

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761123Orig1s000

OTHER REVIEW(S)

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	July 29, 2021
Requesting Office or Division:	Division of Rheumatology and Transplant Medicine (DRTM)
Application Type and Number:	BLA 761123
Product Name and Strength:	Saphnelo (anifrolumab-fnia) Injection, 300 mg/2 mL (150 mg/mL)
Applicant/Sponsor Name:	AstraZeneca Pharmaceuticals LP
OSE RCM #:	2020-1632-2
DMEPA 1 Safety Evaluator:	Teresa McMillan, PharmD
DMEPA 1 Team Leader:	Idalia Rychlik, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised carton labeling received on July 27, 2021 for Saphnelo. The Division of Rheumatology and Transplant Medicine (DRTM) requested that we review the revised carton labeling for Saphnelo (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are AstraZeneca's update to the carton technical layout, which changes where the printing of the serialization/variable data will be placed. The change was made only to the panel of the carton.

2 CONCLUSION

We find the carton labeling revisions acceptable and have no additional recommendations at this time.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON JULY 27, 2021

Carton labeling



(b) (4)

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/

TERESA S MCMILLAN
07/29/2021 01:24:33 PM

IDALIA E RYCHLIK
07/29/2021 01:37:13 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatrics and Maternal Health
Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatric and Maternal Health Memorandum

Date: July 28, 2021

From: Christos Mastroyannis, M.D., Medical Officer, Maternal Health, Division of Pediatrics and Maternal Health (DPMH)

Through: Tamara Johnson, MD, MS, Team Leader, Maternal Health, DPMH
Lynne Yao, MD, Director, DPMH

To: Division of Rheumatology and Transplant Medicine (DRTM)

Drug: Saphnelo (anifrolumab-fnia) for intravenous injection

Drug Class: First in class, type I interferon (IFN) receptor- (b) (4)

BLA: 761123

Applicant: AstraZeneca

Subject: DPMH response to applicant's response to the Lactation PMR

Indication: Treatment of adult patients with moderate to severe systemic lupus erythematosus (SLE) (b) (4)

Materials Reviewed:

- Response to query PMRs 22 Jul 2021, submitted July 26, 2021

Purpose

On July 26, 2021, in response to the July 22, 2021, FDA Communication, AstraZeneca submitted a response to the Agency stating a rationale for lack of agreement related to the postmarketing requirement (PMR) clinical lactation study. DRTM requested DPMH to provide input on the applicant's response. This memorandum documents the Agency rationale regarding the necessity to collect additional data on the use of therapeutic monoclonal antibodies during lactation.

Agency response to applicant's response to the PMR clinical lactation study

We acknowledge your response to the July 22, 2021, FDA Communication and, in particular, the rationale for lack of agreement related to the postmarketing requirement (PMR) clinical lactation study. However, the Agency continues to recommend a PMR for a clinical lactation study to assess concentrations of anifrolumab in human milk.

We understand that the scientific literature describes the current knowledge regarding therapeutic monoclonal antibody (mAB) presence in human breastmilk, however, we disagree that the information supports a generalized assumption that exposure to therapeutic mAB through breastmilk will be minimal. Based on recent Agency review, of the 105 mAB approved between 1960 and 2020, only 15 had clinical data reporting concentrations in breast milk. The literature reports inconsistency of the amount of mAB present in breastmilk; some with minimal amounts, while others demonstrate higher amounts and accumulation over time.^{1,2} Further studies are needed to understand and confirm the safety of mABs in breast milk.

In addition, it is understood that infants absorb antibodies from breast milk, particularly in the first 6 weeks of life, for the development of passive immunity.^{3,4,5} IgG antibody transfer across the GI into blood circulation is facilitated by the neonatal Fc receptor (FcRn).⁶ Furthermore, published studies have reported antibody survivability past the stomach where 10-15% of orally administered IgGs were recovered as intact IgGs in infant's stools.⁷ Thus, it is reasonable that even in small amounts, these biologics may potentially cause adverse reactions in breastfed infants (i.e., diarrhea, skin rash).⁸

There are limited data on the levels of therapeutic mABs in breast milk and their safety during breast feeding. In this regard, the Agency has added a statement to labeling for therapeutic mABs to state that, "[t]he effects of local gastrointestinal exposure and limited systemic exposure to drugname on the breastfed infant are unknown." While the labeling does not specifically advise against breastfeeding, there are insufficient data to evaluate whether anifrolumab is transferred into breastmilk. This information is important to prescribers and their patients and must be confirmed with collection of clinical lactation data.

Based on the lack of available data and the anticipated use of anifrolumab in females of reproductive potential, including lactating women, the Agency is requiring a post-marketing clinical lactation study (milk only) to assess concentration of anifrolumab in human milk. If there is evidence that the drug is transferred into breastmilk additional studies may also be required to further evaluate infant exposure through breast milk.

¹ Ross E, Robinson SE, Amato C, McMillan C, Westcott J, Wolf T, Robinson WA. Therapeutic monoclonal antibodies in human breast milk: a case study. *Melanoma Res.* 2014 Apr;24(2):177-80

² Baker TE, Cooper SD, Kessler L, Hale TW. Transfer of natalizumab into breast milk in a mother with multiple sclerosis. *J Hum Lact.* 2015 May;31(2):233-6

³ Brandtzaeg P. The mucosal immune system and its integration with the mammary glands. *J Pediatr* 2010; 156:S8-S15.

⁴ Hurley WL, Theil PK. Perspectives on immunoglobulins in colostrum and milk. *Nutrients* 2011; 3:442-474.

⁵ Kirkwood JM, Tarhini AA, Panelli MC, Moschos SJ, Zarour HM, Butterfield LH, et al. Next generation of immunotherapy for melanoma. *J Clin Oncol* 2008; 26:3445-3455

⁶ Lawrence, SA et al. Influence of FcRn binding properties on the gastrointestinal absorption and exposure profile of Fc molecules. *Bioorganic & medicinal chemistry* vol. 32 (2021): 115942. doi:10.1016/j.bmc.2020.115942

⁷ Jasion, VS, Burnett BP. Survival and digestibility of orally-administered immunoglobulin preparations containing IgG through the gastrointestinal tract in humans. *Nutr J.* 2015 Mar 7;14:22

⁸ Brennan FR, Morton LD, Spindeldreher S, Kiessling A, Allenspach R, Hey A, et al. Safety and immunotoxicity assessment of immunomodulatory monoclonal antibodies. *MAbs* 2010; 2:233-255

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/

CHRISTOS MASTROYANNIS
07/28/2021 11:59:11 AM

TAMARA N JOHNSON
07/28/2021 12:38:48 PM

LYNNE P YAO
07/28/2021 02:45:01 PM



Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)
Epidemiology: ARIA Sufficiency Memo

Date: 07/21/2021

Reviewer: Yan Li, PhD, B.Pharm
Division of Epidemiology II

Associate Director: Efe Eworuke, PhD, MSc., B.Pharm
Division of Epidemiology II

Deputy Director: Monique Falconer, MD, MS
Division of Epidemiology II

Subject: ARIA Sufficiency Memo

Drug Name: Anifrolumab-fnia (Saphnelo)

Application Type/Number: BLA 761123

Applicant/sponsor: AstraZeneca



Expedited ARIA Sufficiency Template for Pregnancy Safety Concerns

1. BACKGROUND INFORMATION

1.1. Medical Product

BLA 761123 is being reviewed for the new molecular entity anifrolumab-fnia (Saphnelo), a monoclonal antibody (mAb) that inhibits subunit 1 of the type I interferon receptor (IFNAR1), for the proposed indication of treating moderate to severe systemic lupus erythematosus (SLE) in adults who are receiving standard therapy. Type I IFNs play an important role in the pathogenesis of SLE. Approximately 60-80% of adult patients with SLE express elevated levels of type I IFN inducible genes, which are associated with increased disease activity and severity. Anifrolumab can bind to subunit 1 of the IFNAR1 with high specificity and affinity. This binding inhibits IFN responsive gene expression as well as downstream inflammatory and immunological processes. It also blocks plasma cell differentiation and normalizes peripheral T-cell subsets, resulting in decreased disease activity.

1.2. Describe the Safety Concern

SLE is a chronic, multisystem, disabling autoimmune rheumatic disease of unknown etiology, affecting 0.2 to 1.5 million individuals in the United States.¹ The age of disease onset is usually between 15 and 40 years. With a female to male ratio of 8-15 to 1, SLE predominately affects women, especially women of child-bearing age.² Pregnant women with SLE generally have poorer pregnancy outcomes compared to women without the disease. In a meta-analysis that included 2751 pregnancies from 1842 SLE patients in 37 studies, the most frequent maternal complications included lupus flare (25.6%), hypertension (16.3%), nephritis (16.1%), and pre-eclampsia (7.6%). The most common adverse fetal outcomes were spontaneous abortion (16.0%), intrauterine growth restriction (12.7%), induced abortions (5.9%), stillbirth (3.6%) and neonatal deaths (2.5%). Among the live birth deliveries, prematurity occurred in 39.4% of infants.³

In non-clinical animal studies, anifrolumab was given to pregnant cynomolgus monkeys intravenously at doses of 30 or 60 mg/kg every 2 weeks from gestation day 20 to lactation day 28. While anifrolumab is transferable through the placenta, no drug-related adverse effects in maternal animals or infants were noted. The incidence rates of embryo-fetal loss, and the number of stillbirths and live infants in drug-treated groups were comparable to the control group, the testing facility's historical incidence data, and/or literature. No drug-related adverse effects on body growth, behavior, functional, morphological and skeletal development, or T-cell dependent antibody response of the infants were noted.

In the Saphnelo clinical development program, women of childbearing potential were counseled to use two effective methods of birth control during study participation, and had to have a negative serum pregnancy test during screening and a negative urine pregnancy test during the study prior to receiving any study therapy. Despite the mandatory contraception requirement, there were 31 patients with one or more pregnancies in the clinical development program as of August 1, 2019. Of those 31 patients, 20 patients were randomized to receive

¹ Izmirly et al. *Arthritis Rheumatol.* 2021; 73(6): 991-996.

² Murphy et al. *Rheumatology (Oxford).* 2013; 52(12): 2108-2115.

³ Smyth et al. *Clin J Am Soc Nephrol.* 2010; 5(11): 2060-2068.



anifrolumab. Among patients who received anifrolumab and reported a pregnancy, investigational products-associated congenital anomalies and drug-associated adverse events were not observed. These data on pregnancy exposure are insufficient to inform on drug-associated risk.

Although no safety signal has been identified in non-clinical and clinical studies of anifrolumab so far, given the experience with the clinical development program, it is very likely that exposure to anifrolumab during pregnancy will occur post-approval. As a result, there is a need for long term data collection and analysis to monitor and characterize the risk of embryo-fetal toxicity of anifrolumab in real world settings. Such knowledge will inform regulatory actions to ensure the safe use of anifrolumab and prevent maternal and fetal harm.

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

- Please ensure that the selected purpose is consistent with the other PMR documents in DARRTS

Purpose (place an "X" in the appropriate boxes; more than one may be chosen)

Assess a known serious risk	
Assess signals of serious risk	
Identify unexpected serious risk when available data indicate potential for serious risk	X

2. REVIEW QUESTIONS

2.1. Why is pregnancy safety a safety concern for this product? Check all that apply.

- ☐ Specific FDA-approved indication in pregnant women exists and exposure is expected
- ☐ No approved indication, but practitioners may use product off-label in pregnant women
- ☒ No approved indication, but there is the potential for inadvertent exposure before a pregnancy is recognized
- ☒ No approved indication, but use in women of child-bearing age is a general concern

2.2. Regulatory Goal

- ☒ *Signal detection* – Nonspecific safety concern with no prerequisite level of statistical precision and certainty
- ☐ *Signal refinement of specific outcome(s)* – Important safety concern needing moderate level of statistical precision and certainty. [†]
- ☐ *Signal evaluation of specific outcome(s)* – Important safety concern needing highest level of statistical precision and certainty (e.g., chart review). [†]

[†] If checked, please complete **Error! Reference source not found..**

2.3. What type of analysis or study design is being considered or requested along with ARIA? Check all that apply.

- ☒ Pregnancy registry with internal comparison group
- ☐ Pregnancy registry with external comparison group
- ☐ Enhanced pharmacovigilance (i.e., passive surveillance enhanced by with additional actions)

- ☐ Electronic database study with chart review
- ☐ Electronic database study without chart review
- ☒ Other, please specify: Complementary database study

2.4. Which are the major areas where ARIA is not sufficient, and what would be needed to make ARIA sufficient?

- ☐ Study Population
- ☐ Exposures
- ☒ Outcomes
- ☐ Covariates
- ☒ Analytical Tools

For any checked boxes above, please describe briefly:

Outcomes

ARIA lacks access to detailed narratives. Given that the registry study for broad-based surveillance being considered is descriptive and without sample size requirements, having detailed narratives are deemed necessary to identify and validate outcomes, assess exposure-outcome temporality, and to conduct causality assessments. Only a subset of pregnancy and birth outcomes have validated algorithms the ARIA system.

