

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**761037Orig1s000**

**CLINICAL REVIEW(S)**



## DEPARTMENT OF HEALTH & HUMAN SERVICES

### Food and Drug Administration Center for Drug Evaluation & Research

#### Memorandum

**Date:** May 15, 2017

**To:** BLA 761037 sarilumab (KEVZARA<sup>®</sup>)

**From:** Suzette Peng, MD  
Medical Reviewer, CDER/ODEII/DPARP

**Through:** Janet Maynard, MD, MHS  
Cross-Discipline Team Leader, CDER/ODEII/DPARP

**Applicant:** Sanofi-aventis Research & Development and Regeneron  
Pharmaceuticals, Inc.

**Subject:** Sarilumab Resubmission: Response to FDA Complete Response Letter

#### I. Background

Sarilumab is a recombinant human immunoglobulin (IgG)1 monoclonal antibody that binds specifically to both soluble and membrane-bound interleukin-6 (IL-6) receptors (sIL-6R $\alpha$  and mIL-6R $\alpha$ ) and inhibits IL-6-mediated signaling. On October 30, 2015, Sanofi and its partner Regeneron submitted an application for sarilumab for the 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). The proposed dose was 200mg subcutaneously every 2 weeks, and the dose can be reduced to 150mg every 2 weeks for the management of neutropenia, thrombocytopenia, and elevated liver enzymes.

As part of the original application, the pivotal studies to support efficacy of sarilumab in the treatment of RA were two phase 3, randomized, double-blind, placebo-controlled trials evaluating 2 doses of sarilumab (150mg q2w and 200mg q2w) plus DMARDs. Study EFC11072 Part B had a double-blind treatment period of 52 weeks in RA patients who were MTX inadequate responders, and study EFC10832 had a double-blind treatment period of 24 weeks in RA patients who were TNF inhibitor inadequate responders. Both studies met the evidentiary standard. The primary and key secondary efficacy endpoints assessed signs and symptoms (ACR response, DAS28-CRP), physical function (HAQ-DI), and radiographic progression (mTSS). For all these endpoints, sarilumab showed a statistically significant and robust improvement compared to placebo. For ACR response, DAS28-CRP, and mTSS, there was a dose response with a trend toward slightly greater response on sarilumab 200mg compared to 150mg. In

conclusion, the data supported sarilumab's efficacy in the treatment of patients with RA who are inadequate responders or intolerant of one or more DMARD. The efficacy results supported the proposed initial dose of 200mg every 2 weeks.

The safety profile of sarilumab was well-characterized within the clinical trials. The major toxicities of concern with sarilumab are related to significant immunosuppression and are consistent with the safety concerns of tocilizumab, which is also an IL-6R inhibitor, like sarilumab. Sarilumab was associated with an increased risk of serious infections, including opportunistic infections and tuberculosis. While no imbalance in malignancy was seen in the clinical trials, treatment with an immunosuppressant may increase the risk of malignancies. Sarilumab treatment was associated with laboratory abnormalities including decreases in neutrophils and platelets and increases in liver function tests and lipid parameters. In general, laboratory abnormalities appeared to be dose-related. Notably, there did not appear to be an association between neutropenia and the development of infections. There were elevations in LDL, HDL, and triglycerides on sarilumab. There were very few cardiovascular events observed, and, thus, there was limited ability to determine an increased risk or an association with the changes in the lipid profile. Additional safety concerns included hypersensitivity reactions and gastrointestinal perforation.

At the time of the original submission, the clinical team's conclusion based on the review of efficacy and safety data was that the benefit/risk profile of sarilumab was favorable to support the 200 mg dose regimen, with dose reduction to 150 mg as needed for laboratory abnormalities. Compared to the 150 mg dose, the 200 mg dose demonstrated numerical trends suggesting additional benefit on both clinical and radiographic outcomes. While there were some dose-related safety signals, the safety profile of both doses was acceptable given the severity of RA and the demonstrated benefits. The identified safety concerns could be addressed through appropriate product labeling. However, the applicant received a Complete Response letter, dated October 28, 2106, because of a product quality-facility inspections issue. Specifically, the letter noted the following issue, "During a recent inspection of the Sanofi Winthrop Le Trait manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved."

Since that time, the applicant and the Agency have communicated via a telecon (Type A meeting) on December 16, 2016. Discussion included the safety update requirement at the time of application resubmission, a prior approval inspection (PAI), classification of the resubmission, and some labeling questions regarding the radiographic data. A PAI of the Sanofi Le Trait manufacturing facility was completed (b) (4)

In a letter dated March 21, 2017, the Agency indicated that the facility was now classified as acceptable. Accordingly, the applicant submitted the response to the Complete Response letter (i.e., the sarilumab resubmission) on March 22, 2017. The Agency agreed that the resubmission can be classified as a complete class I response with a 2 month PDUFA review and action date.

As part of the clinical review for this resubmission, I will review the Developmental Safety Update Report (DSUR), which reflects a sufficient safety update from the safety database that was submitted with the original application. In addition, I will present some internal discussions that have occurred since the original application review regarding 52-week placebo-controlled studies for RA and the most appropriate analyses of radiographic data.

## II. Review of Safety

The safety database for the original application included all safety data collected through the database lock, April 29, 2015. The 120-day update that was submitted during the course of the review reflected data from ongoing studies through November 16, 2015. For this resubmission, the applicant submits the sixth annual DSUR, which presents safety data from November 15, 2016, to November 14, 2016.

As of the database lock for this DSUR, 3836 RA patients (3611 in phase 2/3 studies and 225 in phase 1 studies) have received sarilumab since the Development International Birth Data of November 15, 2007. (b) (4)

Compassionate use programs are ongoing in Brazil and Australia with which 1 and 3 patients, respectively, have been actively enrolled.

Table 1 shows the completed and ongoing studies during the reporting period. As of the database lock for this DSUR, there are 8 ongoing trials, 6 in subjects with adult RA. There are no ongoing blinded clinical trials.

**Table 1. Ongoing and Completed Trials from November 15, 2015, to November 14, 2016**

Study	Description
<b>Completed</b>	
<b>PDY14191</b> Phase 1 in adult RA	OL, R, PG, SD study to describe the safety of IL-6R blockade with sarilumab or tocilizumab monotherapy in Japanese patients
<b>Ongoing</b>	
<b>Adult RA</b>	
<b>INT12684</b> Phase 1	MC, OL, 2-treatment study to eval the effects of single dose of sarilumab 200mg SC on PK of single dose of simvastatin 40mg with optional 1 year extension on OL sarilumab
<b>LTS11210 (SARIL-RA-EXTEND)</b> Phase 3	MC, uncontrolled extension study to eval efficacy and safety of sariluamb 200mg q2w
<b>EFC14092 (SARIL-RA-MONARCH)</b> Phase 3 <i>24-wk randomized portion complete; OL portion ongoing</i>	R, DB, PG study to assess efficacy and safety of sarilumab monotherapy vs. adalimumab monotherapy
<b>MSC12665 (SARIL-RA-EASY)</b> Phase 3 <i>Study complete, CSR pending</i>	MC, R, OL, PG usability study of sarilumab autoinjector device and prefilled syringe

<b>EFC14059 (SARIL-RA-KAKEHASI)</b> Phase 3 <i>24-wk analysis complete</i>	R, DB, MC study with PC period assessing efficacy and safety of sarilumab + MTX in Japanese patients with RA who are MTX inadequate responders
<b>LTS13618 (SARIL-RA-HARUKA)</b> Phase 3 <i>24-wk analysis complete</i>	R, DB, MC study evaluating safety and efficacy of sarilumab + non-MTX DMARDs or as monotherapy in Japanese patients with RA
(b) (4)	
<b>DRI13925</b>	(b) (4) study of sarilumab in children and adolescents (ages 2-17) (b) (4)
	(b) (4)

Safety findings for ongoing studies as of the database lock were generally similar to what was noted in the safety database of the original application.

- The applicant has identified the following important potential risks:
  - Increased risk of infection secondary to neutropenia
  - Thrombocytopenia and the potential risk of bleeding
  - Clinically evident hepatic injury
  - Impact on CV outcome (MACE) secondary to LDL elevation
  - Gastrointestinal (GI) perforations
  - Malignancy
- The important identified risks are the following:
  - Serious infections
  - Hypersensitivity reactions

Hypersensitivity reaction was added as a new important identified risk in this DSUR after an Investigator in study EFC14092 reported a case of suspect Stevens Johnson Syndrome (SJS). The case was further reviewed by external experts (dermatopathology and clinical dermatology) who concluded that the subject more likely had a severe cutaneous hypersensitivity reaction “with no evidence of SJS.” Because of this event, the applicant reassessed hypersensitivity data from the clinical development program. Much of this was presented in the clinical review of the original application. In the placebo-controlled population (e.g., EFC11072 Part A, EFC11072 Part B, and EFC10832), the number of patients with hypersensitivity adverse events per 100 patient years was 7.0 in the placebo group, 10.7 in the sarilumab 150mg q2w group, and 11.4 in the sarilumab 200mg q2w. The applicant used the MedDRA SMQ hypersensitivity to identify these events, which included preferred terms (PTs) such as injection site rash, rash, urticaria, eczema, rash generalized, rash erythematous, injection site urticarial, and hypersensitivity. Only one patient in the 200mg q2w group had a serious hypersensitivity event. The exposure-adjusted incidence in the long-term safety population was 4.8 in the any sarilumab dose group. The applicant noted that there were no hypersensitivity events with a fatal outcome in either the placebo-controlled or the long-term safety population.

Table 2 presents a brief description of safety findings in the ongoing studies in the database lock period.

**Table 2. Safety Findings in Ongoing Trials**

Study	Safety Summary
<b>Rheumatoid arthritis</b>	
<b>INT12684</b>	<ul style="list-style-type: none"> <li>• Most frequently reported: neutropenia, increased ALT, increased blood cholesterol</li> <li>• 3 SAEs: acute cholecystitis, allergic reaction to cephalosporin, and left sided weakness</li> </ul>
<b>EFC14092</b>	<ul style="list-style-type: none"> <li>• 1 death in sarilumab group (DB period): acute cardiac failure</li> <li>• 1 death in adalimumab group (OL period): pelvic tumor</li> <li>• Most frequent SOC in both treatment groups: Infections and infestations               <ul style="list-style-type: none"> <li>○ Rates of infection similar, sarilumab (28.8%) and adalimumab (27.7%)</li> </ul> </li> <li>• Neutropenia higher in sarilumab (13.6%) vs. adalimumab (0.5%)</li> <li>• Injection site erythema higher in sarilumab (7.6%) vs. adalimumab (3.3%)</li> <li>• TEAEs of HA and worsening of RA more frequent in adalimumab vs. sarilumab</li> <li>• Case of severe cutaneous hypersensitivity in sarilumab group (described above)</li> </ul>
<b>MSC12665</b>	No new clinically important safety finding
<b>EFC14059</b>	<ul style="list-style-type: none"> <li>• No deaths</li> <li>• Most commonly reported SOC:               <ul style="list-style-type: none"> <li>○ Infections and infestations in all 3 treatment groups</li> <li>○ Blood and lymphatic disorders in sarilumab groups</li> </ul> </li> <li>• Most frequent PT:               <ul style="list-style-type: none"> <li>○ Nasopharyngitis in all 3 treatment groups</li> <li>○ Neutropenia and hepatic function abnormal in sarilumab groups</li> </ul> </li> <li>• 14 SAEs (6 PBO, 4 in each dose of sarilumab): gastroenteritis, herpes zoster, PCJ pneumonia, sepsis, organizing pneumonia, pulmonary fibrosis</li> <li>• Most frequently reported AESIs in all 3 arms: infections               <ul style="list-style-type: none"> <li>○ Serious infections: PBO (1), sarilumab (3)</li> <li>○ Decreased in neutrophil count not associated with increase in infection</li> <li>○ Grade 3-4 neutropenia limited to sarilumab arms</li> </ul> </li> <li>• AEs leading to discontinuation: thrombocytopenia (1) and atypical pneumonia (1)</li> </ul>
<b>LTS13618</b>	<ul style="list-style-type: none"> <li>• No deaths</li> <li>• Most frequent reported AEs: Infections</li> <li>• 4 SAEs (sarilumab 200mg + DMARD): 2 malignancies (breast cancer, gastric cancer) and 2 serious infections (chronic sinusitis and periorbital abscess)</li> </ul>

	<ul style="list-style-type: none"> <li>• Most frequent AESIs <ul style="list-style-type: none"> <li>○ (sarilumab + DMARD) infections and leukopenia</li> <li>○ (sarilumab monotherapy) infection and injection site reaction</li> </ul> </li> </ul>
<b>LTS11210</b>	No new safety findings with long-term administration identified
	(b) (4)
<b>DRI13925</b>	(b) (4) patients exposed to sarilumab, no SAEs or AEs leading to discontinuation
(b) (4)	

A review of the cumulative serious adverse events (SAEs) in all RA studies to date is consistent with what was already described in the review of the original application. The most commonly reported SOC for these SAEs were Infections and Infestations with the top 3 PTs of pneumonia, cellulitis, and erysipelas.

