APPLICATION NUMBER:

761037Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW
## Cross-Discipline Team Leader Review

<table>
<thead>
<tr>
<th>Date</th>
<th>May 15, 2017</th>
</tr>
</thead>
<tbody>
<tr>
<td>From</td>
<td>Janet Maynard, MD, MHS</td>
</tr>
<tr>
<td>Subject</td>
<td>Cross-Discipline Team Leader Review</td>
</tr>
<tr>
<td>NDA/BLA #</td>
<td>761037</td>
</tr>
<tr>
<td>Supplement#</td>
<td></td>
</tr>
<tr>
<td>Applicant</td>
<td>sanofi-aventis U.S. LLC</td>
</tr>
<tr>
<td>Date of Submission</td>
<td>March 22, 2017</td>
</tr>
<tr>
<td>PDUFA Goal Date</td>
<td>May 22, 2017</td>
</tr>
<tr>
<td>Proprietary Name / Non-Proprietary Name</td>
<td>KEVZARA / Sarilumab</td>
</tr>
<tr>
<td>Dosage form(s) / Strength(s)</td>
<td>200 mg/1.14 mL or 150 mg/1.14 mL solution in a single-dose pre-filled syringe</td>
</tr>
<tr>
<td>Applicant Proposed Indication(s)/Population(s)</td>
<td>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</td>
</tr>
<tr>
<td>Recommendation on Regulatory Action</td>
<td>Approval</td>
</tr>
<tr>
<td>Recommended Indication(s)/Population(s) (if applicable)</td>
<td>Treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response or intolerance to one or more Disease-Modifying Anti-Rheumatic Drugs (DMARDs)</td>
</tr>
</tbody>
</table>
1. Background

Sanofi-aventis U.S. LLC, A SANOFI COMPANY (sanofi) submitted this complete response to biologics license application (BLA) 761037 on March 22, 2017, for the new molecular entity (NME) sarilumab for the treatment of adult patients with moderate to severely active rheumatoid arthritis (RA) who had an inadequate response or intolerance to one or more disease modifying anti-rheumatic drugs (DMARDs). The BLA was originally submitted on October 30, 2015, and received a complete response on October 28, 2016, due to inspectional deficiencies at the manufacturing facility. This resubmission does not contain any manufacturing changes and was classified as a type 1 submission. For details regarding the original application, please see my CDTL review dated September 16, 2016. This document focuses on considerations during the current review.

As background, the proposed dose is 200 mg once every two weeks. The dose should be modified to 150 mg once every two weeks to manage decreased neutrophil count, decreased platelet count or elevated liver transaminases. The product is a subcutaneous (SC) injection in 200 mg and 150 mg single-dose pre-filled syringes.

Sarilumab is a recombinant human IgG1 monoclonal antibody that binds both soluble and membrane-bound IL-6 receptors. If approved, sarilumab would be the second IL-6 inhibitor for rheumatoid arthritis. Tocilizumab (Actemra®, BLA 125276) was initially approved as an intravenous IL-6 inhibitor for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more tumor necrosis factor (TNF) antagonist therapies on January 8, 2010. This indication was subsequently broadened to the treatment of adult patients with moderate to severely active rheumatoid arthritis who have had an inadequate response to one or more DMARDs on October 11, 2012. Tocilizumab solution for subcutaneous injection (BLA 125472) was subsequently approved for the same indication as intravenous Actemra on October 21, 2013. The proposed indication for sarilumab is the same as that currently approved for Actemra. Therefore, sarilumab would be another choice in the class of IL-6 inhibitor agents for RA.

