Taiwan Food and Drug Administration

Assessment Report

Trade Name：莎芙諾注射劑 150 毫克/毫升 / SAPHNELO 150 mg/mL Concentrate for Solution for Infusion

Active Ingredient：Anifrolumab

License Number：MOHW-BI-001231

Applicant：臺灣阿斯特捷利康股份有限公司

Approval Date：112/4/10

Indication：
與標準治療併用，適用於在標準治療下仍為中度至重度的自體免疫抗體陽性之全身性紅斑性狼瘡成年病人。
使用限制：
目前尚未有臨床試驗顯示本品用於嚴重狼瘡腎炎或嚴重中樞神經系統狼瘡之療效與安全性。

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

Limitations of Use:
The efficacy of SAPHNELO has not been evaluated in patients with severe active lupus nephritis or severe active central nervous system lupus.

Background Information

Trade Name	莎芙諾注射劑 150 毫克/毫升 / SAPHNELO 150 mg/mL Concentrate for Solution for Infusion
Active Ingredient(s)	Anifrolumab
Applicant	臺灣阿斯特捷利康股份有限公司
Dosage Form & Strengths	注射液劑 300 mg concentrate for solution for injection, one vial of 2.0 mL concentrate contains 300 mg of anifrolumab (150 mg/mL)
Indication	與標準治療併用，適用於在標準治療下仍為中度至重度的自體免疫抗體陽性之全身性紅斑性狼瘡成年病人。 使用限制： 目前尚未有臨床試驗顯示本品用於嚴重狼瘡腎炎或嚴重中樞神經系統狼瘡之療效與安全性。 Saphnelo is indicated as an add-on therapy for the treatment of adult patients with moderate to severe, active autoantibody-positive systemic lupus erythematosus, despite standard therapy. Limitations of Use: The efficacy of SAPHNELO has not been evaluated in patients with severe active lupus nephritis or severe active central nervous system lupus.
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Pharmacological Category **ATC Code**	L04AA51

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug Substance (DS)

The general information and the chemical structure, the manufacturing process, control of materials, in-process controls, characterization, specifications, container closure system, and stability data of the anifrolumab are provided.

General information

Anifrolumab is a human IgG1κ mAb directed against subunit 1 of the type I interferon receptor (IFNAR). It is composed of 2 identical light chains and 2 identical heavy chains, with an overall molecular weight of approximately 148 kDa. Anifrolumab binds to subunit 1 of the IFNAR1 with high specificity and affinity. This binding inhibits type I interferon (IFN) signaling by blocking the biologic activity of type I IFNs.

Manufacture

Anifrolumab DS is manufactured under current good manufacturing practice. The manufacturing process is described including the material inputs, critical process parameters, and process outputs (in-process controls, microbial controls, and performance attributes) and supported process robustness, as demonstrated during process validation. The raw materials used during the production of anifrolumab are either of compendial quality or are tested according to in-house specifications to ensure their quality. Cholesterol is the only animal-derived raw material. However, the Certificate of Analysis (CoA), Certificate of Origin and Transmissible spongiform encephalopathies Certificate of Suitability demonstrate cholesterol has low safety issues. There are three DS process variants in the manufacturing process history. To evaluate comparability of manufacturing process change, comparability studies were performed such as lot release tests, process-related impurity, characterization tests, and stability. The comparability results demonstrated the process changes doesn't impact DS quality.

Characterization

Characterization tests are physicochemical and biological properties of the product, including primary structure, higher order structure, carbohydrate structure, charge and size heterogeneity, and biological properties. Process-related impurities and product-related impurities were within the specification for release and stability tests.

Control of DS

The specification of DS was provided and the acceptance criteria is well-justified. All batch results were within acceptable criteria to demonstrate DS quality consistency. In addition, CoAs showed that analytical results meet specification requirements.

Stability

The proposed self-life is 60 months at -45°C to -35°C (long-term storage condition) and 12 months at 2-8 °C (short-term storage condition). The long-term stability test is on-going. Three commercial process performance qualifications were conducted in stability test. The results showed the DS was stable at -45°C to -35°C for 48 months and at 2-8 °C for 12 months.

