypersensitivity and anaphylactic reactions are identified risks and well-known reactions that can occur with protein-based infusion therapies. These reactions are managed as per routine clinical practice (see SmPC Section 4.4). In the placebo-controlled Phase II and III SLE studies, numerically more patients in the anifrolumab 300 mg group had AEs reported as hypersensitivity than in the placebo group; most were mild or moderate in intensity and non-serious. There was one case of anaphylactic reaction in an anifrolumab- treated patient in the anifrolumab SLE programme.

- Drug/ADA immune complex formation (type III hypersensitivity) can occur with protein-based infusion therapies. Anifrolumab 300 mg administered as an IV infusion is poorly immunogenic in patients with moderate to severe SLE. In the anifrolumab programme, there was no evidence that the formation of ADAs had an impact on any safety variable.

2.7.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP and missing information

Important Potential Risk: Malignancy

Published studies have identified an increased frequency of some malignancies among patients with SLE, particularly for non-Hodgkin's lymphoma, leukaemia, and cancer of the vulva, lung, thyroid, and liver. Although there is a decreased risk of other select types of cancer for patients with SLE, the overall cancer risk in SLE is slightly greater compared with the general population (SIR 1.14 per Bernatsky et al 2013; refer to Section 2.1, Module SI, for more details). Serious malignancies can result in decreased quality of life, disability, or mortality.

Treatments that induce immune suppression may impair immune surveillance and thereby increase the risk for initiation or growth acceleration of malignancies. In cynomolgus monkey toxicology studies of up to 39-weeks dosing duration, there were no malignancies observed. No malignancy type was identified in more than one patient enrolled in the anifrolumab development programme to date, with the exception of non-melanoma skin cancers (7 patients) and breast cancer (3 patients), commonly observed in both the general and predominantly female SLE populations.
Malignancies have the potential to result in serious consequences such as disability, fatality, or a detrimental impact on a patient's quality of life, and therefore could impact the benefit-risk profile of anifrolumab.

Important potential risk: Serious infection

The incidence of serious infection was similar between the anifrolumab 300 mg and placebo groups in the supportive safety pool. Across the anifrolumab program, up to 19 March 2020, 4 pneumonia deaths were reported in anifrolumab-treated patients. Serious infections have the to result in serious consequences such as disability, fatality, or a detrimental impact on a patient's quality of life, and therefore could impact the benefit-risk profile of anifrolumab.

Missing information: Use in pregnant and breastfeeding women

Systemic lupus erythematosus affects more females than males, with the female:male ratio

of 8 to 15:1 (Pons-Estel et al 2017). Incidence is highest from 24 to 32 years of age (Pons-Estel et al 2017), while maximal prevalence of SLE is between 45 to 64 years of age for females (Rees et al 2017).

Since SLE affects a high percentage of women who are of child-bearing potential age, it is important to further evaluate the impact of anifrolumab in pregnant or breastfeeding women. For ethical reasons, this potentially vulnerable population was excluded in all anifrolumab clinical studies. In the anifrolumab development programme, females of child-bearing potential were counselled to use 2 effective methods of avoiding pregnancy during study participation. All patients were required to have a negative serum pregnancy test during screening to enroll and a negative urine pregnancy test prior to each administration of IP to continue in the study. However, some patients reported pregnancy. All pregnant patients were discontinued from IP.

Twenty-four (24) patients randomised to receive anifrolumab reported pregnancy during the study period. As patients were discontinued from IP once their pregnancy was known, there are no data of patients taking anifrolumab throughout the entirety of their pregnancy, and there are no data on the effect of anifrolumab on patients who are breastfeeding or their offspring.
As such, use of anifrolumab in pregnant women will be collected in the post-marketing setting through a non-interventional pregnancy study.

Missing information: Effects on responses to inactivated vaccines

The use of inactivated vaccines was not restricted in the study protocols; however, there is insufficient data on whether use of anifrolumab impacts the response to these vaccines. In the Phase II and III studies, vaccine data, such as receipt of the seasonal flu vaccine, were only collected as part of the routine collection of concomitant medications during the studies. It is unknown if the blockade of IFN receptors could have an effect on vaccination responses. As there is insufficient knowledge to determine whether the safety profile for this utilisation differs from that characterised so far, it is considered missing information. The effects on responses to inactivated vaccines are being collected and investigated through an externally-sponsored study.

2.7.2 New safety concerns and reclassification with a submission of an updated RMP

Not Applicable

2.7.3 Details of important identified risks, important potential risks and missing information

2.7.3.1 Presentation of important identified risks and important potential risks

Important Potential Risk: Malignancy

Potential mechanisms:

Type I IFNs may play a role in tumour surveillance. Neutralisation of IFN α/β with a polyclonal antibody in mice has been reported to enhance the growth of transplanted, syngeneic tumour cells that grow progressively in immune-competent hosts (Affabris et al 1987, Gresser et al 1974, Gresser et al 1983). In addition, an antitumor function for exogenously administered type I IFN has been described and used to treat a range of malignancies, including hairy cell leukaemia, melanoma, renal cell carcinoma, and Kaposi sarcoma (Belardelli et al 2002). While blocking type I IFN might be beneficial in controlling IFN-driven autoimmune diseases, the same pathway of suppression might increase the development of malignancies or neoplasms.