Analytical tools

The requested PMR targets more than one outcome, including major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, small for gestational age, preterm birth, and others. ARIA might address the complexity presented by multiple discrete outcomes by means of an appropriate data mining approach. However, a suitable data mining approach (e.g., TreeScan) is not yet available for signal detection of birth defects and other pregnancy outcomes in ARIA.

2.5. Please include the proposed PMR language in the approval letter.

Conduct a prospective, registry based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to Saphnelo (anifrolumab-fnia) during pregnancy to an unexposed control population. The registry will detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, small for gestational age, preterm birth, and any other adverse pregnancy outcomes. These outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life. This pregnancy registry study may be conducted as part of a multiple-product or disease-based pregnancy registry.

Conduct an additional pregnancy study that uses a different design from the Pregnancy Registry (for example a retrospective cohort study using claims or electronic medical record data or a case control study) to assess major congenital malformations, spontaneous abortions, stillbirths, and small for gestational age and preterm birth in women exposed to Saphnelo (anifrolumab-fnia) during pregnancy compared to an unexposed control population.



APPEARS THIS WAY ON ORIGINAL

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/

YAN LI
07/21/2021 12:24:24 PM

EFE EWORUKE
07/21/2021 12:34:23 PM

MONIQUE FALCONER
07/21/2021 01:01:23 PM

JUDITH W ZANDER
07/21/2021 01:02:42 PM

SARAH K DUTCHER
07/21/2021 02:27:13 PM

ROBERT BALL
07/21/2021 02:30:49 PM

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: July 20, 2021

To: Christine Ford
Regulatory Project Manager
**Division of Rheumatology and Transplant Medicine
(DRTM)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Nydera Booker, PharmD. MPH
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

From: Mary Carroll, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Kyle Snyder, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): SAPHNELO (anifrolumab-fnia)

Dosage Form and Route: injection, for intravenous use

Application Type/Number: BLA 761123

Applicant: AstraZeneca

1 INTRODUCTION

On July 22, 2020, AstraZeneca submitted for the Agency's review an original Biologics License Application (BLA) 761123 for SAPHNELO (anifrolumab-fnia) injection, for intravenous use. SAPHNELO (anifrolumab-fnia) is a New Molecular Entity (NME) with a proposed indication for the treatment of adult patients with moderate to severe systemic lupus erythematosus. (b) (4)

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Rheumatology and Transplant Medicine (DRTM) on December 21, 2020, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for SAPHNELO (anifrolumab-fnia) injection, for intravenous use.

2 MATERIAL REVIEWED

- Draft SAPHNELO (anifrolumab-fnia) PPI received on July 22, 2020 and received by DMPP and OPDP on July 8, 2021.
- Draft SAPHNELO (anifrolumab-fnia) Prescribing Information (PI) received on July 22, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on July 8, 2021.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APhont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

4 Pages of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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/

MARY E CARROLL
07/20/2021 02:34:32 PM

KYLE SNYDER
07/20/2021 02:45:56 PM

NYEDRA W BOOKER
07/20/2021 03:02:12 PM

LASHAWN M GRIFFITHS
07/20/2021 03:04:22 PM

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: July 14, 2021

To: Christine Ford, Regulatory Project Manager
Division of Rheumatology and Transplant Medicine (DRTM)

From: Kyle Snyder, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Matthew Falter, Team Leader, OPDP

Subject: OPDP Labeling Comments for SAPHNELO (anifrolumab-fnia) injection, for intravenous use

BLA: 761123

In response to DRTM's consult request dated December 18, 2020, OPDP has reviewed the proposed Prescribing Information (PI), Patient Package Insert (PPI), and carton and container labeling for the original BLA submission for SAPHNELO (anifrolumab-fnia) injection, for intravenous use.

Labeling: OPDP's comments on the proposed PI are based on the draft labeling received by electronic mail from DRTM on July 8, 2021, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed for the proposed PPI, and comments will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling received by electronic mail from DRTM on July 7, 2021, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Kyle Snyder at (240) 402-8792 or kyle.snyder@fda.hhs.gov.

24 Pages of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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/

KYLE SNYDER
07/14/2021 10:25:48 AM

Clinical Outcome Assessment Review Memorandum

From	Susan Pretko, PharmD, MPH Clinical Outcome Assessment (COA) Reviewer Division of Clinical Outcome Assessment (DCOA) David Reasner, PhD Director DCOA
To	Division of Rheumatology & Transplant Medicine
COA tracking number	C2020459
BLA#	761123 (ref IND: 101849)
Drug Sponsor	AstraZeneca
Meeting type	BLA Review
Indication:	Systemic Lupus Erythematosus (SLE) Please check all that apply: <input type="checkbox"/> Rare Disease/Orphan Designation <input type="checkbox"/> Pediatric
Instrument(s) reviewed:	Functional Assessment of Chronic Illness Therapy – FATIGUE (FACIT-F) <input checked="" type="checkbox"/> Patient-reported outcome (PRO)

This memo is in response to the clinical outcome assessment (COA) consult request filed in DARRTS by the Division of Rheumatology & Transplant Medicine (DRTM) on October 21, 2020 (DARRTS Reference ID: 4689867) for BLA 761123 regarding Saphnelo (anifrolumab) injection for the treatment of systemic lupus erythematosus (SLE).

This COA consult response is related to proposed labeling claims for the Functional Assessment of Chronic Illness Therapy – FATIGUE (FACIT-F), participation in the Medical Policy and Program Review Council (MPPRC) meeting, and BLA review milestone meetings.

High-level review conclusions:

1. Based on the evidence provided, we agree that fatigue appears to be an important and common symptom in patients with SLE. However, the applicant did not submit sufficient evidence to support interpretation FACIT-F scores. It is unclear whether changes in the FACIT-F total score are clinically meaningful. The threshold for clinically meaningful within-patient change to assess fatigue severity in the clinical trials could not be estimated using anchor-based methods as the clinical trials did not include appropriate anchor scales.

2. Based on the empirical distribution function (eCDF) curves and item-level analyses, there does not appear to be a difference in the change from baseline at Week 52 in FACIT-F total scores between treatment arms in the phase 3 studies.
3. FACIT-F items have limitations related to content validity that present additional challenges to interpreting FACIT-F data in the applicant's clinical trials.
4. For future clinical trials in patients with SLE, we recommend that sponsors conduct patient interviews to determine the relevance and importance of the different aspects of fatigue in the clinical trial target population. It is important to evaluate patients' understanding of the content of the instrument. We recommend that sponsors include appropriate anchor scales in their clinical trials to facilitate determination of clinically meaningful changes in scores from the patient perspective using anchor-based methods. Early engagement with FDA during drug development on clinical outcome assessments is highly encouraged.

Sponsors should refer to the FDA Guidance for Industry, Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims,¹ regarding evidence required to support labeling claims.

Background

The sponsor completed two 52-week, multicenter, randomized, double-blind, placebo-controlled, phase 3 studies (Study 04 and Study 05) evaluating the efficacy and safety of anifrolumab in adult subjects aged 18-70 years with active SLE. The studies had different primary endpoints; however, both studies proposed the FACIT-F total score to support an exploratory endpoint (not adjusted for multiplicity and defined as the change from baseline at week 52).

The primary endpoint in Study 05 was the SLE Responder Index (SRI-4), a composite endpoint defined by the following criteria:

- Reduction from baseline of ≥ 4 points in the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) score
- No new organ system clinical manifestations as defined by British Isles Lupus Assessment Group (BILAG) grade
- No worsening from baseline in subjects' lupus disease activity, where worsening is defined by an increase ≥ 0.30 points on a 3-point physician global assessment (PGA) visual analogue scale (VAS)
- No discontinuation of investigational product and no use of restricted medications beyond the protocol-allowed threshold before assessment

The primary endpoint in Study 04 was the composite endpoint (British Isles Lupus Assessment Group-based Composite Lupus Assessment (BICLA)) defined by the following:

¹ U.S. Food and Drug Administration. Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. December 2009. Available from: <https://www.fda.gov/regulatory-information/search-fdaguidance-documents/patient-reported-outcome-measures-use-medical-product-development-support-labeling-claims>

- Reduction in severity of all baseline clinical manifestations and no worsening in other organ systems, as defined by BILAG grade
- No worsening from baseline in SLEDAI-2K score
- No worsening from baseline in subjects' lupus disease activity, where worsening is defined by an increase ≥ 0.30 points on the PGA VAS
- No discontinuation of investigational product
- No use of restricted medications beyond the protocol-allowed threshold before assessment

The FACIT-F is a 13-item patient-reported outcome measure assessing symptoms and impacts of fatigue. A total score is calculated from the FACIT-F with a potential score range of 0-52 (based on reversed scoring, lower scores indicate greater fatigue). The FACIT-F is in Attachment 1.



Reviewer's Comment(s):

The results of the applicant's first phase 3 study (study 05) found that the study did not meet the primary endpoint of proportion of SRI-4 responders at Week 52. For the applicant's second phase 3 study (study 04), the applicant proposed using the BICLA response rate at Week 52. The issue of different primary endpoints in the phase 3 studies was discussed with the MPPRC to determine whether there is substantial evidence of efficacy to support approval of anifrolumab for active SLE.

Review Findings

Efficacy Results

Table 29 from the Summary of Clinical Efficacy in the original BLA submission shows the efficacy results for FACIT-F scores at week 52 for the phase 3 studies.

Table 29 FACIT-fatigue response at Week 52—study 04, study 05, and phase III pool (full analysis set)							
BICLA response at Week 52	FACIT-Fatigue response at Week 52	Study 04		Study 05		Phase III pool	
		Anifrolumab 300 mg (N = 180)	Placebo (N = 182)	Anifrolumab 300 mg (N = 180)	Placebo (N = 184)	Anifrolumab 300 mg (N = 360)	Placebo (N = 366)
All patients	n	180	182	180	184	360	366
	Number (%) responders	60 (33.2)	45 (24.7)	64 (35.4)	52 (28.4)	124 (34.3)	97 (26.5)
	Number (%) non-responders	120 (66.8)	137 (75.3)	116 (64.6)	132 (71.6)	236 (65.7)	269 (73.5)
	95% CI responder rate	26.2, 40.1	18.3, 31.1	28.4, 42.5	21.7, 35.0	29.4, 39.2	21.9, 31.1
	Comparison with placebo						
	Difference in response rate	8.5		7.1		7.8	
	95% CI of difference in response rate	-0.9, 17.9		-2.6, 16.7		1.0, 14.5	
BICLA responder	FACIT-fatigue responder	47 (26.1)	29 (15.9)	50 (27.8)	29 (15.8)	97 (26.9)	58 (15.8)
	FACIT-fatigue non-responder	36 (20.0)	24 (13.2)	34 (18.9)	22 (12.0)	70 (19.4)	46 (12.6)
BICLA non-responder	FACIT-fatigue responder	13 (7.2)	16 (8.8)	14 (7.8)	23 (12.5)	27 (7.5)	39 (10.7)
	FACIT-fatigue non-responder	57 (31.7)	71 (39.0)	48 (26.7)	71 (38.6)	105 (29.2)	142 (38.8)

Derived from: Table 2.3.3.3 and Table 2.3.3.4, Appendix 2.7.3.6.1 in Module 5.3.5.3.
Percentages are based upon all patients in the full analysis set within the respective treatment group.
Phase III pool includes study 04 and study 05 (excluding the 150 mg group from study 05).
A response in FACIT-fatigue is defined as an improvement from baseline to Week 52 of > 3 points (ie, change from baseline < -3). Patients treated with restricted medication beyond protocol-allowed threshold, and those who discontinued investigational product, are regarded as non-responders.
Results are based on the study 04 rules for restricted medications. For additional information see Section 1.2.1.7.
The FACIT-fatigue responder/non-responder rates, the difference in estimates and associated 95% CI are calculated using a stratified CMH approach, with stratification factors SLEDAI-2K score at screening, Day 1 OCS dose, type I IFN gene signature test result at screening, and study (study 04 vs study 05).
BICLA response is defined in Section 1.2.1.7.
BICLA British Isles Lupus Assessment Group-based Composite Lupus Assessment; BILAG-2004 British Isles Lupus Assessment Group-2004; CI Confidence interval; CMH Cochran-Mantel-Haenszel; CSR Clinical study report; FACIT-fatigue Functional Assessment of Chronic Illness Therapy-fatigue; IFN Interferon; n Number of patients in analysis; N Number of patient in treatment group; OCS Oral corticosteroids; PGA Physician Global Assessment; SLEDAI-2K Systemic Lupus Erythematosus Disease Activity Index 2000; VAS Visual analog scale.

