

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761037Orig1s000

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

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

Application Type	BLA
Application Number	761037
Reviewer Name	Charlotte Jones, MD, PhD., MSPH
Team Leader	Donella Fitzgerald, Pharm.D.
Deputy Div. Director	Jamie Wilkins Parker, Pharm.D.
Date	May 22, 2017
Subject	Risk Management Review Memorandum
Established Name	Sarilumab
Proposed Trade Name	Kevzara
Name of Applicant	Sanofi-Aventis U.S. LLC
Therapeutic Class	Immunomodulator; interleukin-6 (IL-6) receptor antagonist
Formulation(s)	Prefilled syringe (PFS), 150 mg and 200 mg
Dosing Regimen	200 mg every 2 weeks

1 Introduction and Background

This memorandum by the Division of Risk Management (DRISK) provides an updated evaluation of whether a risk mitigation strategy (REMS) for the new molecular entity (NME) Sarilumab is necessary to ensure the benefits of this product outweigh its risks. Sanofi-Aventis submitted a Biologic Licensing Application (BLA # 761037) for Sarilumab with the proposed indication of the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to one or more Disease-Modifying Anti-Rheumatic drugs (DMARDs) on October 30, 2015. A complete response (CR) was subsequently issued on October 28, 2016 due to deficiencies identified during the facility inspection. On March 24, 2017, Sanofi submitted a Type 1 resubmission. Sarilumab, a new molecular entity, is a fully human IgG1 mAb to the interleukin-6 (IL-6) receptor.

DRISK completed a REMS review during the previous review cycle for this product on September 29, 2016.¹ Since the completion of the DRISK review, a developmental safety update report (DSUR) was submitted by the sponsors in January of 2017.² No new efficacy data was submitted in the Type 1 resubmission, therefore this memorandum only pertains to the DSUR as it informs DRISK's evaluation on the necessity of a REMS for Sarilumab.

2 Discussion

At the time of the initial review by DRISK in September of 2016 the risks associated with the use of Sarilumab included serious infections and laboratory abnormalities, including neutropenia, thrombocytopenia, hepatic transaminase and lipid elevations. It was determined that the risks could be communicated through professional labeling, including a boxed warning for serious infection. Rheumatologists who are the expected prescribing population for Sarilumab are familiar with the risks seen with Sarilumab.¹

During the initial review cycle in October 2016, the clinical reviewer, analyzed and assessed the risk of hypersensitivity. She stated, "As a biologic DMARD, hypersensitivity is an anticipated adverse event. In conclusion, there were more hypersensitivity events and injection site reactions in the Sarilumab treatment arms. Therefore, the safety data support a risk of hypersensitivity events with Sarilumab treatment. There does not appear to be a dose-response. Importantly, for the entire Sarilumab program, there were no cases of anaphylaxis, and no subjects experienced Sanofi's definition of a "severe hypersensitivity event."³

In the developmental safety update, which covered the period from November 15, 2015- November 14, 2016, the applicant identified an additional case of severe hypersensitivity.² This was a case of investigator identified suspected Stevens-Johnson syndrome (SJS), which after review by external experts, selected by the applicant without agency input, was considered to be a severe cutaneous reaction and not SJS.

The prescribing population for Sarilumab is already familiar with the risk of hypersensitivity reactions associated with biologic DMARDs used for the treatment of severe rheumatoid arthritis.^{4,5} The hypersensitivity risk associated with Sarilumab will be addressed in the Warnings and Precautions section of the Prescribing Information.⁶ The addition of the hypersensitivity case does not alter DRISK's conclusion documented September 29, 2016 in review RCM 2016-2461.¹

3 Conclusion

After review of the Developmental Safety Update Report submitted by Sanofi-Aventis on January 12, 2017, DRISK and the Division of Pulmonary, Allergy, and Respiratory Products (DPARP) remain in agreement that a REMS is not needed to ensure the benefits of Sarilumab outweigh its risks.⁷ In general, healthcare providers who treat rheumatoid arthritis should be familiar with the risks associated with biologic DMARDs, including the risk of severe hypersensitivity for Sarilumab.