Evidence source(s) and strength of evidence:

There is a plausible mechanism of action for how anifrolumab may increase the risk of developing malignancy, although malignancy was not observed in non-clinical primate studies.

Characterisation of the risk:

Across the completed Phase II and III SLE controlled and uncontrolled IV studies of anifrolumab (studies 02, 04, 05, 09, 1013, and 1145), there were 17 malignancies reported in patients who received any dose of anifrolumab. Of those, only non-melanoma skin cancers (n = 7) and breast cancers (n = 3) were reported in more than one patient.

In the 52-week placebo-controlled SLE studies (studies 04, 05, and 1013) at any dose (150, 300, and 1000 mg), malignancies (excluding non-melanoma skin cancers) were observed in 0.67% (5/657) and 0.64% (3/466) of patients receiving anifrolumab and placebo, respectively. Among the 5 malignancies (excluding non-melanoma skin cancers) reported in anifrolumab-treated patients in studies 04, 05, and 1013, there were 2 malignancies reported within 180 days of the first exposure to anifrolumab, which were likely pre-existing. Malignant neoplasm (including non-melanoma skin cancers) was reported for 8/657 (1.2%) patients receiving anifrolumab, compared with 3/466 (0.6%) patients receiving placebo.

The Phase III long-term safety data evaluated in the completed Phase III long-term study, did not suggest any change in the rate of malignancies reported with long-term exposure to anifrolumab, with no temporal patterns observed by yearly intervals of malignancies during

treatment. Over up to 4 years of treatment in the Phase III long-term data, the EAIR of any malignancy (including non-melanoma skin cancers) was 0.7 per 100 patient-years in the anifrolumab 300 mg group and 0.7 per 100 patient-years in the placebo group.

Risk factors and risk groups

Patients with SLE are also at increased risk of certain malignancies compared with the general population. Patients with SLE are reported to have an increased risk of haematologic malignancies, particularly non-Hodgkin's lymphoma and leukaemia. In addition, increased risks of cancer of the vulva, lung, thyroid, and possibly liver were suggested (Bernatsky et al 2013). Patients < 40 years old with SLE have a higher relative cancer risk compared with sex and age-appropriate general population rates (Bernatsky et al 2013).

Persistence of viral infections with HPV may occur with increased frequency in patients with SLE. Female patients with SLE have an increased risk of developing abnormal cervical cytology and squamous intraepithelial lesions (and cervical intraepithelial neoplasia) (Nath et al 2007).

Preventability

The general risk of malignancy can be reduced by managing lifestyle factors such as smoking and alcohol use. There is currently no evidence of an increased risk of malignancy for anifrolumab specifically and, therefore, no specific requirements for prevention are recommended. Patients with SLE should be screened (breast and cervix) and vaccinated (ie, HPV) according to national guidelines.

Impact on the risk-benefit balance of the product:

Malignancies have the potential to result in serious consequences such as disability, fatality, or a detrimental impact on a patient's quality of life, and could therefore impact the benefit-risk profile of anifrolumab.

Public health impact

As the impact is to the treated population of patients with SLE only, there is no public health impact.

Important potential risk: Serious infections

Potential mechanisms:

Anifrolumab binds to IFNAR1 and blocks dimerization with IFNAR2; and reduces the number of available IFNAR1 by inducing receptor internalization (Riggs et al 2018). Type I IFNs, including IFN-α and IFN-β, constitute a potent innate defense system against viral infections. Type I IFN (IFN-α and IFN-β) is secreted by virus-infected cells while type II,

immune or IFN-gamma is mainly secreted by T cells, natural killer cells, and macrophages (Le Page et al 2000). Interferons interact with specific cellular receptors, which promote production of second messengers, ultimately leading to expression of antiviral and immune modulatory genes. Therefore, there is a theoretical risk of increased susceptibility to serious infections caused by viruses, bacteria, and fungi during treatment with anifrolumab.

Evidence source(s) and strength of evidence:

Due to the mechanism of action of anifrolumab, it is plausible that anifrolumab may increase the risk of developing certain serious infections. However, the incidence of serious infection was similar between treatment groups in the controlled Phase II and Phase III clinical studies.

Characterisation of the risk:

In clinical studies, a serious infection is any infection that fulfils the regulatory criteria for seriousness: death, life-threatening, in-patient hospitalisation or prolongation of hospitalisation, significant disability, congenital abnormality, or important medical event.