Key Regulatory Interactions

Key regulatory interactions after the complete response are listed:

December 16, 2016 – Type A meeting
- Agreement on planned content of complete response submission
- Agency noted that one inspection for both sarilumab and (b) (4) would be considered given that a prior approval inspection was already scheduled for (b) (4).
2. **Product Quality**

### Quality Review Team

<table>
<thead>
<tr>
<th>Discipline</th>
<th>Reviewer</th>
<th>Branch/Division</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product Quality</td>
<td>Gerald Feldman</td>
<td>OBP/DBRRIV</td>
</tr>
<tr>
<td>Manufacturing Facilities</td>
<td>Laura Fontan</td>
<td>OBP/DBRRIV</td>
</tr>
<tr>
<td>Microbiology</td>
<td>DMA-DS: Candace Gomez-Broughton</td>
<td>OPF/DIA</td>
</tr>
<tr>
<td></td>
<td>DMA-DP: Lakshmi Narasimhan</td>
<td>OPF/DIA</td>
</tr>
<tr>
<td>Regulatory Business Process Manager</td>
<td>Melinda Bauerlien</td>
<td>OPQ/OPRO</td>
</tr>
<tr>
<td>Application Technical Lead</td>
<td>Joel Welch</td>
<td>OBP/DBRRIV</td>
</tr>
</tbody>
</table>

- **General product quality considerations**

Sarilumab is a human IgG1 monoclonal antibody of the IgG1 kappa isotype. Sarilumab binds to human interleukin-6 receptor (IL-6R). Binding of sarilumab to IL-6R blocks the interaction of IL-6R with its natural ligand the cytokine interleukin 6 (IL-6), thereby preventing ligand-induced receptor activation and subsequent downstream IL-6 signaling.

The site for manufacture of the drug product is Sanofi Winthrop Industrie (LeTrait, France). The initial OPQ recommendation of the original submission was a complete response based on the provisional official action indicated (pOAI) status of the Le Trait, France facility. The status of this site is now acceptable per the review of the Division of Inspectional Assessment. The current submission contains no new product quality data and the original conclusion of its adequacy remains unchanged. The Office of Pharmaceutical Quality recommends approval of sarilumab.

3. **Nonclinical Pharmacology/Toxicology**

No issues during this review.

4. **Clinical Pharmacology**

No issues during this review.

5. **Clinical Microbiology**

Not applicable

6. **Clinical/Statistical- Efficacy**

*Clinical Primary Reviewer: Suzette Peng, MD*

*Statistical Reviewer: Yongman Kim, PhD; Statistical Team Leader: Gregory Levin, PhD*
During the current review, there were two main clinical and statistical considerations: the design of the 52-week placebo-controlled study (EFC11072) and the methodology for analyzing radiographic data from that study.

**Design of study EFC11072**

In terms of the design of study EFC11072, patients randomized to the placebo group could have remained on placebo for up to 52 weeks. There were provisions for escape during the study, but approximately 49% of patients remained on placebo for 52 weeks. Sanofi was asked to justify that patients who remained on placebo for 52 weeks in the study were provided treatment appropriate and consistent with the severity of their disease and acceptable at the time of the study. In addition, the Division requested an ethics consultation from the Office of Good Clinical Practice (OGCP) within the Office of Medical Products and Tobacco (OMPT).

The ethics consultation concluded that the trial was not ethically unacceptable for consideration by the review division. It was noted that the trial included a reasonably robust rescue plan. Starting at Week 16, patients with a lack of efficacy, defined as less than 20% improvement compared to baseline in swollen joints count (SJC) or tender joints count (TJC) for 2 consecutive visits (consecutive visits: 4 weeks apart [week 16-28] and 8 weeks apart [weeks 28-52]), or any other clear lack of efficacy based on Investigator judgment, could be rescued by permitting the patient to take open-label sarilumab at the highest available dose at the time of transfer into the rescue treatment arm. The rescue medications included the sarilumab 200 mg every other week dose or any non-study rescue medications as listed below:

- Initiated glucocorticoids for the treatment of RA, only if the patient received more than 1 intra-articular or intramuscular injection or received at least 10 mg per day of prednisone or equivalent for a period of at least 4 weeks
- Initiated use of any biologic (etanercept, adalimumab, infliximab, anakinra, rituximab, abatacept, tocilizumab, certolizumab, or golimumab) for the treatment of RA
- Initiated use of any DMARD other than MTX (gold, penicillamine, sulfasalazine, hydroxychloroquine, azathioprine, cyclophosphamide, leflunomide, cyclosporine, sulfasalazine, hydroxychloroquine, or cyclophosphamide) for the treatment of RA.