The following Information Request (IR) was sent to the sponsor on January 5, 2021:

“Submit the following:

- 1. Evidence of content validity of the FACIT-F in the SLE population (e.g., evidence from the published literature and/or qualitative research with SLE patients)**
- 2. Item-level analyses of the FACIT-F**
- 3. Treatment arms empirical cumulative distribution function (eCDF) and probability density function (PDF) curves for the FACIT-F**
- 4. Evidence to support a threshold for clinically meaningful within patient change based on input from SLE patients. The proposed 3-point threshold was derived from a population of cancer patients.**
 - a. Clarify if a verbal rating global anchor scale was included in your pivotal studies to aid with post-hoc anchor-based analyses for a meaningful change threshold for the FACIT-F in SLE patients.”**

The sponsor submitted the requested information on January 13, 2021. The eCDF curves using pooled data from the phase 3 studies for FACIT-F score change from baseline at week 52 are in Attachment 2. Results from item-level analyses of the FACIT-F are in Attachment 3.

Reviewer’s Comment(s):

The eCDF curves showing FACIT-F score change from baseline at Week 52 by treatment arm did not demonstrate clear separation between the anifrolumab and placebo arms, suggesting there was not a meaningful difference in FACIT-F scores between the study arms.

The FACIT-F item level analyses found the pooled data 95% Confidence Interval for the difference in response rate for FACIT-F response at Week 52 between the study arms included 0 for all FACIT-F items except items 4 (“I feel tired”), 6 (“I have trouble finishing things because I am tired”), and 10 (“I am too tired to eat”). Thus, the item level analyses suggests there is not a statistically significant difference between treatment arms, which is consistent with the eCDF curves.

There is clear separation between the treatment arms by BICLA responder, suggesting BICLA responders experienced meaningful improvement in FACIT-F scores compared to BICLA non-responders. However, a BICLA responder is based on clinical manifestation of SLE on organ systems and it is unclear how closely fatigue and clinical manifestations of SLE on organ systems correlate.

Content Validity of the FACIT-F

The sponsor referenced existing literature to support the content validity of the FACIT-F as an assessment of fatigue in the SLE population.²⁻⁶ The referenced literature did not demonstrate relevancy/importance of all concepts included in the FACIT-F.

Reviewer’s Comment(s):

The submitted evidence does not support the content validity of the FACIT-F in the SLE population. Although the applicant’s submitted literature describes the relevance of the FACIT-F instrument as an assessment of fatigue in SLE patients, some items of the FACIT-F appear to be problematic. Specific concerns on the content validity of the FACIT-F based on interviews with SLE patients as described by Kosinski et al include:

- 1. For item 3 (“feeling listless/washed out”) interpretation of the term “listless/washed out” varied, ranging from consideration of listlessness as “an emotional or mental state in which they were uninterested in engaging in activities” to “a physical state in which they lacked energy and were incapacitated”. Additionally, not all patients understood the meaning of the word “listless”.*
- 2. For item 5 (“I have trouble starting things because I am tired”), factors contributing to participant response were not all related to SLE.*
- 3. For item 10 (“I am too tired to eat”), the majority of participants interviewed indicated that meal avoidance was not due to their SLE-related fatigue; rather, “it was the effort required to buy and prepare food that was more relevant to SLE-related fatigue”.*

² Kosinski M, Gajria K, Fernandes AW, Cella D. Qualitative validation of the FACIT-fatigue scale in systemic lupus erythematosus. *Lupus* 2013;22:422–30.

³ Mannix S, Beyer A, Strand V, Hanrahan L, Abel C, Flamion B. Assessment of fatigue in adults with moderate to severe systemic lupus erythematosus (SLE): a qualitative study to explore what patients feel should be measured in clinical trials. *Ann Rheum Dis*. 2020;79(Suppl 1):1916.

⁴ Park J, Raymond K, White M, Joshi A. Patient insights of fatigue in systemic lupus erythematosus and content validation of the FACIT-Fatigue. *Lupus Science & Medicine*. 2019;6(Suppl 1):A37-A38

⁵ Strand V, Levy RA, Cervera R, et al. Improvements in health-related quality of life with belimumab, a B-lymphocyte stimulator-specific inhibitor, in patients with autoantibodypositive systemic lupus erythematosus from the randomised controlled BLISS trials. *Ann Rheum Dis*. 2014;73(5):838-844.

⁶ Strand V, Simon LS, Meara AS, Touma Z. Measurement properties of selected patient-reported outcome measures for use in randomised controlled trials in patients with systemic lupus erythematosus: a systematic review. *Lupus Science & Medicine*. 2020;7.

4. *The majority of patients that were cognitively interviewed on the FACIT-F instrument based their responses on health conditions either related or unrelated to SLE or on external circumstances (i.e., job stress or family illness).*

Interpretation of FACIT-F Scores

The applicant proposed a responder definition from baseline to Week 52 in FACIT-F total score using a threshold of > 3 points to reflect clinically meaningful improvement. The 3-point threshold is based on existing literature and was derived from a population of cancer patients receiving some form of chemotherapy at baseline.⁷ The applicant referenced additional publications to support the meaningful change threshold. **Error! Bookmark not defined.**⁸⁻¹⁰ A verbal rating global anchor scale was not used to collect data in the phase 3 studies, although subjects were asked to complete a patient Global Assessment (PtGA) that used a 100mm VAS to assess patient perceived global health status. The PtGA is in Attachment 4.

Reviewer's Comment(s):

The evidence submitted by the applicant is insufficient to support a threshold for clinically meaningful within-patient change given an inappropriate context of use^{7,10} or inappropriate methods^{5,8-9}. From a regulatory standpoint, we are more interested in what constitutes a clinically meaningful within-patient change in scores (i.e., improvement threshold), from the patient perspective, rather than a minimal clinically important difference (MCID) across all patients.

Anchor-based methods are the primary methods we use to interpret meaningful within-patient score changes in COA endpoints. A VAS is an inappropriate anchor scale given the difficulty differentiating a clinically meaningful difference on the VAS line, hence presenting limitations for interpretation.

Attachments

- Attachment 1. Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue
- Attachment 2. Empirical Cumulative Distribution Function curves
- Attachment 3. FACIT-F Item-level Analyses
- Attachment 4. Patient Global Assessment

⁷ Cella DF, Eton DT, Lai JS, Peterman AH, Merkel DE. Combining anchor and distribution-based methods to derive minimal clinically important differences on the functional assessment of cancer therapy (FACT) anaemia and fatigue scales. *J Pain Symptom Manage.* 2002;24:547-61.

⁸ Goligher EC, Pouchot J, Brant R, Kherani R, Aviña-Zubieta, J, Lacaille, D. Minimal clinically important difference for 7 measures of fatigue in patients with systemic lupus erythematosus. *J Rheumatol.* 2008;35(4):635-642.

⁹ Lai JS, Beaumont JL, Ogale S, Brunetta P, Cella D. Validation of the functional assessment of chronic illness therapy-fatigue scale in patients with moderately to severely active systemic lupus erythematosus, participating in a clinical trial. *J Rheumatol.* 2011;38(4):672-679.

¹⁰ Cella D, Yount S, Sorensen M, Chartash E, Sengupta N, Grober J. Validation of the Functional Assessment of Chronic Illness Therapy Fatigue Scale relative to other instrumentation in patients with rheumatoid arthritis. *J Rheumatol.* 2005;32(5):811-819.

For internal use only (do not convey to sponsor)

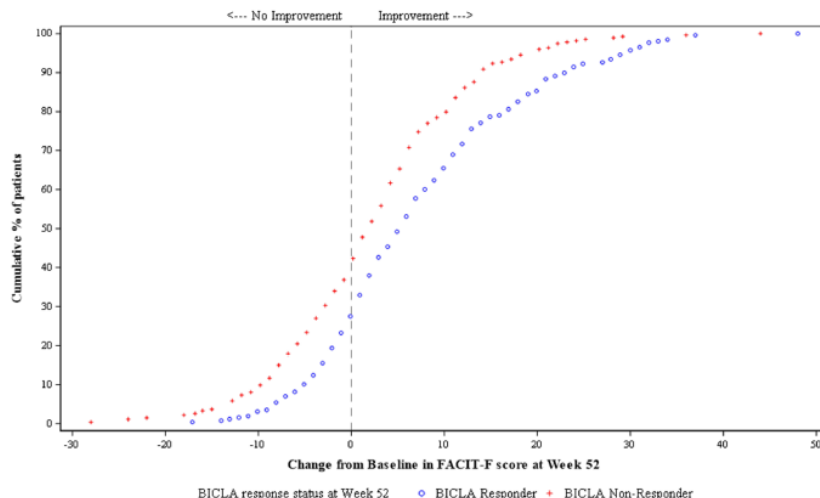
Attachments

Attachment 1. Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue

FACIT Fatigue Scale (Version 4)						
Below is a list of statements that other people with your illness have said are important. Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u> .						
		Not at all	A little bit	Some- what	Quite a bit	Very much
Hi7	I feel fatigued	0	1	2	3	4
Hi12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble <u>starting</u> things because I am tired	0	1	2	3	4
An4	I have trouble <u>finishing</u> things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4

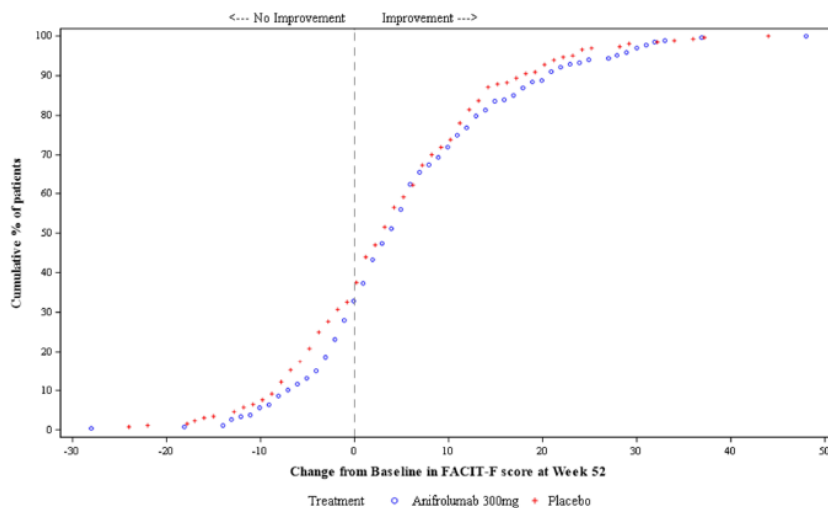
Attachment 2. Empirical Cumulative Distribution Function curves

Figure 1 Cumulative distribution function of FACIT-F score change from baseline at Week 52, by BICLA response status at Week 52 (study 04 and study 05; pooled data)



BICLA, British Isles Lupus Assessment Group based Composite Lupus Assessment; FACIT-F, Functional Assessment of Chronic Illness Therapy-fatigue
Baseline is defined as the measurement prior to randomization and dose administration on Day 1.
Pooled data excludes 150 mg dose group from study 05.
Positive change from baseline values indication improvement.
Missing data are not imputed.

Figure 2 Cumulative distribution function of FACIT-F score change from baseline at Week 52, by treatment arm (study 04 and study 05; pooled data)



FACIT-F, Functional Assessment of Chronic Illness Therapy-fatigue
Baseline is defined as the measurement prior to randomization and dose administration on Day 1.
Pooled data excludes 150 mg dose group from study 05.
Positive change from baseline values indication improvement.
Missing data are not imputed.

