CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761123Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	BLA
Application Number	761123
PDUFA Goal Date	July 31, 2021
OSE RCM #	2020-1633
Reviewer Name(s)	Brian Caruth, Pharm.D., BCPS
	Theresa Ng, Pharm.D., BCPS, CDE
Team Leader	Laura Zendel, Pharm.D., BCPS
Division Director	Cynthia LaCivita, Pharm.D.
Review Completion Date	July 21, 2021
Subject	Evaluation of Need for a REMS
Established Name	Anifrolumab-fnia
Trade Name	Saphnelo
Name of Applicant	AstraZeneca Pharmaceuticals LP (AstraZeneca)
Therapeutic Class	Type I interferon (IFN) receptor antagonist
Formulation(s)	Solution for Injection
Dosing Regimen	Anifrolumab-fnia 300 mg intravenous (IV) infusion over 30 minutes every 4 weeks

Table of Contents

EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Saphnelo (anifrolumab-fnia) is necessary to ensure the benefits outweigh its risks. AstraZeneca Pharmaceuticals LP (Applicant) submitted a Biologic Licensing Application (BLA) 761123 for anifrolumab-fnia with the proposed indication for the treatment of adult patients with moderate to severe systemic lupus erythematosus (SLE) who are receiving standard therapy. Anifrolumab-fnia is associated with an increased risk for potentially fatal infections and hypersensitivity and infusion related reactions. The Applicant did not submit a proposed REMS or risk management plan with this application.

The Division of Risk Management (DRM) has determined that a REMS is not needed to ensure the benefits of anifrolumab-fnia outweigh its risks. The increased risk for potentially fatal infections and hypersensitivity and infusion related reactions are similar to another approved targeted immunosuppressive therapy for SLE. Anifrolumab-fnia is likely to be prescribed by rheumatologists familiar with SLE and administered in an outpatient infusion setting. Prescribers and outpatient infusion settings are expected to screen patients for signs and symptoms of infection and treat hypersensitivity and infusion related reactions accordingly. The safety profile of anifrolumab-fnia, consistent with predicted risks, will be communicated in the Warnings and Precautions section in labeling.

1 Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Saphnelo (anifrolumab-fnia) is necessary to ensure the benefits outweigh its risks. AstraZeneca Pharmaceuticals LP (Applicant) submitted a Biologic Licensing Application (BLA) 761123 for anifrolumab-fnia with the proposed indication for the treatment of adult patients with moderate to severe SLE who are receiving standard therapy. This application is under review in the Division of Rheumatology and Transplant Medicine (DRTM). The Applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

Anifrolumab-fnia, a new molecular entity,[a] is a first-in-class type I interferon (IFN) receptor antagonist proposed for the treatment of adult patients with moderate to severe SLE who are receiving standard therapy. Blockade of receptor mediated type I IFN signaling inhibits interferon responsive gene expression and downstream inflammatory and immunological processes. Inhibition of type I IFN blocks plasma cell differentiation and normalized peripheral T-cell subsets, restoring the balance between adaptive and innate immunity that is dysregulated in multiple autoimmune disorders.[1]

Anifrolumab-fnia is proposed to be available as an injection for intravenous infusion in a 300 mg/2 mL single dose vial. The product is diluted in 100 mL of 0.9% sodium chloride and intravenously infused over

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

30 minutes every 4 weeks. Duration of treatment with anifrolumab-fnia is expected to be long term and administered in an outpatient infusion setting.[b] Anifrolumab-fnia is not currently approved in any jurisdiction.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for BLA 761123 relevant to this review:

- 08/22/2014: IND 101849 submitted with Breakthrough Therapy request
- 10/17/2014: FDA denied Breakthrough Therapy citing a lack of clinical evidence demonstrating substantial improvement over existing therapy
- 07/23/2015: IND 101849 submitted with Fast Track designation request
- 08/13/2015: FDA granted Fast Track designation
- 07/31/2020: BLA 761123 received for anifrolumab-fnia
- 01/29/2021: Mid-Cycle Communication meeting held and FDA informed the Applicant that no safety issues that may require a REMS for anifrolumab-fnia have been identified