In conclusion, the safety findings in this DSUR are consistent with what was summarized/reviewed in the original application for approval. Hypersensitivity reaction was added as an important identified risk because of a case of severe cutaneous hypersensitivity reaction. Hypersensitivity reactions were described in the original application, and there is a Warning related to Hypersensitivity in Section 5 of the current labeling. This one event does not change the previous assessment. The safety concerns associated with the use of sarilumab are adequately captured in the proposed labeling. No REMS are recommended.

### III. Study Design: 52-week placebo-controlled studies

As noted, one of the pivotal studies is Study EFC 11072 Part B, a 52-week, randomized, double-blind, placebo-controlled study to confirm safety and efficacy of sarilumab in subjects with RA who are taking MTX. Efficacy data were derived specifically from Cohort 2, where subjects were randomized to 2 doses of sarilumab (150mg q2w and 200mg q2w) and placebo. Starting at Week 16, patients were assessed for lack of efficacy, which was defined as less than 20% improvement compared to baseline in swollen joint counts (SJC) or tender joint counts (TJC) for 2 consecutive visits or any other clear lack of efficacy based on Investigator judgment. Subjects with lack of

efficacy could be rescued by permitting the subjects to take open-label sarilumab at the highest available dose at the time of transfer into the rescue treatment arm. It was noted that 196 subjects (49.2%) who started on placebo remained on placebo through 52 weeks, whereas 156 placebo subjects (39.2%) were rescued and 46 placebo subjects (11.6%) discontinued during the double-blind period.

Since the time of the review of the original submission, there have been internal discussions regarding the placebo subjects who remained in the study through the treatment period (52 weeks). Specifically, the appropriateness of patients receiving 52-weeks of placebo (with concomitant MTX) has come into question. Appropriateness of the 52-week placebo-controlled data would influence whether any of the efficacy endpoints assessed at Week 52 (in particular, the radiographic endpoints) would be interpretable.

The internal questions arose from the fact that, with the availability of multiple biologic disease modifying anti-rheumatic drugs (bDMARDs) that are effective for prevention of structural progression, the rheumatology community has questioned whether it is appropriate to conduct randomized placebo-controlled trials that last 12 months. In 2010, the American College of Rheumatology (ACR) organized a clinical trial priorities and design conference to discuss the evolving treatment landscape for RA. Trial design issues discussed included “the need for active comparator trials, the ethical use of placebos, the duration of treatment needed to address clinically relevant questions, the need for the collection of biospecimens in all trials, the duration of blinding, and the patient populations studied.”<sup>1</sup> The ACR conference participants were in “broad agreement” that the use of placebo may be an “ethically questionable trial feature.”<sup>2</sup> Because early treatment to target (low disease activity or remission) is a “central tenet of current state-of-the art therapy for RA,” use of placebo for prolonged period “does not provide clinically useful information and is not ethically defensible.”<sup>3</sup> However, the Conference did note that, in some scenarios (new molecular entities), a placebo-trial may be necessary. If so, “placebo exposure should be kept to a minimum and early rescue therapy should be provided (in most cases at the 12-16 week time point or sooner).”<sup>4</sup> Following this conference, in 2012, the ACR updated the 2008 guidelines for the use of conventional DMARDs (cDMARDs) and bDMARDs in the treatment of RA. These guidelines reiterated the importance of early treatment to target (low disease activity or remission). In established RA, if a patient has moderate or high disease activity after 3 months of MTX or cDMARD combination therapy, adding or switching to a bDMARD (anti-TNF) should be considered.<sup>5</sup> In fact, even in early RA (<6 months duration), combination cDMARD and bDMARD could be considered as initial therapy for patients with poor prognostic features with high disease activity.<sup>6</sup> To reflect the evolving

---

<sup>1</sup> ACR RA Clinical Trial Investigators Ad Hoc Task Force. Conference Summary: ACR Clinical Trial Priorities and Design Conference, July 22-23, 2010. *Arthritis Rheum.* 2011; 63: 2151-2156.

<sup>2</sup> Ibid.

<sup>3</sup> Ibid.

<sup>4</sup> Ibid.

<sup>5</sup> Singh JA, et al. 2012 Update of the 2008 ACR Recommendations for the Use of DMARDs and Biologic Agents in the Treatment of Rheumatoid Arthritis. *Arthritis Care Res.* 2012; 64: 625-639.

<sup>6</sup> Ibid.

treatment paradigm in clinical practice and the Agency's more current recommendations, the 2013 draft *Guidance for Industry: Rheumatoid Arthritis: Developing Drug Products for Treatment* states that exposure to placebo or ineffective therapies should be limited. "Use of placebo as a control in long-term trials (usually 6 months or longer for trials done in the past to demonstrate effect on radiographic outcome) is no longer feasible."<sup>7</sup> Study EFC11072 Part B initiated in 2011 and was completed in 2013, thus, in the midst of these evolving recommendations.

An ethics consult was requested on March 13, 2017, with the question whether receipt of placebo for 52 weeks was appropriate and consistent with the severity of the subjects' disease and was acceptable at the time of the study. The Office of Good Clinical Practice (OGCP) completed the consult on March 29, 2017, and concluded that study EFC11072 Part B is ethically acceptable for consideration. The OCGP consultant utilized the ethical principles of social value, scientific validity, fair selection of subjects, respect for persons, independent review, and favorable risk-to-benefit ratio to consider whether it was ethically appropriate to use a 52-week placebo-controlled efficacy endpoint (specifically, the radiographic endpoint). The consultant determined that, at the time the trial was initiated in 2011, there were many differences in opinion on the acceptable timing of radiographic assessment. In addition, the consultant felt that EFC11072 Part B provided a "reasonably robust rescue plan" at Week 16, consistent with recommendations by ACR for timing of modification of therapy. Noting that as many as 4 different bDMARDs have been approved after demonstrating radiographic benefit at 6 months, "it is likely becoming increasingly difficult to justify a 12 month radiographic endpoint for future clinical trials."

The question of the appropriateness of the 52-week placebo-controlled trial was also addressed to the applicant directly via a telecom on April 13, 2017. The applicant responded on April 24, 2017, with a "white paper" detailing the rationale for the EFC11072 study design, how the applicant ensured patients' interests were addressed, and other external input received on the design. The applicant noted that, in developing study EFC11072, many factors were considered. These included the following: (1) standard of drug development between 2000 to 2010 (such as the clinical trials of abatacept, adalimumab, infliximab, and tocilizumab); (2) direct and indirect feedback from Health Authorities including FDA guidance documents, FDA meetings, and European Medicines Agency (EMA) Scientific Advice; (3) recommendations from clinical RA experts in the US and EU as well as Sanofi and Regeneron internal review committees. Study EFC11072 was designed in early 2009. The applicant concludes that the study design was consistent with the thinking at the time and implementation of studies for patients with RA. There was a low threshold to receive rescue treatment with sarilumab or to withdraw and receive alternative treatment outside of the study. The study design was scientifically valid to demonstrate that a novel disease-modifying therapy could inhibit or reduce progression of joint damage in patients with moderately to severely active RA. Study EFC11072 was acceptable to health authorities, IRBs/IECs, the independent data monitoring committee, and the participating investigators.

---

<sup>7</sup> FDA Draft *Guidance for Industry: Rheumatoid Arthritis: Developing Drug Products for Treatment*, issued May 2013, at [www.fda.gov](http://www.fda.gov).

Lastly, the Center Director, Dr. Woodcock, was briefed on the study design and placebo-controlled period of this RA study on April 21, 2017. The general consensus was that the study was conducted at a time of transition regarding the appropriate length of placebo control. Therefore, although it is not anticipated that future studies with 52-week placebo-controlled periods would be acceptable, the study design of EFC11072 Part B Cohort 2 was reasonable at the time of study conduct.

In conclusion, the 52-week placebo-controlled period in study EFC11072 Part B is acceptable, and, thus, efficacy endpoints (in particular, radiographic assessments) can be interpreted.

#### **IV. Analysis of Radiographic Data**

A review of the radiographic assessments in study EFC11072 was presented in the clinical review of the original application of sarilumab for RA. Briefly, the applicant sought the claim of inhibition of structural progression by assessing the mean change in the van de Heijde modified Total Sharp Score (mTSS) at Week 52. The pre-specified, primary analysis of this endpoint was linear extrapolation which was applied to escapers or any other missing data. Sensitivity analysis used post-rescue data from subjects who crossed over to sarilumab after Week 16. Additionally, the statistical team assessed mean change in mTSS at Week 24 when there was less missing data. All statistical analysis of the radiographic endpoint showed less progression in treatment arms receiving sarilumab, and the difference from placebo was statistically significant. At the time of the original review, it was noted that there were limitations to linear extrapolation. Although linear extrapolation was pre-specified and has been used historically in other bDMARD labeling, the Agency recommended that the results be displayed for analyses including data collected after escape/rescue and treatment discontinuation, as this would be a more reliable assessment of the intention-to-treat (ITT) estimand. As noted in Dr. Kim's review (primary statistical reviewer), "the linear extrapolation approach requires the strong and unverifiable assumption that patients' scores would have continued to change at exactly the same linear rate that was observed through the time of withdrawal." Dr. Kim also noted that "linear extrapolation is a single imputation approach that does not appropriately take into account the uncertainty in the imputation process." After several iterations with the applicant, the proposed labeling was amended to utilize analyses including data after rescue or discontinuation from treatment, without linear extrapolation.