Attachment 3. FACIT-F Item-level Analyses

Table A3.1. Summary statistics at baseline and estimated change from baseline at week 52 for FACIT-F item scores (Full analysis set, Phase III pool)

Variable	Timepoint		Study 04		Study 05		Phase III Pool	
			Anifrolumab 300mg (N=180)	Placebo (N=182)	Anifrolumab 300mg (N=180)	Placebo (N=184)	Anifrolumab 300mg (N=360)	Placebo (N=366)
Item 1. Feel fatigued	Baseline	n	170	175	171	174	341	349
		Mean (SD)	1.553 (1.1967)	1.423 (1.1515)	1.404 (1.2058)	1.603 (1.2577)	1.478 (1.2018)	1.513 (1.2072)
		Median	1.000	1.000	1.000	2.000	1.000	1.000
		Min, Max	0.00, 4.00	0.00, 4.00	0.00, 4.00	0.00, 4.00	0.00, 4.00	0.00, 4.00
	Week 52	n	137	126	131	138	268	264
		LSMean (SE)	0.400 (0.0967)	0.313 (0.0988)	0.524 (0.1033)	0.461 (0.1012)	0.468 (0.0704)	0.407 (0.0704)
		COMPARISON WITH PLACEBO:						
		LSMean difference	0.087		0.063		0.061	
95% CI	(-0.162, 0.336)		(-0.200, 0.326)		(-0.120, 0.241)			
Item 2. Feel weak all over	Baseline	n	170	175	171	174	341	349
		Mean (SD)	1.965 (1.1961)	1.800 (1.1497)	1.678 (1.2159)	1.845 (1.2465)	1.821 (1.2128)	1.822 (1.1974)
		Median	2.000	2.000	2.000	2.000	2.000	2.000
		Min, Max	0.00, 4.00	0.00, 4.00	0.00, 4.00	0.00, 4.00	0.00, 4.00	0.00, 4.00
	Week 52	n	137	126	131	138	268	264
		LSMean (SE)	0.349 (0.0963)	0.245 (0.0988)	0.535 (0.1014)	0.490 (0.0993)	0.450 (0.0695)	0.377 (0.0697)
		COMPARISON WITH PLACEBO:						
		LSMean difference	0.103		0.045		0.073	
95% CI	(-0.146, 0.352)		(-0.213, 0.303)		(-0.106, 0.251)			
Item 3. Feel Listless (Washed out)	Baseline	n	170	175	171	174	341	349
		Mean (SD)	2.106 (1.4060)	2.063 (1.2961)	1.860 (1.3254)	2.075 (1.3344)	1.982 (1.3697)	2.069 (1.3134)
		Median	2.000	2.000	2.000	2.000	2.000	2.000
		Min, Max	0.00, 4.00	0.00, 4.00	0.00, 4.00	0.00, 4.00	0.00, 4.00	0.00, 4.00
	Week 52	n	137	126	131	138	268	264
		LSMean (SE)	0.287 (0.0985)	0.134 (0.1010)	0.448 (0.1021)	0.311 (0.0999)	0.372 (0.0707)	0.231 (0.0707)
		COMPARISON WITH PLACEBO:						
		LSMean difference	0.153		0.137		0.140	
95% CI	(-0.103, 0.410)		(-0.122, 0.396)		(-0.041, 0.322)			
Item 4. Feel Tired	Baseline	n	170	175	171	174	341	349
		Mean (SD)	1.441 (1.2063)	1.326 (1.1949)	1.199 (1.1612)	1.443 (1.2043)	1.320 (1.1884)	1.384 (1.1993)
		Median	1.000	1.000	1.000	1.000	1.000	1.000
		Min, Max	0.00, 4.00	0.00, 4.00	0.00, 4.00	0.00, 4.00	0.00, 4.00	0.00, 4.00
	Week 52	n	137	126	131	138	268	264
		LSMean (SE)	0.451 (0.0934)	0.251 (0.0959)	0.604 (0.0983)	0.435 (0.0960)	0.534 (0.0677)	0.357 (0.0678)
		COMPARISON WITH PLACEBO:						
		LSMean difference	0.200		0.170		0.177	
95% CI	(-0.042, 0.443)		(-0.077, 0.417)		(0.004, 0.350)			

Table A3.1. cont. Summary statistics at baseline and estimated change from baseline at week 52 for FACIT-F item scores (Full analysis set, Phase III pool)

Variable	Timepoint		Study 04		Study 05		Phase III Pool	
			Anifrolumab 300mg (N=180)	Placebo (N=182)	Anifrolumab 300mg (N=180)	Placebo (N=184)	Anifrolumab 300mg (N=360)	Placebo (N=366)
Item 5. Trouble Starting Things due to Tiredness	Baseline	n	170	175	171	174	341	349
		Mean (SD)	2.006 (1.2475)	1.971 (1.2055)	1.766 (1.2849)	1.931 (1.2049)	1.886 (1.2702)	1.951 (1.2036)
		Median	2.000	2.000	2.000	2.000	2.000	2.000
		Min, Max	0.00, 4.00	0.00, 4.00	0.00, 4.00	0.00, 4.00	0.00, 4.00	0.00, 4.00
	Week 52	n	137	126	131	138	268	264
		LSMean (SE)	0.423 (0.0993)	0.154 (0.1011)	0.547 (0.1002)	0.498 (0.0979)	0.472 (0.0704)	0.323 (0.0703)
		COMPARISON WITH PLACEBO:						
		LSMean difference	0.269		0.049		0.150	
		95% CI	(0.012, 0.525)		(-0.204, 0.303)		(-0.031, 0.330)	
Item 6. Trouble Finishing Things due to Tiredness	Baseline	n	170	175	171	174	341	349
		Mean (SD)	1.947 (1.2699)	1.920 (1.2569)	1.702 (1.2457)	1.868 (1.2116)	1.824 (1.2619)	1.894 (1.2330)
		Median	2.000	2.000	2.000	2.000	2.000	2.000
		Min, Max	0.00, 4.00	0.00, 4.00	0.00, 4.00	0.00, 4.00	0.00, 4.00	0.00, 4.00
	Week 52	n	137	126	131	138	268	264
		LSMean (SE)	0.431 (0.0945)	0.150 (0.0966)	0.472 (0.1003)	0.350 (0.0982)	0.456 (0.0686)	0.257 (0.0686)
		COMPARISON WITH PLACEBO						
		LSMean difference	0.281		0.122		0.200	
		95% CI	(0.037, 0.525)		(-0.131, 0.375)		(0.025, 0.374)	
Item 7. Have Energy	Baseline	n	170	175	171	174	341	349
		Mean (SD)	1.429 (0.9780)	1.326 (0.9174)	1.211 (0.9775)	1.483 (1.0185)	1.320 (0.9824)	1.404 (0.9709)
		Median	1.000	1.000	1.000	1.000	1.000	1.000
		Min, Max	0.00, 4.00	0.00, 4.00	0.00, 4.00	0.00, 4.00	0.00, 4.00	0.00, 4.00
	Week 52	n	137	126	131	138	268	264
		LSMean (SE)	0.196 (0.0838)	-0.077 (0.0861)	0.168 (0.0908)	0.213 (0.0886)	0.174 (0.0615)	0.077 (0.0616)
		COMPARISON WITH PLACEBO						
		LSMean difference	0.273		-0.044		0.097	
		95% CI	(0.053, 0.493)		(-0.275, 0.187)		(-0.062, 0.255)	
Item 8. Able to Do Usual Activities	Baseline	n	170	175	171	174	341	349
		Mean (SD)	2.000 (1.0824)	1.943 (1.1075)	1.825 (1.1081)	1.856 (1.0069)	1.912 (1.0973)	1.900 (1.0579)
		Median	2.000	2.000	2.000	2.000	2.000	2.000
		Min, Max	0.00, 4.00	0.00, 4.00	0.00, 4.00	0.00, 4.00	0.00, 4.00	0.00, 4.00
	Week 52	n	137	126	131	138	268	264
		LSMean (SE)	0.113 (0.0923)	0.079 (0.0952)	0.292 (0.0934)	0.270 (0.0914)	0.209 (0.0654)	0.186 (0.0657)
		COMPARISON WITH PLACEBO						
		LSMean difference	0.034		0.023		0.023	
		95% CI	(-0.211, 0.278)		(-0.219, 0.264)		(-0.148, 0.194)	

Table A3.1. cont. Summary statistics at baseline and estimated change from baseline at week 52 for FACIT-F item scores (Full analysis set, Phase III pool)

Variable	Timepoint		Study 04		Study 05		Phase III Pool	
			Anifrolumab 300mg (N=180)	Placebo (N=182)	Anifrolumab 300mg (N=180)	Placebo (N=184)	Anifrolumab 300mg (N=360)	Placebo (N=366)
Item 9. Need to Sleep During the Day	Baseline	n	170	175	171	174	341	349
		Mean (SD)	2.206 (1.2399)	2.240 (1.2729)	2.456 (1.2519)	2.184 (1.3259)	2.331 (1.2504)	2.212 (1.2980)
		Median	2.000	2.000	3.000	2.000	3.000	2.000
		Min, Max	0.00, 4.00	0.00, 4.00	0.00, 4.00	0.00, 4.00	0.00, 4.00	0.00, 4.00
	Week 52	n	137	126	131	138	268	264
		LSMean (SE)	0.166 (0.0874)	0.302 (0.0894)	0.244 (0.0883)	0.054 (0.0874)	0.210 (0.0621)	0.166 (0.0622)
		<u>COMPARISON WITH PLACEBO</u>						
		LSMean difference	-0.136		0.190		0.044	
		95% CI	(-0.359, 0.088)		(-0.035, 0.415)		(-0.113, 0.202)	
Item 10. Too Tired to Eat	Baseline	n	170	175	171	174	341	349
		Mean (SD)	3.182 (1.1341)	3.034 (1.1392)	3.070 (1.0714)	3.063 (1.0920)	3.126 (1.1029)	3.049 (1.1144)
		Median	4.000	3.000	3.000	3.000	4.000	3.000
		Min, Max	0.00, 4.00	0.00, 4.00	0.00, 4.00	0.00, 4.00	0.00, 4.00	0.00, 4.00
	Week 52	n	137	126	131	138	268	264
		LSMean (SE)	0.127 (0.0811)	0.070 (0.0831)	0.145 (0.0825)	-0.109 (0.0811)	0.135 (0.0576)	-0.025 (0.0577)
		<u>COMPARISON WITH PLACEBO</u>						
		LSMean difference	0.057		0.254		0.161	
		95% CI	(-0.153, 0.267)		(0.044, 0.464)		(0.013, 0.308)	
Item 11. Need Help Doing Usual Activities	Baseline	n	170	175	171	174	341	349
		Mean (SD)	2.735 (1.2237)	2.617 (1.1971)	2.515 (1.1850)	2.586 (1.1978)	2.625 (1.2078)	2.602 (1.1958)
		Median	3.000	3.000	3.000	3.000	3.000	3.000
		Min, Max	0.00, 4.00	0.00, 4.00	0.00, 4.00	0.00, 4.00	0.00, 4.00	0.00, 4.00
	Week 52	n	137	126	131	138	268	264
		LSMean (SE)	0.117 (0.0797)	0.152 (0.0816)	0.245 (0.0874)	0.206 (0.0858)	0.181 (0.0588)	0.183 (0.0589)
		<u>COMPARISON WITH PLACEBO</u>						
		LSMean difference	-0.035		0.039		-0.003	
		95% CI	(-0.239, 0.168)		(-0.181, 0.259)		(-0.151, 0.146)	
Item 12. Frustrated by Being Too Tired	Baseline	n	170	175	171	174	341	349
		Mean (SD)	2.206 (1.4304)	1.926 (1.3219)	1.842 (1.3520)	1.954 (1.3804)	2.023 (1.4015)	1.940 (1.3495)
		Median	2.000	2.000	2.000	2.000	2.000	2.000
		Min, Max	0.00, 4.00	0.00, 4.00	0.00, 4.00	0.00, 4.00	0.00, 4.00	0.00, 4.00
	Week 52	n	137	126	131	138	268	264
		LSMean (SE)	0.372 (0.1012)	0.333 (0.1037)	0.613 (0.1028)	0.395 (0.1008)	0.487 (0.0715)	0.382 (0.0717)
		<u>COMPARISON WITH PLACEBO</u>						
		LSMean difference	0.039		0.219		0.105	
		95% CI	(-0.219, 0.298)		(-0.040, 0.478)		(-0.076, 0.287)	

Table A3.1. cont. Summary statistics at baseline and estimated change from baseline at week 52 for FACIT-F item scores (Full analysis set, Phase III pool)

Variable	Timepoint	Study 04		Study 05		Phase III Pool		
		Anifrolumab 300mg (N=180)	Placebo (N=182)	Anifrolumab 300mg (N=180)	Placebo (N=184)	Anifrolumab 300mg (N=360)	Placebo (N=366)	
Item 13. Have to Limit Social Activity	Baseline	n	170	175	171	174	341	349
		Mean (SD)	2.218 (1.3256)	2.097 (1.2625)	1.936 (1.2795)	2.126 (1.3151)	2.076 (1.3084)	2.112 (1.2873)
		Median	2.000	2.000	2.000	2.000	2.000	2.000
		Min, Max	0.00, 4.00	0.00, 4.00	0.00, 4.00	0.00, 4.00	0.00, 4.00	0.00, 4.00
	Week 52	n	137	126	131	138	268	264
		LSMean (SE)	0.322 (0.0960)	0.311 (0.0982)	0.613 (0.0949)	0.271 (0.0930)	0.466 (0.0672)	0.296 (0.0673)
		<u>COMPARISON WITH PLACEBO:</u>						
		LSMean difference	0.011		0.341		0.170	
		95% CI	(-0.236, 0.258)		(0.103, 0.580)		(-0.001, 0.341)	

N=Number of subjects in treatment group. N=Number of subjects in analysis. SD=Standard deviation. Min=Minimum. Max=Maximum. CI=Confidence Interval. LSMean=Least Squares Mean. SE=Standard Error. FACIT-F=Functional Assessment of Chronic Illness Therapy-FATIGUE.
Phase III pool includes studies D3461C00004 and D3461C00005 (excluding the 150 mg group from study D3461C00005).
Baseline is defined as the last measurement prior to randomization and dose administration on Day 1.