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Systemic lupus erythematosus (SLE) is an autoimmune disease that affects many organ systems, is more prevalent in females, and has no known etiology. The systems commonly involved include muscle and joints, brain and peripheral nervous system, lungs, heart, kidneys, skin, serous membranes, and components of the blood. The pathogenetic factors causing lupus remain enigmatic, and while predominantly immunological, are influenced and modified by multiple systems such as the endocrine or clotting systems.[2] Clinical presentation ranges from mild joint and skin involvement to life-threatening renal, hematologic, or central nervous system involvement. The prevalence ranges from 20 to 150 cases per 100,000 in the United States and appears to be increasing as the disease is recognized more readily and survival increases.[c] In the United States, people of African, Hispanic, or Asian ancestry, as compared with those of other racial or ethnic groups, tend to have an increased prevalence of SLE and greater involvement of vital organs. The 10-year survival rate is about 70%.[3]

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

Non pharmacologic interventions for management of SLE include lifestyle modifications (balanced diet, exercise, smoking cessation) and avoidance of direct sunlight and ultraviolet light sources. Table 1 lists current FDA-approved treatments for SLE.

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

[c] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

Table 1: FDA-Approved Treatment Options for SLE

Product Trade Name (Generic)	Year of Approval	Indication	Dosing and Administration	Important Safety and Tolerability Issues
(aspirin)	1948	Treatment of arthritis and pleurisy of SLE	3 grams daily in divided doses	Gastrointestinal Bleeding, Tinnitus
Deltasone (prednisone)	1955	During an exacerbation or as maintenance therapy in selected cases of SLE	5 – 60 mg daily	Glucose Intolerance, Osteoporosis, Glaucoma, Increased Infection Risk
Plaquenil (hydroxychloroquine)	1955	Treatment of discoid and SLE	200 – 400 mg daily or in two divided doses	Retinal and Cornea Deposits
Benlysta (belimumab IV)	2011	Treatment of active, autoantibody positive systemic SLE despite standard of care	10 mg/kg every 2 weeks for 3 doses, then 10 mg/kg every 4 weeks	Increased Infection Risk, Progressive Multifocal Leukoencephelopathy

No safety issues warranting a REMS have been identified for current FDA-approved treatments for SLE. Three oral agents are FDA-approved treatments for SLE. Effectiveness varies depending on organ system disease involvement and is limited by toxicities. Hydroxychloroquine is the most frequently used therapy for relief of constitutional symptoms, musculoskeletal manifestations, and mucocutaneous manifestations. Low dose prednisone is used for the treatment of mild SLE symptoms while high dose regimens may be used for moderate to severe SLE flares. Only one injectable agent, belimumab, is FDA-approved for SLE at this time. The approval of belimumab contains a limitation of use to avoid in combination with other biologics as efficacy has not been evaluated and is not recommended in patients with severe active central nervous system lupus.

Immunosuppressive agents are used off-label as treatments for SLE due to the unpredictable disease course, resistance to established treatments, and desire to minimize long-term adverse effects of glucocorticoid therapy. Common therapeutic options include azathioprine, cyclophosphamide, mycophenolate, and rituximab. Nonspecific immunosuppression, insufficient disease control, and a lack of targeted therapies to further improve treatment of SLE represent an unmet medical need.