Since the review of the original application, questions have arisen regarding the most appropriate way to analyze radiographic endpoints in RA trials. Given the amount of missing data in the placebo arm at Week 52, there are limitations to most methods utilized to analyze the data. Limitations of linear extrapolation of the missing data are described above. However, utilization of post-rescue/post-discontinuation data (i.e., when placebo subjects have crossed over to sarilumab itself) may underestimate the true treatment effect. For sarilumab, the question regarding statistical methodology was not to determine whether there was a treatment effect but rather how to display the radiographic

endpoints in labeling. Multiple discussions have occurred at the Office level. Please see the reviews by the statistical team and the CDTL for details. Based on these discussions, it was determined that the estimand of interest is the difference in mean progression at Week 52 between sarilumab and control if escape therapy on placebo was not available or ethically necessary, rather than an ITT estimand. It is with this estimand in mind that the statistical team requested the applicant to utilize a linear mixed effects regression model that includes all radiographic data observed prior to escape. The results with this analysis continued to show a statistically significant difference from placebo but with a magnitude slightly larger than that utilizing observed data and smaller than that utilizing linear extrapolation.

**Table 3. Change of mTSS from baseline at Week 52 in Study EFC11072 Part B**

	<b>Placebo + MTX (N=398)</b>	<b>Sarilumab 150mg + MTX (N=400)</b>	<b>Sarilumab 200mg + MTX (N=399)</b>
<b>Observed Data</b>			
Mean change at Week 52	2.02	0.58	0.15
Difference from PBO + MTX (95% CI)		-1.43 (-2.01, -0.85)	-1.86 (-2.45, -1.28)
<b>Linear Extrapolation</b>			
Mean change at Week 52	2.53	0.65	0.01
Difference from PBO + MTX (95% CI)		-1.88 (-2.74, -1.01)	-2.52 (-3.18, -1.88)
<b>Linear Mixed Effects Regression Model</b>			
Mean change at Week 52	2.24	0.64	0.23
Difference from PBO + MTX (95% CI)		-1.60 (-2.20, -1.00)	-2.01 (-2.61, -1.41)

Source: FDA statistical team (Drs. Kim and Levine)

These data were presented and discussed internally. The primary review team (stats and clinical) felt that, given the limitations with linear extrapolation and the revised estimand of interest, the results analyzed by linear mixed effects regression model might be the most appropriate for labeling. The label should indicate the method of analysis used. Additionally, since this method is different from what has been used historically in the label of other biologics, it is appropriate to indicate that these results should not be compared to other approved drugs. There was general concurrence in this plan amongst members of the Office.

## **V. Clinical Reviewer’s Final Recommendation**

With the resubmission of the sarilumab application, the clinical review focused on the safety update and the internal discussions regarding the interpretation of the radiographic data (52-week placebo-controlled studies and method of analyses for labeling). The benefit/risk profile of sarilumab continues to support the 200 mg q2w, with dose reduction to 150 mg as needed for laboratory abnormalities, for the treatment of adult patients with moderately to severely active RA. There are no new safety issues that require further assessment. No REMS are recommended. The currently proposed

labeling reflects all the safety concerns with sarilumab therapy. Hypersensitivity reactions, already in Section 5, should be added to the Highlights portion of the USPI. Labeling should also be amended to reflect the changes to the analyses and interpretation of radiographic data, i.e., linear mixed effects regression model instead of observed data or linear extrapolation.

APPEARS THIS WAY ON ORIGINAL

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

SUZETTE W PENG  
05/16/2017

JANET W MAYNARD  
05/16/2017

## Summary Basis for Regulatory Action

<b>Date</b>	October 28, 2016
<b>From</b>	Curtis J Rosebraugh, MD, MPH Director, Office of Drug Evaluation II
<b>Subject</b>	Summary Review
<b>NDA/BLA #</b> <b>Supp #</b>	BLA 761037
<b>Applicant Name</b>	Sanofi-Aventis U.S. LLC
<b>Proprietary / Established (USAN) Names</b>	Kevzara Sarilumab
<b>Dosage Forms / Strength/Dose</b>	Pre-filled syringe 200 mg/1.14 mL every 2 weeks. Reduction of dose to 150 mg/1.14 mL every 2 weeks for management of neutropenia, thrombocytopenia, and elevated liver enzymes
<b>Proposed Indication(s)</b>	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)
<b>Action:</b>	<i>Complete Response</i>

# 1. Benefit-Risk Assessment

## Benefit-Risk Summary and Assessment

Patients with rheumatoid arthritis (RA) have a chronic progressive disease that is associated with morbidity and mortality. There are multiple drugs and biologics approved for the treatment of RA, but existing therapies are not effective for all RA patients. Thus, another biologic therapy would be a desirable addition to the treatment options available for RA. Sarilumab is a monoclonal antibody that binds to human interleukin-6 receptor (IL-6R). Tocilizumab is approved for the treatment of RA and also binds to IL-6R target as sarilumab.

Efficacy of sarilumab at doses of 150 mg and 200 mg every two weeks was established in two phase 3 trials in patients with RA. These trials showed efficacy of sarilumab for reducing signs and symptoms of RA, based on the proportion of patients experiencing favorable American College of Rheumatology (ACR) response and reduction in Disease Activity Score (DAS28-CRP), improved physical function as measured by Health Assessment Questionnaire-Disability Index (HAQ-DI), and structural progression prevention as assessed by radiograph. Comparison of the two sarilumab doses showed that the proportion of patients experiencing improvement in ACR response was numerically higher with the 200 mg dose compared to the 150 mg dose. For HAQ-DI, the level of improvement was similar for the 150 mg and 200 mg dose groups. Structural progression was assessed in one study, which showed trends towards more inhibition of radiographic progression with the 200 mg dose as compared to the 150 mg dose. Although there was only a single study assessing radiographic progression, the evidence is sufficient due to the highly statistically significant result and the consistency of the results across the two doses.

The safety profile of sarilumab was well characterized in the clinical program. Major safety concerns are related to immunosuppression and are consistent with the safety concerns of tocilizumab, which has the same target. Sarilumab was associated with an increased risk of serious infections, including opportunistic infections and tuberculosis compared to placebo. While no imbalance in malignancy was seen in the clinical trials, treatment with an immunosuppressant may increase the risk of malignancies. Sarilumab treatment was associated with laboratory abnormalities including decreases in neutrophils and platelets and increases in liver function tests and lipid parameters. Laboratory abnormalities appeared to be dose-related. There were elevations in LDL, HDL, and triglycerides on sarilumab, but there was no clear increase in the risk of cardiovascular events on sarilumab. Additional safety concerns included hypersensitivity reactions and gastrointestinal perforation.

Based on the data in this submission, the benefit/risk profile of sarilumab is adequately favorable to support the 200 mg dose regimen, with dose reduction to 150 mg as needed. Compared to the 150 mg dose, the 200 mg dose demonstrated numerical trends suggesting additional benefit on both clinical and radiographic outcomes. While there were some dose-related safety signals, the safety profile of both doses was acceptable.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<b>Analysis of Condition</b>	<ul style="list-style-type: none"> <li>• RA is an autoimmune disease that causes chronic symmetric inflammation of joints. RA impacts the lives of patients due to pain and decreased physical function and, ultimately, irreversible joint damage.</li> </ul>	Most patients with RA have chronic progressive disease.
<b>Current Treatment Options</b>	<ul style="list-style-type: none"> <li>• There are multiple drugs approved for RA. RA patients are treated with disease modifying antirheumatic drugs (DMARDs). Generally, methotrexate (MTX) is the first line of therapy for RA. The next line of therapy is a TNF-antagonist. There are multiple TNF-antagonists approved for RA. In addition, there are other drug classes approved for RA, such as IL-6R antagonist, IL-1R antagonist, JAK inhibitors, etc.</li> </ul>	Current treatment options for this condition are effective. An addition to the treatment armamentarium would provide another choice for patients with RA.
<b>Benefit</b>	<ul style="list-style-type: none"> <li>• Reducing signs and symptoms of RA based on ACR response</li> <li>• Improvement in physical function based on HAQ-DI</li> <li>• Inhibition of structural damage progression</li> <li>• Sarilumab 200 mg was associated with numerically higher response compared to 150 mg</li> </ul>	In controlled clinical studies, sarilumab 200 mg and 150 mg were both effective with response rates numerically higher for the 200 mg dose compared to the 150 mg dose. The magnitude of the effects sizes were comparable to other DMARDs approved for RA.
<b>Risk</b>	<ul style="list-style-type: none"> <li>• Major safety concerns were infections, including opportunistic infection and tuberculosis; risk of malignancy with known immunosuppression; gastrointestinal perforation; laboratory parameter change of decrease in neutrophil and platelet count and increases in liver function tests and lipid parameters; and hypersensitivity reactions.</li> </ul>	The safety profile of sarilumab is well characterized and consistent with the safety profile of another IL-6R antagonist tocilizumab.

<b>Dimension</b>	<b>Evidence and Uncertainties</b>	<b>Conclusions and Reasons</b>
<b>Risk Management</b>	<ul style="list-style-type: none"><li>• The safety findings of sarilumab are well characterized and are consistent with other DMARDs approved for the treatment of RA.</li></ul>	The safety risks will be communicated in labeling, including a Medication Guide and a boxed warning for infection.

## 1. Introduction

This review will be a brief summary of the basis for the regulatory action regarding sarilumab, and I refer the reader to the other reviews in the action package for a more detailed discussion. Sarilumab is a human immunoglobulin antibody IgG1 that binds to soluble and membrane bound human interleukin 6 receptor alpha (IL-6R $\alpha$ ) to inhibit IL-6 mediated signaling. Sarilumab was developed for use in the treatment of adult patients with moderate to severely active rheumatoid arthritis (RA) who have had an inadequate response or intolerance to one or more disease modifying anti-rheumatic drugs (DMARDs). Overproduction of IL-6 has been suggested to play pathological roles in RA, and the theory that blocking IL-6 activity can be effective therapy has been validated with the approval of tocilizumab (which also targets IL-6R) for RA in 2010.

During the review of this application, efficacy with appropriate safety was demonstrated as will be discussed below. The review team is recommending approval if manufacturing issues are resolved. I agree with this recommendation. Unfortunately, the sponsor has not resolved manufacturing deficiencies associated with the Sanofi Winthrop Industrie (LeTrait, France) site, so we will issue a complete response.<sup>1</sup> Please see the other reviews for details concerning product quality, nonclinical pharmacology/toxicology, clinical pharmacology, and clinical microbiology.

### Efficacy

Efficacy has been thoroughly covered in reviews authored by Drs. Kim, Peng, Maynard, and Chowdhury. Two principal trials (11072, 10832) were submitted as evidence of efficacy. The primary efficacy outcome was response rate as measured by change in ACR20. Several other outcome measures (HAQ-DI, ACR50, ACR70, SF-36 etc.) were common to both trials and evaluated. Study 11072 included a radiographic outcome evaluation evaluated by modified Sharp Score. Drs. Maynard and Chowdhury have thorough discussions of the criteria associated with each efficacy endpoint. The results for ACR20 are presented in the table below copied from Dr. Maynard's review (Page 38).

---

<sup>1</sup>

(b) (4)

**Table 1: Summary of ACR20 Response Rates at Week 24 in phase 3 RA studies**

Treatment group	n/N (%)	Comparison	Odds Ratio	95% CI	p-value
<b>EFC11072 Part B</b>					
SAR 150mg (N=400)	232/400 (58)	vs. placebo	2.8	(2.1, 3.7)	<0.0001
SAR 200mg (N=399)	265/399 (66)	vs. placebo	4.0	(3.0, 5.3)	<0.0001
Placebo (N=398)	133/398 (33)	--	--	--	--
<b>EFC10832</b>					
SAR 150mg (N=181)	101/181 (56)	vs. placebo	2.7	(1.7, 4.2)	<0.0001
SAR 200mg (N=184)	112/184 (61)	vs. placebo	3.3	(2.1, 5.1)	<0.0001
Placebo (N=181)	61/181 (34)	--	--	--	--

SAR=sarilumab; ACR=American College of Rheumatology; NRI=nonresponder imputation; CI=confidence interval

Primary analysis with NRI

Study EFC11072: p-value based on CMH test stratified by prior biologic use and region

Study EFC110832: CMH test stratified by number of previous anti-TNFs and region.