Attachment 4. Patient Global Assessment

Patient Assessment

Considering all the ways in which illness and health conditions may affect you at this time, please make a mark below to show how you are doing:

Very Well |—————| Very Poorly

APPEARS THIS WAY ON ORIGINAL

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/

SUSAN M PRETKO
06/03/2021 08:34:05 AM

DAVID S REASNER
06/03/2021 09:19:51 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatrics and Maternal Health
Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatric and Maternal Health Review

Date: May 19, 2021 **Date consulted:** April 21, 2021

From: Christos Mastroyannis, M.D., Medical Officer, Maternal Health, Division of Pediatrics and Maternal Health (DPMH)

Through: Tamara Johnson, MD, MS, Team Leader, Maternal Health, DPMH
Lynne Yao, MD, Director, DPMH

To: Division of Rheumatology and Transplant Medicine (DRTM)

Drug: Saphnelo (anifrolumab-fnia) for intravenous injection

Drug Class: First in class, type I interferon (IFN) receptor- (b) (4)

BLA: 761123

Applicant: AstraZeneca

Subject: Recommendations for PMR for Pregnancy Registry and Lactation Study

Indication: Treatment of adult patients with moderate to severe systemic lupus erythematosus (SLE), (b) (4)

Consult Question:

DRTM would like DPMH-Maternal Health to provide input on the pregnancy and lactation PMRs, including Pregnancy Registry. Benlysta (belimumab), an approved comparator for SLE, has a Pregnancy Registry.

Materials Reviewed:

- July 31, 2020: Original submission for BLA 761123 for first in class, type I interferon (IFN) receptor- (b) (4)
- April 21, 2021: DRTM consult, DARRTS Reference ID 4782882
- January 19, 2017: Kasten CH Review of Benlysta, in DARRTS, January 19, 2017,

INTRODUCTION

On July 31, 2020, AstraZeneca submitted an original BLA 761123 for Saphnelo (anifrolumab-fnia), first in class, type I interferon (IFN) receptor-(b) (4) for intravenous injection, under the 351(a) pathway. The Division of Rheumatology and Transplant Medicine (DRTM) consulted the Division of Pediatrics and Maternal Health (DPMH) on April 21, 2021, to assist to determine if pregnancy and lactation Post Marketing Requirements (PMRs) are required.

BACKGROUND

Drug Characteristics

Saphnelo (anifrolumab-fnia) is a human IgG1kAb directed against subunit 1 of the type I interferon receptor (IFNAR1). It is composed of 2 identical light chains and 2 identical heavy chains.

Systemic Lupus Erythematosus (SLE)²

SLE is a chronic disease that is life-long and may be life threatening.³ The pathogenesis of SLE is cellular and humoral immune dysregulation manifested by B cell hyperactivity, autoreactive T cells, immune complex deposition in organs and abnormal apoptosis.⁴ Prevalence rates vary by country; estimates of prevalence in the U.S. range from 4.8 to 78.5 per 1000,000 individuals. SLE affects women predominantly with almost 90% of patients diagnosed with SLE being female.^{5,6,7} The age of onset of SLE is usually between 15 and 40 years of age. One publication found that approximately 15% of patients developed SLE symptoms before 16 years of age.⁴ Juvenile-onset SLE appears to be more severe and the 10-year survival may be only 85%, according to one publication.⁴ The goal of SLE management is to minimize the risk of permanent organ damage and the impact of adverse, treatment-related events. Common adverse effects that result from disease progression and drug treatment are damage to renal, hepatic and neuronal organ systems. Other common

¹ DPMH did not rely on data in the Benlysta by Human genome Sciences, Inc NDA or the Agency's findings of safety and effectiveness for Benlysta to support labeling sections of this NDA. Rather, the cross-reference to the Benlysta consult is included to avoid duplicating background information relevant to this class of products.

² Kasten CH Review of Benlysta, in DARRTS, January 19, 2017, Reference ID: 4044159

³ Singh J, Noorbaloochi S, Tucker M. Belimumab for systemic lupus erythematosus. Cochrane Database of Systematic Reviews 2013, Issue 7. Art. No: CD010668. DOI: 10.1002/14651858.CD010668.

⁴ Craig J, Pain C, Beresford M: Disease modifying immunosuppressant drugs for juvenile onset systemic lupus erythematosus. Cochrane Database of Systematic Reviews 2010, Issue 7. Art. No.: CD008617. DOI:10.1002/14651858.CD008617

⁵ Craig J, Pain C, Beresford M .Disease modifying immunosuppressant drugs for juvenile onset systemic lupus erythematosus. Cochrane Database of Systematic Reviews 2010, Issue 7. Art. No.: CD008617. DOI:10.1002/14651858.CD008617

⁶ Hahn B. Systemic Lupus Erythematosus. In: Kasper D, Fauci A, Hauser S, Longo D, Jameson J, Loscalzo J. eds. Harrison's Principles of Internal Medicine, 19e. New York, NY: McGraw-Hill; 2015. <http://accessmedicine.mhmedical.com/content.aspx?bookid=1130&Sectionid=79749933> Accessed July 08, 2016.

⁷ Cunningham F, Leveno K, Bloom S, Spong C, Dashe J, Hoffman B, Casey B, Sheffield J. Connective-Tissue Disorders. In: Cunningham F, Leveno K, Bloom S, Spong C, Dashe J, Hoffman B, Casey B, Sheffield J. eds. Williams Obstetrics, Twenty-Fourth Edition. New York, NY: McGraw-Hill; 2013. <http://accessmedicine.mhmedical.com/content.aspx?bookid=1057&Sectionid=59789204>. Accessed July 08, 2016.

adverse effects of SLE are osteoporosis, premature ovarian failure and infertility. Co-morbidities include hypertension, atherosclerosis and severe infections.

Systemic Lupus Erythematosus and Pregnancy

Pregnant women with SLE generally have poorer pregnancy outcomes than women without the disease; however, studies of the outcomes of pregnancies in women with SLE are frequently limited by small numbers of SLE patients and a retrospective design that may lead to conflicting results. A meta-analysis by Smyth, et al.,⁸ reviewed 37 studies with 1842 SLE patients and 2751 pregnancies reported the most common complications were: lupus flare (25.6%), anti-phospholipid antibodies (APAs)⁹ (23.6%), hypertension (16.3%), spontaneous abortion (SAb) (16.0%) and preeclampsia (7.6%). The most common fetal complications were intrauterine growth restriction (12.7%), stillbirth (3.6%) and neonatal deaths (2.5%). Among the live births of women with SLE, the most frequent complication was prematurity (39.4%). For pregnant women with SLE who also had APAs, the rate of SAbs appears to be increased; however, reporting differences make it difficult to identify the rate of SAbs for pregnant women with SLE and APAs.¹⁰

APAs in women with SLE may cross the placenta during pregnancy and may produce congenital heart block (CHB) in the fetus. It is thought that anti-Sjögren's-syndromerelated antigen A (anti-SSA antibodies) and anti-Sjögren's-syndrome-related antigen B (anti-SSB antibodies) induce an inflammatory, autoimmune reaction in fetal cardiocytes which appears to lead to fibrosis of the cardiac conduction system.¹¹ The damage to the conduction system is reported to be permanent.

REVIEW

From nonclinical studies in pregnant cynomolgus monkeys who received anifrolumab-fnia at IV doses of 30 or 60 mg/kg every 2 weeks from Gestation Day 20 throughout the gestation period and 1-month postpartum (approximately Lactation Day 28), there was no evidence of maternal toxicity, embryo-fetal toxicity, or postnatal developmental effects at exposure approximately 18 times the MRHD of 300 mg IV on an AUC basis.

There are no adequate or well-controlled studies of anifrolumab-fnia in pregnant women. There was no use of anifrolumab-fnia in pregnant women during the drug development program. There are risks to the mother and fetus associated with systemic lupus erythematosus (SLE).

DISCUSSION ON POSTMARKETING REQUIREMENT (PMR) STUDIES

There is anticipated use of Saphnelo in females of reproductive potential or during pregnancy. The CDC reports that 10% of females of reproductive potential become pregnant each year, and half of all pregnancies are unintended. Therefore, it is likely that

⁸ Smyth A, Oliveira G, et al. A Systematic Review and Meta-Analysis of Pregnancy Outcomes in Patients with Systemic Lupus Erythematosus and Lupus Nephritis Clin J Am Soc Nephrol 5: 2060–2068, 2010.

⁹ Anti-phospholipid antibodies (APA) are antibodies directed against anionic membrane phospholipids such as cardiolipin and phosphatidylserine. Anti-SSA autoantibodies (Anti-Sjögren's-syndrome-related antigen A are also called anti-Ro antibodies


¹⁰ Østensen M, Andreoli L, et al., State of the art: Reproduction and pregnancy in rheumatic diseases. Autoimmunity Reviews.2015;14:376–386.

¹¹ Peart E, Clowse M. Systemic lupus erythematosus and pregnancy outcomes: an update and review of the literature. Curr Opin Rheumatol. 2014 Mar;26(2):118-23.

exposures during pregnancy will occur. Postmarketing studies to assess maternal and infant outcomes following exposure in pregnancy are important to help characterize Saphnelo's safety in pregnancy.

A pregnancy exposure registry is the Agency's preferred method for post-marketing data collection in pregnant women due to the prospective method of data collection, which minimizes the biases of retrospective data collection.¹² In addition, pregnancy registries allow collection of patient level detailed data on potential confounders. However, pregnancy registries are limited by their lack of power to assess specific (rare) birth defects and the long duration that may be needed to accumulate data. As discussed by the expert panel at the 2014 FDA public meeting on pregnancy registries and other post-approval safety studies in pregnant women, combining two study methods addresses limitations inherent to each study design.¹³ Combining a pregnancy registry with a complementary study with a different study design that relies on large databases may address the potential low enrollment in a registry. Examples of complementary study designs include a case control study or a retrospective cohort study using claims or electronic medical record data.

Further, collection of outcomes through a multiple-drug or disease-based pregnancy exposure registry may reduce burden on patients, physicians, and the healthcare system when compared to many single-drug pregnancy registries.¹² Multiple-drug registries easily allow for inherent comparison groups. Sponsors should be encouraged to work together directly or through consortiums to develop or support multiple-drug pregnancy exposure registries. An approved comparator drug, Benlysta, was issued a pregnancy exposure registry PMR in 2011. The final report has been delayed (b) (4)



DPMH recommends a PMR pregnancy exposure registry in combination with a complementary study to collect any safety information with the use of Saphnelo during pregnancy. The Saphnelo sponsor may be encouraged to explore opportunities for collaboration in a disease-based or multiple-drug pregnancy exposure registry vs. a single-drug pregnancy exposure registry. Together, the goal of the post-approval pregnancy safety studies are to provide clinically relevant human safety data that can inform healthcare providers treating or counseling patients who are pregnant or anticipating pregnancy about the safety of drugs and biological products through inclusion of information in a product's labeling.

A PMR for a milk only lactation study is also in order because the drug is an NME and use of Saphnelo is anticipated in females of reproductive potential; therefore, additional data are required to evaluate the quantity of drug, if any, that is transferred into human breastmilk.

¹² FDA Guidance for Industry Postapproval Pregnancy Safety Studies, July 2019.

¹³ FDA webpage Study Approaches and Methods To Evaluate the Safety of Drugs and Biological Products During Pregnancy in the Post-Approval Setting; Public Meeting <http://www.fda.gov/Drugs/NewsEvents/ucm386560.htm>

RECOMMENDATION

DPMH recommends the following language for the PMR study description in the action letter:

1. Conduct a prospective, registry based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to Saphnelo (anifrolumab-fnia) during pregnancy to an unexposed control population. The registry will detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, small for gestational age, preterm birth, and any other adverse pregnancy outcomes. These outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life.
2. Conduct an additional pregnancy study that uses a different design from the Pregnancy Registry (for example a retrospective cohort study using claims or electronic medical record data or a case control study) to assess major congenital malformations, spontaneous abortions, stillbirths, and small for gestational age and preterm birth in women exposed to Saphnelo (anifrolumab-fnia) during pregnancy compared to an unexposed control population.