Should DPARP have any concerns or questions, or feel that a REMS is warranted for this product, or if new safety information becomes available; please send a consult to DRISK.

4 References

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6. Ford C. Sarilumab BLA 761037 Labeling PMR/PMC Discussion Comments. *DAARTS*. (May 15, 2017).
7. Peng S. Sarilumab BLA 761037 Clinical Review. *DAARTS*. (May 16, 2017).

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/s/

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05/22/2017

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

Application Type: BLA

Application Number: 761037

PDUFA Goal Date: October 30, 2016

OSE RCM # 2016-2461

Reviewer Name(s): Elizabeth Everhart, MSN, RN, ACNP
Division of Risk Management (DRISK)

DRISK Team Leader: Jamie Wilkins Parker, PharmD, DRISK

Division Director: Cynthia LaCivita, PharmD, DRISK

Review Completion Date: September 29, 2016

Subject: Evaluation to determine if a REMS is necessary

Established Name: Sarilumab (SAR153191)

(Proposed) Trade Name: Kevzara

Applicant: Sanofi-Aventis U.S. LLC

Therapeutic Class: Immunomodulator; interleukin-6 (IL-6) receptor antagonist

Formulation(s): Prefilled syringe (PFS), 150 mg and 200 mg

Dosing Regimen:

- 200 mg every 2 weeks
- Reduction of dose to 150 mg every 2 weeks for management of neutropenia, thrombocytopenia, and elevated liver enzymes

Table of Contents

1

2 EXECUTIVE SUMMARY3

3 1 Introduction.....3

4 2 Background3

5 2.1 Product Information.....3

6 2.2 Regulatory History4

7 3 Therapeutic Context and Treatment Options4

8 3.1 Description of the Medical Condition.....4

9 3.2 Description of Current Treatment Options4

10 4 Benefit Assessment.....5

11 5 Risk Assessment & Safe-Use Conditions.....7

12 5.1 [Serious Adverse Reactions]8

13 6 Expected Postmarket Use.....10

14 7 Evaluating the Need for a REMS.....10

15 8 Risk Management Activities Proposed by the Applicant.....11

16 8.1 Other Proposed Risk Management Activities11

17 9 Conclusion & Recommendations12

18 10 Appendices12

19 10.1 Materials Reviewed.....12

20

EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Sarilumab is necessary to ensure the benefits of this product outweigh its risks. Sanofi-Aventis submitted a Biologic Licensing Application (BLA #761037) for sarilumab with the proposed indication of the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to one or more Disease-Modifying Anti-Rheumatic drugs (DMARDs). The risks associated with the use of Kevzara are serious infections, and laboratory abnormalities, including neutropenia, thrombocytopenia, hepatic transaminase and lipid elevations. The applicant's proposed REMS consists of [REDACTED] (b) (4) [REDACTED]. The Applicant voluntarily proposed a Medication Guide as part of product labeling, as well as a non-REMS pregnancy registry.

Based on current data, risks can be adequately communicated through professional labeling. The prescribing population is familiar with monitoring for the risks associated with other biologic DMARDs, which include serious infections, neutropenia, thrombocytopenia, hepatic transaminase and lipid elevations, and GI perforations. DRISK and the Division of Pulmonary, Allergy, and Respiratory Products (DPARP) agree that a REMS is not needed to ensure the benefits of sarilumab outweigh its risks because in general, healthcare providers who treat rheumatoid arthritis are familiar with risks associated with other biologic DMARDs, which include serious infections, neutropenia, thrombocytopenia, hepatic transaminase and lipid elevations, and GI perforations, and the importance of patient monitoring.

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) sarilumab is necessary to ensure the benefits of this product outweigh its risks. Sanofi-Aventis submitted a Biologic Licensing Application (BLA # 761037) for sarilumab with the proposed indication of the treatment of rheumatoid arthritis in adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to one or more Disease-Modifying Anti-Rheumatic drugs (DMARDs) on October 30, 2015. The Applicant's proposed REMS consists of [REDACTED] (b) (4) [REDACTED] [REDACTED] [REDACTED]. The Applicant proposed a Medication Guide as part of product labeling, as well as a pregnancy registry that is not part of a REMS.