Source: Clinical Study Report for Study EFC11072 (page 103) and 15.2 (page 4) and Clinical Study Report for Study EFC10832 (page 81) & 15.2 (page 83), submitted 10/30/15

Overall ACR response is provided in the table below copied from Dr. Chowdhury's review (page 15).

**Table 2. ACR response rates (% patients with ACR response) at primary analysis time point**

Study *	Time	Treatment †	ACR 20	ACR 50	ACR 70	OR (CI) vs placebo ACR 20
			%	%	%	
11072	Week 24	Sar 150 Q2wk	58	47	20	2.8 (2.1, 3.7)
		Sar 200 Q2wk	66	46	25	4.0 (3.0, 5.3)
		Placebo	33	17	7	
10832	Week 24	Sar 150 Q2wk	56	37	20	2.7 (1.7, 4.2)
		Sar 200 Q2wk	66	41	16	3.3 (2.1, 5.1)
		Placebo	34	18	7	

\* Study ID shown as Sanofi's study number

† Sar = Sarilumab

Dr. Kim performed many additional analyses that were generally consistent with the results above. No single component of the ACR20 drove the results demonstrated above.

Secondary endpoints for both trials also reflected the results demonstrated by the primary endpoint, supporting efficacy. Sarilumab 150 and 200 mg doses were effective in the population tested with trends favoring the 200 mg dose as being more efficacious. As noted in Dr. Maynard's review, data from study 11072 were also supportive of the treatment effect of sarilumab on preventing structural damage progression with the 200mg dose having a greater effect than the 150 mg dose.

### Safety

Safety findings have been thoroughly reviewed by Drs. Peng, Maynard and Chowdhury. Please refer to their reviews for a detailed analysis. Evaluations for leukopenia (specifically, neutropenia), thrombocytopenia, infections, hepatic disorders, GI perforations, evaluation of lipids, anaphylaxis, hypersensitivity, injection site reactions, malignancy, lupus-like syndrome,

demyelinating disorders, major adverse cardiovascular events (MACE), and immunogenicity were performed. The most common serious adverse event was infections and infestations, which is expected for this class. Both sarilumab treatment arms were numerically higher than that of placebo (0.7% vs 1.0%) but were of equal incidence despite increased neutropenia and leukopenia with the 200 mg dose.<sup>2</sup> Adverse events were similar to those seen with the other approved immunosuppressive agents.

Use of sarilumab resulted in elevations of lipids levels, as has been seen with the approved IL-6 agent, tocilizumab. There were too few cardiovascular events to evaluate if this elevation is of clinical consequence. Although for the few events that occurred, there were more (exposure adjusted) in those receiving the 200 mg dose compared to those receiving 150 mg and more in those receiving sarilumab than those receiving placebo. I would note that Dr. Maynard mentions a Safety Outcome Trial (SOT) meeting where this was discussed and that some on the panel voiced that a trial was infeasible because of the large size necessary to ‘answer the question’ regarding whether an increase in cholesterol is associated with sarilumab. In reality, the role of a safety outcome trial, at least in this context, is not to ‘prove’ whether something may cause a safety issue but, rather, to rule out the level of risk with which it does not occur. This is a critical distinction and separates this type of trial from ‘efficacy’ trials where the goal is to prove that something has a favorable effect. Safety trials are not designed to ‘prove’ safety issues because, statistically, it is extremely hard to ‘prove a negative,’ should the drug not cause a problem, and trying to would result in a trial of infeasibly large size. However, one can statistically assign a level of risk that may be ruled out and which does result in a practical trial size (dependent upon various parameters). Indeed, it is the reasoning mentioned above that has allowed for the requirement of the sponsors of tocilizumab to perform a cardiovascular outcome trial (CVOT). If the logic stated in Dr. Maynard’s review summary of the SOT meeting were applied, a CVOT study of tocilizumab would be infeasible as well. Instead, we are requiring that there is a demonstration that the use of tocilizumab is not associated with a certain level of risk of increased cardiovascular events.

Since it has been demonstrated that the use of a drug that works through an IL-6 blocking mechanism is associated with increased levels of cholesterol and it is unknown whether increasing cholesterol in this manner will result in clinically important increases in cardiovascular events, the issue is really whether to require two drugs in the same class, that both elevate cholesterol (as a proposed mechanism for cardiovascular harm concern), to perform a CVOT. Whether to require a CVOT for like agents has received a great deal of discussion (outside of weight loss or diabetic drugs), and there is not widespread agreement on when CVOTs should be required.<sup>3</sup> An example of where we have not required a CVOT while awaiting results of a trial from an agent in the same class is the anticholinergic agent umeclidinium for use in chronic obstructive pulmonary disease.<sup>4</sup> These types of decisions generally require considerations of the level of concern of possibility of risk balanced against practicality of trial and possibility of other data being generated to inform the decision. The

---

<sup>2</sup> Although the rate per 100 patient years for serious infections was higher for the 200 mg dose (placebo, 150 mg, 200mg, 3.2, 2.7 and 4.3 respectively).

<sup>3</sup> This may vary if there is some theoretical concern that individual agents themselves may carry different absolute risks based on off-target activities.

<sup>4</sup> I have a detailed discussion of this issue in the approval memo for Anoro Ellipta, NDA 203975

CVOT for tocilizumab is very near complete and could certainly inform our thinking about further requirements of other rheumatologic agents (where CVOTs are not routinely performed)<sup>5</sup>, much like the results for tiotropium influenced the decision for umeclidinium and the results for the aclidinium CVOT may influence further actions. As such, I believe it is acceptable to await the results of that trial and then revisit this issue.

### Advisory Committee Meeting

An Advisory Committee meeting was not held as this drug is not the first in its class. The safety profile is similar to that of other drugs approved for this indication in this class, and the clinical study is acceptable.

## **2. Conclusions and Recommendations**

The use of sarilumab for the population of patients with RA as studied in this application has demonstrated efficacy with appropriate safety. Sarilumab will add another option to the armamentarium of health care providers. I recommend a CR action at present pending resolution of manufacturing deficiencies.

---

<sup>5</sup> Especially since the concern is through the activity of IL-6 blockade causing the increase in cholesterol and not an off-site activity that would be specific to one drug and not the other. Antibodies developed for specific targets should not be as permissive in off-site activity as is the case with small molecules.

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

CURTIS J ROSEBRAUGH  
10/28/2016

Clinical Review  
 Reviewer: Suzette Peng, MD  
 NME/BLA 761037  
 Sarilumab/Kevzara

### CLINICAL REVIEW

<b>Application Type</b>	BLA
<b>Application Number(s)</b>	761037
<b>Priority or Standard</b>	Standard
<b>Submit Date(s)</b>	October 30, 2015
<b>Received Date(s)</b>	October 30, 2015
<b>PDUFA Goal Date</b>	October 28, 2016
<b>Division/Office</b>	DPARP/ODE II
<b>Reviewer Name(s)</b>	Suzette Peng, MD
<b>Review Completion Date</b>	September 21, 2016
<b>Established Name</b>	Sarilumab
<b>(Proposed) Trade Name</b>	KEVZARA
<b>Applicant</b>	Sanofi
<b>Formulation(s)</b>	Pre-filled syringe
<b>Dosing Regimen</b>	200 mg every 2 weeks. Reduction of dose to 150 mg every 2 weeks for management of neutropenia, thrombocytopenia, and elevated liver enzymes
<b>Applicant Proposed Indication(s)/Population(s)</b>	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)
<b>Recommendation on Regulatory Action</b>	Approve
<b>Recommended Indication(s)/Population(s) (if applicable)</b>	Adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to one or more DMARD

## Table of Contents

Glossary.....	13
1 Executive Summary .....	16
1.1. Product Introduction .....	16
1.2. Conclusions on the Substantial Evidence of Effectiveness .....	16
1.3. Benefit-Risk Assessment .....	16
2 Therapeutic Context .....	23
2.1. Analysis of Condition .....	23
2.2. Analysis of Current Treatment Options .....	25
3 Regulatory Background .....	26
3.1. U.S. Regulatory Actions and Marketing History .....	27
3.2. Summary of Presubmission/Submission Regulatory Activity .....	27
3.3. Foreign Regulatory Actions and Marketing History .....	30
4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety.....	30
4.1. Office of Scientific Investigations (OSI) .....	30
4.2. Product Quality .....	31
4.3. Clinical Microbiology .....	34
4.4. Nonclinical Pharmacology/Toxicology .....	34
4.5. Clinical Pharmacology .....	35
4.5.1. Mechanism of Action .....	35
4.5.2. Pharmacodynamics.....	35
4.5.3. Pharmacokinetics.....	36
4.6. Devices and Companion Diagnostic Issues .....	37
4.7. Consumer Study Reviews.....	37
5 Sources of Clinical Data and Review Strategy .....	37
5.1. Table of Clinical Studies.....	37
5.2. Review Strategy.....	43
6 Review of Relevant Individual Trials Used to Support Efficacy .....	43
CDER Clinical Review Template 2015 Edition	2
<i>Version date: November 5, 2015 for initial rollout (NME/original BLA reviews)</i>	

Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

6.1.	EFC11072 (MOBILITY) Part A.....	43
6.1.1.	Study Design .....	43
6.1.2.	Study Results.....	67
6.2.	EFC11072 (MOBILITY) Part B.....	86
6.2.1.	Study Design .....	86
6.2.2.	Study Results.....	109
6.3.	EFC10832 (SARIL-RA-TARGET).....	120
6.3.1.	Study Design .....	120
6.3.2.	Study Results.....	132
6.4.	SFY13370 (SARIL-RA-ASCERTAIN).....	141
6.4.1.	Study Design .....	141
6.4.2.	Study Results.....	148
6.5.	EFC13752 (SARIL-RA-ONE) .....	159
6.5.1.	Study Design .....	159
6.5.2.	Study Results.....	165
6.6.	EFC11574 (SARIL-RA-COMPARE).....	174
6.6.1.	Study Design .....	174
6.6.2.	Study Results.....	180
6.7.	MSC12665 (SARIL-RA-EASY).....	180
6.7.1.	Study Design .....	180
6.7.2.	Study Results.....	185
6.8.	ACT11575 .....	185
6.8.1.	Study Design .....	185
6.8.2.	Study Results.....	188
6.9.	LTS11210 (SARIL-RA-EXTEND).....	188
6.9.1.	Study Design .....	188
6.9.2.	Study Results.....	193
7	Integrated Review of Effectiveness.....	195
7.1.	Assessment of Efficacy Across Trials.....	195
7.1.1.	Primary Endpoints.....	195