In the supportive safety pool in the 52-week clinical SLE studies, 4.8% (22/459; EAIR: 5.4/100 patient-years) and 5.6% (26/466; EAIR: 6.6/100 patient-years) of patients had any serious infection during treatment in the anifrolumab 300 mg group and the placebo group, respectively; the EAIR risk difference was -1.3 (95% CI: -4.7, 2.1). The most common serious infection by preferred term was pneumonia and similar proportions of patients experienced a serious pneumonia event in the anifrolumab 300 mg group (1.7%) and the placebo group (1.9%).

In the combined data from the 2 Phase III 52-week (studies 04 and 05) trials and the long-term extension study, 11.7% (42/358; EAIR: 4.3/100 patient-years) and 8.9% (32/360; EAIR: 5.8/100 patient-years) of patients had any serious infection through up to 4 years of treatment in the anifrolumab 300 mg group and the placebo group, respectively.

In the Phase III LTE data (studies 04, 05, and 09), there have been 4 reports of pneumonia with fatal outcomes [1]. All 4 patients received anifrolumab. All 4 patients also had concomitant

[1] For one patient in study 09, thrombocytopenia was listed as the primary event as of 31 December 2023, but the outcome of pneumonia has been updated to fatal in the database. Accordingly, this event is counted here as a fatal pneumonia event.

medication, such as corticosteroids, hydroxychloroquine, and methotrexate, which could contribute to the immunosuppression over time as well as subsequent infections.

The risk of serious infection has been evaluated in the anifrolumab SLE program, including in 3 randomised, placebo-controlled studies.

Risk factors and risk groups:

The risk factors for serious infection in patients treated with anifrolumab are unknown. Infection is a risk of prolonged immunosuppression and high-dose corticosteroid therapy in patients with SLE, even in the absence of other impairments of host defenses. Infection is one of the most common causes of morbidity and mortality among patients with SLE and may contribute to disease exacerbations (Navarra and Leynes 2010). The probability of developing a given infectious disease depends on the risk for exposure to potential pathogens, the virulence of the pathogen, and the level of immunosuppression of the patient.

Preventability:

In Section 4.4 of the SmPC, as a general precaution, it is recommended that prior to initiating therapy with anifrolumab, consideration should be given to completion of all appropriate immunisations according to current immunisation guidelines. Patients are informed in the Patient Information Leaflet to contact their healthcare provider as soon as possible in the event that they develop signs/symptoms of an infection.

Impact on the benefit-risk balance of the product:

Serious infections have the potential to result in serious consequences such as hospitalisation, fatality, or a detrimental impact on a patient's quality of life, and could therefore impact the benefit-risk profile of anifrolumab.

Public health impact

As the impact is to the treated population of patients with SLE only, there is no public health impact.

2.7.3.2 Presentation of missing information

Missing information: Use in pregnant and breastfeeding women

Evidence source:

Non-clinical findings suggest that reproductive risks and developmental toxicity risks associated with anifrolumab administration are low (Section 2.2.1). In the enhanced peri- and post-natal developmental toxicology study in cynomolgus monkeys with IV anifrolumab, there were embryo-fetal losses, but the values were within the testing facility's historical control range and did not attain statistical significance (Section 2.2.1). Therefore, it cannot be concluded that the apparent increases in abortion resulted from treatment with anifrolumab.

However, because there is no clinical data for patients taking anifrolumab throughout the entirety of their pregnancy, these risks cannot be excluded.

It is unknown whether anifrolumab or its metabolites are excreted in human or animal milk; therefore, risk to the breastfed child cannot be excluded. There is no clinical trial data on the effect of anifrolumab on patients who are breastfeeding.

Population in need of further characterisation:

Use of anifrolumab in pregnant women will be studied in a post-marketing pregnancy study.

Missing information: Effects on responses to inactivated vaccines

Evidence source

The use of inactivated vaccines was not restricted in the study protocols; however, there is insufficient data on whether use of anifrolumab effects the response to these vaccines. In the Phase II and III studies, vaccine data, such as receipt of the seasonal flu vaccine, were only collected as part of the routine collection of concomitant medications during the studies. It is unknown if the blockade of IFN receptors could have an effect on vaccination responses. As there is insufficient knowledge to determine whether the safety profile for this utilisation differs from that characterised so far, it is considered missing information.

Population in need of further characterisation:

Effects on responses to inactivated vaccines are being further characterised through an ongoing externally-sponsored study of patients who have received quadrivalent flu vaccination.

2.8 MODULE SVIII: SUMMARY OF THE SAFETY CONCERNS

2.8.1 Summary of the safety concerns

Table 2-6 Summary of safety concerns

Important potential risks	Malignancy Serious infection
Missing information	Use in pregnant and breastfeeding women
	Effects on responses to inactivated vaccines

3 PART III: PHARMACOVIGILANCE PLAN

3.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

Specific adverse reaction follow-up questionnaires for malignancy:

Follow-up questionnaires will be used to facilitate the post-marketing safety data collection for malignancy. The purpose is to collect additional information related to the management and outcome of these events, which will allow for more accurate assessment of the post-marketing safety profile of anifrolumab.