2 Background

2.1 PRODUCT INFORMATION

Sarilumab, a new molecular entity, is a fully human IgG1 mAb to the interleukin-6 (IL-6) receptor. Elevated levels of IL-6 are found in the synovial fluid of patients with rheumatoid arthritis (RA) and they are important in the inflammation and joint destruction that are key features of RA.

The proposed indication for sarilumab is as a treatment of adult patients with moderately to severely active RA who have had an inadequate response or intolerance to one or more DMARDs. Sarilumab maybe be used as monotherapy or in combination with methotrexate (MTX) or other traditional DMARDs as a subcutaneous injection. The proposed dose is 200 mg in a prefilled syringe (PFS) by the subcutaneous route every 2 weeks with a dose modification to 150 mg subcutaneously every 2 weeks for the management of neutropenia, thrombocytopenia, or elevated hepatic transaminases. Kevzara is not currently approved in any jurisdiction.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for BLA #761037 relevant to this review:

- 10/30/2015: BLA 761037 submission for treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to one or more Disease-Modifying Anti-Rheumatic Drugs (DMARDs)received. The submission included a CP REMS, a Medication Guide as part of product labeling, and a pregnancy registry.
- 04/06/2016: Mid-cycle meeting was held between Agency and Applicant. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for sarilumab.
- 07/25/2016: Late-cycle meeting was held between the Agency and the Applicant. The Agency informed the Applicant that the need for post-marketing safety data concerning serious cardiovascular events is still under discussion internally. The Agency also informed the Applicant that a warning concerning hypersensitivity events will need to be added to product labeling.

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Rheumatoid arthritis (RA) is an autoimmune disease involving inflammation of the synovium that affects approximately 1.3 million Americans. The inflammation causes progressive bone erosion leading to joint misalignment, loss of function and disability.^a Health-related quality of life is significantly impaired in patients with RA due to pain, deficits in function, and RA-associated fatigue. Generally, mortality rates are 1.5 to 1.6 fold higher in RA patients than in the general population.

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

The goal of treatment of RA is to treat to target – either decreased disease activity or remission. Non-biologic DMARDs such as methotrexate are the recommended first line of therapy in RA. For patients who do not respond to non-biologic DMARD therapy, or progress while on treatment, an oral kinase

^a Donahue KE, Jonas D, Hansen RA, Roubey R, Jonas B, Lux LJ, Gartlehner G, Harden E, Wilkins T, Peravali V, Bangdiwala SI, Yuen A, Thieda P, Morgan LC, Crotty K, Desai R, Van Noord M. Drug Therapy for Rheumatoid Arthritis in Adults: An Update. Comparative Effectiveness Review No. 55. (Prepared by RTI-UNC Evidence-based Practice Center under Contract No. 290-02-0016-I.) AHRQ Publication No. 12-EHC025-EF. Rockville, MD: Agency for Healthcare Research and Quality. April 2012.

inhibitor, tofacitinib (Xeljanz) or injectable biologic treatment is recommended as add-on or monotherapy.^b Currently approved biologic treatments include the oral biologic product, tofacitinib (Xeljanz), as well as injectable biologics etanercept (Enbrel), infliximab (Remicade), adalimumab (Humira), certolizumab pegol (Cimzia), golimumab (Simponi), Orencia (abatacept), rituximab (Rituxan), anakinra (Kineret), and tocilizumab (Actemra).

Many RA patients relapse or are intolerant to DMARDs, and so there remains an unmet medical need for effective treatment for RA. Currently, Actemra (tocilizumab) is the only other FDA-approved biologic in the same class as sarilumab.

Actemra, a first-in-class IL-6 receptor inhibitor, was approved in 2010 with a CP REMS for risks of serious infections, GI perforations, changes in liver function, decreases in peripheral neutrophil counts, decreases in platelet counts, elevations in lipid parameters in peripheral blood, demyelinating disorders, and malignancies; the REMS was subsequently released in September, 2015.