DPMH recommends the following language for the PMR study description in the action letter:

1. Perform a lactation study, milk only, in lactating women who have received TRADENAME (anifrolumab-fnia) to assess concentrations of anifrolumab-fnia in breast milk using a validated assay.

Any further discussion about the study designs and study population will be discussed after approval, at the time of the draft study protocol review.

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/

CHRISTOS MASTROYANNIS
05/24/2021 08:26:30 AM

TAMARA N JOHNSON
05/24/2021 08:49:33 AM

LYNNE P YAO
05/24/2021 09:02:41 AM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	May 21, 2021
Requesting Office or Division:	Division of Rheumatology and Transplant Medicine (DRTM)
Application Type and Number:	BLA 761123
Product Name and Strength:	Saphnelo (anifrolumab-fnia) Injection, 300 mg/2 mL (150 mg/mL)
Applicant/Sponsor Name:	AstraZeneca Pharmaceuticals LP
OSE RCM #:	2020-1632-1
DMEPA Safety Evaluator:	Teresa McMillan, PharmD
DMEPA Team Leader:	Idalia Rychlik, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on April 20, 2021 and May 19, 2021 for Saphnelo. Division of Rheumatology and Transplant Medicine (DRTM) requested that we review the revised Prescribing Information, container label and carton labeling for Saphnelo (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

The Applicant implemented all of our recommendations except for the following recommendation for the container labels:

If space permits, consider adding the following statement: "For intravenous infusion after dilution. Discard any unused portion."

Per AstraZeneca, the current vial size is 2 mL and there is not enough space to accommodate additional statements on the container label. We defer to OBP labeling for the acceptability of this statement.

^a McMillan T. Label and Labeling Review for Saphnelo (BLA 761123). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 MAR 26. RCM No.: 2020-1632.

Additionally, per the information request response received via email from AstraZeneca on May 12, 2021, AstraZeneca has removed (b) (4) from this application and there are no plans (b) (4)

Thus, we find the submitted Prescribing Information, trade container labels and carton labeling acceptable from a medication error perspective. We have no additional recommendations at this time.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON APRIL 20, 2021 and May 19, 2021

Container labels

<\\CDSESUB1\evsprod\bla761123\0027\m1\us\draft-label-vial-sales.pdf>

Carton labeling

<\\CDSESUB1\evsprod\bla761123\0027\m1\us\draft-carton-sales.pdf>

<\\CDSESUB1\evsprod\bla761123\0035\m1\us\draft-carton-sales.pdf>

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/

TERESA S MCMILLAN
05/21/2021 08:48:24 AM

IDALIA E RYCHLIK
05/21/2021 12:10:39 PM

Clinical Inspection Summary

Date	May 18, 2021
From	Tina Chang, M.D., Reviewer Karen Bleich, M.D., Team Leader Kassa Ayalew, M.D., M.P.H, Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Amit Golding, M.D., Ph.D., Medical Officer Raj Nair, M.D., Clinical Team Leader Christine Ford, M.S., RPh, Regulatory Project Manager Division of Rheumatology and Transplant Medicine (DTRM)
BLA #	761123
Applicant	AstraZeneca Pharmaceuticals, L.P.
Drug	Anifrolumab (MEDI-546)
NME (Yes/No)	Yes
Therapeutic Classification	Type I IFN inhibitor
Proposed Indication(s)	A Type I IFN inhibitor indicated for the treatment of adult patients with moderate to severe, auto-antibody positive, systemic lupus erythematosus (b) (4)
Consultation Request Date	November 3, 2020
Summary Goal Date	April 1, 2021 (Original); June 15 (Extension)
Action Goal Date	July 30, 2021
PDUFA Date	July 31, 2021

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from three studies (D3461C0004, D3461C00005, and CD-IA-MEDI-546-1013) were submitted to the Agency in support of a biologics licensing application (BLA) 761123 for anifrolumab to treat adult patients with moderate to severe, auto-antibody positive systemic lupus erythematosus (SLE) (b) (4). Clinical inspections of the sponsor AstraZeneca Pharmaceuticals L.P., and four clinical investigators (Dr. Anurekha Chadha, Dr. Sabeen Najam, Dr. Phillip Waller, and Dr. Eric Lee) were conducted in support of this application.

Based on the results of the clinical investigators and sponsor inspections, Protocols D3461C0004, D3461C00005, and CD-IA-MEDI-546-1013 appear to have been conducted adequately, and the data generated appear acceptable in support of the proposed indication. However, based on the findings from the CI inspections, OSI has significant data reliability concerns regarding the data generated from Dr. Sabeen Najam and Dr. Phillip Waller because of their significant failure to prepare and maintain adequate and accurate source records for

Study D3461C00004. Therefore, OSI recommends conducting a sensitivity analysis to assess the validity and robustness of the results from the primary analysis by excluding the data generated by Dr. Najam and Dr. Waller.

II. BACKGROUND

Anifrolumab is a human immunoglobulin G1 kappa (IgG1 κ) monoclonal antibody (mAb) directed against type I interferon receptor (IFNAR1). AstraZeneca Pharmaceuticals, L.P., submitted data from three clinical trials in support of the use of anifrolumab for the treatment of moderate to severe systemic lupus erythematosus (SLE). The following describes briefly the Protocols D3461C00004, D3461C00005, and CD-IA-MEDI-546-1013.

Protocol D3461C00004 (TULIP 2)

Study Title: A Multicentre, Randomised, Double-blind, Placebo-controlled, Phase 3 Study Evaluating the Efficacy and Safety of Anifrolumab in Adult Subjects with Active Systemic Lupus Erythematosus

The primary objective of the study was to evaluate the effect of anifrolumab 300 mg compared to placebo on disease activity as measured by the difference in the proportion of patients who achieved a British Isles Lupus Assessment Group-based Composite Lupus Assessment (BICLA) response at Week 52.

The primary efficacy endpoint was the BICLA response at Week 52.

Note: AstraZeneca re-evaluated the primary and key secondary endpoints, and the primary efficacy endpoint was changed from Systemic Lupus Erythematosus (SLE) Responder Index ≥ 4 (SRI[4]) to the BICLA response at Week 52 before study D3461C00004 was unblinded.

A BICLA response at Week 52 was defined as:

- Reduction of all baseline British Isles Lupus Assessment Group (BILAG) 2004 A to B/C/D and baseline BILAG-2004 B to C/D, and no BILAG-2004 worsening in other organ systems (worsening defined as ≥ 1 new BILAG-2004 A or ≥ 2 new BILAG-2004 B); and
- No worsening from baseline in Systemic Lupus Erythematosus Disease Activity Index (SLEDAI-2K) with worsening defined as an increase of >0 points; and
- No worsening from baseline in the patients' lupus disease activity with worsening defined as an increase ≥ 0.30 points on a 3-point patient global assessment (PGA) visual analog scale (VAS); and
- No discontinuation of investigative product (IP); and
- No use of restricted medications beyond the protocol-allowed threshold before assessment

The study randomized 365 subjects from 119 sites in 15 countries. The first subject was enrolled on 9 July 2015 and the last subject completed the study on 6 December 2018.

Protocol D3461C00005 (TULIP 1)

Study Title: A Multicentre, Randomised, Double-blind, Placebo-controlled, Phase 3 Study Evaluating the Efficacy and Safety of Two Doses of Anifrolumab in Adult Subjects with Active Systemic Lupus Erythematosus

The primary objective of the study was to evaluate the effect of anifrolumab 300 mg compared to placebo on disease activity as measured by the difference in the proportion of patients who achieve an SLE Responder Index of ≥ 4 (SRI[4]) at Week 52.

The primary efficacy endpoint was the Systemic Lupus Erythematosus Disease Responder Index (SRI [4]) at Week 52.

SRI (4) is a composite score defined as:

- Reduction from baseline of ≥ 4 points in the SLEDAI-2K; and
- No new organ system affected as defined by 1 or more BILAG-2004 A or 2 or more BILAG-2004 B items compared to baseline using BILAG-2004; and
- No worsening from baseline in the patients' lupus disease activity defined by an increase ≥ 0.30 points on a 3-point PGA VAS; and
- No discontinuation of IP or use of restricted medications beyond the protocol-allowed threshold before assessment.

BICLA response at Week 52 was a key secondary efficacy endpoint in this study.

The study randomized 457 subjects from 123 sites in 18 countries. The first subject was enrolled on 9 June 2015 and the last subject completed the study on 17 July 2018.

Protocol CD-IA-MEDI-546-1013 (MUSE)

Study Title: A Phase 2, Randomized Study to Evaluate the Efficacy and Safety of MEDI-546 in Subjects with Systemic Lupus Erythematosus

The primary study objective was to evaluate the efficacy of anifrolumab compared to placebo at Day 169 (Week 24) in subjects with chronic, moderately-to-severely active SLE with an inadequate response to standard of care treatment for SLE.

The primary efficacy endpoints were the following:

- Proportion of subjects achieving an SLE responder index (SRI [4]) response at Day 169 with a sustained reduction of oral corticosteroids (OCS) defined as < 10 mg/day prednisone or equivalent and less than or equal to the dose received on Day 1 maintained between Days 85 and 169
- Proportion of type I IFN signature diagnostic test positive (i.e., type I IFN test high) subjects achieving an SRI (4) response at Day 169 with a sustained reduction of OCS (< 10 mg/day prednisone or equivalent and less than or equal to the dose received on

Day 1) maintained between Days 85 and 169

BICLA response at Week 52 was an exploratory efficacy endpoint.

The study randomized 307 subjects from 101 sites in 15 countries (Brazil, Bulgaria, Colombia, Czech Republic, Hong Kong, Hungary, India, Mexico, Peru, Poland, Romania, South Korea, Taiwan, Ukraine, and United States of America). The first subject was enrolled in January 2012 and the last subject completed the study in April 2015.

Rationale for Site Selection

The clinical investigators Dr. Anurekha Chadha, Dr. Sabeen Najam, Dr. Phillip Waller, and Dr. Eric Lee were selected for clinical site inspections using risk-based approach that also considers numbers of enrolled subjects and treatment effect. Dr. Eric Lee was added later to follow-up on data integrity concerns with the initial inspections of Dr. Najam and Dr. Waller for study D3461C00004.

III. RESULTS (by site):

1. Dr. Anurekha Chadha

Austin Regional Clinic
6811 Austin Center Blvd, Suite 300
Austin, TX 78731-3295
Study D3461C00005, Site 07904
Inspection dates: December 1-3, 2020

Dr. Chadha was inspected as a surveillance inspection for study D3461C00005. This was the first FDA inspection for this clinical investigator.

For study D3461C00005, Dr. Chadha screened 17 subjects and randomized nine subjects. Of the nine randomized subjects, three subjects discontinued the study and six subjects completed the study. Records for all nine subjects that were enrolled in the study were reviewed comprehensively during the inspection.

The inspection evaluated the following documents: comparison of all source documents with protocol requirements as well as all informed consent forms, and adverse event records.

The primary efficacy endpoint data and components of the secondary efficacy endpoint, BICLA response (SLEDAI-2K, BILAG 2004, PGA, investigational product administration, and rescue medication use) were verified for all subjects by comparison of source documents at the site to the submitted subject data line listings. There was no evidence of underreporting of adverse events.

This clinical investigator appeared to be in compliance with Good Clinical Practices. A

Form FDA 483 (Inspectional Observations) was not issued. Data submitted by this clinical site appear acceptable in support of this application.

2. Dr. Sabeen Najam

Accurate Clinical Management
1610 W Baker Road, Suite C
Baytown, TX 77521-2279
Study D3461C00004, Site 07834
Inspection dates: January 11-20, 2021

Dr. Najam was inspected as a surveillance inspection for study D3461C00004. This was the first FDA inspection for this clinical investigator.

For study D3461C00004, Dr. Najam screened 19 subjects. Seven subjects were enrolled and randomized. Among the 7 enrolled subjects, six subjects completed the study. Records for all seven subjects that were enrolled in the study were reviewed comprehensively during the inspection.

The inspection evaluated the overall control and administration of the clinical trial, adherence to the study protocols, an audit of relevant records such as informed consents, protocols and amendments, signed Statement of Investigator, financial disclosure statements, IRB submissions and correspondence, adverse event reporting, clinical source data, study test article accountability, concomitant medication, and sponsor monitoring activities.