3.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Anifrolumab Pregnancy Study

Study short name and title:

D3461R00028 – Retrospective Pregnancy Study, A Non-Interventional Multi-Database Post Authorisation Study to Assess Pregnancy-Related Safety Data from Women with SLE Exposed to Anifrolumab

Rationale and study objectives:

Systemic lupus erythematosus affects a high proportion of women of child-bearing potential age. However, there is limited information on pregnancy and birth outcomes in women who are exposed to anifrolumab during pregnancy.

The study includes 2 stages, a feasibility assessment (conducted in parallel with protocol development) and a main study.

The objective of the feasibility assessment (Stage 1) was to conduct a full feasibility assessment of existing electronic data sources suitable for pregnancy studies.

The primary, secondary, and exploratory objectives of the main study (Stage 2) are:

Primary Objectives

- To describe and estimate the risk of MCM in live and non-live offspring from:
  - women with moderate/severe SLE, exposed to anifrolumab during the first trimester of pregnancy.
  - comparable population of women with moderate/severe SLE, exposed to SOC and unexposed to anifrolumab during the first trimester of pregnancy.
- To estimate the relative risk of MCM in live and non-live offspring from women with moderate/severe SLE exposed to anifrolumab during the first trimester of pregnancy compared to women with moderate/severe SLE exposed to SOC and

unexposed to anifrolumab during the first trimester of pregnancy.

- To describe and estimate the risk of select pregnancy loss outcomes (composite of spontaneous abortion and stillbirth) in pregnancies occurring in:
  - women with moderate/severe SLE exposed to anifrolumab anytime during pregnancy.
  - comparable population of women with moderate/severe SLE exposed to SOC and unexposed to anifrolumab anytime during pregnancy.
- To estimate the relative risk of select pregnancy loss outcomes (composite of spontaneous abortion and stillbirth) in pregnancies occurring in women with moderate/severe SLE exposed to anifrolumab anytime during pregnancy compared to women with moderate/severe SLE exposed to SOC and unexposed to anifrolumab anytime during pregnancy.

Secondary Objectives

- To describe demographic and clinical characteristics of:
  - live and non-live offspring (separately) and their mothers with moderate/severe SLE exposed to anifrolumab during the first trimester of pregnancy.
  - live and non-live offspring (separately) and their mothers with moderate/severe SLE exposed to SOC and unexposed to anifrolumab during the first trimester of pregnancy.
  - live and non-live offspring (separately) and their mothers with moderate/severe SLE exposed to anifrolumab anytime during pregnancy.
  - live and non-live offspring (separately) and their mothers with moderate/severe SLE exposed to SOC and unexposed to anifrolumab anytime during pregnancy.
- To describe and estimate the risk of mCM in live and non-live offspring from:
  - women with moderate/severe SLE exposed to anifrolumab anytime during pregnancy.
  - comparable population of women with moderate/severe SLE exposed to SOC and unexposed to anifrolumab anytime during pregnancy.
- To estimate the relative risk of mCM in live and non-live offspring from women with moderate/severe SLE exposed to anifrolumab anytime during pregnancy compared to women with moderate/severe SLE exposed to SOC and unexposed to anifrolumab anytime during pregnancy.
- To describe and estimate the risk of adverse pregnancy outcomes separately (ectopic pregnancy, spontaneous abortion, elective termination of pregnancy, stillbirth, infections requiring hospitalisation during pregnancy, emergency caesarean section) and as a composite of foetal loss (composite of spontaneous abortion, ectopic pregnancy, elective termination of pregnancy, and stillbirth) in pregnancies from:

  - women with moderate/severe SLE exposed to anifrolumab anytime during pregnancy.
  - comparable population of women with moderate/severe SLE exposed to SOC and unexposed to anifrolumab anytime during pregnancy.

- To estimate the relative risk of adverse pregnancy outcomes separately (ectopic pregnancy, spontaneous abortion, elective termination of pregnancy, stillbirth, infections requiring hospitalisation during pregnancy, emergency caesarean section) and as a composite of foetal loss (composite of spontaneous abortion, ectopic pregnancy, elective termination of pregnancy, and stillbirth) in pregnancies from women with moderate/severe SLE exposed to anifrolumab anytime during pregnancy compared to women with moderate/severe SLE exposed to SOC and unexposed to anifrolumab anytime during pregnancy.
- To describe and estimate the risk of adverse birth outcomes (preterm birth, SGA) in live offspring from:
  - women with moderate/severe SLE exposed to anifrolumab anytime during pregnancy.
  - comparable population of women with moderate/severe SLE exposed to SOC and unexposed to anifrolumab anytime during pregnancy.
- To estimate the relative risk of adverse birth outcomes (preterm birth, SGA) in live offspring from women with moderate/severe SLE exposed to anifrolumab anytime during pregnancy compared to women with moderate/severe SLE exposed to SOC and unexposed to anifrolumab anytime during pregnancy.