Similarly, sanofi cited the availability of rescue treatments and the option to withdraw and receive alternative treatment outside of the study. Sanofi noted that the study design was acceptable to health authorities, institutional review boards, independent ethics committees, the independent data monitoring committee, and the participating investigators.

There were internal discussions, including a briefing with the Center Director on April 21, 2017, regarding the study design and placebo-controlled period of the study. The general consensus was that the study in the BLA was conducted at a time of transition. Specifically, at the time the study was conducted, the thinking was changing about the length of placebo-control. It is not anticipated that future RA trials will have a 52-week placebo-controlled period, but the study design was reasonable at the time it was conducted. There were no concerns regarding inclusion of data from the study in the product label.

**Considerations Related to Radiographic Progression Analyses**
Background

An additional issue that was raised during the review was the presentation of radiographic progression results in the KEVZARA (sarilumab) label. For additional details regarding the statistical methodology, please see the Statistical Review.

As background, whether or not a given therapy inhibits radiographic progression is a key consideration in rheumatoid arthritis drug development since progression of structural changes is irreversible and is associated with functional decline. Drugs for rheumatoid arthritis are approved based on evidence of an effect on signs and symptoms of disease. However, signs and symptoms of disease do not necessarily predict radiographic damage. Further, a drug’s impact on signs and symptoms may not correlate with an impact on radiographic progression. This is a significant clinical consideration given that a product could improve a patient’s signs and symptoms, but the patient could develop joint destruction. There are drugs approved for rheumatoid arthritis, such as nonsteroidal anti-inflammatory drugs (NSAIDs) that impact signs and symptoms but do not modify radiographic progression.

Given this context, information regarding the impact of a drug on structural damage has only been included in previous product labeling if there was a robust effect. There have been previous applications where efficacy was shown in one trial but not another (BLA 125289, golimumab SC), and the radiographic results were not included in labeling, or there were concerns with the robustness of the results given the impact of outliers (NDA 203214 tofacitinib), and the radiographic results were only included in labeling after corroborating evidence from another study was provided.

A challenge in the analysis of radiographic progression in rheumatoid arthritis is the appropriate methodology to handle missing and post-rescue data. Generally, radiographs are assessed at 6 and 12 months to allow adequate time for differences to be seen in radiographic progression between treatment groups. However, most trials in rheumatoid arthritis include escape criteria beginning at approximately 3 months. The escape criteria allow an escalation of therapy for patients who continue to have significant disease activity, based on an assessment of swollen and tender joints. These escape criteria lead to either missing radiographic data or radiographic data that is obtained after the patient changes therapy. As more patients on placebo than active drug escape, there is differential missing data. In recent placebo controlled trials, approximately 50% of patients on placebo escaped by 52 weeks.

A variety of methodologies have been utilized to analyze radiographic data given these challenges. Previous product labeling has included data based on linear extrapolation. Linear extrapolation assumes that patients continue to have radiographic progression at the same linear rate as was observed throughout the time of escape/withdrawal. There are clear limitations of this analysis. From the clinical perspective, the primary concern is that it is not possible for patients to have linear radiographic progression throughout their disease course.

Further, from a clinical and physiologic perspective, it is unlikely that radiographic progression is linear throughout the disease. In two recent placebo-controlled 52-week studies, radiographic progression in the placebo group was not linear in either. The primary concern from a clinical perspective is that this analysis method may overestimate true progression.