There was no evidence of underreporting of adverse events.

Source records were created and maintained electronically at the site using Egnyte Data Control software system. The source records of the components of the efficacy endpoints (SLEDAI-2K and BILAG 2004 assessments) included physical exam assessments, medical history assessments, and lab assessments. Data related to physical exam and medical history were entered directly into the source electronic system at the time of the assessment; these data were not reliably captured elsewhere. Data related to lab results were initially captured as results generated by the testing laboratory and were subsequently entered into the electronic source record when available.

The electronic source record of each assessment timepoint was found to have been initially created, signed, and dated by Dr. Najam. Each assessment, however, was also subsequently modified at multiple time points. All versions of the assessments appear to have been retained. However, in most cases only the initial version of the assessment was signed by Dr. Najam. Subsequent versions of the assessments did not include information regarding who made the changes, when the changes were made, and whether Dr. Najam or another qualified member of the study staff approved of the changes. For the reasons described above, the accuracy and the integrity of the data from Dr. Najam's site are questionable.

Deficiencies with the electronic source documentation of adverse events were additionally identified. For example, according to the electronic source records, Subject # (b) (6) (placebo arm) experienced the adverse event bronchitis. The source record was electronically signed by Dr. Najam on 4/7/2016. The stop date of the adverse event was documented as (b) (6). There was no record of when the stop date was reported and by whom.

In order to further evaluate the inspectional findings regarding the lack of adequate documentation of changes to the electronic source records, an information request was sent to the study sponsor for an audit trail summary to allow comprehensive review of changes made to the source records relevant to the primary endpoint. The documents submitted by the study sponsor supported the initial inspectional findings; i.e., in many cases changes were made to the initial signed version of the source document without adequate documentation of the changes to the data.

The documentation submitted by the study sponsor additionally raised concerns about the adequacy of subject identification. Specifically, for the baseline visit (Visit 1) for Subject # (b) (6) (anifrolumab arm), there are copies of the electronic source records that indicate that the Subject's initials are (b) (6) and that the baseline visit occurred on (b) (6). The submission includes other copies of electronic source records that indicate that the Subject's initials are (b) (6) and that the baseline visit occurred on (b) (6).

Table 1 below details examples of changes to source records for which there is inadequate documentation to ensure the reliability of the data. Not included in the table are multiple instances in which laboratory results relevant to the rheumatologic assessments (renal labs, hematology labs, urinalysis, complement, and DNA binding) and assessments as to whether abnormal lab results were attributable to SLE were added to the electronic source records in unsigned versions of the record.

Table 1: Examples of unattributable changes to rheumatologic assessments in electronic source records for Dr. Najam's site

Subject/ Treatment arm	Visit	Data point	Result reported in initial signed version of e- source record	Result reported in current unsigned version of e-source record
(b) (6) Anifrolumab	Visit 1/ Baseline	BILAG 2004 (multiple fields)	<i>Blank</i>	Skin eruption – mild, same Mucosal ulceration – mild, same Alopecia – mild, same All other fields - No findings

(b) (6) Anifrolumab	Week 52	Physical exam, skin	Abnormal	Normal
(b) (6) Placebo	Visit 0/ Screening	Signs or symptoms of active TB	<i>Blank</i>	No
		Joint count, right elbow swelling	<i>Blank</i>	Present
		Joint count, left PIP4 swelling	<i>Blank</i>	Absent
		Arthritis	≥2 joints, basic ADLs affected	≥1 joint, some loss of function
	Week 52	Joint count, right knee swelling	Absent and present	Present
		Myositis	Not present	Mild, same

Reviewer's comment: The electronic source records are unreliable because unattributed changes were made after Dr. Najam had signed the initial version. According to the protocol, the SLEDAI-2K and the BILAG-2004 must be administered by the clinical investigator or another qualified physician. According to the site delegation log, no duties pertaining to clinical assessments were delegated to anyone other than Dr. Najam. There is no record that Dr. Najam was aware of or approved of the changes made to the source records after her initial sign-off of the document. Additionally, there is inconsistent identification of Subject # (b) (6), and we are unable to determine if some of the records labeled as belonging to Subject # (b) (6) may be for an unidentified subject.

Dr. Najam did not provide a corrective action plan in her written response to address the deficiencies in the electronic source documents she generated for this study. Her preventive action plan includes the use of a different electronic source documentation system. We did not evaluate records from the new system during this inspection and are thus unable to assess the adequacy of her preventive action plan. Dr. Najam did not propose actions to ensure that any changes made to source records are documented and attributable, regardless of unforeseen software difficulties that may be encountered.

At the conclusion of the inspection, a Form FDA-483, Inspectional Observations, was issued for regulatory violations related to the described findings. Based on the inspection findings, the data submitted by Dr. Najam may not be reliable.

3. Dr. Philip Waller

11003 Research Parkway, Suite 2012
Houston, TX 77089
Study D3461C00004, Site 07815
Study CD-IA-MEDI-546-1013, Site 1323501

Inspection dates: January 11-14, 2021

Dr. Waller was inspected as a surveillance inspection for study D3461C00004 and study CD-IA-MEDI-546-1013. Dr. Waller has been previously inspected on 2/15/2015 and classified as NAI.

For study D3461C00004, Dr. Waller screened 16 subjects. Ten subjects were randomized. Among the ten randomized subjects, eight subjects completed the study. Records for all ten subjects that were enrolled in the study were reviewed comprehensively during the inspection.

For study CD-IA-MEDI-546-1013, Dr. Waller screened 26 subjects and enrolled 12 subjects. Among the 12 enrolled subjects, ten completed the study treatment. Records for all 12 subjects that were enrolled in the study were reviewed comprehensively during the inspection.

The inspection included an evaluation and adherence to study protocol and site SOPs, sponsor monitoring of study conduct, subject's medical records, and GCP regulations applicable to the Clinical Investigator.

There was no evidence of underreporting of adverse events for both studies D3461C00004 and CD-IA-MEDI-546-1013.

For study D3461C00004, as mentioned above with Dr. Najam's site, source records were created and maintained electronically using Egnyte Date Control software system. The audit trail information provided by the Sponsor for Dr. Waller's site revealed similar issues where in most cases only the initial version of the assessment was signed by Dr. Waller and subsequent versions of the assessments did not include information regarding who made the changes, when the changes were made, and whether Dr. Waller or another qualified member of the study staff approved of the changes. The table below details examples of changes to source records for which there is inadequate documentation to ensure the reliability of the data. Not included in the table are multiple instances in which laboratory results relevant to the rheumatologic assessments (renal labs, hematology labs, urinalysis, complement, and DNA binding) and assessments as to whether abnormal lab results were attributable to SLE were added to the electronic source records in unsigned versions of the record.

Table 2: Examples of unattributable changes to rheumatologic assessments in electronic source records for Dr. Waller's site

Subject/ Treatment arm	Visit	Data point	Result reported in initial signed version of e-source record	Result reported in current unsigned version of e- source record	Comments

(b) (6) Placebo	Week 52	Entire Week 52 assessment			One version of the full assessment that occurred on (b) (6) provided with a signature date of (b) (6) but no signature and no information regarding version or changes.
(b) (6) Anifrolumab	Visit 1/ Baseline	BILAG 2004, blood pressure (BP)	Blank	103/84	
		CLASI, hand erythema	0	1	
	Week 52	Entire Week 52 assessment			Documents submitted in folder for Subject # (b) (6) Week 52 are for Subject # (b) (6). No results received for Subject # (b) (6) Week 52.
(b) (6) Placebo	Visit 1/ Baseline	Physical exam, thyroid	Normal	Abnormal	
		SLEDAI-2K, pleurisy	Not present	Present	
(b) (6) Anifrolumab	Week 52	BILAG 2004, BP	Blank	109/68	
(b) (6) Anifrolumab	Week 52	BILAG 2004, BP	Blank	114/72	
(b) (6) Placebo	Week 52	BILAG 2004, BP	Blank	118/73	
(b) (6) Anifrolumab	Week 52	BILAG 2004, BP	Blank	109/78	

Reviewer's comment: The data in the electronic source records are unreliable because unattributed changes were made after Dr. Waller had signed the initial version. Additionally, there is no record for the Week 52 visit for Subject # (b) (6) and there is no signed version of the Week 52 assessment for Subject # (b) (6).

For study D3461C00004, the following discrepancies were discovered when comparing the source documents at the site submitted by the sponsor in the audit trail summary to the submitted subject data line listings for the SLEDAI-2K:

Table 3. SLEDAI-2K score discrepancies to submitted subject data listings

Subject	Treatment arm	Visit	Date	Source result	Data line listing entry
(b) (6)	Placebo	Baseline	(b) (6)	10	14
	Placebo	Week 52	(b) (6)	10	blank
	Anifrolumab	Week 52	(b) (6)	10	blank

Reviewer's comment: All data discrepancies in Table 3 are relevant to the determination of the composite primary endpoint which includes the SLEDAI-2K score at baseline and at Week 52.

At the conclusion of the inspection, a Form FDA-483, Inspectional Observations, was not issued. Based on the inspection findings, the data submitted by Dr. Waller for study D3461C00004 may not be reliable.

4. Dr. Eric Lee

Inland Rheumatology and Osteoporosis Medical Group
1238 East Arrow Highway
Upland, CA 91786
Study D3461C00004, Site 7825
Inspection dates: May 2-7, 2021

Dr. Lee was inspected as a surveillance inspection for study D3461C00004. Dr. Lee has been previously inspected on 4/20/2016 and classified as NAI.

For study D3461C00004, this site screened 14 subjects and enrolled eight subjects. All eight subjects completed the study. Records for all eight subjects that were enrolled in the study were reviewed comprehensively during the inspection.

The inspection evaluated the following documents: informed consents, protocols and amendments, protocol training, signed Statement of Investigator, financial disclosure statements, IRB submissions and correspondence, adverse event reporting, clinical source data, study test article accountability, concomitant medications, and sponsor monitoring activities.

This site only used paper source records and does not use electronic software. The SLEDAI-2K, BILAG 2004 Index, and PGA VAS scores at Baseline (Visit 1) and Week 52 (Visit 14) were verified for all subjects by comparison of source documents at the site

to the submitted subject data line listings. o subjects discontinued the study drug. There were no instances of use of restricted medications by any subject. There was no evidence of underreporting of adverse events.

This clinical investigator appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (Inspectional Observations) was not issued. Data submitted by this clinical site appear acceptable in support of this application.

5. AstraZeneca Pharmaceuticals, LP

1 Medimmune Way
Gaithersburg, MD 20878-2204
Inspection dates: February 22-26, 2021

The inspection covered review of investigational sites, monitoring practices, sponsor study oversight, electronic records, and drug accountability records.

For study DC346C0004, one site was closed due to sustained GCP non-compliance, and for study DC3461C00005, one site was closed due to GCP non-compliance.

- For study D3461C0004, Site 7835 under Dr. Abdeinaser Elkhilili was closed due to sustained noncompliance with protocol procedures and specifications. This included but was not limited to failure to follow protocol stipulated inclusion/exclusion criteria, failure to maintain proper documentation in patient source files, and failure to maintain proper investigator oversight. This site was excluded from all analysis sets, and the site closure were reported to the FDA in the clinical study report. Data from the 13 screened and/or randomized patients were not included in analyses and summaries

For study D3461C00005, Site 7857 under Dr. Aaron Eggebeen was closed due to noncompliance with protocol procedures and specifications. This included but was not limited to lack of adherence to the blinding plan and delegation log by the unblinded pharmacist and lack of adherence by the site study coordinator and unblinded pharmacist to their roles and responsibilities for accountability of IP including reconstitution and preparation leading to potential risk of unblinding study data. This site was excluded from all analysis sets, and the site closure were reported to the FDA in the clinical study report. Data from 3 randomized patients as well as 1 screen failure were not included in analyses and summaries

Reviewer comment: The site closures are reported in the clinical study report and the data generated from the sites was in the submission. The sites have been reported to the GCP Oversight Branch of OSI for evaluation of regulatory compliance.

At Dr. Phillip Waller's site, for study CD-IA-MEDI-546-1013, 12 subjects were enrolled and 10 subjects completed the study. The components of the BICLA response (SLEDAI-2K, the full BILAG analysis set, Visual Analog Score) were verified for nine subjects by comparison of Dr. Waller's records in AstraZeneca's electronic data capture (EDC) to the submitted subject data line listings.