7.1.2. Secondary and Other Endpoints .....	199
7.1.3. Subpopulations .....	216
7.1.4. Dose and Dose-Response.....	220
7.1.5. Onset, Duration, and Durability of Efficacy Effects .....	221
7.2. Additional Efficacy Considerations.....	225
7.2.1. Considerations on Benefit in the Postmarket Setting .....	225
7.2.2. Other Relevant Benefits.....	225
7.3. Integrated Assessment of Effectiveness .....	226
8 Review of Safety .....	227
8.1. Safety Review Approach .....	227
8.2. Review of the Safety Database .....	233
8.2.1. Overall Exposure .....	233
8.2.2. Relevant characteristics of the safety population:.....	241
8.2.3. Adequacy of the safety database: .....	247
8.3. Adequacy of Applicant’s Clinical Safety Assessments.....	247
8.3.1. Issues Regarding Data Integrity and Submission Quality .....	247
8.3.2. Categorization of Adverse Events.....	250
8.3.3. Routine Clinical Tests .....	257
8.4. Safety Results .....	260
8.4.1. Deaths .....	260
8.4.2. Serious Adverse Events.....	264
8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects .....	288
8.4.4. Significant Adverse Events .....	294
8.4.5. Treatment Emergent Adverse Events and Adverse Reactions .....	294
8.4.6. Laboratory Findings .....	299
8.4.7. Vital Signs .....	331
8.4.8. Electrocardiograms (ECGs).....	335
8.4.9. QT .....	335
8.4.10. Immunogenicity.....	336
8.5. Analysis of Submission-Specific Safety Issues .....	345

Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

8.5.1. Infections .....	345
8.5.2. Lipid Abnormalities .....	362
8.5.3. Cardiovascular Events.....	373
8.5.4. Malignancy.....	384
8.5.5. Gastrointestinal (GI) Perforations.....	395
8.5.6. Hypersensitivity .....	401
8.5.7. Lupus-like Disorders/Autoimmunity.....	409
8.5.8. Demyelinating disorders.....	411
8.6. Safety Analyses by Demographic Subgroups .....	412
8.7. Specific Safety Studies/Clinical Trials .....	417
8.8. Additional Safety Explorations .....	430
8.8.1. Human Carcinogenicity or Tumor Development.....	430
8.8.2. Human Reproduction and Pregnancy.....	430
8.8.3. Pediatrics and Assessment of Effects on Growth.....	432
8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound .....	432
8.9. Safety in the Postmarket Setting.....	433
8.9.1. Safety Concerns Identified Through Postmarket Experience .....	433
8.9.2. Expectations on Safety in the Postmarket Setting .....	433
8.10. Additional Safety Issues From Other Disciplines.....	434
8.11. Integrated Assessment of Safety.....	434
9 Advisory Committee Meeting and Other External Consultations.....	437
10 Labeling Recommendations .....	437
10.1. Prescribing Information.....	437
10.2. Patient Labeling .....	439
10.3. Nonprescription Labeling .....	439
11 Risk Evaluation and Mitigation Strategies (REMS) .....	439
11.1. Safety Issue(s) that Warrant Consideration of a REMS.....	439
11.2. Conditions of Use to Address Safety Issue(s) .....	439
11.3. Recommendations on REMS .....	439

Clinical Review  
Reviewer: Suzette Peng, MD  
NME/BLA 761037  
Sarilumab/Kevzara

12	Postmarketing Requirements and Commitments.....	439
13	Appendices .....	440
13.1.	References .....	440
13.2.	Financial Disclosure .....	442
13.3.	Schedule of Assessments.....	446

## Table of Tables

Table 1. Clinical Trials Relevant to BLA 761037 .....	38
Table 2. EFC11072 Part A Patient Disposition .....	69
Table 3. Demographics and Patient Characteristics at Baseline in Study EFC11072 Part A.....	71
Table 4. Disease Characteristics at Baseline in Study EFC11072 Part A .....	74
Table 5. ACR20 Response at Week 12 in Study EFC11072 Part A .....	79
Table 6. Overview of Adverse Events in Study EFC11072 Part A.....	84
Table 7. Most Common Adverse Events in Study EFC11072 Part A .....	84
Table 8. SFY13370 Patient Disposition.....	149
Table 9. Baseline Demographics and Patient Characteristics (Study SFY13370) .....	151
Table 10. Baseline Disease Characteristics (SFY13370) .....	154
Table 11. Efficacy Assessments at Week 24 for study SFY13370 .....	156
Table 12. Summary of ACR Components and DAS-28 at Week 24 (Study SFY13370).....	158
Table 13. Summary of Safety Populations .....	228
Table 14. Number of Patients by Study Contributing to Pool 1 .....	230
Table 15. Number of Patients by Study Contributing to Pool 2 .....	231
Table 16. Number of Patients by Study Contributing to Pool 3 .....	232
Table 17. Patient Disposition for Pool 1 (Placebo-Controlled Population) .....	234
Table 18. Patient Disposition of Any Sarilumab Dose Group in Pool 2 (Long-Term Safety Population).....	236
Table 19. Exposure to Sarilumab in Pool 1 (Placebo-Controlled Population) .....	237
Table 20. Exposure to Sarilumab in Pool 1a (Phase 3 Placebo-Controlled Population) .....	238
Table 21. Exposure to Sarilumab in Pool 2 (Long-Term Safety Population).....	239
Table 22. Exposure to Sarilumab in Pool 3 (Monotherapy Population) .....	241
Table 23. Demographics and Patient Characteristics at Baseline (Pool 1) .....	243
Table 24. Disease Characteristics at Baseline (Pool 1) .....	245
Table 25. Baseline Medications for RA in Pool 1 .....	246
Table 26. Definition of TEAE Period for Each Safety Population .....	251
Table 27. AESIs and MedDRA Search Criteria for Adverse Events.....	253
Table 28. Additional Safety Analyses of Placebo-Controlled Studies .....	255
Table 29. Summary of All Deaths.....	262
Table 30. Summary of Deaths by Study and Treatment at time of Death .....	263
Table 31. Number (%) of Patients with SAEs during the Pre-Rescue Period (Pool 1a) .....	266
Table 32. Overview of SAEs in the Double-Blind Treatment Period (Pool 1) .....	283
Table 33. Overview of SAEs in $\geq 3$ patients in the Entire TEAE Period (Pool 2).....	285
Table 34. Overview of Adverse Events Leading to Discontinuation in the Double-Blind Period (SOCs and PTs reported in $\geq 2$ patients, Pool 1) .....	290
Table 35. Overview of Adverse Events Leading to Discontinuation in the Entire TEAE Period (SOCs and PTs in $\geq 3$ patients, Pool 2) .....	292

Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

Table 36. Summary of Common TEAEs (incidence >2% subjects in one of the treatment groups) by PT during the Pre-Rescue Period (Pool 1a) .....	294
Table 37. Number (%) of Patients with Elevated ALT by Maximum Grade during the Pre-Rescue Period (Pool 1a).....	301
Table 38. Number (%) of Patients with ALT >3x ULN during the Pre-Rescue Period (Pool 1a)..	301
Table 39. Number of Patients with PCSA in Liver Enzymes during the Double-Blind Period (Pool 1) .....	306
Table 40. Model-based Analyses on Patients with at least one ALT >3x ULN during the TEAE period .....	308
Table 41. Number (%) of Patients with Hepatic Disorders during the Pre-Rescue Period (Pool 1a) .....	309
Table 42. Dose Reduction for Elevated ALT in Study LTS11210 .....	311
Table 43. Summary of ALT for Patients on 200mg q2w who Dose Reduced due to ALT Increase in Study LTS11210.....	312
Table 44. Number (%) of Patients with Decreased ANC by Maximum Grade during the Pre-Rescue Period (Pool 1a) .....	314
Table 45. Summary of ANC < 1.0 Giga/L in the Pre-Rescue Period (Pool 1a).....	315
Table 46. Model-based Analyses on Patients with at least one Absolute Neutrophil Count <1.0 Giga/L during the TEAE period.....	318
Table 47. Incidence of Infection in Subjects with and without ANC < LLN in the Long-Term Safety Population (Pool 2) .....	319
Table 48. Summary of Adverse Events in Leukopenia and Neutropenia in the Pre-Rescue Period (Pool 1a) .....	320
Table 49. Dose Reduction in Study LTS11210 Secondary to Neutrophil Count Decrease .....	322
Table 50. Summary of ANC for Patients on 200mg q2w who Required Dose Reduction in Study LTS11210.....	323
Table 51. Summary of Thrombocytopenia during the Pre-Rescue Period (Pool 1a).....	328
Table 52. Overview of ADA during the Double-Blind Period (Pool 1) .....	337
Table 53. Number of Patients with Hypersensitivity Events by ADA Status during the Entire TEAE Period (Pool 2) .....	338
Table 54. Number of Patients with Lack or Loss of Efficacy by ADA status (Neutralizing and Persistent) during the Entire TEAE Period (Pool 2).....	339
Table 55. Overview of Incidence of Positive ADA in Study EFC13752.....	341
Table 56. Overview of ADA Status in Study EFC13752 .....	342
Table 57. Number of Patients with AEs Leading to Discontinuation by ADA Status in Study EFC13752 .....	343
Table 58. Number of Patients with Lack or Loss of Efficacy in Study EFC13752 .....	343
Table 59. Incidence of ACR20 Response at Week 24 by ADA Status in Study EFC13752.....	344
Table 60. Summary of Overall Infections during the Pre-Rescue Period (Pool 1a) .....	347
Table 61. Overview of Infections in the Entire Double-blind Treatment Period (Pool 1) .....	348
Table 62. Overview of Serious Infections in the Double-Blind Treatment Period (Pool 1) .....	349

Table 63. Overview of Opportunistic Infections in the Double-blind Treatment Period (Pool 1)	350
Table 64. Overview of All Infections for the Entire TEAE Period (Pool 2)	352
Table 65. Overview of Serious Infections in the Entire TEAE Period (Pool 2)	354
Table 66. Sensitivity Analyses of Infections during the TEAE Period (Week 0-52, Pool 1a)	359
Table 67. Model-based Analyses on Patients with at least one Serious Infection during the TEAE Period	360
Table 68. Model-based Analyses on Number of Serious Infections during the Entire TEAE Period	361
Table 69. Summary of Serious Infections in Pivotal Studies and OLE (EFC11072, EFC10832, LTS11210)	362
Table 70. Elevation in Lipids during Pre-Rescue Period (Pool 1a)	367
Table 71. Elevation in Lipids during the Double-Blind Treatment Period (Pool 1)	368
Table 72. Number of Patients by NCEP ATPIII LDL Classification according to Baseline Status and Post-Baseline Values during Double-Blind Treatment Period (Pool 1)	369
Table 73. Elevation in Lipids in Long-Term Safety Population (Pool 2)	371
Table 74. Cardiovascular History in the Placebo-Controlled Population (Pool 1)	374
Table 75. Summary of CV Events during Pre-Rescue Period (Pool 1a)	375
Table 76. Sensitivity Analyses of CV Events during TEAE Period (Weeks 0-52, Pool 1a)	377
Table 77. Number of CV Events (per 100 pt-yrs) in the Long-Term Safety Population (Pool 2)	378
Table 78. Model-based Analyses on Patients with at least one MACE during the TEAE period	379
Table 79. Summary of CV Events in Pivotal Studies and OLE (EFC11072, EFC10832, LTS11210)	380
Table 80. Summary of Malignancies in the Pre-Rescue Period (Pool 1a)	385
Table 81. Overview of Malignancy TEAEs in Entire Double-Blind Treatment Period (Pool 1)	386
Table 82. Sensitivity Analyses of Malignancies during TEAE period (Week 0-52, Pool 1a)	388
Table 83. Overview of Malignancy TEAEs in the Long-Term Safety Population (Pool 2)	389
Table 84. Model-based Analyses on Patients with at least one Malignancy during the TEAE Period	392
Table 85. Summary of Malignancies in Pivotal Studies and OLE (EFC11072, EFC10832, LTS11210)	393
Table 86. Standard Incidence Ratios for Malignancies in the Sarilumab + DMARD (any dose) Long-Term Safety Population (Pool 2): Rheumatoid Arthritis Patients (Clinformatics 2000-2014)	395
Table 87. Summary of GI Perforations and Ulcerations in the Pre-Rescue Period (Pool 1a)	397
Table 88. Sensitivity Analyses of GI Perforations and Ulcerations during TEAE period (Week 0-52, Pool 1a)	398
Table 89. Overview of Diverticulitis/GI perforations in the Entire TEAE Period (Pool 2)	399
Table 90. Overview of GI Ulcerations in the Entire TEAE Period (Pool 2)	400
Table 91. Number (%) of Patients with Potential GI Perforation and GI Ulcerations	401
Table 92. Overview of Hypersensitivity Events in the Pre-Rescue Period (Pool 1a)	403

Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

Table 93. Sensitivity Analyses of Hypersensitivity Events during the TEAE Period (Weeks 0-52, Pool 1a) .....	404
Table 94. Overview of Hypersensitivity in the Double-Blind Period (Pool 1) .....	405
Table 95. Overview of Hypersensitivity in the Entire TEAE Period (Pool 2) .....	406
Table 96. Overview of Injection Site Reactions in the Double-Blind Period (Pool 1) .....	407
Table 97. Overview of Demyelinating Disorders in the Pre-Rescue Period (Pool 1a) .....	411
Table 98. SFY13370 Exposure to Investigational Medicinal Product .....	418
Table 99. Overview of Adverse Events in SFY13370 .....	419
Table 100. Number (%) of Patients with SAEs by SOC and PT in study SFY13370 .....	420
Table 101. SFY13370 Number of Patients with AEs Leading to Permanent Discontinuation ....	421
Table 102. SFY13370 Number of Patients with AEs of Special Interest (AESI) .....	423
Table 103. Overview of Adverse Events in Study EFC13752 .....	427
Table 104. Number of Patients with AESI in Study EFC13752 .....	429
Table 105. EFC11072 Part A Study Flow Chart .....	446
Table 106. EFC11072 Part B Study Flow Chart .....	449
Table 107. EFC10832 Study Flow Chart .....	453
Table 108. LTS11210 Study Flow Chart (Subjects from ACT11575, EFC11072 Part A and B Cohort 1) .....	457
Table 109. LTS11210 Study Flow Chart (Subjects from EFC10832, EFC11072 Part B Cohort 2, SFY13370, EFC13752).....	461
Table 110. SFY13370 Study Flow Chart .....	465
Table 111. EFC13752 Study Flow Chart .....	469
Table 112. EFC11574 Study Flow Chart (Open Label Phase) .....	474
Table 113. EFC11574 Study Flow Chart (Randomized Control Phase) .....	477
Table 114. EFC11574 Substudy Flow Chart (1-year OL Study) .....	480
Table 115. MSC12665 Study Flow Chart.....	483

## Table of Figures

Figure 1. Study Schema of EFC11072 Part A.....	45
Figure 2. Incidence of ACR20 Response at Each Visit (EFC11072 Part A).....	80
Figure 3. Incidence of ACR50 Response at Each Visit (Study EFC11072 Part A).....	82
Figure 4. ANC at Each Visit in Study EFC11072 Part A.....	85
Figure 5. Study Schema of EFC11072 Part B Cohort 1.....	88
Figure 6. Study Schema of EFC11072 Part B Cohort 2.....	89
Figure 7. Study Schema of EFC10832.....	122
Figure 8. Study Schema of SFY13370.....	142
Figure 9. Incidence of ACR20 Response at Each Visit.....	157
Figure 10. Study Schema of EFC13752.....	160
Figure 11. Study Schema of EFC11574.....	176
Figure 12. Study Schema of EFC11574 Substudy.....	177
Figure 13. Study Schema of MSC12665.....	181
Figure 14. Kaplan-Meier Plot for Time to Treatment Discontinuation or Rescue (Pool 1).....	235
Figure 15. Contribution of Doses to Any Sarilumab Dose Arm Over Entire TEAE Period (Pool 2) .....	240
Figure 16. Sanofi-Aventis General Guidance for Follow-up of Neutropenia.....	258
Figure 17. Sanofi-Aventis General Guidance for Follow-up of an Increase in ALT.....	259
Figure 18. Sanofi-Aventis General Guidance for Follow-up on Acute Renal Failure (ARF).....	260
Figure 19. Exposure-adjusted Rate of Death by 6-month Intervals during the Entire TEAE and Post-Study Periods (Pool 2).....	264
Figure 20. Exposure-Adjusted Rate of SAEs by 6-month Interval during the Entire TEAE Period (Pool 2).....	287
Figure 21. Summary of Adverse Events Leading to Discontinuation in the Pre-Rescue Period (Pool 1a).....	288
Figure 22. Kaplan-Meier Plot for Time to Discontinuation due to Adverse Events (Pool 2).....	293
Figure 23. Mean ALT across Visits during the Double-Blind Period (Pool 1).....	302
Figure 24. Mean AST across Visits during the Double-Blind Period (Pool 1).....	303
Figure 25. Mean T Bili across Visits during the Double-Blind Period (Pool 1).....	304
Figure 26. Mean ALP across Visits during the Entire Double-Blind Period (Pool 1).....	305
Figure 27. Scatter Plot of Peak Values of ALT vs. Peak Value of T Bili during the Entire TEAE Period (Pool 2).....	307
Figure 28. Mean ANC across Visits during the Double-Blind Treatment Period (Pool 1).....	316
Figure 29. Exposure-adjusted Rate of Patients with at least 1 ANC <1.0 Giga/L by 6 month Interval during the Entire TEAE Period (Pool 2).....	317
Figure 30. Mean Platelets Across Visits during the Double-Blind Period (Pool 1).....	325
Figure 31. Exposure-adjusted Rate of Patients with at least 1 Platelet Count < 100 Giga/L by 6- month Intervals during the Entire TEAE Period (Pool 2).....	326

Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

Figure 32. Mean Change from Baseline in BUN across Visits during the Double-Blind Period (Pool 1) .....	329
Figure 33. Mean Change from Baseline in SCr Across Visits during the Entire Double-Blind Period (Pool 1) .....	330
Figure 34. Mean Weight Change from Baseline Across Visits during the Double-Blind Period (Pool 1) .....	332
Figure 35. Mean Supine SBP Across Visits during the Double-Blind Period (Pool 1) .....	333
Figure 36. Mean Supine DBP Across Visits during the Double-Blind Period (Pool 1) .....	334
Figure 37. Mean Supine Heart Rate Across Visits during the Double Blind Period (Pool 1) .....	335
Figure 38. Exposure-Adjusted Rate of Serious Infections by 6-month Intervals During the Entire TEAE Period (Pool 2) .....	358
Figure 39. Mean LDL across Visits during the Double-Blind Treatment Period (Pool 1) .....	364
Figure 40. Mean HDL across Visits during the Double-Blind Treatment Period (Pool 1) .....	365
Figure 41. Mean Triglycerides across Visits during the Double-Blind Treatment Period (Pool 1) .....	366
Figure 42. Mean Change from Baseline in LDL at Each Visit during the TEAE Period (SFY13370) .....	372
Figure 43. Exposure-adjusted Rate of MACE (primary) by 6-month Intervals During the Entire TEAE Period (Pool 2) .....	381
Figure 44. Exposure-adjusted Rate of Injection Site Reactions by 6-month Interval during the Entire TEAE Period (Pool 2) .....	409
Figure 45. Mean Change from Baseline in ANC at Each Visit for Study SFY13370 .....	424
Figure 46. Mean Change from Baseline in ALT at Each Visit for Study SFY13370 .....	425

## Glossary

---

AC	advisory committee
ACR	American College of Rheumatology
AE	adverse event
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRP	C-reactive protein
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMARD	disease modifying anti-rheumatic drug
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
EOP2	end of phase 2
ETASU	elements to assure safe use
EULAR	European League against Rheumatism
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
HAQ-DI	Health Assessment Questionnaire-Disability Index
HCQ	hydroxychloroquine
HLGT	High Level Grouped Term
HLT	High Level Term
hs-CRP	high sensitivity C-reactive protein

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

ICF	informed consent form
ICH	International Conference on Harmonization
IL-6R	interleukin 6 receptor
IMP	investigational medicinal product
IND	Investigational New Drug
iPSP	initial Pediatric Study Plan
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
IVRS	interactive voice response system
LEF	leflunomide
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
MTX	methotrexate
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
NSAID	nonsteroidal anti-inflammatory drug
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
pcJIA	polyarticular-course juvenile idiopathic arthritis
pJIA	polyarticular juvenile idiopathic arthritis
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PPSR	Proposed Pediatric Study Report
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
PT	Preferred Term
RA	rheumatoid arthritis
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan

Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

SGE	special government employee
SOC	standard of care
SOC	System Organ Class
SSZ	sulfasalazine
TEAE	treatment emergent adverse event
TNF $\alpha$	tumor necrosis factor alpha
VAS	visual analog scale

## 1 Executive Summary

---

### 1.1. Product Introduction

Sarilumab (KEVZARA) is a recombinant human immunoglobulin (IgG)1 monoclonal antibody that binds specifically to both soluble and membrane-bound interleukin-6 (IL-6) receptors (sIL-6R $\alpha$  and mIL-6R $\alpha$ ) and inhibits IL-6-mediated signaling. It is a new molecular entity (NME).

Sanofi proposes that "sarilumab is indicated for 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)."

Sarilumab may be used as monotherapy or in combination with methotrexate (MTX) or other traditional DMARDs as a subcutaneous injection. The recommended dose of sarilumab is 200 mg once every 2 weeks (q2w) given as a subcutaneous (SC) injection. Reduction in the dose from 200 mg q2w to 150 mg q2w is recommended for management of elevated liver enzymes, neutropenia, and thrombocytopenia.

### 1.2. Conclusions on the Substantial Evidence of Effectiveness

To support efficacy of sarilumab in the treatment of patients with RA, Sanofi performed two phase 3, randomized, double-blind, placebo-controlled trials evaluating 2 doses of sarilumab (150mg q2w and 200mg q2w) plus DMARDs. Study EFC11072 Part B had a double-blind treatment period of 52 weeks in RA patients who were MTX inadequate responders, and study EFC10832 had a double-blind treatment period of 24 weeks in RA patients who were TNF inhibitor inadequate responders. Both studies met the evidentiary standard. The primary and key secondary efficacy endpoints assessed signs and symptoms (ACR response, DAS28-CRP), physical function (HAQ-DI), and radiographic progression (mTSS). For all these endpoints, sarilumab showed a statistically significant and robust improvement compared to placebo. For ACR response, DAS28-CRP, and mTSS, there was a dose response with a trend toward slightly greater response on sarilumab 200mg compared to 150mg. In conclusion, the data support sarilumab's efficacy in the treatment of patients with RA who are inadequate responders or intolerant of one or more DMARD. The efficacy results support the proposed initial dose of 200mg every 2 weeks.

### 1.3. Benefit-Risk Assessment

### Benefit-Risk Summary and Assessment

Rheumatoid arthritis (RA) is a serious disease that can cause pain, stiffness, and functional impairment. The majority of patients with RA have a chronic, progressive disease that is associated with increased morbidity and mortality. There are multiple approved drugs to treat RA, but there remains unmet need since existing therapies are not effective for all patients with RA and all therapies have potential side effects. Thus, another biologic therapy would be a desirable addition to the therapeutic options available for RA.