4 Benefit Assessment

The efficacy and safety of anifrolumab-fnia were evaluated in two phase 3 studies (Study 04 [NCT02446899] and Study 05 [NCT02446912]) and one phase 2 study (Study 1013 [NCT01438489]). The three studies represented a total of 1129 randomized patients, of whom 658 were randomized to treatment with anifrolumab-fnia, from approximately 200 sites in 30 countries. All patients were ≥ 18 years of age and had moderate to severe disease, despite receiving standard SLE therapy consisting of either one or any combination of oral corticosteroids (OCS), antimalarials, or immunosuppressants at baseline. Patients with severe lupus nephritis and severe CNS disease were excluded from the studies. All three studies were similar in design: 52-week, multicenter, multinational, randomized, double-blind, parallel-group, and placebo-controlled. The three studies evaluated a 300 mg dose administered intravenously every 4 weeks for 52 weeks (13 doses) and had the same predefined primary efficacy

endpoint: evaluation of disease activity using the Systemic Lupus Erythematosus Responder Index of ≥ 4 (SRI[4]) disease activity index (DAI). The primary endpoint switched from SRI(4) to the British Isles Lupus Assessment Group-2004-based Combined Lupus Assessment (BICLA) DAI prior to unblinding in Study 04. In addition, Study 05 and Study 1013 evaluated 150 mg and 1000 mg doses, respectively. Table 2 summarizes the studies contributing to the primary efficacy data of anifrolumab-fnia.

Table 2: Summary of Studies Contributing to the Primary Efficacy Data of Anifrolumab-fnia

Study	Study Design	Dose Evaluated	Patients	Primary Endpoint	Nominal p-value
Phase 3 Studies					
Study 04	Randomized (1:1), double-blind, placebo-controlled	300 mg or placebo	Total: n = 365 181 (300 mg) 184 (placebo)	BICLA at week 52	0.0013
Study 05	Randomized (1:2:2), double-blind, placebo-controlled	150 mg, 300 mg, or placebo	Total: n = 457 93 (150 mg) 180 (300 mg) 184 (placebo)	SRI(4) at week 52 (original)	0.412
				SRI(4) week 52 (post-hoc)	0.455
Phase 2 Study					
Study 1013	Randomized (1:1:1), double-blind, placebo-controlled	300 mg, 1000 mg, or placebo	Total: n = 307 100 (300 mg) 104 (1000 mg) 103 (placebo)	SRI(4) + OCS tapering at week 24	0.014
				SRI(4) + OCS tapering in IFN test-high patients at week 24	0.004

Similar proportions of patients completed anifrolumab-fnia across the three studies: Study 04 (78.2%), Study 05 (80.1%), and Study 1013 (80.1%). Baseline demographics, disease characteristics, and SLE-related treatments in the three studies were generally representative of the target patient population of patients with moderate to severe SLE, despite standard therapy. The Applicant provided BICLA and SRI(4) response rates using original restricted medication rules for Study 05 and revised (post-hoc) restricted medication rules for Study 05 and amended for Study 04 after the pre-BLA Type B Meeting, due to the different study results observed in studies 04 and 05. Table 3 summarizes the BICLA and SRI(4) response rates using different restricted medication rules.

Table 3: BICLA and SRI(4) Response Rates Using Different Restricted Medication Rules

Study	Restricted Medication Study Rules	Anifrolumab-fnia 300 mg n/N (Response Rate)	Placebo n/N (Response Rate)	Difference (95% CI)
BICLA at Week 52				
Study 04	Study 04	86/180 (48%)	57/182 (32%)	16% (6 – 26)
Study 04	Study 05	70/180 (39%)	48/182 (27%)	12% (3 – 22)
Study 05	Study 05	67/180 (37%)	49/184 (27%)	10% (1 – 20)
Study 05	Study 04	85/180 (47%)	55/184 (30%)	17% (7 – 27)
SRI(4) at Week 52				
Study 04	Study 04	100/180 (56%)	68/182 (37%)	18% (8 – 28)
Study 04	Study 05	83/180 (46%)	62/182 (34%)	12% (3 – 22)
Study 05	Study 05	65/180 (36%)	74/184 (40%)	-4% (-14 – 6)
Study 05	Study 04	88/180 (49%)	79/184 (43%)	6% (-4 – 16)