<u>Exploratory Objectives</u>

- To describe and estimate the risk of adverse outcome related to infant growth up to one year of age of live offspring from:
  - women with moderate/severe SLE exposed to anifrolumab anytime during pregnancy.
  - comparable population of women with moderate/severe SLE exposed to SOC and unexposed to anifrolumab anytime during pregnancy.
- To describe and estimate the risk of select pregnancy loss outcomes (composite of spontaneous abortion and stillbirth) in pregnancies occurring in:
  - women with moderate/severe SLE exposed to anifrolumab during specific pregnancy trimesters (trimester 1 only; trimester 1and 2 only; trimester 2 and 3 only; trimester 3 only; all trimesters 1, 2, and3).
  - comparable population of women with moderate/severe SLE exposed to SOC during specific pregnancy trimesters (trimester 1 only; trimester 1 and 2 only; trimester 2 and 3 only; trimester 3 only; all trimesters 1,2, and 3) and unexposed to anifrolumab anytime during pregnancy.

- To estimate the relative risk of select pregnancy loss outcomes (composite of spontaneous abortion and stillbirth) in pregnancies occurring in women with moderate/severe SLE exposed to anifrolumab during specific pregnancy trimesters (trimester 1 only; trimester 1 and 2 only; trimester 2 and 3 only; trimester 3 only; all trimesters 1,2, and 3) compared to women with moderate/severe SLE exposed to SOC in the same pregnancy trimesters and unexposed to anifrolumab anytime during pregnancy.
- To describe and estimate the risk of MCM by target body system organ class in live and non-live offspring from:
  - women with moderate/severe SLE exposed to anifrolumab during the first trimester of pregnancy.
  - comparable population of women with moderate/severe SLE exposed to SOC and unexposed to anifrolumab during the first trimester of pregnancy.

Study design:

This study will be an observational cohort study of anifrolumab-exposed and non-exposed pregnancies in patients with moderate/severe SLE. The study will utilise data extracts from multiple secondary data collected and maintained within established secondary observational data sources in the EU and US with mother-baby linkage. Pregnancy outcomes (including live births and non-live births) and infant outcomes (including congenital anomalies/birth defects) will be collected and followed up on for one year.

The study will include a feasibility assessment of suitable secondary observational data sources, including existing SLE disease registries as well as established electronic medical records and other secondary data sources. The study period will start with the first anifrolumab prescription in each data source and will end at the latest date for which data are needed to complete the analyses in the desired sample size. Throughout the study period, the number of anifrolumab-exposed pregnancies and live births will be monitored annually in all data sources to inform the study size, to update the predicted statistical precision, and to determine the study data set creation.

Data from the selected data sources will be analysed retrospectively according to a common protocol and statistical analysis plan during Stage 2.

Study population:

The study population will include pregnant women exposed to anifrolumab and a comparable group of pregnant women with moderate/severe SLE not exposed to anifrolumab.

Pregnancy outcomes (including live births and non-live births) and infant outcomes (including congenital anomalies/birth defects) will be collected and followed up on for one year.

Pregnancy will be identified using appropriate coding for pregnancy and antenatal and postnatal care, depending on the database. Where possible, the profiles of a sample of patients who were potentially pregnant will be reviewed to evaluate the performance of and refine the electronic algorithm used to identify pregnancy.

Women who were prescribed a known teratogenic drug during pregnancy will be excluded

Milestones

- **Completion of the feasibility study (Stage 1):** Q1 2023
- **Study protocol submission:** Q2 2023
- **Interim report 1:** Q4 2027
- **Interim report 2:** Q4 2030
- **Final report submission:** Q1 2032

Anifrolumab Serious Infection and Malignancy Study

Study short name and title:
D3461R00046 – Anifrolumab Serious Infections and Malignancies Study, A non-interventional multi-country post-authorisation safety study (PASS) to assess the incidence of serious infections & malignancies in systemic lupus erythematosus (SLE) patients exposed to anifrolumab.

Rationale and study objectives:

Anifrolumab is a mAb with a novel mechanism of action. In the absence of sufficient data from clinical studies to determine the risk of malignancy and serious infections among moderate/severe SLE patients, AstraZeneca will conduct a PASS to assess the risk of serious infections and malignancies in a population of patients receiving treatment with anifrolumab compared to a comparable population of SLE patients who receive standard therapy.
The study will include 2 study cohorts - one for the evaluation of malignancy outcomes and the other for the evaluation of serious infection outcomes.

Primary Objectives

The following primary objectives pertain to serious infection and malignancy outcomes:

- To compare hazard rates of new malignancies (as a composite outcome) in moderate/severe SLE patients initiating anifrolumab versus comparable moderate/severe SLE patients who do not initiate anifrolumab (exposed to SLE

SOC).