For several years, FDA has consistently told sponsors that there are limitations to linear extrapolation given its strong and unverifiable assumptions. FDA has asked sponsors to evaluate radiographic data utilizing different methodologies. One methodology that was utilized and incorporated into the draft labels of two recent applications included observed data. In this analysis, x-ray data are analyzed according to randomized treatment group, regardless of treatment discontinuation or escape. This methodology also has limitations given that it analyzes x-ray data from placebo patients who cross-over to active drug. While radiographic changes that were accrued during the time on placebo would not be anticipated to resolve after switching to active drug, it would be anticipated that there would not be significant additional progression after switching to active drug. Thus, this methodology is anticipated to be more conservative than assuming linear progression.

**Radiographic Analyses in Sarilumab (Kevzara)**

During the initial review cycle of this BLA, the review team had numerous discussions with the applicant on the analyses utilized for the radiographic results. The pre-specified radiographic analysis evaluated the mean change in modified total Sharp score (mTSS) from baseline to Week 52. The linear extrapolation method was the primary method used to impute missing or post-rescue Week 52 modified total Sharp scores. The data collected after treatment discontinuation + 14 days or rescue were set to missing before linear extrapolation. Sanofi and the FDA performed numerous sensitivity analyses to explore the impact of missing data and assess the robustness of the findings with different assumptions. Each methodology for handling missing and post-rescue data has limitations. Both doses of sarilumab had statistically significantly less radiographic progression than placebo at both 24 and 52 weeks, regardless of the analysis method utilized. Thus, sarilumab has robust evidence of inhibition of radiographic progression. A focus of the review was consideration of the most appropriate statistical methodology to display the data in the labeling. Based on concerns with the strong and unverifiable assumptions of linear extrapolation, the review team recommended inclusion of analyses based on observed data in the first review cycle, and Sanofi agreed to this. These data are in the version of the label submitted by Sanofi in the complete response.

During the current review of the complete response submission, there have been additional discussions regarding the optimal presentation of inhibition of radiographic progression results in the Kevzara labeling. Concerns were raised with using observed data given that it would analyze x-ray data from placebo patients who cross-over to active drug. A meeting was held with the Office Director and review team on April 27, 2017, to discuss these issues. The relative strengths and limitations of the different methodologies were discussed. The statistical team proposed an alternative methodology, and an information request was sent to the Applicant. This methodology uses a linear mixed effects model that includes all radiographic data observed prior to escape (+14 days), including such data collected at any time point.
during the 52-week double-blind period. Patient data on the placebo arm after escape were considered missing. See the statistical review for additional details of the analyses. Similar to linear extrapolation, this analysis still relies on strong and unverifiable assumptions. Specifically, the analysis assumes that missing values after escape in placebo patients who escape are similar to observed values in placebo patients who do not escape, conditional on a linear model of the baseline covariates and the time of the x-ray and the observed value prior to escape. However, the statistical team noted that there were improvements in this methodology compared to linear extrapolation since it is not a single imputation method. A comparison of the different methodologies is shown in Table 1.

**Summary**

Each methodology for handling missing and post-rescue data has limitations. Thus, the FDA review team and the Applicant have utilized multiple sensitivity analyses to assess the robustness of the effect. In the current application, the consideration is not whether or not sarilumab impacts radiographic progression but what the optimal methodology to display the data is. Based on concerns with the strong and unverifiable assumptions of linear extrapolation, the review team recommended inclusion of analyses based on observed data in the first review cycle, and the Applicant agreed to this. The Applicant has now performed an additional analysis that the statistical review team feels is a reasonable alternative methodology. From a clinical perspective, I think it would be reasonable to include data from these analyses. An additional discussion of these issues with the Office Director occurred on May 11, 2017. The consensus was to include data based on the linear mixed effects model. Labeling negotiations with Sanofi are ongoing at the time of this review.