4 Benefit Assessment

The efficacy and safety of sarilumab were demonstrated in two pivotal phase 3 studies, EFC11072 Part B, Cohort 2 and EFC10832. Persistence of efficacy was evaluated in a long-term extension study (LTS11210) that allowed assessment of efficacy and safety through approximately 3 years of continuous treatment.

Both Phase 3 studies were similar in design: multicenter, randomized, double-blind, and placebo-controlled, fixed dose, parallel group trials which differed in duration (52 weeks and 24 weeks, respectively). Both studies had the same co-primary efficacy endpoints: the proportion of patients who achieved an ACR20 response at Week 24 and change from baseline HAQ-DI score (at Week 16 in EFC11072 Part B, Cohort 2 and at Week 12 in EFC10832). ACR20 is an American College of Rheumatology Criteria that assesses improvement in tender or swollen joint counts and improvement in three of the following five parameters: acute phase reactant (such as sedimentation rate), patient assessment, physician assessment, pain scale, and disability/functional questionnaire.^c HAQ-DI, or the Health Assessment Questionnaire for Rheumatoid Arthritis, is a questionnaire that is used for measuring functional status in RA. Change from baseline in modified total Sharp score (mTSS) at Week 52 was the third co-primary endpoint in EFC11072 Part B, Cohort 2 only. The mTSS score is a radiographic

^b Singh, JA, Saag, KG, Bridges, SL, Akl, EA, Bannuru, RR, Sullivan, M. C., Vaysbrot, E, McNaughton, C, Osani, M, Shmerling, RH, Curtis, JR, Furst, DE, Parks, D, Kavanaugh, A, O'Dell, J, King, C, Leong, A, Matteson, EL, Schousboe, JT, Drevlow, B, Ginsberg, S, Grober, J, St.Clair, EW, Tindall, E, Miller, AS and McAlindon, T (2016), 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. *Arthritis Care & Research*, 68: 1–25. doi:10.1002/acr.22783

^c ACR Preliminary Definition of Improvement in Rheumatoid Arthritis. Felson, David T. *Arthritis & Rheumatism*. June 1995. American College of Rheumatology. 17 Nov 2006.

assessment for joint damage. It is an accepted endpoint and has been utilized as support for the labeling claim of inhibition of structural progression^d.

Additionally, preliminary safety and efficacy of sarilumab in RA were demonstrated by a Phase 2 placebo-controlled dose-ranging study, EFC11072 Part A. EFC11072 Part A was the initial stage of the Phase 2/3 study that provided the clinical data to select the dose regimens to be tested and provide supportive evidence of efficacy in Phase 3 testing.

In pivotal study EFC11072 Part B, Cohort 2, subjects with an inadequate response to methotrexate (MTX) or patients previously treated with biologic DMARDs for RA were enrolled. 1197 subjects were randomized to receive placebo + MTX (n=398), sarilumab 150 mg q2 weeks + MTX (n=400), or sarilumab 200 mg q2 weeks + MTX (n=399) over a 52-week treatment period. Per the medical officer's review, the number (%) of who achieved an ACR20 response was 133 (33.4), 232 (58), and 265 (66.4) in the placebo +MTX, sarilumab 150 mg q2 weeks + MTX, and sarilumab 200 mg q2 weeks + MTX arms, respectively; p-value vs placebo was <0.0001 for both treatment arms. The LS mean change (SED) from baseline in HAQ-DI was -0.29 (0.03), -0.53 (0.03), and -0.55 (0.03) in the placebo + MTX, sarilumab 150 mg q2 weeks + MTX, and sarilumab 200 mg q2 weeks + MTX arms, respectively; p-value vs placebo was <0.0001 for both treatment arms. The LS mean change from baseline at Week 52 in mTSS (SE) was 2.78 (7.73), 0.90 (4.66), and 0.25 (4.61) in the placebo + MTX, sarilumab 150 mg q2 weeks, and sarilumab 200 mg q2 weeks arms, respectively; p-value vs placebo was <0.0001 for both treatment arms.

