Unit: Technical Assessment Unit

Public assessment report for biological products

Saphnelo 120

Administrative information:

Trade name of the medicinal product:	Saphnelo 120
INN (or common name) of the active substance(s):	Anifrolumab
Manufacturer of the finished product	AstraZeneca AB, Gartunavagen SE-152 57 Sodertalje Sweden - SWEDEN ;
Marketing Authorization holder	AstraZeneca AB, SE-151 85, Sodertalje - SWEDEN;
Applied Indication(s):	Saphnelo is indicated as an add-on therapy for the treatment of adult patients with moderate to severe, active autoantibody-positive systemic lupus erythematosus (SLE), despite standard therapy.
Pharmaceutical form(s) and strength(s):	Solution for injection, 120 mg (150 mg/mL).
Route of administration	Subcutaneous (SC injection)
Type of registration (EMA/FDA – Local)	EMA

List of abbreviations

ADA	Anti-Drug Antibody
AI	Autoinjector
APFS	Accessorized Pre-filled Syringe
AUC	area under the concentration-time curve
BICLA	BILAG-Based Composite Lupus Assessment
CI	Confidence Interval
Cmax	maximal concentration
Fc	fragment crystallizable
GLP	Good Laboratory Practice
IFN	interferon
IFNAR1	type I interferon receptor (IFNAR1).
IgG1κ	human immunoglobulin G1 kappa

IV	Intravenous
mAb	monoclonal antibody
MRHD	Maximum Recommended Human Dose
NOAEL	no-observable adverse effect level
PD	Pharmacodynamics
PK	Pharmacokinetics
SC	subcutaneous
SLE	Systemic Lupus Erythematosus
TLR	Toll-like Receptor

Table of contents

1. General introduction about the product including brief description of the AI, its mode of action and indications……2
2. Quality aspects……...……..2
2.2 Drug Substance (Active ingredient) …… ……...……..... 2
2.3 Drug product……..….2
3. Non-clinical aspects…….……...…..3
4. Clinical aspect…….…….……....6
5. General Conclusion and Recommendations if any……...8

1. Introduction:

The file evaluated according to EDA Reliance Model & the company submitted data which are the following:

1. Quality module-3 from the CTD file.
2. EMA Unredacted Assessment.

2. Quality aspects:

Manufacturer (s):

• Drug Substance

- AstraZeneca Pharmaceuticals LP, Frederick Manufacturing Center (FMC), 633 Research Court, Frederick, Maryland, 21703 United States - UNITED STATES OF AMERICA ;

• Drug product

- AstraZeneca AB , Gartunavagen SE-152 57 Sodertalje Sweden - SWEDEN ;

Stability of

- **Drug substance**

Approved Storage Conditions	**Long term storage at -45°C to -35°C Short term storage: 2-8°C.**
Approved Shelf Life	**-60 months long term at -45°C to -35°C -12 months short term at 2-8°C**

- **Drug product**

Approved Storage Conditions	**-Store in a refrigerator (2 °C – 8 °C). -Store in the original package in order to protect from light. -Do not freeze, shake or expose to heat.**
Approved Shelf Life	**48 months.**

3. **Non –clinical aspect:**

Systemic lupus erythematosus (SLE) is a complex, chronic, and heterogeneous autoimmune disease that can affect any organ system which means patients with SLE present with a variety of clinical manifestations. These clinical manifestations can be devastating for patients with SLE and can lead to reduced physical function, loss of employment, a major impact on health-related quality of life, frequent hospitalizations, cumulative and irreversible organ damage, and early mortality. Organ damage accumulates from SLE disease activity itself and from treatment-related adverse effects associated with the chronic use of steroids and other immunosuppressive agents.

Anifrolumab is a human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody (mAb) directed against subunit 1 of the type I interferon receptor (IFNAR1) with high specificity and affinity. This binding inhibits type I IFN signaling and blocks the biologic activity of all type I IFNs, including IFN α, IFN β, and IFN ω. Anifrolumab also induces the internalization of IFNAR1, thereby reducing the levels of cell surface IFNAR1 available for receptor assembly. Blockade of receptor-mediated type I IFN signaling inhibits IFN responsive gene expression and downstream inflammatory and immunological processes and events. Anifrolumab was engineered to reduce binding to fragment crystallizable (Fc) gamma receptor to prevent Fc-mediated effector functions.