Sarilumab is a human monoclonal antibody of the IgG1 kappa isotype that binds to human interleukin-6 receptor (IL-6R). Two doses of sarilumab (150 mg and 200 mg) were studied in two phase 3 trials in patients with RA. These trials were adequate and well-controlled, and provided corroborating evidence of the efficacy of sarilumab for reducing signs and symptoms of RA, based on the proportion of patients experiencing an American College of Rheumatology (ACR) response criteria and reduction in DAS28-CRP. Comparison of the two sarilumab doses indicates that the proportion of patients experiencing improvement in the sarilumab 200 mg once every two week group was numerically higher than the 150 mg group. Both of the phase 3 trials provided corroborating evidence of sarilumab for improving physical function, as measured by Health Assessment Questionnaire-Disability Index (HAQ-DI). The level of improvement was similar for the 150 mg and 200 mg dose groups. The effect of sarilumab on structural damage progression was assessed by radiographs in one study, which provided evidence of efficacy of sarilumab on structural damage progression and suggested trends towards more inhibition of radiographic progression with the 200 mg dose as compared to the 150 mg dose. Although there was only a single study assessing radiographic progression, the evidence is sufficient due to the highly statistically significant p-values and the consistency of the results across the two doses and with different analysis techniques.

The safety profile of sarilumab is well-characterized within the clinical trials. Based on this profile, the major toxicities of concern with sarilumab are related to significant immunosuppression and are consistent with the safety concerns of tocilizumab, which has the same mechanism of action. Sarilumab was associated with an increased risk of serious infections, including opportunistic infections and tuberculosis. While no imbalance in malignancy was seen in the clinical trials, treatment with an immunosuppressant may increase the risk of malignancies. Sarilumab treatment was associated with laboratory abnormalities including decreases in neutrophils and platelets and increases in liver function tests and lipid parameters. In general, laboratory abnormalities appeared to be dose-related. Notably, there did not appear to be an association between neutropenia and the development of infections. There were elevations in LDL, HDL, and triglycerides on sarilumab, but there was no clear increase in the risk of cardiovascular events on sarilumab during the time frame of the clinical trials. That being said, there were very few events observed overall and we therefore have limited ability to rule out increases in risk based on the currently available clinical data. Additional safety concerns included hypersensitivity reactions and gastrointestinal perforation.

Based on the data in this submission, the seriousness of RA, and the need for additional therapeutic options for RA, the benefit/risk profile of sarilumab is adequately favorable to support the 200 mg dose regimen, with dose reduction to 150 mg as needed for laboratory abnormalities. Compared to the 150 mg dose, the 200 mg dose demonstrated numerical trends suggesting additional benefit on both clinical and radiographic outcomes. While there were some dose-related safety signals, the safety profile of both doses is acceptable given the severity of this disease and the demonstrated benefits. The identified safety concerns can be addressed through appropriate product labeling. Sarilumab appears to provide benefit similar to other available therapies and represents an additional treatment option for patients with RA.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<a href="#">Analysis of Condition</a>	<ul style="list-style-type: none"> <li>Rheumatoid arthritis (RA) is an autoimmune disease that causes chronic symmetric inflammation of joints. It can also cause inflammation outside of the joints in a variety of locations, such as the lungs, heart, and blood vessels.</li> <li>RA affects 1% of the adult population in the United States (US) and is the most common type of inflammatory arthritis.</li> <li>RA significantly impacts the lives of patients due to pain and decreased physical function. In addition, patients with RA have higher mortality rates than the general population.</li> <li>The goal of treatment is early and aggressive use of medications to try to prevent functional impairment and irreversible joint damage.</li> </ul>	<p><b>Rheumatoid arthritis is a serious condition and is the most common type of inflammatory arthritis. Most patients have a chronic progressive disease that is associated with morbidity and increased mortality.</b></p>
<a href="#">Current Treatment Options</a>	<ul style="list-style-type: none"> <li>All patients with RA are generally treated with disease modifying antirheumatic drugs (DMARDs). There are multiple drugs approved by the FDA for the treatment of RA. Generally, methotrexate (MTX) is the first line of therapy for RA. Treatment with a tumor necrosis factor-alpha (TNF-<math>\alpha</math>) antagonist as add-on or as monotherapy is generally the recommended next line of treatment. However, between 30% and 40% of patients fail to respond or become intolerant to anti-TNF-<math>\alpha</math> therapy. For these patients, additional</li> </ul>	<p>There are multiple current treatment options for patients with RA. However, despite this fact, some subjects continue to have active disease either due to inadequate response or due to intolerance of therapy.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>anti-TNF-<math>\alpha</math> therapies or therapies that target different pathways can be used.</p> <ul style="list-style-type: none"> <li>• Tocilizumab is approved for the treatment of RA and has the same target as sarilumab (interleukin-6).</li> </ul>	
<p><u>Benefit</u></p>	<ul style="list-style-type: none"> <li>• Sarilumab is proposed for treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more DMARDs.</li> <li>• The efficacy of sarilumab was established in two phase 3 clinical trials. One trial was placebo controlled for 52 weeks (n=1197) and one trial was placebo controlled for 24 weeks (n=546).</li> <li>• The primary endpoint in both phase 3 trials was the proportion of patients who achieved an ACR20 response at Week 24.</li> <li>• The ACR20 response is calculated as a &gt;20% improvement in:             <ul style="list-style-type: none"> <li>○ tender joint count and</li> <li>○ swollen joint count and</li> <li>○ 3 of the 5 remaining ACR core set measures                 <ul style="list-style-type: none"> <li>▪ Patient Global Assessment of Arthritis on a visual analog scale (VAS)</li> <li>▪ Physician Global Assessment of Arthritis on a VAS</li> <li>▪ Patient Assessment of Pain on a VAS</li> <li>▪ Patient Assessment of Physical Function</li> <li>▪ Acute Phase Reactant</li> </ul> </li> </ul> <p>Fifty percent and 70 percent improvement (ACR50 and ACR70) are similarly calculated using these higher levels of improvement.</p> <li>• In both studies, patients treated with either 200 mg or 150 mg of sarilumab + MTX/DMARD every two weeks had higher ACR20,</li> </li></ul>	<p>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.</p> <p>Although the two pivotal phase 3 studies did not include an active comparator, the degree in reduction in signs and symptoms of RA and inhibition of radiographic progression appears to be similar to other DMARDs approved for RA. Without effective treatment, joint damage progresses chronically and irreversibly and results in impaired physical function and disability. Thus, effective therapies are needed for RA.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>ACR50, and ACR70 response rates versus placebo-treated patients at Week 24. In study EFC11072 Part B the difference (95% confidence interval) from placebo for ACR20 at 24 weeks was 25% (18%, 31%) and 33% (27%, 40%) for the 150 mg and 200 mg dose groups, respectively. In study EFC10832, the difference (95% confidence interval) from placebo for ACR20 at 24 weeks was 22% (13%, 32%) and 27% (18%, 37%).</p> <ul style="list-style-type: none"> <li>• Both studies demonstrated that patients receiving sarilumab 200 mg or 150 mg every two weeks had greater improvement from baseline in physical function, as measured by the Health Assessment Questionnaire-Disability Index (HAQ-DI) compared to placebo.</li> <li>• Results from Study EFC11072 Part B showed that both doses of sarilumab were associated with significantly less radiographic progression of structural damage as compared to placebo. Although there was only a single study assessing radiographic progression, the evidence is sufficient due to the highly statistically significant p-values and the consistency of the results across the two doses and with different analysis techniques.</li> <li>• For the vast majority of endpoints, sarilumab 200 mg was associated with numerically higher responses than 150 mg. The data suggest trends towards more radiographic inhibition with the 200 mg dose as compared to the 150 mg dose.</li> </ul>	
<b>Risk</b>	<ul style="list-style-type: none"> <li>• The safety of sarilumab in combination with DMARDs was evaluated in phase 2 and phase 3 studies, consisting of 3,019 patients, which included 132 patients on sarilumab monotherapy. The drug exposure data are considered adequate.</li> </ul>	<p>The size of the safety database for sarilumab is adequate. Its safety profile is well characterized and consistent with the safety profile of tocilizumab, a medication approved</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<ul style="list-style-type: none"> <li>• The safety profile for sarilumab was consistent with the known safety profile of tocilizumab.</li> <li>• Major safety concerns:               <ul style="list-style-type: none"> <li>○ <b>Serious infections:</b> Serious and sometimes fatal infections due to bacterial, mycobacterial, fungal, viral, or other opportunistic pathogens were reported in patients receiving sarilumab for RA.</li> <li>○ <b>Laboratory parameters:</b> Sarilumab is associated with decreases in neutrophils and platelet counts. In addition, sarilumab is associated with increases in liver enzymes and lipid parameters, such as LDL cholesterol, HDL cholesterol, and triglycerides. In general, these laboratory abnormalities appeared to be dose-related. While neutropenia appeared to be dose-related, there did not appear to be an association between neutropenia and the development of infections. Liver enzyme elevations were mostly mild, and no cases were consistent with Hy’s law criteria.</li> <li>○ <b>Gastrointestinal perforation:</b> Events of gastrointestinal perforation were reported in clinical studies, primarily as complications of diverticulitis. However, the numbers were low.</li> <li>○ <b>Immunosuppression:</b> While no imbalance in malignancy was seen in the clinical trials, treatment with immunosuppressants may increase the risk of malignancies.</li> <li>○ <b>Hypersensitivity reactions:</b> Hypersensitivity reactions, such as rash and urticaria, have been reported in association with sarilumab.</li> </ul> </li> </ul>	<p>for RA.</p> <p>The main safety concerns associated with sarilumab are immunosuppression and laboratory parameter changes, including neutropenia, thrombocytopenia, and elevations in lipid parameters and liver function tests. Overall, the risks observed are deemed acceptable with proper warnings.</p> <p>Each drug approved for RA is associated with toxicities and the toxicities associated with these approved drugs are similar to those observed with sarilumab.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<ul style="list-style-type: none"> <li>Other safety issues include infections, immunogenicity, upper respiratory tract infection, and nasopharyngitis.</li> </ul>	
<p><u>Risk Management</u></p>	<ul style="list-style-type: none"> <li>The safety concerns with sarilumab are well-characterized. Healthcare providers are familiar with treatments for RA associated with immunosuppression and lipid elevations.</li> <li>Tocilizumab has a boxed warning for serious infections, including active tuberculosis, invasive fungal infections, and bacterial, viral and other infections due to opportunistic pathogens.</li> </ul>	<p>Safety risks can be communicated to healthcare professionals through labeling (including a Medication Guide). The labeling will include a boxed warning for serious infections. In addition, the labeling will contain Warnings and Precautions for the major safety signals. The safety section of the label will be similar to that of tocilizumab. Routine pharmacovigilance and labeling are adequate to address the safety issues associated with sarilumab.</p>

## 2 Therapeutic Context

---

### 2.1. Analysis of Condition

Rheumatoid arthritis (RA) is a chronic, symmetric inflammatory polyarthritis that primarily involves synovial joints. In RA, synovial tissues become inflamed and proliferate, forming pannus that invades bone, cartilage, and ligament and leads to joint damage and deformities. Destruction of synovial joints can lead to severe disability and premature mortality (Scott, et al. “Long-term outcome” 1108; Mitchell, et al. 706). The joints most commonly involved first are the metacarpophalangeal (MCPs), proximal interphalangeal (PIPs), wrist, and metatarsophalangeal (MTPs) joints. The disease onset is usually insidious, with tenderness, warmth, and swelling of many joints. Patients frequently report joint stiffness that is worse in the mornings and after inactivity. Systemic symptoms, such as fatigue, fever, and weight loss can be present. Larger joints generally become symptomatic after small joints. Extra-articular manifestations occur in about 40% of patients with RA (Tueresson, et al. 722). Extra-articular manifestations include rheumatoid nodules, pleurisy, interstitial lung disease, pericarditis, myocarditis, and rheumatoid vasculitis (Nyhall-Wahlin, et al. 416).