**Table 1: Overview of Sarilumab Radiographic Results Utilizing Various Methodologies for Handling Missing and Post-Escape Data**

<table>
<thead>
<tr>
<th>Mean change in mTSS at Week 52</th>
<th>Placebo+MTX (n=398)</th>
<th>Sarilumab 150 mg q2w+MTX (N=400)</th>
<th>Sarilumab 200mg q2w+MTX (N=399)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Linear extrapolation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean change</td>
<td>2.78</td>
<td>0.90</td>
<td>0.25</td>
</tr>
<tr>
<td>LS mean difference (95% CI)</td>
<td>--</td>
<td>-1.88 (-2.74, -1.01)</td>
<td>-2.52 (-3.38, -1.66)</td>
</tr>
<tr>
<td><strong>Observed data</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean change</td>
<td>2.04</td>
<td>0.60</td>
<td>0.17</td>
</tr>
<tr>
<td>LS mean difference (95% CI)</td>
<td>--</td>
<td>-1.43 (-2.01, -0.85)</td>
<td>-1.86 (-2.45, -1.28)</td>
</tr>
<tr>
<td><strong>Linear mixed effects model</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean change</td>
<td>2.24</td>
<td>0.64</td>
<td>0.23</td>
</tr>
<tr>
<td>LS mean difference (95% CI)</td>
<td>--</td>
<td>-1.60 (-2.20, -1.00)</td>
<td>-2.01 (-2.61, -1.41)</td>
</tr>
</tbody>
</table>

CI=confidence interval; MTX=methotrexate; mTSS=modified total Sharp Score

**7. Safety**

Sanofi submitted a Development Safety Update Report covering the period November 15, 2015 to November 14, 2016. No new safety issues were identified in this submission that
were not previously identified in the initial review. No labeling changes were recommended based on the safety information in this submission.

8. Advisory Committee Meeting

No issues were identified that would warrant an advisory committee meeting. Thus, an advisory committee meeting was not held for this submission.

9. Pediatrics

Polyarticular juvenile idiopathic arthritis (PJIA) has been considered the juvenile equivalent of adult rheumatoid arthritis, and thus a study in PJIA patients would be required by the Pediatric Research Equity Act (PREA) if this BLA in RA patients is approved. With this BLA, sanofi submitted a request for a partial waiver for children under 2 years of age, because studies in this age group are impossible or highly impracticable due to the rarity of PJIA in children under 2 years of age. A deferral was requested in children ages 2 to <17 years of age because studies in adults are complete and ready for approval.

The proposed pediatric assessment is the same as the information contained in the Initial Pediatric Study Plan (iPSP) agreed to by the Agency on January 10, 2014. The agreed pediatric study plan includes:

- Study DRI13925: A dose-finding study of sarilumab, aged 2 to 17,
- EFC11783: A study to assess the efficacy and safety of sarilumab in children and adolescents, aged 2 to 1

The sarilumab pediatric program was discussed at the Pediatric Review Committee (PeRC) meeting on June 15, 2016. The PeRC agreed with the requested waiver and deferral.

10. Other Relevant Regulatory Issues

No issues.

11. Labeling

- Proprietary name
The proposed proprietary name for sarilumab is Kevzara. This name has been reviewed by the Division of Medication Error Prevention and Analysis (DMEPA) and by the Office of Prescription Drug Promotion (OPDP) and was found to be acceptable.

- **Physician labeling**

The primary change to the labeling is the analysis used for the presentation of radiographic data in Section 14. See Section 6 of this review for additional details regarding the analyses of the radiographic data. The Agency has proposed the data be displayed using a linear mixed effects model; however, labeling negotiations are ongoing at the time of this review.

- **Patient labeling (i.e., Medication Guide, Patient Information, Instructions for Use)**

No issues.

- **Carton and container labeling**

No issues.

12. **Postmarketing Recommendations**

See Section 9 regarding the PREA PMR studies. No additional post marketing requirements or commitments are recommended.

13. **Recommended Comments to the Applicant**

None
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JANET W MAYNARD
05/16/2017