- **Pharmacology**:

Pharmacology studies showed that anifrolumab binds to the IFNAR1 subunit of the type I IFNα/β receptor with high affinity and blocks type I IFN mediated signaling. Anifrolumab competitively inhibits the binding of type I IFN to the receptor and blocks ligand mediated

dimerization of the IFNAR1/2 heterodimer and signal transduction. Anifrolumab also rapidly internalizes IFNAR1, reducing the levels of IFNAR1 on the surface available for receptor mediated signaling. Anifrolumab potently inhibits the signal transduction and interferon sensitive response element activity by all recombinant type I IFNs, type I IFNs produced by plasmacytoid dendritic cells, and type IFNs present in lupus patient's serum. Blockade of the type I IFN suppressed the activation, differentiation and inflammatory cytokine production of monocytes and dendritic cells, and the differentiation of B cells into plasma cells. It is therefore predicted that anifrolumab will diminish inflammation and suppress adaptive autoimmune responses that drive tissue pathology in SLE. Anifrolumab inhibited the induction of the type I IFN 21-gene signature by an average of 86% in the presence of endosomal Toll-like Receptor (TLR) agonist stimulation which indicated that suppression of the type I IFN gene signature will provide a valuable pharmacodynamic marker in vivo.

There were no anifrolumab-related adverse findings in any of the safety pharmacologic parameters assessed in any non-clinical studies. The cynomolgus monkey was selected as the pharmacologically relevant toxicology model for anifrolumab nonclinical safety assessment.

- **Pharmacokinetics**:

  Kinetics of anifrolumab were assessed in six nonclinical safety studies conducted in cynomolgus monkeys following single and repeated IV and SC administrations at dose levels up to 100 mg/kg. In general, for IV infusion and SC injection, C_{max} was dose proportional, while a more-than-dose-proportional increase in AUC was observed. The elimination half-life ($t_{1/2}$) of anifrolumab increased with dose. Following SC injection, absorption of anifrolumab from the dosing site was slow, with the peak serum concentration occurring approximately 2 days after administration. The slopes of the terminal phases for IV infusion and SC injection were similar. Distribution of anifrolumab from maternal plasma to neonates was consistent with placental transfer from maternal into fetal circulation. No significant gender difference was observed.

- **Toxicology**:

  At single doses up to 100 mg/kg, no adverse anifrolumab findings were evident; minimal receptor occupancy and target neutralization were evident at a dose of 0.3 mg/kg. In a cohort of 3 animals that received 5 mg/kg re-doses of anifrolumab 35 and 49 days after initial dose, one animal exhibited signs consistent with a hypersensitivity response that worsened with each re-dose and was relieved by administration of intravenous anti-histamine. This isolated case of hypersensitivity-like reaction was not observed in the subsequent one month and 9-month (39-week) repeat dose studies.

  In A GLP one month repeat IV infusion dose toxicity study in cynomolgus a NOAEL was 30 mg/kg. In a 9-month (39-week) repeat IV infusion or SC injection dose toxicity study and at the terminal necropsy at the end of the dosing phase, 2 males given 50 mg/kg IV had anifrolumab-related inflammation of arteries in multiple organs (arteritis). At the end of the recovery phase, 3 males had anifrolumab-related inflammation of arteries: one each given 5 mg/kg IV, 50 mg/kg

IV, and 60 mg/kg SC. While evident in more animals, the inflammatory changes in the recovery phase males were less pronounced and generally less widespread than in those of dosing phase males. 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 with no known vascular targets. In those cases, the findings were considered likely due to deposits of ADA/drug complexes. However, a possibility of other factors than production of antibodies to anifrolumab cannot be ruled out. The NOAEL for males is less than 5 mg/kg IV and 15 mg/kg SC if arteritis finding were considered. If the observed arteritis is not factored into the NOAEL determination, the NOAEL of anifrolumab for males is at least 50 mg/kg IV and 60 mg/kg SC, the highest doses tested.