2.1.2 Drug Product (DP)

Description of DP

The DP is a sterile, preservative-free, liquid dosage form intended for intravenous infusion after dilution. The container closure system of anifrolumab consists of 2R type I glass vials which is closed with an elastomeric stopper, sealed with an aluminum. It is supplied as a single-dose vial in one presentation: 300 mg of anifrolumab per vial. Each vial contains 150 mg/mL anifrolumab in 25 mM L-histidine/L-histidine hydrochloride monohydrate, L-lysine hydrochloride, α,α-trehalose dihydrate, polysorbate 80, pH 5.9.

Pharmaceutical Development

There are no significant changes during manufacturing process development. There are at least three batches of each process used in comparability studies. Comparability studies contain lot release test, characterization test, stability test. All results were within acceptance criteria. The compatibility and safety of the container closure system were demonstrated by stability study, extractable and leachable study. The manufacturers and batch formula of DP are shown. The process controls and parameters are presented in manufacturing process description. The process validation results of three batches met the acceptance criteria to support process consistent quality.

Control of DP

The specification of DP was provided and the acceptance criteria is well-justified. Release results and CoA were within acceptance criteria.

Stability

The results of accelerated stability and long-term stability data were provided and supported 36 months of shelf-life for DP stored at 2-8°C, protected from light.

The quality results include the manufacturing process, control of materials, in-process controls, characterization, specifications, container closure system, and stability. These results adequately support that the manufacturing of DP is well-controlled and quality consistency.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

Anifrolumab is a human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody (mAb) directed against subunit 1 of the type I interferon receptor (IFNAR1). Anifrolumab blocks type I IFN-induced cell signaling by competitively inhibiting type I IFN binding to IFNAR1. Pharmacology studies showed that anifrolumab binds to subunit 1 of the IFNAR1 with high

specificity and affinity. This binding inhibits type I IFN signaling and blocks the biological activity of all type I IFNs, including IFN α, IFN β, and IFN ω.

By using a surrogate anti-murine IFNAR Ab,5A3, it has been shown that blockade of the type I IFNAR1 suppressed the induction of type I IFN-induced genes and reduced the onset and severity of kidney damage in an accelerated NZB/W F1 murine model of lupus nephritis. Besides, 5A3 administration inhibited cutaneous inflammation, vascular injury, and dermal fibrosis in a Graft-vs-host-induced systemic sclerosis (GVH-SSc) model. There were no anifrolumab-related adverse findings in safety pharmacologic parameters assessed in non-clinical studies.

2.2.2 Toxicological Studies

The cynomolgus monkey was selected as the pharmacologically relevant toxicology model for anifrolumab nonclinical safety assessment. In a GLP 9-month (39-week) repeat IV infusion or SC injection dose toxicity study of cynomolgus monkeys, only arteritis finding was found in male animals, which may be a consequence of species-specific immunogenicity, and its relevance to human safety is unknown. By the most conservative approach (based on exposure at MRHD in IFN gene signature test low subjects), safety margins are approximately 58 for AUC and 33 for $C_{max.}$

The absence of genotoxicity studies is acceptable since aducanumab is an antibody not expected to interact directly with DNA or chromosomal material. There was also no anifrolumab-related increase in tumors in the toxicology studies with monkeys. However, the potential hazard can be addressed in product labeling and risk management practices without performing additional in vivo studies in animal (ICH S6 (R1). In an enhanced pre- and post-natal development study, following IV administration of anifrolumab, no adverse effects on maternal animals or their offspring were observed up to the highest weekly dose tested (60 mg/kg weekly), and no teratogenicity potential was noted.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

SAPHNELO contains anifrolumab and is indicated for the treatment of adult patients with moderate to severe systemic lupus erythematosus (SLE). Anifrolumab is a monoclonal antibody (mAb) that inhibits subunit 1 of the type I interferon receptor (IFNAR1). The recommended dose of SAPHNELO is 300 mg, administered as an intravenous infusion over a 30 minutes period, every 4 weeks.