- To compare hazard rates of the first occurrence of a serious infection (as a composite outcome) in moderate/severe SLE patients initiating anifrolumab versus comparable moderate/severe SLE patients who do not initiate anifrolumab (exposed to SLE SOC).

Secondary Objectives

The following secondary objective pertain to the malignancy and serious infection outcome cohorts:

- To describe the demographic and clinical characteristics of patients in each study cohort (malignancy cohort and serious infection cohort) at index date, by exposure status (exposed to anifrolumab versus exposed to SLE SOC).

The following secondary objectives pertain to the malignancy outcomes:

- To compare hazard rates of new pre-specified malignancy sub-types (separately) in moderate/severe SLE patients initiating anifrolumab versus comparable moderate/severe SLE patients who do not initiate anifrolumab (exposed to SLE SOC).

The following secondary objectives pertain to the serious infection outcomes:

- To compare hazard rates of the first occurrence of opportunistic serious infections, other serious infections, pneumonia (overall), fatal and non-fatal pneumonia (separately) in moderate/severe SLE patients initiating anifrolumab versus comparable moderate/severe SLE patients who do not initiate anifrolumab (exposed to SLE SOC), where feasible (i.e., if sample size is sufficient).

Exploratory Objectives

The following objectives pertain to the serious infection outcomes:

- To compare the hazard rates of recurrent infections leading to hospitalisation in moderate/severe SLE patients initiating anifrolumab and in comparable moderate/severe SLE patients who do not initiate anifrolumab (exposed to SLE SOC), when feasible.

Study design:

This study will be a non-interventional, multi-country, long-term PASS based on secondary use of data from Denmark, France, Germany, and Spain, allowing the inclusion of a large number of patients and enhancing representativeness across Europe. This PASS will evaluate the risk of malignancies and serious infections in patients who receive anifrolumab in addition to SLE SOC compared to a similar population who are on SLE SOC alone, using a

prevalent-new-user design and propensity score approach. Multiple observational data sources in Europe will be analysed separately and, subsequently, a meta-analysis will be performed (where feasible).

The study includes a feasibility assessment of suitable secondary observational data sources, including existing SLE disease registries as well as established electronic medical records and other secondary data sources.

The study will start with the first anifrolumab prescription in each data source and will end on the last possible day of follow-up when all patients still in the study are censored.

Study population

The study population will include patients ≥ 18 years of age with a diagnosis of moderate/severe SLE who receive anifrolumab plus standard of care or standard of care in four European countries. The anifrolumab-treated cohort will be compared with a cohort of patients with SLE treated with standard of care (including biologics) using propensity score methods focusing on current and treatment history, disease severity, and other factors.

Milestones

- **Completion of feasibility study (Stage 1):** Q1 2023
- **Study protocol submission:** Q3 2022
- **Interim report 1 (serious infection and malignancy):** Q2 2027
- **Final report of study results (serious infection):** Q4 2028
- **Interim report 2 (malignancy):** Q2 2030
- **Final report of study results (malignancy)**: Q4 2032

3.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Table 3-1 Ongoing and planned additional pharmacovigilance activities

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 Non-Interventional Multi-Database Post Authorisation Study to Assess Pregnancy-Related Safety Data from Women with SLE Exposed to Anifrolumab Planned	The aim of this study is to describe the congenital malformations, adverse pregnancy and birth outcomes in pregnancies/offspring from women with moderate/severe SLE exposed to anifrolumab during pregnancy and to compare with outcomes in women with moderate/severe SLE who are exposed to other SOC but not anifrolumab. Adverse outcomes related to infant growth up to one year of age will also be investigated.	Use in pregnant women	Completion of the feasibility study	Q1 2023
			Study protocol submission	Q2 2023
			Interim report 1	Q4 2027
			Interim report 2	Q4 2030
			Final report submission	Q1 2032
D3461R00046 A non-interventional multi-country post-authorisation safety study (PASS) to assess the incidence of serious infections & malignancies in systemic lupus erythematosus (SLE) patients exposed to anifrolumab.	To compare hazard rates of new malignancies (as a composite outcome) in moderate/severe SLE patients initiating anifrolumab versus comparable moderate/severe SLE patients who do not initiate anifrolumab (exposed to SLE SOC). To compare hazard rates of the first occurrence of a serious infection (as a composite outcome) in moderate/severe SLE patients initiating anifrolumab versus comparable moderate/severe SLE patients who do not initiate anifrolumab (exposed to SLE SOC).	Serious infection and malignancies	Completion of feasibility study (Stage 1)	Q1 2023
			Study protocol submission	Q3 2022
			Interim report 1 (serious infections and malignancy)	Q2 2027