Since non-SLE vasculitis has not been a clinical safety finding attributed to anifrolumab in the completed clinical studies to date, and since anifrolumab has not been nearly as immunogenic in humans as it has been in monkeys (based on immunogenicity rates and relative titers), the applicant proposes using the IV NOAEL from this study when the observed arteritis is not factored into consideration (50 mg/kg) for safety margin calculations in relation to the MRHD.

There were no anifrolumab-related adverse findings noted for maternal animals or offspring in an enhanced pre- and post-natal development study in cynomolgus monkeys with IV anifrolumab, resulting in a NOAEL of 60 mg/kg, the highest dose tested. Female and male fertility was indirectly assessed as components of the GLP 9-month (39-week) repeat dose study and there were no anifrolumab-related adverse effects noted for females. However, there were testicular findings noted for two anifrolumab-treated males, and associated data for the two males argues against these testicular findings being attributable to anifrolumab. This is consistent with available type I IFN literature that appears suggestive that over-expression (not neutralization) of type I IFN could impair spermatogenesis.

- **Overall conclusion**:

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

(Saphnelo 120mg)

Meanwhile, the Toxicokinetics data characterised the PK profile in cynomolgus monkeys.
The toxicological program is considered appropriate and sufficient to characterize the toxicity profile of anifrolumab. Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology or repeated dose toxicity studies in cynomolgus monkeys. Anifrolumab is a monoclonal antibody, as such genotoxicity and carcinogenicity studies have not been conducted. In rodent models of IFNAR1 blockade, increased carcinogenic potential has been observed. The clinical relevance of these findings is unknown. This risk is reflected in the SmPC and is followed by the routine risk management activities.
Animal studies show no adverse effects of anifrolumab on indirect measures of fertility. However, the risk to reproduction cannot be excluded based on the available nonclinical data. Given that it is unlikely that further animal studies would provide clinically meaningful data to inform about the risk in SLE patients, Saphnelo is not recommended during pregnancy and in women of childbearing potential not using contraception, unless the possible benefit justifies the potential risk.

4. Clinical aspect:

Clinical Overview

The clinical development program for the subcutaneous (SC) formulation of anifrolumab comprised two studies supporting the proposed presentation. A Phase I, randomized, open-label bridging study evaluated the pharmacokinetics (PK), safety, tolerability, and immunogenicity of anifrolumab administered via an autoinjector (AI) compared with an accessorized pre-filled syringe (APFS) in healthy volunteers. The pivotal Phase III TULIP SC study was a multicenter, randomized, double-blind, placebo-controlled trial evaluating the efficacy and safety of weekly SC anifrolumab in adult patients with moderate-to-severe, active, autoantibody-positive systemic lupus erythematosus (SLE) receiving standard therapy.
The clinical pharmacology data demonstrated comparable systemic exposure between the AI and APFS devices and supported transition between the approved intravenous (IV) regimen and the proposed SC regimen. Pharmacodynamic analyses showed rapid and sustained suppression of the type I interferon gene signature comparable to that previously observed with IV anifrolumab. Overall, the submitted clinical package supported the efficacy, safety, pharmacokinetic profile, and low immunogenicity of the SC formulation.

Clinical Efficacy

Clinical efficacy was primarily demonstrated in the pivotal Phase III TULIP SC study. The study met its primary endpoint, with a higher proportion of patients receiving SC anifrolumab achieving a BILAG-Based Composite Lupus Assessment (BICLA) response at Week 52 compared with placebo (59.4% vs. 43.9%), corresponding to a treatment difference of 15.5% (95% CI: 2.3, 28.6).
Secondary efficacy outcomes consistently favored anifrolumab, including improvement in disease activity, reduction in oral corticosteroid use, earlier achievement of sustained clinical response, and delayed disease flare. Following the completion of the study, formal multiplicity-

controlled statistical testing of the key secondary endpoints will be performed as part of the final analysis; the final analysis is now complete, and submission of the final Clinical Study Report will enable further regulatory confirmation. The interim results have shown efficacy trends generally consistent with the established efficacy profile of intravenous anifrolumab.