During the dose range of 100 mg to 1000 mg, anifrolumab exhibits non-linear PK (more than

dose-proportional). Steady-state was reached by Day 85 following the 300 mg every 4 weeks IV infusion. Based on population PK analysis, the estimated Vd,ss for a typical patient with SLE weighing 69.1 kg is 6.23 L. Also, the estimated systemic clearance (CL) for anifrolumab was 0.193 L/day (IIV=33.0%), and it decreases slowly over time. Since anifrolumab is an IgG1κ monoclonal antibody, it predominantly eliminated via catabolism and were not expected to undergo hepatic metabolism. The incidence of ADA (ie. treatment-emergent) was 1.7% (6/359), 4 patients were persistently positive ADA. Overall, no notable difference in anifrolumab concentrations between patients who were ADA positive (at any time) and those who were ADA negative.

2.3.2 Interaction Studies

No formal drug-drug interaction studies were conducted.

2.3.3 Special Populations

Based on the population PK analysis, age (18~69 years of age), gender, body weight or IFN status did not have significant impact on the PK of anifrolumab. No dose adjustment was required based on these intrinsic factors. No dedicated renal or hepatic dysfunction study were conducted since anifrolumab is not expected to clear via renal route and undergo hepatic metabolism.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

Three randomized, double-blind, and placebo-controlled clinical studies in patients with moderate to severe SLE (measured by: SLEDAI-2K ≥ 6, plus at least 1A or 2B BILAG-2004, plus PGA ≥ 1) were reviewed to evaluate the efficacy of anifrolumab: a phase II study (study 1013) and two phase III studies (study 05 and study 04). The primary endpoint of study 1013 was SRI(4) response with oral corticosteroid (OCS) tapering at Week 24. As for the phase III studies, the primary endpoint was SRI(4) response at Week 52 for Study 05 and BICLA response at Week 52 for Study 04.

In Study 1013 (phase II), two-sided significance level of 0.10 was used. In mITT population, the proportion of subjects who had an SRI (4) response with OCS tapering at Week 24 was 34.3% (odds ratio [OR] 2.38, 90% confidence interval [CI]: 1.33 to 4.26; p=0.014) for the 300 mg anifrolumab group and 28.8% (OR 1.94, 90% CI: 1.08 to 3.49; p=0.063) for the 1000 mg anifrolumab group compared to the placebo group (17.6%). Anifrolumab 300 mg was selected for further evaluation in the phase III studies.

The primary objective in Study 05 (phase III) was not met as there was no statistically

significant difference in overall disease activity, as measured by SRI(4) response rate, between the anifrolumab 300 mg and placebo groups at Week 52 (difference -4.2%, 95% CI: -14.2 to 5.8; adjusted p-value =0.412). When the overall disease activity was measured by another composite endpoint, BICLA, numerically greater rates of improvements were observed for anifrolumab 300 mg compared with placebo (difference 10.1%, 95% CI: 0.6 to 19.7 in the original prespecified analysis).

Study 04 (phase III) met its primary endpoint plus a number of key secondary endpoints. Patients treated with anifrolumab 300 mg had a statistically significant difference in BICLA response rates at Week 52, compared with patients in the placebo group (47.8% vs 31.5%; difference 16.3%, 95% CI: 6.3 to 26.3; p=0.0013). For type I IFN gene signature test high patients, the BICLA response rates at Week 52 were consistent with those in the overall population (difference 17.3%, 95% CI: 6.5 to 28.2; p=0.0022). For the subgroup of patients with OCS ≥10 mg/day at baseline, a higher proportion of patients in the anifrolumab 300 mg group able to taper their OCS dose to ≤7.5 mg/day at Week 40 and maintain this lower dose through Week 52 compared with the placebo group (difference 21.2%, 95% CI: 6.8 to 35.7; adjusted p-value =0.0135). For patients with baseline CLASI activity score ≥10, more patients were able to achieve a ≥50% reduction from baseline in CLASI activity score at Week 12 in the anifrolumab 300 mg group compared with the placebo group (difference 24.0%; 95% CI: 4.3 to 43.6; p=0.0392).

Study 04, an adequate and well controlled phase III trial, demonstrated favorable and statistically significant changes on the clinically meaningful primary endpoint (BICLA response rate) and secondary endpoints when comparing anifrolumab versus placebo. While study 05, the first phase III trial, failed on its primary endpoint (SRI -4 response rate), the study showed a numerically higher proportion of BICLA responders at Week 52 in the anifrolumab 300 mg group compared with the placebo group. In all three studies (04, 05 and 1013), additional supportive evidence was noted in the analyses of the secondary endpoints, including a greater proportion of subjects on anifrolumab than placebo able to reduce oral corticosteroid use and a lower proportion of subjects on anifrolumab experiencing a flare of SLE disease activity, further supporting the effectiveness of anifrolumab. When these trials are considered in combination, the totality of evidence is supportive of beneficial treatment effects of anifrolumab.