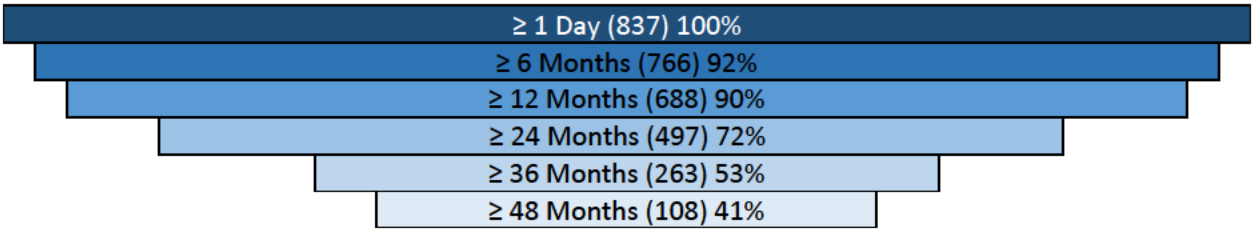
Source: Adapted from Applicant's original submission July 31, 2020; Figure 0000.175.10, Appendix 2.7.3.6.8 in Module 5.3.5.3

With acknowledgment of the failed primary endpoint of SRI(4) in Study 05, as well as the change in primary endpoint and amended restricted medication rules in Study 04, the clinical reviewer concluded that substantial evidence of effectiveness supported the benefit of anifrolumab-fnia. This determination relied on the statistically significant and clinically meaningful results of Study 04, consistency with Study 1013, and improved clinical outcome over placebo in post-hoc analysis for BICLA in Study 05. The Medical Policy and Program Review Council (MPPRC) reviewed discrepant efficacy data from the three studies and determined the evidence for effectiveness was persuasive for anifrolumab-fnia.[4]

5 Risk Assessment & Safe-Use Conditions

The primary safety analysis of anifrolumab-fnia 300 mg IV every 4 weeks for 52 weeks, referred to as the supportive safety pool, relies on pooled data from all three pivotal studies (Study 1013, Study 04, and Study 05). The supportive safety pool represents 459 patients with SLE who received at least one 300 mg dose of anifrolumab-fnia. The safety profile assessment of anifrolumab-fnia is adequate given the estimated disease prevalence and total duration of exposure in patients with SLE.[5] The overall extent of exposure represented by the target number of patients receiving ≥ 6 months and ≥ 12 months of anifrolumab-fnia is sufficient to support a safety conclusion according to recommendations from the International Conference on Harmonization (ICH). The data pool for cumulative duration of exposure over time represents 837 patients with SLE who received at least one dose ≥ 150 mg of anifrolumab-fnia and is summarized in Figure 1.

Figure 1: Cumulative Duration of Exposure to Anifrolumab-fnia Over Time (Number of Patients)



Source: Adapted from Applicant's original submission July 31, 2020; Table 3.1.2, Appendix 2.7.4.7.1 in Module 5.3.5.3

The four most common adverse events (≥ 5% difference or at least 5% incidence in the anifrolumab-fnia group and twice the frequency as the placebo group) include nasopharyngitis, upper respiratory tract infection, bronchitis, and herpes zoster. Common and select adverse events related to the mechanism of action and therapeutic drug class of anifrolumab-fnia, and an SLE patient cohort are listed in Table 4.

Table 4: Summary of Adverse Events During Treatment – Supportive Safety Pool

Adverse Event (AE) Category	Anifrolumab-fnia 300 mg (N = 459)	Placebo (N = 466)
	n (%) patients	
Any AE with Outcome of Death	2 (0.4)	0
Anaphylaxis	0	0
Hypersensitivity Reactions	13 (2.8)	3 (0.6)
Infusion Related Reactions	43 (9.4)	33 (7.1)
Bronchitis	49 (10.7)	24 (5.2)
Nasopharyngitis	75 (16.3)	44 (9.4)
Herpes Zoster	28 (6.1)	6 (1.3)
Influenza	12 (2.6)	9 (1.9)
Latent Tuberculosis	4 (0.9)	1 (0.2)
Pneumonia	15 (3.3)	16 (3.4)
Upper Respiratory Tract Infection	158 (34.4)	108 (23.2)
Depression	14 (3.1)	9 (1.9)
Malignancy	6 (1.3)	3 (0.6)