Table 3-1 Ongoing and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Planned	To describe the demographic and clinical characteristics of patients in each study cohort (malignancy cohort and serious infection cohort) at index date, by exposure status (exposed to anifrolumab vs. exposed to SLE SOC). To compare hazard rates of new pre-specified malignancy sub-types (separately) in moderate/severe SLE patients initiating anifrolumab versus comparable moderate/severe SLE patients who do not initiate anifrolumab (exposed to SLE SOC). To compare hazard rates of the first occurrence of opportunistic serious infections, other serious infections, pneumonia (overall), fatal and non-fatal pneumonia (separately) in moderate/severe SLE patients initiating anifrolumab versus comparable moderate/severe SLE patients who do not initiate anifrolumab (exposed to SLE SOC), where feasible (i.e., if sample size is sufficient). To compare the hazard rates of recurrent infections leading to hospitalisation in moderate/severe SLE patients initiating anifrolumab and in comparable moderate/severe SLE patients who do not initiate anifrolumab (exposed to SLE SOC), when feasible.		Final report of study results (serious infections)	Q4 2028
			Interim report 2 (malignancy)	Q2 2030
			Final report of study results (malignancies)	Q4 2032

Table 3-1 Ongoing and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
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	Q2 2024

EMA European Medicines Agency; Q1 Quarter 1; Q2 Quarter 2; Q3 Quarter 3; Q4 Quarter 4; SLE Systemic lupus erythematosus; SOC Standard of care

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4 PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

This section is not applicable since there are no post-authorisation efficacy studies planned

5 PART V: RISK MINIMISATION MEASURES

5.1 ROUTINE RISK MINIMISATION MEASURES

Table 5-1 Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important potential risks	
Malignancy	Routine risk communication: • SmPC Section 4.4 • Package leaflet Section 2 Other routine risk minimisation measures beyond the Product Information: • Legal status: Restricted medical prescription
Serious infection	Routine risk communication: • SmPC Section 4.4 • Package leaflet Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: • SmPC Section 4.4 Other routine risk minimisation measures beyond the Product Information: • Legal status: Restricted medical prescription
Missing information	
Use in pregnant and breastfeeding women	Routine risk communication: • SmPC Section 4.6, package leaflet Section 2
Effects on responses to inactivated vaccines	Routine risk communication: • SmPC Sections 4.4 and 4.5 • Package leaflet Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: • SmPC Section 4.4

SmPC Summary of Product Characteristics.

5.2 ADDITIONAL RISK MINIMISATION MEASURES

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

5.3 SUMMARY OF RISK MINIMISATION MEASURES

Table 5-2 Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

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

<< SLE Systemic lupus erythematosus; SmPC Summary of Product Characteristics.>>

6 PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN FOR ANIFROLUMAB

This is a summary of the RMP for anifrolumab. The RMP details important risks of anifrolumab, how these risks can be minimised, and how more information will be obtained about anifrolumab's risks and uncertainties (missing information).

Anifrolumab's SmPC and its package leaflet give essential information to healthcare professionals and patients on how anifrolumab should be used.

This summary of the RMP for anifrolumab should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR)>.

Important new concerns or changes to the current ones will be included in updates of anifrolumab's RMP.

6.1 THE MEDICINE AND WHAT IT IS USED FOR

The indication of anifrolumab is as an add-on therapy for the treatment of adult patients with moderate to severe, active, autoantibody-positive, systemic lupus erythematosus, despite standard therapy (see SmPC for full indication). It contains anifrolumab as the active substance and is administered as an IV infusion.

Further information about the evaluation of anifrolumab’s benefits can be found in anifrolumab’s EPAR, including in its plain-language summary, available on the EMA website, under the medicine’s webpage:

https://www.ema.europa.eu/en/medicines/human/EPAR/saphnelo

6.2 RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

Important risks of anifrolumab , together with measures to minimise such risks and the proposed studies for learning more about anifrolumab's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and <SmPC/PI> addressed to patients and healthcare professionals;
- Important advice on the medicine’s packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine’s legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

Information about adverse reactions is collected continuously and regularly analysed, including in the Periodic Safety Update Report, so that immediate action can be taken as

necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of anifrolumab is not yet available, it is listed under 'missing information' below.

6.2.1 List of important risks and missing information

Important risks of anifrolumab are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of anifrolumab. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

Table 6-1 List of important risks and missing information

Important potential risks	Malignancy Serious infection
Missing Information	Use in pregnant and breastfeeding women
	Effects on responses to inactivated vaccines

6.2.2 Summary of important risks

Table 6-2 Important potential risk: Malignancy

Evidence for linking the risk to the medicine	There is a plausible mechanism of action for how anifrolumab may increase the risk of developing malignancy
Risk factors and risk groups	Patients with SLE are reported to have an increased risk of haematologic malignancies, particularly non-Hodgkin's lymphoma and leukaemia. In addition, increased risks of cancer of the vulva, lung, thyroid, and possibly liver were suggested (Bernatsky et al 2013). Female patients with SLE also have an increased risk of developing abnormal cervical cytology and squamous intraepithelial lesions.
Risk minimisation measures	Routine risk minimisation measures • SmPC Section 4.4 • Package leaflet Section
Additional pharmacovigilance activities	Study D3461R00046 - A non-interventional multi-country post-authorisation safety study (PASS) to assess the incidence of serious infections & malignancies in systemic lupus erythematosus (SLE) patients exposed to anifrolumab.