Per the medical officer's clinical review, pivotal study EFC10832 was a randomized, double-blind, parallel, placebo-controlled study assessing the efficacy and safety of sarilumab added to non-biologic DMARD therapy in patients with RA who are inadequate responders to or intolerant of TNF α antagonists. The co-primary endpoints in this study were ACR20 response rate at Week 24 and change from baseline in HAQ-D1 at Week 12. Patients were randomized in a 1:1:1 ratio to receive SC injections of sarilumab 150mg q2weeks (n=181) or sarilumab 200 mg q2weeks (n=184) or placebo q2weeks (n=181). From Week 12 onwards, patients were evaluated with lack of efficacy, defined as less than 20% improvement from baseline in either swollen joint count or tender joint count for 2 joint assessments that were at least 4 weeks apart. Patients who met criteria for "lack of efficacy" were allowed to be rescued with open-label sarilumab in the ongoing open-label extension study. The number (%) of who achieved an ACR20 response was 61 (34), 101 (56), and 112 (61) in the placebo +DMARD, sarilumab 150 mg q2 weeks + DMARD, and sarilumab 200 mg q2 weeks + DMARD arms, respectively; p-value vs placebo was <0.0001 for both treatment arms. The LS mean change (SE) from baseline in HAQ-DI was -0.26 (0.04), -0.46(0.04), and -0.47 (0.04)in the placebo + DMARD, sarilumab 150 mg q2 weeks + DMARD, and sarilumab 200 mg q2 weeks + DMARD arms, respectively; p-value vs placebo was 0.0007 in the 150 mg arm and 0.0004 in the 200 mg arm.

More patients treated with sarilumab than with placebo completed the studies; this was due to a higher incidence of rescue in the placebo groups. The baseline and disease characteristics of the study

^d Peng, S., Clinical Review of Sarilumab, 9/22/16

population were representative of the target population of patients with moderately to severely active RA. Clinically meaningful improvements in the components of the ACR response criteria were achieved for extended periods of time with sarilumab treatment in both pivotal studies, with the magnitude of improvements favoring the 200 mg q2 week arm over the 150 mg q2 week arm. In both studies, compared to placebo, sarilumab 200 mg q2 weeks resulted in significantly higher proportions of patients with HAQ-DI improvement ≥ 0.3 units at Weeks 12, 24, and 52 in EFC11072 Part B, Cohort 2 (these improvements remained stable for up to 2 years) and Weeks 12 and 24 in EFC10832. When compared to placebo, significantly higher proportions of patients receiving the 150 mg q2 weeks dose had with HAQ-DI improvement > 0.3 units at Week 24 in EFC11072 Part B, Cohort 2; the difference, however, from placebo at Week 12 in EFC10832 was numerically, but not statistically, greater than placebo in that study. Regarding radiographic progression, both doses of sarilumab were statistically superior to placebo ($p < 0.0001$) for the co-primary endpoint of change from baseline in mTSS at weeks 52.

Based upon the Cross Discipline Team Leader (CDTL) summary review, the sarilumab clinical trials were adequate and well-controlled. Sarilumab 150 mg and 200 mg were both effective in reducing signs, symptoms, and radiographic progression in patients with RA. For the vast majority of endpoints, the response rates were numerically higher for the 200 mg than the 150 mg dose. This is especially notable for inhibition of radiographic progression, which is irreversible.

5 Risk Assessment & Safe-Use Conditions

The safety data include observations from 3019 patients in all the Phase 2 and Phase 3 RA studies who received at least one dose of sarilumab through the CTD cutoff; however, information on serious adverse events was included as of July 31, 2015. Per the medical officer, Dr. Peng's, review, as of April 29, 2015, there were a total of 26 deaths reported in sarilumab's RA clinical development program, specifically from the phase 2 and 3 studies. Of these deaths, 22 of the subjects were receiving sarilumab. Two additional deaths were reported after April 29, 2015. All 28 deaths are described in Table 57 in the Dr. Peng's review. Table 57 was created from the narratives for each of the deaths and then categorizing the deaths by treatment at the time of death into 4 main categories: infection, cardiovascular events (CV), malignancy, and other. Overall, the rate and etiologies of deaths in the sarilumab population were consistent with what is expected from RA patients with underlying co-morbid disease. The Applicant noted that the mortality rate in patients with rheumatoid arthritis is 2.7 deaths per 100 patient-years.