Source: Adapted from Applicant's original submission July 31, 2020; Table 3.2.1.1.1, 3.2.2.2.1, and 178.4.1, Appendix 2.7.4.7.1 in Module 5.3.5.3

5.1 Serious Infections

Serious infections are a predicted risk of immunosuppression therapy.[d] Two on-treatment deaths due to pneumonia occurred in the anifrolumab-fnia group (0.4% [2/459]) compared to zero deaths in the placebo group (0/466) within the supportive safety pool. One death related to anifrolumab-fnia therapy occurred in Study 04 in a 53 year-old woman 26 days after her eighth dose of anifrolumab-fnia. The other death, unrelated to anifrolumab-fnia therapy, occurred in Study 05 in a 65 year-old woman 36 days after her second dose of anifrolumab-fnia.

Herpes zoster occurred more frequently in the anifrolumab-fnia group (6.1% [28/459]) compared to placebo (1.3% [6/466]). Moderate or severe cases occurred in 19 patients in the anifrolumab-fnia group and 2 patients discontinued therapy due to herpes zoster. None of the herpes zoster adverse events in the placebo group were serious or led to discontinuation of therapy. The Applicant proposed precautionary language in the Warnings and Precautions section of the label for an increased infection risk of herpes zoster. The clinical reviewer proposed elevating the labeled risk of infection to include serious and sometimes fatal infections.

5.2 Hypersensitivity and Infusion Related Reactions

Hypersensitivity reactions occurred more frequently in the anifrolumab-fnia group (2.8% [13/459]) compared to placebo (0.6% [3/466]). Events were mild or moderate in intensity and no serious hypersensitivity reactions were reported. Infusion related reactions occurred more frequently in the anifrolumab-fnia group (9.4% [43/459]) compared to placebo (7.1% [33/466]) and were also mild or moderate in intensity with no serious infusion related reactions reported. No cases of anaphylaxis were reported in the supportive safety pool.

[d] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

The Applicant proposed inclusion of hypersensitivity reactions in the Warnings and Precautions section of the label to address this safety concern.

The clinical reviewer concluded the safety profile of anifrolumab-fnia is consistent with predicted risks of targeted immunosuppressive therapy and the overall benefit-risk profile appears acceptable.

6 Expected Postmarket Use

Anifrolumab-fnia is likely to be prescribed by rheumatologists familiar with SLE and administered in an outpatient infusion setting. The likely prescribers and outpatient infusion settings are expected to be familiar with predicted risks of targeted immunosuppressive therapy and be able to screen patients for signs and symptoms of infection and treat hypersensitivity and infusion related reactions accordingly.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for anifrolumab-fnia beyond routine pharmacovigilance and labeling.

8 Discussion of Need for a REMS

The clinical reviewer recommends approval of anifrolumab-fnia citing the efficacy and safety data from the three pivotal studies (Study 1013, Study 04, and Study 05), the seriousness of SLE, and an adequately favorable benefit-risk profile.

The following statutory factors were considering in determining if a REMS was necessary for the benefits of anifrolumab-fnia to outweigh its risks: the estimated size of the population likely to use the drug, the seriousness of the disease or condition that is to be treated, the expected benefit of the drug, expected or actual duration of treatment, the seriousness of any known or potential adverse events that may be related to anifrolumab-fnia and the background incidence of such events in the population likely to use the drug and if the drug is a new molecular entity.

Systemic lupus erythematosus is an autoimmune disease that affects many organ systems, is more prevalent in females, and has no known etiology. The systems commonly involved include muscle and joints, brain and peripheral nervous system, lungs, heart, kidneys, skin, serous membranes, and components of the blood. Clinical presentation ranges from mild joint and skin involvement to life-threatening renal, hematologic, or central nervous system involvement. The prevalence ranges from 20 to 150 cases per 100,000 in the United States and 10-year survival rate is about 70%.