Maintenance of blinding was adequate throughout for all three studies (DC346C00004,

DC346100005, CD-IA-MEDI-546-1013.) The data and safety monitoring board (DSMB) consisted of multi-disciplinary group of two rheumatologists, one infectious disease, one nephrologist, and one biostatistician. On 1/25/2019, DSMB minutes document how study D3461C00005 did not meet the primary efficacy endpoint. Study D3461C00005 was closed out and high level, aggregate efficacy and safety data were presented to the full DSMB, (b) (4) attendees. The Sponsor and (b) (4) medical team remained blinded to study D3461C00004. The DSMB reviewed the Closed Report (partially unblinded by masked treatment arms) for study D3461C00004 during the closed session.

In general, the sponsor appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (Inspectional Observations) was not issued. Data submitted by this sponsor appear acceptable in support of this biologic license application.

{ See appended electronic signature page }

Suyoung Tina Chang, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{ See appended electronic signature page }

Karen Bleich, M.D.
Team Leader,
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{ See appended electronic signature page }

Kassa Ayalew, M.D., M.P.H.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CC:

Central Doc. Rm.
Review Division /Division Director/
Review Division /Medical Team Leader/
Review Division /Project Manager/
Review Division/MO/
OSI/Office Director/
OSI/DCCE/ Division Director/
OSI/DCCE/Branch Chief/
OSI/DCCE/Team Leader/
OSI/DCCE/GCP Reviewer/
OSI/ GCP Program Analysts/
OSI/Database PM/Dana Walters

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/

SUYOUNG T CHANG
05/18/2021 02:27:47 PM

KAREN B BLEICH
05/18/2021 02:51:18 PM

KASSA AYALEW
05/18/2021 02:58:22 PM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	March 26, 2021
Requesting Office or Division:	Division of Rheumatology and Transplant Medicine (DRTM)
Application Type and Number:	BLA 761123
Product Name, Dosage Form, and Strength:	Saphnelo (anifrolumab-fnia) Injection, 300 mg/2 mL (150 mg/mL)
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	AstraZeneca Pharmaceuticals LP
FDA Received Date:	July 31, 2020
OSE RCM #:	2020-1632
DMEPA Safety Evaluator:	Teresa McMillan, PharmD
DMEPA Team Leader:	Idalia Rychlik, PharmD

1 REASON FOR REVIEW

As part of the approval process for Saphnelo (anifrolumab-fnia) Injection, the Division of Rheumatology and Transplant Medicine (DRTM) requested that we review the proposed Saphnelo prescribing information (PI), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 FINDINGS AND RECOMMENDATIONS

Table 2: Identified Issues and Recommendations for Division of Rheumatology and Transplant Medicine (DRTM)

Prescribing Information (Highlights and Full Prescribing Information)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
General Issues			
1.	The 'TRADENAME' placeholder for the proposed proprietary name and the '(Anifrolumab-xxxx)' proposed suffix placeholder for the nonproprietary name	Both the proposed proprietary name, 'Saphnelo', and the proposed suffix, 'fnia', for the nonproprietary name (anifrolumab-fnia), were found conditionally acceptable on October 20,	To minimize confusion, replace all instances of the placeholders 'TRADENAME' and '(Anifrolumab-xxxx)' to Saphnelo and (anifrolumab-fnia).

	appear throughout the Prescribing Information.	2020 and November 3, 2020. Both should be presented throughout the Prescribing Information to minimize confusion.	
Full Prescribing Information			
1.	Use of trailing zero for dosing statements in Section 2, Dosage and Administration	Trailing zeros have led to ten-fold overdoses	Remove the trailing zeros throughout this section (e.g. change 2.0 mL to 2 mL

Table 3: Identified Issues and Recommendations for AstraZeneca Pharmaceuticals LP (entire table to be conveyed to Applicant)

Container Labels and Carton Labeling (Trade and Professional Sample)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
1.	The 'TRADENAME' placeholder for the proposed proprietary name appears on the container labels and carton labeling.	The proposed proprietary name, 'Saphnelo', was found conditionally acceptable on November 3, 2020. It should be presented throughout the container labels and carton labeling to minimize confusion.	To minimize confusion, replace all instances of the placeholder 'TRADENAME' to Saphnelo.
Container Labels (Trade and Professional Sample)			
2.	The route of administration has been omitted from the principal display panel.	Omission of the route of administration from the principal display panel may lead to wrong route of administration medication errors.	If space permits, consider adding the following statement: "For intravenous infusion after dilution. Discard any unused portion."
3.	The package type has been omitted from the principal display panel.	Omission of the package type from the principal display panel may prevent the medication from being safely handled and used.	Add "single dose vial" to the bottom of the principal display panel.
4.	The "Rx only" statement appears more prominent	Increase prominence and close proximity of the "Rx	Decrease the prominence of and relocate the "Rx only"

	than other important information (e.g. proprietary name, established name or nonproprietary name, strength) on the principal display panel and is in close proximity to this information.	only" statement to other important information on the principal display panel may lead to confusion.	statement to the lower left-hand corner or a different area on the PDP to avoid confusion with strength and nonproprietary name.
Carton Labeling (Trade and Professional Sample)			
1.	The recommended dosage and administration and storage statements are inconsistent with the Prescribing Information.	Inconsistency with the prescribing information may lead to dosing and administration and storage medication errors.	To ensure consistency with the Prescribing Information, revise the dosage and administration statement, to read "Recommended Dosage: See prescribing information." Revise and bold the storage statement to read "Store refrigerated at 2°C to 8°C (36°F to 46°F). Keep vial in original carton to protect from light. Do not shake or freeze." We recommend this to increase the prominence of this important information and minimize the risk of the storage information being overlooked.

4 CONCLUSION

Our evaluation of the proposed Prescribing Information, container labels and carton labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 2 for the Division and Table 3 for the Applicant. We ask that the Division convey Table 3 in its entirety to AstraZeneca so that recommendations are implemented prior to approval of this BLA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Saphnelo received on July 31, 2020 from AstraZeneca Pharmaceuticals LP.

Table 2. Relevant Product Information for Saphnelo	
Initial Approval Date	N/A
Nonproprietary Name	anifrolumab-fnia
Indication	<ul style="list-style-type: none"> Treatment of adult patients with moderate to severe systemic lupus erythematosus (SLE) (b) (4)
Route of Administration	Intravenous
Dosage Form	Injection
Strength	300 mg/2 mL (150 mg/mL)
Dose and Frequency	300 mg every four weeks. Dilute and administer as an intravenous infusion over a period of 30 minutes.
How Supplied	<ul style="list-style-type: none"> 2 mL of concentrate in a (b) (4) clear (b) (4) glass vial closed by a (b) (4) elastomeric stopper sealed with an aluminum overseal.
Storage	(b) (4)

APPENDIX B. PREVIOUS DMEPA REVIEWS

On January 12, 2021, we searched for previous DMEPA reviews relevant to this current review using the terms, anifrolumab. Our search did not identify any previous reviews that were relevant to this review..

APPENDIX C. HUMAN FACTORS STUDY-N/A

APPENDIX D. ISMP NEWSLETTERS-N/A

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)-N/A

APPENDIX F. N/A

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^a along with postmarket medication error data, we reviewed the following Saphnelo labels and labeling submitted by AstraZeneca Pharmaceuticals LP.

- Container label received on July 31, 2020
- Carton labeling received on July 31, 2020
- Prescribing Information (Image not shown) received on July 31, 2020, available from <\\CDSESUB1\evsprod\bla761123\0001\m1\us\nonannotated-draft-label-anifrolumab-sle.pdf>

G.2 Label and Labeling Images

Container Labels- Professional Sample and Trade



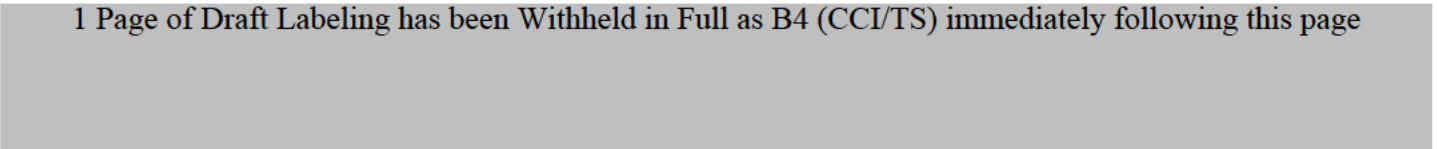
^a Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

Carton Labeling Professional Sample and Trade

(b) (4)



1 Page of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page



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/

TERESA S MCMILLAN
03/26/2021 11:20:32 AM

IDALIA E RYCHLIK
03/26/2021 12:11:25 PM



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III
Division of Dermatology and Dentistry
Silver Spring, MD 20993

Tel: 301 796-2110
Fax: 301 796-9894

MEMORANDUM

Date: March 11, 2021

From: Brenda Carr, M.D., Medical Officer/DDD

Through: Snezana Trajkovic, M.D., Clinical Team Leader/DDD
Kendall Marcus, M.D., Division Director/DDD

To: Christine Ford, RPM/DRTM

Cc: H.F. Van Horn, III, RPM/DRO/DDD
Barbara Gould/Chief, Project Management Staff/DRO/DDD

Re: DDD Consult #2079 – BLA 761123

Material Reviewed: Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) instrument

Background: On July 22, 2020, AstraZeneca submitted a Biologics License Application (BLA) proposing anifrolumab intravenous injection for “treatment of adult patients with moderate to severe systemic lupus erythematosus, (b) (4).” Per the cover letter to the BLA, anifrolumab is a monoclonal antibody directed against subunit 1 of the type I interferon receptor (IFNAR1).

The Division of Rheumatology and Transplant Medicine (DRTM) submitted a consult to the Division of Dermatology and Dentistry (DDD), as below:

This is a consult for assignment and DDD review of new BLA for anifrolumab proposed for the treatment of systemic lupus erythematosus (SLE). Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) has been used as a secondary endpoint (b) (4). A Medical Policy & Program Review Council (MPPRC) meeting has been scheduled for 12/2/2020. DDD review team participation for the MPPRC, a planned AC, and milestone meetings is requested.

In 2014, the then Division of Dermatology and Dental Products (DDDP) provided consult #1593 to the then Division of Pulmonary, Allergy, and Rheumatology Products, on use of the CLASI in the anifrolumab development program for SLE (IND 101849). In that consult, DDDP stated that,

We do not agree that the Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) is an acceptable tool for the measurement of reduction of skin disease in SLE subjects [REDACTED] (b) (4)

[REDACTED] (b) (4)

DTRM and DDD agreed that DDD would not review any portion of BLA 761123 in detail for the current consult and would provide high-level advice regarding concerns with the CLASI. DDD's position is unchanged from consult #1593 [REDACTED] (b) (4) and we do not consider the instrument to be fit-for-purpose as utilized in AstraZeneca's development program. As communicated in the previous consult (#1593):

The presentations of cutaneous LE are highly variable, and each CLASI score represents a bundling of different cutaneous signs into a single score. Each subject's activity score may represent a different combination of clinical signs. For example, there are several possible ways for arriving at a Total Activity Score of, say, "12": This total could reflect the presence of erythema at several sites; it could reflect erythema with mucous membrane involvement, erythema with scale and alopecia, etc. Therefore, a decrease in CLASI might reflect improvement in different elements of the scale (e.g. improvement in alopecia or erythema) depending on what elements on the scale contributed to an individual's baseline score. Simply reporting a decrease in the CLASI does not permit or present a clinical picture of the nature of improvement, as one would not be able to determine what elements on the CLASI were impacted by study treatment and made for the reduction in score. Therefore, [REDACTED] (b) (4)

[REDACTED] a reduction in the CLASI score is not interpretable. Reporting of a reduction would not convey what elements on the CLASI were impacted, e.g. is the reduction driven by a decrease in erythema or improvement of mucosal lesions or improvement in some combination of signs?

***Comment:** Consult #1593 references MedImmune as the sponsor of IND 101849, while AstraZeneca submitted the BLA. Per the BLA cover letter, MedImmune "is a wholly-owned subsidiary of AstraZeneca and is a member of the AstraZeneca Group."*

Clinical Outcome Assessments Qualification Program

The CDER Clinical Outcome Assessments (COA) Qualification Program received a Letter of Intent (LOI) for Drug Development Tool (DDT) COA #000135 on May 4, 2020 for the CLASI, proposed for the presence and severity of signs of cutaneous manifestations in patients with SLE. The submitter was "the CLASI Working Group," composed of individuals from academia, the Lupus Foundation of America, and industry (Biogen, Bristol-Myers Squibb, and Celgene). The FDA accepted the LOI into the CDER COA Qualification Program on 08/05/2020, and the outcome of that process is pending.

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/

BRENDA CARR
03/17/2021 09:30:35 AM

SNEZANA TRAJKOVIC
03/17/2021 09:32:40 AM

KENDALL A MARCUS
03/17/2021 09:56:04 AM