2.4.2 Safety Results

As of 01 August 2019, at least 837 SLE patients exposed to IV anifrolumab (150, 300, or 1000 mg), of which at least 766 patients were exposed for ≥ 24 weeks, 688 patients for ≥ 52 weeks, and 108 patients for ≥ 208 weeks (~ 4 years). Of these 459 were exposed to the proposed dose of 300 mg for at least 52 weeks.

In two phase III study pool, 360 SLE patients exposed to IV anifrolumab 300mg and 365 SLE patients exposed to placebo, of which 326 patients (90.6%) were treated with anifrolumab for ≥ 24 weeks and 299 patients (83.1%) were treated with anifrolumab for ≥ 48 weeks. Fewer patients in the anifrolumab 300 mg group had any SAE during treatment than patients in the placebo group (11.1% vs 16.4%). The incidence of AEs leading to discontinuation were balanced between the treatment groups (4.7% in anifrolumab 300mg group vs. 4.9% in placebo group). More patients in the anifrolumab 300 mg group than the placebo group had an AE in the SOC of Infections and infestations (71.7% vs 57.8%). Patients in the anifrolumab 300 mg group had an increased incidence of herpes zoster compared with patients in the placebo group (6.4% vs 1.4%). Higher incidence of bronchitis AEs were reported in the anifrolumab 300 mg group than placebo group (10.6% vs. 4.4%). There were 6 patients with latent tuberculosis AEs during the study: 4 patients (1.1%) in the anifrolumab 300 mg group and 2 patients (0.5%) in the placebo group. The incidence of hypersensitivity and infusion related reaction were also higher in anifrolumab 300 mg group compared with placebo: hypersensitivity (3.3 % vs. 0.8%), infusion related reaction (11.4% vs. 7.4%).

Anti-anifrolumab antibodies were detected in 6 of 352 (1.7%) patients who received anifrolumab at the recommended dosing regimen during the 60-week study period. The clinical relevance of the presence of antianifrolumab-fnia antibodies is not known.

2.5 Bridging Study Evaluation

Based on the cross-study comparison, the observed C_{trough} in Asian population were higher than those in non-Asian population, this may be due to lower body weight in Asian population. In population PK analysis, Asia-pacific region patients with type 1 IFN test-high have similar CL to Europe patients, but lower CL than North America patients. After adjusted CL with body weight, the body weight-adjusted CL in Asian patients was within that in other race patients. Overall, the ethnic difference between East Asian and non-East Asian population was negligible according to the PK characteristic and performance of anifrolumab.

In Phase III study pool (Study 04, 05), excluding Anifrolumab 150 mg group from study 05, the East Asian subpopulation included 66 subjects from sites in Taiwan, Japan and Korea. The East Asian subpopulation were around 9.1% of 726 overall population.

Efficacy:

In East Asian subpopulation, the difference between the treatment groups in BICLA response rate in favor of anifrolumab is consistent with that observed in the overall population.

Safety
The safety profile of anifrolumab in the East Asian subpopulation were generally similar to those in the overall population, except higher incidence of herpes zoster in East Asian subpopulation [11.1% (4/36) vs. 5.9% (19/324)]. No additional safety signal was identified in the East Asian population.

In summary, the submitted PK, clinical efficacy and safety data can support the proposed dosage of Anifrolumab for the claimed indication for Taiwanese patients. No further bridging study was needed.

2.6 Conclusion
Based on review of the submitted package, the review team considered anifrolumab demonstrated a favorable risk-benefit profile with adequate evidence to support regular approval for the following indication:
Saphnelo is indicated as an add-on therapy for the treatment of adult patients with moderate to severe, active autoantibody-positive systemic lupus erythematosus, despite standard therapy.

Limitations of Use:
The efficacy of SAPHNELO has not been evaluated in patients with severe active lupus nephritis or severe active central nervous system lupus.

3. Post-Marketing Requirements
(1). RMP is required.