. SLE Systemic lupus erythematosus; SmPC Summary of Product Characteristics

Table 6-3 Important potential risk: Serious infection

Evidence for linking the risk to the medicine	Due to the mechanism of action of anifrolumab, it is plausible that anifrolumab may increase the risk of developing certain serious infections. However, the incidence of serious infection was similar between treatment groups in the controlled Phase II and Phase III clinical studies.
Risk factors and risk groups	The risk factors for serious infection in patients treated with anifrolumab are unknown. Infection is a risk of prolonged immunosuppression and high-dose corticosteroid therapy in patients with SLE, even in the absence of other impairments of host defences. Infection is one of the most common causes of morbidity and mortality among patients with SLE and may contribute to disease exacerbations (Navarra and Leynes 2010). The probability of developing a given disease depends on the risk for exposure to potential pathogens, the virulence of the pathogen, and the level of immunosuppression of the patient.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.4 • Package leaflet Section 2

Table 6-3 Important potential risk: Serious infection

Evidence for linking the risk to the medicine	Due to the mechanism of action of anifrolumab, it is plausible that anifrolumab may increase the risk of developing certain serious infections. However, the incidence of serious infection was similar between treatment groups in the controlled Phase II and Phase III clinical studies.
Additional pharmacovigilance activities	Study D3461R00046 - A non-interventional multi-country post-authorisation safety study (PASS) to assess the incidence of serious infections & malignancies in systemic lupus erythematosus (SLE) patients exposed to anifrolumab.

SLE Systemic lupus erythematosus; SmPC Summary of Product Characteristics.

Table 6-4 Missing information: Use in pregnant and breastfeeding women

Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.6 • Package leaflet Section 2
Additional pharmacovigilance activities	D3461R00028 - A Non-Interventional Multi-Database Post Authorisation Study to Assess Pregnancy-Related Safety Data from Women with SLE Exposed to Anifrolumab

SLE Systemic lupus erythematosus; SmPC Summary of Product Characteristics.

Table 6-5 Missing information: Effects on responses to inactivated vaccines

Risk minimisation measures	Routine risk minimisation measures: • SmPC Sections 4.4 and 4.5 • Package leaflet Section 2
Additional pharmacovigilance activities	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.

SmPC Summary of Product Characteristics.

6.2.3 Post-authorisation development plan

6.2.3.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of anifrolumab.

6.2.3.2 Other studies in post-authorisation development plan

Anifrolumab pregnancy study (D3461R00028)

Study title: Retrospective Pregnancy Study, A Non-Interventional Multi-Database Post Authorisation Study to Assess Pregnancy-Related Safety Data from Women with SLE

Exposed to Anifrolumab.

Purpose of the study: Systemic lupus erythematosus affects a high proportion of women of child-bearing potential age. However, there is limited information on pregnancy and birth outcomes in women who are exposed to anifrolumab during pregnancy.

The aim of this study is to describe the congenital malformations, adverse pregnancy and birth outcomes in pregnancies/offspring from women with moderate/severe SLE exposed to anifrolumab during pregnancy and to compare with outcomes in women with moderate/severe SLE who are exposed to other SOC but not anifrolumab. Adverse outcomes related to infant growth up to one year of age will also be investigated.

Anifrolumab serious infections and malignancy study (D3461R00046)

Study title: A non-interventional multi-country post-authorisation safety study (PASS) to assess the incidence of serious infections & malignancies in systemic lupus erythematosus (SLE) patients exposed to anifrolumab.

Purpose of the study: In the absence of sufficient data from clinical studies to determine the risk of malignancy and serious infections among moderate/severe SLE patients exposed to anifrolumab, AstraZeneca will conduct a PASS to compare the risk of serious infections and malignancies, separately, in a population of patients receiving treatment with anifrolumab and a comparable population of SLE patients receiving standard therapy.

This is an observational study, in which the main research question is to evaluate the risk of malignancies and serious infections among moderate/severe SLE patients who receive anifrolumab compared with a comparable population of moderate/severe SLE patients on SOC who do not initiate anifrolumab. To address this research question, 2 study cohorts will be defined - one for the evaluation of malignancy outcomes and the other for the evaluation of serious infection outcomes.

The NAÏVE study (D3461C00023)

Study title: 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.

Purpose of the study: To better understand the impact of anifrolumab on vaccination responses, including measuring antibody concentrations; an external partner (Oklahoma Medical Research Foundation) is conducting a study.

The study has the following objectives:

- 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.

7 PART VII: ANNEXES

7.1 ANNEX 4: Specific adverse drug reaction follow-up forms

- *Malignancy Adverse Event Report Questionnaire*

7.2 ANNEX 6: Details of proposed additional risk minimisation activities

Not applicable

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