VI. 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.

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

VI.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

VI.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 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 (eg, 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.

VI.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 (eg, on the long-term use of the medicine).

Table 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

VI.2.2 Summary of important risks

Table 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 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. D3461C00009 - A multicentre, randomised, double-blind, placebo- controlled Phase III extension study to characterise the long-term safety and tolerability of anifrolumab in adult subjects with active systemic lupus erythematosus.

SLE Systemic lupus erythematosus; SmPC Summary of Product Characteristics.

Table 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 3 Important potential risk: Serious infection

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. D3461C00009 - A multicentre, randomised, double-blind, placebo- controlled Phase III extension study to characterise the long-term safety and tolerability of anifrolumab in adult subjects with active systemic lupus erythematosus.

SLE Systemic lupus erythematosus; SmPC Summary of Product Characteristics.

Table 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 multiple database study of the use (and safety) of anifrolumab in women with SLE during pregnancy

SLE Systemic lupus erythematosus; SmPC Summary of Product Characteristics.

Table 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.

VI.2.3 Post-authorisation development plan

VI.2.3.1 Studies that are conditions of the marketing authorisation

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

VI.2.3.2 Other studies in post-authorisation development plan

Anifrolumab pregnancy study (D3461R00028)

Study title: A multiple database study of the use (and safety) of anifrolumab in women with systemic lupus erythematosus during pregnancy.

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 objectives of the study are the following:

- To describe pregnancy outcomes (including live births and non-live births) and infant outcomes (including congenital anomalies/birth defects) in pregnancies among women with SLE exposed to anifrolumab anytime during pregnancy, including within 12 weeks of LMP.
- To compare outcomes in pregnancies exposed to anifrolumab among women with SLE with the outcomes in pregnancies not exposed to anifrolumab among women with SLE.
- To compare outcomes in pregnancies exposed to anifrolumab among women with SLE with the outcomes in pregnancies among women without SLE.

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.

The objectives of the study are the following:

- To compare hazard rates of new malignancies (as a composite outcome) in moderate/severe SLE patients initiating anifrolumab versus comparable moderate/severe SLE patients who do not initiate anifrolumab (exposed to SLE SOC).
- To compare hazard rates of the first occurrence of a serious infection (as a composite outcome) in moderate/severe SLE patients initiating anifrolumab versus comparable moderate/severe SLE patients who do not initiate anifrolumab (exposed to SLE SOC).
- To describe the demographic and clinical characteristics of patients in each study cohort (malignancy cohort and serious infection cohort) at index date, by exposure status (exposed to anifrolumab versus 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.

- 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.

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.

Anifrolumab Phase III long-term extension study (D3461C00009)

Study title: A multicentre, randomised, double-blind, placebo-controlled Phase III extension study to characterise the long-term safety and tolerability of anifrolumab in adult subjects with active systemic lupus erythematosus.

Purpose of the study: The primary objective of the study is to characterise the long-term safety and tolerability of IV anifrolumab. Outcome measures will include rates of malignancy and serious infections.