Dr. Peng notes in her review that, in general, the standardized mortality ration is 2:1 to 2.5:1 compared with people of the same sex and age without RA. Her analysis was if just using the 19 deaths during the treatment emergent period, the rate of death in the sarilumab groups was 0.4 deaths per 100 patient years (95% CI: 0.26-0.66), and the rate of death in the placebo group was 0.8 deaths per 100 patient-years (95% CI: 0.16, 2.28). She concluded that the rates of death do not seem to exceed that of the general RA population. Similarly, the most common causes of death in the RA population are cardiovascular disease (42%, frequency increased twofold over the general population), infections (especially pneumonias, 9%), and cancer and lymphoproliferative malignancies (14%, specifically,

lymphoma and leukemia, lung cancer, and melanoma). The deaths that occurred in the sarilumab RA clinical trials were consistent with that of the general RA population with the majority of causing being an infection, CV event, or malignancy. Additional findings were that there were not any unusual infections or malignancies leading to death. There were 3 subjects with interstitial lung disease (ILD) (2 on sarilumab 200mg q2 week and 1 on sarilumab 100mg q week). Upon review, the number of subjects with interstitial lung disease on any dose of sarilumab was low (9 subjects, 0.3%, in the long-term safety population with the PTs of “idiopathic pulmonary fibrosis,” “interstitial lung disease,” and “pulmonary fibrosis”). Therefore, it does not appear that ILD should be considered a safety signal.^e

According to the CDTL summary review, the size of the safety database for sarilumab is adequate. Its safety profile is well characterized and consistent with the safety profile of Actemra, another medication in the same class approved for RA.

Per the CDTL summary review, the safety data submitted for sarilumab suggest it is associated with immunosuppression, as manifested by increased risks of serious infection, as well as important laboratory abnormalities, such as neutropenia and lipid parameter elevations. Some of these risks appeared to have a dose-response, but there was no evidence of increased risk with longer duration of exposure.^f There were also events of GI perforation and hypersensitivity, however there was only one event of GI perforation in a sarilumab-treated patient in the 52-week pivotal trial; with regard to hypersensitivity, there were injection site reactions, rash, and urticaria, but no anaphylaxis events reported.

Adverse events of special interest are discussed in the subsections below.

5.1.1 LABORATORY ABNORMALITIES

Sarilumab was associated with changes in certain hematologic, hepatobiliary, and lipid parameters. The phase 3 protocols incorporated pre-specified criteria for monitoring or discontinuation due to laboratory abnormalities as follows:

- Absolute neutrophil count (ANC) <0.5 Giga/L (i.e., Grade 4 neutropenia)
- Platelet count < 50 Giga/L
- ALT > 5x ULN
- ALT > 3x ULN
- Total bilirubin >2x ULN (unless patient has known Gilbert’s disease)

Neutropenia

More patients reported a decrease in ANC below LLN (1.96 Giga/L) in the sarilumab treatment groups compared to the placebo group (5%), with a numerically higher occurrence in the 200 mg q2 week group (41%) compared to the 150 mg q2 week group (32%), although in the majority of patients the

^e Peng, Suzette. Clinical Review of Sarilumab dated 9/22/16.

^f Maynard, Janet. Cross Discipline Team Leader Review of Sarilumab dated 9/16/16.

lowest ANC value remained above ≥ 1.0 Giga/L. The incidence was similar in the 2 dose groups with regard to ANC < 0.5 Giga/L (0.9-1.1%), as well as the rate of discontinuations due to neutropenia (2.3%). Based on the timing of a maximum decrease within 2 to 4 weeks prior to stabilizing, ANC should be obtained within 4-8 weeks after initiation of sarilumab and then every 3 months to assess the change in ANC secondary to sarilumab administration and determine if a modification to the dose regimen is warranted. The Applicant's proposed Package Insert (PI) recommends monitoring of neutrophils after 4-8 weeks of therapy and every 3 months thereafter; labeling also includes dose modifications based on ANC results.