Clinical Immunogenicity

The overall immunogenicity of subcutaneous anifrolumab was low across the clinical development program. In the device bridging study, the incidence of anti-drug antibodies (ADAs) was low and comparable between administration devices. Although neutralizing antibodies were detected in a small number of healthy participants, no clinically meaningful differences were observed between the AI and APFS devices.

In the pivotal TULIP SC study, the incidence of treatment-emergent ADAs remained low, and no treatment-emergent neutralizing antibodies were detected among ADA-positive patients. Due to the limited number of ADA-positive subjects, the impact of immunogenicity on pharmacokinetics, efficacy, or safety could not be conclusively evaluated; however, no clinically meaningful effect was identified. Overall, the immunogenicity profile of the SC formulation was consistent with the established low immunogenicity profile of intravenous anifrolumab.

Clinical Safety

Subcutaneous anifrolumab administered once weekly for 52 weeks was generally well tolerated in patients with moderate-to-severe active SLE. The overall incidence of adverse events, serious adverse events, and adverse events leading to treatment discontinuation was low and broadly comparable to placebo.

The safety profile was consistent with the known safety profile of intravenous anifrolumab, with no new safety signals identified. The most frequently reported adverse events included upper respiratory tract infections, nasopharyngitis, bronchitis, COVID-19, and herpes zoster. An increased incidence of herpes zoster was observed with anifrolumab compared with placebo, consistent with previous clinical experience, with most events being localized, non-serious, and manageable with antiviral treatment.

Injection-site reactions occurred at similar frequencies in the anifrolumab and placebo groups, were predominantly mild or moderate, transient, and did not result in treatment discontinuation. Based on the available evidence, a causal relationship between SC anifrolumab and injection-site reactions could not be established. Rates of major adverse cardiovascular events, tuberculosis, hypersensitivity reactions, and serious infections remained low and were consistent with the established safety profile of intravenous anifrolumab.

Benefit–Risk Assessment

The submitted clinical evidence demonstrates that the SC formulation of anifrolumab provides clinically meaningful efficacy in adult patients with moderate-to-severe, active, autoantibody-positive SLE despite standard therapy. Pharmacokinetic and pharmacodynamic data support the proposed SC dosing regimen and demonstrate exposure and biological activity comparable to the approved IV formulation.

The safety and immunogenicity profiles were consistent with the established experience for intravenous anifrolumab, with no new clinically relevant safety concerns identified. The availability of a subcutaneous formulation provides an additional treatment option that may improve convenience and facilitate administration outside the infusion setting.

Although the pivotal efficacy evaluation is currently based on a pre-specified interim analysis and the final analysis is now complete, and submission of the final Clinical Study Report will enable further regulatory confirmation. The totality of evidence indicates a favorable benefit-risk balance for the proposed subcutaneous formulation.

Overall Conclusion

The submitted clinical data support the use of Saphnelo® (anifrolumab) 120 mg/0.8 mL solution for subcutaneous injection as an add-on therapy for adult patients with moderate-to-severe, active, autoantibody-positive systemic lupus erythematosus despite standard therapy.

The clinical development program demonstrated comparable pharmacokinetics between the proposed administration devices, sustained pharmacodynamic activity, clinically relevant efficacy, a safety profile consistent with the approved intravenous formulation, and low immunogenicity. Overall, the available evidence supports a positive benefit–risk profile for the subcutaneous formulation. Submission of the final Clinical Study Report following completion of the pivotal study will provide additional confirmation of the long-term efficacy and safety findings

5. General Conclusion and Recommendations if any:

Based on the review of CTD modules and other supplementary documents, the product is approved.

https://www.ema.europa.eu/en/documents/product-information/saphnelo-epar-product-information_en.pdf

(Saphnelo 120mg)