Two phase 3 studies (Study 04 and Study 05) and one phase 2 study (Study 1013) evaluated efficacy of anifrolumab-fnia in adults with active SLE. Studies 1013 and 04 evaluated patients with moderate to severe disease while receiving standard SLE therapy and achieved a statistically significant and clinically meaningful result in SRI-4 and BICLA primary endpoints, respectively, in the anifrolumab-fnia group compared to placebo. Study 05 demonstrated improved clinical outcome over placebo in post-hoc analysis for BICLA.

The serious risks associated with anifrolumab-fnia include an increased risk for serious and sometimes fatal infections and hypersensitivity and infusion related reactions. The proposed prescribing information, at this time, includes precautionary language in the Warnings and Precautions section of

the label for these risks. Upper respiratory tract infections, bronchitis, and herpes zoster infections, consistent with predicted risks of targeted immunosuppressive therapy, will be described as adverse reactions in the label.

Anifrolumab-fnia is an NME; however, the safety concerns associated with anifrolumab-fnia use are similar to other FDA approved IV targeted immunosuppressive therapy for SLE, which are not approved with a REMS. In general, healthcare providers who treat SLE should be familiar with monitoring and treating infections and hypersensitivity and infusion related reactions associated with immunosuppressive therapies. Therefore, this reviewer is not recommending a REMS for the management of the risks of anifrolumab-fnia therapy.

9 Conclusion & Recommendations

Relying on the data available, a REMS is not necessary to ensure the benefits of anifrolumab-fnia outweigh the risks for serious and sometimes fatal infections and hypersensitivity and infusion related reactions. The safety concerns associated with anifrolumab-fnia use are similar to other FDA approved IV targeted immunosuppressive therapy for SLE and they are not approved with a REMS. Healthcare providers who treat SLE should be familiar with monitoring and treating infections and hypersensitivity and infusion related reactions. The risks of serious infections and hypersensitivity reactions will be communicated in labeling in Warnings and Precautions. At the time of this review, labeling is still under negotiation and the clinical review is ongoing. Should DRTM have any concerns or questions or if new safety information becomes available, please send a consult to DRM.

10 Appendices

10.1 References

1 Riggs et al 2018 Riggs JM, Hanna RN, Rajan B, Zerrouki K, Karnell JL, Sagar D et al. Characterisation of anifrolumab, a fully human anti-interferon receptor antagonist antibody for the treatment of systemic lupus erythematosus. Lupus Sci Med 2018;5(1):e000261.

2 Duarte C, Couto M, Ines L, Liang MH. Epidemiology of systemic lupus erythematosus. In: Lahita RG, Tsokos G, Buyon J, Koike T, eds. Systemic lupus erythematosus. 5th ed. London: Elsevier, 2011:525-39.

3 Tsokos GC. Systemic lupus erythematosus. N Engl J Med. 2011;365:2110-2121.

4 FDA Medical Policy and Program Review Council Meeting. January, 22, 2021. BLA 761123 Anifrolumab-fnia. Available at https://fda.sharepoint.com/:b:/r/sites/CDER-Boards-MPC/Medical%20Policy%20Council%20Topic/Clinical%20Evidence%20of%20Effectiveness%20or%20Safety/January%2022,%202021%20-%20Anifrolumab%20for%20Systemic%20Lupus/012221%20anifrolumab%20for%20SLE_Final%20Minutes.pdf?csf=1&web=1&e=JvWM6s

5 Pons-Estel GJ, Ugarte-Gil MF, Alarcón GS. Epidemiology of systemic lupus erythematosus. Expert Rev Clin Immunol 2017;13(8):799-814.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

BRIAN J CARUTH
07/21/2021 11:32:56 AM

LAURA A ZENDEL
07/21/2021 01:11:21 PM

CYNTHIA L LACIVITA
07/21/2021 05:33:45 PM