Thrombocytopenia

Sarilumab was associated with thrombocytopenia compared with placebo in clinical trials. The thrombocytopenia was not associated with bleeding and the only event reported in a platelet count < 100 Giga/L was an ecchymosis at the injection site. The applicant's proposed PI recommends against initiating treatment with sarilumab in patients with a platelet count below $150,000/\text{mm}^3$ and discontinuing treatment if the platelet count falls below $50,000/\text{mm}^3$; the applicant recommends monitoring platelet counts 4 to 8 weeks after starting therapy and every 3 months thereafter.

Liver enzymes

Sarilumab was associated with elevations in liver enzymes when compared to placebo in clinical trials. In the long-term safety population, the ALT elevations $> 3x$ upper limit of normal (ULN) were transient and no cases met Hy's law criteria as the cases that met the laboratory abnormality criteria had alternative reasons for elevated liver enzymes. The applicant's proposed PI recommends against treatment patients who have elevated transaminases (ALT or AST) greater than $1.5 x$ ULN. Treatment discontinuation is recommended in patients who develop elevated ALT $> 5x$ ULN; monitoring ALT and AST 4 to 8 weeks after starting therapy and every 3 months thereafter is recommended.

Lipid abnormalities and Major Cardiovascular Events

Lipid parameters (LDL, HDL, and triglycerides) were found to increase by week 4 compared to placebo. After week 4, no additional increases were observed. The increases are associated with IL-6 blockade. Despite the elevations, the observed rate of confirmed major cardiovascular events (MACE) was not higher than the background rate for the RA population. The applicant's proposed PI recommends assessing lipid parameters approximately 4 to 8 weeks after treatment initiation and approximately every 6 months thereafter while on treatment. The Agency determined, based on the current safety profile of sarilumab, that a post-marketing cardiovascular outcomes trial would not be required.

5.1.2 SERIOUS INFECTIONS

In the medical officer's integrated safety analysis in the clinical review, for overall infections in the pre-rescue period (Pool 1a – placebo-controlled population) and the double-blind, 52-week treatment period (Pool 1 – Phase 3 placebo-controlled population), there were more infections in the sarilumab arms without a significant difference between doses. For serious infections, though, there were

numerically more subjects on the higher doses with serious infections. The most common serious infections in the sarilumab arms were soft tissue/skin infections (erysipelas, cellulitis) and pulmonary infections (pneumonia, bronchitis). Thus, there were no unusual or unexpected serious infections. There were very low numbers of opportunistic infections in general, and there was actually little difference between treatment arms. Most of these opportunistic infections were secondary to Herpes Zoster and Candida. No subjects developed tuberculosis during the double-blind treatment period. However, in the long-term safety population, there were 2 cases of tuberculosis in subjects on sarilumab. Per the CDTL review, in the entire RA development program, 5 patients had infections leading to death. All events occurred during the open-label study LTS11210 with 4 patients on 200 mg and 1 patient on 150 mg at the time of the event. The pattern of serious infections and deaths related to infections is consistent with the conclusion that sarilumab is associated with significant immunosuppression⁸. The Applicant's proposed prescribing information includes a boxed warning regarding the risk of serious infections leading to hospitalization or death and recommends interrupting sarilumab treatment if a serious infection develops until it is controlled. It is also recommended in labeling to test for latent tuberculosis prior to starting treatment with sarilumab. The review division agreed with the inclusion of the Boxed Warning in labeling for the risk of serious infections, including deaths and hospitalizations.

6 Expected Postmarket Use

Sarilumab has similar risks to other biologic treatments approved for the treatment of RA. The drug will be administered by the subcutaneous route, primarily in the home setting by patients or their caretakers. The likely prescribers for sarilumab will be rheumatologists who are familiar with the risks associated with immunomodulatory treatments for RA.

7 Evaluating the Need for a REMS

Based on the results of the Phase 3 trials, sarilumab was found to be efficacious compared to placebo in terms of clinical improvement and durability of response. The potential risks identified include neutropenia, thrombocytopenia, elevated hepatic transaminases, hyperlipidemia with cardiovascular outcomes, serious infections, and GI perforations; however, the only risk on this list that will be included in a Boxed Warning is the risk of serious infections, the remaining risks will be communicated in the Warnings and Precautions section of the label. These risks are consistent with IL-6 receptor blockade and other biologic treatments, and are similar to the other approved RA treatments.

Of the approved treatments for RA, only Actemra was approved with a REMS. The REMS included a Medication Guide and a communication plan. The goals of the REMS were:

- To inform healthcare providers about the risks of serious infections, gastrointestinal ~~perforations, changes in~~ liver function, decreases in peripheral neutrophil counts, decreases in

⁸ Maynard, Janet. Cross Discipline Team Leader Review of Sarilumab dated 9/16/16.

platelet counts, elevations in lipid parameters in peripheral blood, demyelinating disorders, and malignancies associated with Actemra.

- To inform patients about the serious risks associated with Actemra treatment.

The Actemra REMS was found to have met its goals in September, 2015 and was released.

Overall, the prescribing population is likely to be rheumatologists who are familiar with the risks associated with immunomodulatory treatments for RA.

8 Risk Management Activities Proposed by the Applicant

The Applicant submitted (b) (4) REMS as part of the BLA. The goal of the proposed REMS is:

(b) (4)

(b) (4)

As sarilumab has the same safety profile as Actemra, the Applicant voluntarily submitted a REMS with the BLA. Currently approved treatments for RA with similar risk profiles include the oral product, tofacitinib (Xeljanz), as well as injectable biologics etanercept (Enbrel), infliximab (Remicade), adalimumab (Humira), certolizumab pegol (Cimzia), golimumab (Simponi), Orencia (abatacept), rituximab (Rituxan), anakinra (Kineret), and tocilizumab (Actemra). If approved, sarilumab would join other biologics indicated for the treatment of RA that have similar known risks and offers another treatment option for RA patients who have an inadequate response or are intolerant to one or more DMARDs.

8.1 OTHER PROPOSED RISK MANAGEMENT ACTIVITIES

The Applicant also proposed the following risk management activities:

- Pregnancy registry
- Medication Guide to educate patients on the risks associated with Kevzara
- Boxed Warning regarding the risk of serious infections

DRISK notes that we defer to the Division of Epidemiology and DPARP for review and input on the other Risk Management Activities.

9 Conclusion & Recommendations

Based on the available data, risk mitigation measures beyond professional labeling are not warranted for sarilumab and a REMS is not necessary to ensure the benefits outweigh the risks. In general, healthcare providers who treat rheumatoid arthritis are familiar with risks associated with other biologic DMARDs, which include serious infections, neutropenia, thrombocytopenia, hepatic transaminase and lipid elevations, and GI perforations, and the importance of patient monitoring.

Should DPARP have any concerns or questions, or feel that a REMS is warranted for this product, or if new safety information becomes available, please send a consult to DRISK.

10 Appendices

10.1 MATERIALS REVIEWED

The following is a list of materials informing this review:

1. Sanofi-Aventis. Risk Evaluation and Mitigation Strategy for Kevzara, dated October 30, 2015.
2. Sanofi-Aventis. Proposed Prescribing Information for Kevzara, dated October 30, 2015.
3. Sanofi-Aventis. Clinical Overview for Kevzara, dated October 6, 2015.
4. Sanofi-Aventis. Summary of Clinical Safety for Kevzara, dated October 6, 2015.
5. Erin Hachey South, Division of Risk Management. REMS discussion meeting for BLA 761037 presentation slides, dated March 10, 2016.
6. Suzette Peng, Division of Pulmonary, Allergy, and Respiratory Products. Midcycle Meeting: Clinical presentation slides, dated March 23, 2016.
7. Janet Maynard, Division of Pulmonary, Allergy, and Respiratory Products. Cross Discipline Team Leader Summary review, dated September 16, 2016.
8. Suzette Peng, Division of Pulmonary, Allergy, and Respiratory Products. Clinical review, dated September 22, 2016.

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/s/

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