RA affects approximately 1% of the adult population in North America and Northern Europe (Gabriel, et al. 229). The disease is three times more frequent in women than men. Prevalence rises with age and is highest in woman older than 65 years.

While the exact etiology of RA is unknown, complex interactions between genetic and environmental factors appear to play a role in the development of RA. RA is an autoimmune disease, and certain autoantibodies, including rheumatoid factor (RF) and anti-citrullinated protein antibody (ACPA), can precede the clinical manifestations of RA by many years (Nielen, et al. 380). Cytokines are important contributors in synovial inflammation and proliferation resulting in joint pain and swelling, autoantibody production, bone erosions, joint space narrowing and joint destruction. There are multiple cytokines involved, such as interleukin (IL)-1 and IL-6, and tumor necrosis factor (TNF)-alpha.

While there is heterogeneity in the natural history of RA, it is generally a chronic, progressive disease. Patients can develop joint destruction, severe physical disability and multiple co-morbidities. Risk factors for joint damage and disability are rheumatoid factor status and disease activity (Scott DL, et al. Joint damage and disability in RA. S20). One study found that mortality was increased more than two fold in patients with RA as in the general population (Wolfe F, et al. 481). Disease activity in RA fluctuates secondary to the disease process itself and therapeutic interventions. Patients with RA can develop radiographic changes, including joint space narrowing and bony erosions. In contrast to clinical symptoms, structural damage is

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

irreversible and cumulative (Scott DL. Radiographic progression in established RA. 55).

The prognosis of RA has improved over the last two decades for a variety of reasons, including changes in drug therapy and approaches to treatment. Specific changes include more aggressive disease management, earlier treatment, and the availability of more therapies, such as targeted biologic agents since the later part of the 1990s. Currently, the course of RA is variable. Approximately 15% of patients have intermittent disease with a relatively good prognosis. However, the majority of patients have progressive disease.

In 2010, the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) collaborated to create new classification criteria for RA (Aletaha, et al. 1580). The goal of these classification criteria was to facilitate the identification of patients with RA at earlier stages of disease. Recommendations for the treatment of patients with RA have been developed by major professional organizations, including the ACR and EULAR (Singh, et al. 2012 update of the 2008 ACR recommendations. 625; Smolen, et al. EULAR recommendations for the management of RA. 492; Singh, et al. 2015 ACR guideline for treatment of RA. 1). Since irreversible structural damage can occur if inflammation persists, early recognition and treatment of RA is key, with a goal of low disease activity or remission.

All patients diagnosed with RA are generally treated with disease-modifying antirheumatic drugs (DMARDs). Non-biologic DMARDs, such as methotrexate (MTX), are the first line of therapy for RA (Katchamart, et al. CD008495). Treatment with a tumor necrosis factor-alpha (TNF- $\alpha$ ) antagonist is generally the next line of treatment for patients with ongoing disease activity. However, between 30% and 40% of patients fail to respond or become intolerant to anti-TNF- $\alpha$  therapy (Smolen, et al. RA therapy reappraisal. 276). For patients with ongoing disease activity, the therapeutic strategy usually involves trying another TNF- $\alpha$  antagonist or switching to a medication with a different mechanism of action. Approved alternative therapies include an orally bioavailable Janus kinase (JAK) inhibitor (tofacitinib), and biological DMARDs targeting the B-cell antigen CD-20 (rituximab), cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4; abatacept), and the pro-inflammatory cytokines IL-1 (anakinra) and IL-6 (tocilizumab).

The goal of treatment is prevention of irreversible joint destruction and functional impairment given the significant impact on patients and public health. RA imposes a substantial economic burden not only on patients but also on family members, employers, and the government. One study estimated a total annual cost of \$19.3 billion and \$39.2 billion (in US 2005 dollars) without and with intangible costs, respectively (Birnbaum, et al. 77). Because many RA patients remain inadequately treated or have intolerance to available medications, there remains a continuing unmet medical need for alternative, effective medications for RA.

## 2.2. Analysis of Current Treatment Options

Several therapies have been already approved for the treatment of patients with RA as listed in Table 1 and Table 2. The classes of drugs used for treatment of RA include: nonsteroidal anti-inflammatory drugs (NSAIDs) and selective COX-2 inhibitors, corticosteroids, and disease modifying antirheumatic drugs (DMARDs). NSAIDs and COX-2 inhibitors are utilized primarily for symptomatic relief of pain and are useful adjunct therapies because of their anti-inflammatory and analgesic effects. Corticosteroids also have anti-inflammatory effects, but their use is limited by long-term toxicity.

DMARDs are therapeutic agents that reduce signs and symptoms of RA and decrease radiographic progression of joint damage. DMARDs are frequently divided into two categories: small molecules and biologics. Methotrexate (MTX) is a small molecule and the most commonly used DMARD because of its well-established safety and efficacy profile. In the treatment of RA, methotrexate is often the initial DMARD used. For patients with ongoing disease activity, other small molecule drugs or biologic DMARDs are frequently added to MTX.

**Table 1. Small Molecule DMARDs Approved for the Treatment of RA in the United States**

Product Name (Trade Name) [Sponsor]	Year of First Approval for RA	Dosing/ Administration	Mechanism of Action in RA
Sulfasalazine (AZULFIDINE) [Pfizer]	1950	Oral	Anti-inflammatory and antimicrobial
Methotrexate sodium (METHOTREXATE SODIUM) [Multiple]	1988	Oral, SC (autoinjectors)	Anti-metabolite
Hydroxychloroquine (PLAQUENIL) [Sanofi-Aventis]	1955	Oral	Interference with antigen processing (?)
Azathioprine (IMURAN) [Prometheus Labs]	1968	Oral	Cytostatic
Penicillamine (CUPRIMINE) [Alton]	1970	Oral	Unknown
Auranofin (RIDAURA) [Prometheus Labs]	1985	Oral	Unknown
Cyclosporine (NEORAL) Cyclosporine (SANDIMMUNE) [Novartis]	1995 1990	Oral	T-cell activation inhibitor
Leflunomide (ARAVA) [Sanofi-Aventis]	1998	Oral	Anti-metabolite

Steroids and NSAIDs are approved for the reduction of the signs and symptoms of RA.

Clinical Review  
 Reviewer: Suzette Peng, MD  
 NME/BLA 761037  
 Sarilumab/Kevzara

**Table 2. Biologic DMARDs and JAK Inhibitors Approved for the Treatment of RA in the United States**

Product Name (Trade Name)	Year approved for RA	BLA/NDA (sponsor)	ROA	Description	MOA
Etanercept (ENBREL)	1998	103795 (Immunex/Amgen)	SC	Fusion protein consisting of tumor necrosis factor receptor (TNFR) linked to human IgG1 Fc	TNF inhibitor
Infliximab (REMICADE)	1999	103772 (Centocor)	IV	Chimeric IgG1k mAb	TNF inhibitor
Anakinra (KINERET)	2001	103950 (Amgen)	SC	Recombinant polypeptide	IL-1 receptor antagonist
Adalimumab (HUMIRA)	2002	125057 (Abbott/Abbvie)	SC	Human IgG1k mAb	TNF inhibitor
Abatacept (ORENCIA)	2005 2011	125118 (Bristol-Myers Squibb)	IV SC	Fusion protein consisting of CTLA-4 and human IgG1 Fc	T cell activation inhibitor
Rituximab (RITUXAN)	2006	103705 (Genentech & Biogen Idec)	IV	Chimeric murine/human IgG1k mAb	AntiCD20, B cell depletor
Golimumab (SIMPONI)	2009	125289 (Centocor and Janssen)	SC	Humanized IgG1k mAb	TNF inhibitor
Certolizumab Pegol (CIMZIA)	2009	125160 (UCB Inc)	SC	Humanized Fab fragment	TNF inhibitor
Tocilizumab (ACTEMRA)	2010 2013	125276 125472 (Genentech/Roche)	IV SC	Humanized IgG1k mAb	IL-6 receptor inhibitor
Tofacitinib (XELJANZ)	2012	203214 (Pfizer/PF Prism CV)	PO	Citrate salt	JAK inhibitor
Golimumab IV (SIMPONI ARIA)	2013	125433 (Janssen)	IV	Humanized IgG1k aAb	TNF inhibitor
Tofacitinib (XELJANZ XR)	2016	208246 (Pfizer/PF Prism CV)	PO	Citrate salt	JAK inhibitor
Infliximab-DYYB (INFLECTRA)	2016	125544 (Celltrion Inc)	IV	Chimeric IgG1k mAb	TNF inhibitor

Abbreviations: ROA = Route of administration; MOA= Mechanism of action; TNF=tumor necrosis factor; IL=interleukin; JAK=janus kinase; mAb=monoclonal antibody; CTLA-4=cytotoxic T-lymphocyte-associated protein 4; SC=subcutaneous; IV=intravenous

### 3 Regulatory Background

Clinical Review  
Reviewer: Suzette Peng, MD  
NME/BLA 761037  
Sarilumab/Kevzara

### 3.1. U.S. Regulatory Actions and Marketing History

Sarilumab is a new molecular entity and is currently not marketed in the U.S. It is currently being developed for the treatment of rheumatoid arthritis (this application). (b) (4)

(b) (4) Sarilumab was also investigated for the treatment of patients with ankylosing spondylitis (AS); however, it failed to show a difference from placebo on the primary endpoint. At that point, Sanofi terminated the clinical development for AS.

Regeneron Pharmaceuticals, Inc (Regeneron) initially developed sarilumab under codename REGN88. Sanofi acquired sarilumab in 2009 and continued development under codename SAR153191.

### 3.2. Summary of Presubmission/Submission Regulatory Activity

Key regulatory interactions are listed below by date. Points of discussion or Division recommendations are provided as a bulleted list for each meeting or interaction. The development program for sarilumab occurred under IND 100632.

August 2, 2007 – Pre-IND meeting

- Agreement on initial clinical study design and CMC data to support initial development

September 29, 2009 – Type C meeting (Discussion of design of EFC11072 (Phase 2/3) study)

- Expectations for Study EFC11072, which contains an operationally seamless design, were established. Potential adaptive study design proposals were considered and the sponsor elected not to utilize an adaptive design
- FDA indicated that patients in Part B cohort 1 should not be included in efficacy analyses, but should be included in safety analyses
- Safety database at time of BLA submission is expected to include at least 1,000-1,500 patients treated for 1 year at the proposed dose
- Agreement that it was reasonable to evaluate different patient populations (MTX-IR and DMARD-IR)
- Agreement for waiver for thorough QT study

February 23, 2011 – Type C meeting (Comparability of Phase 2 ((b) (4)F2) and Phase 3 ((b) (4)F3) drug product)

- Agreement that the planned switch to the ((b) (4)F3) drug product in the phase 3 portion of Study EFC11072 could proceed based on data provided. FDA noted that data linking the ((b) (4)F2) and ((b) (4)F3) formulations should be submitted in the BLA.

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

- Concerns were raised regarding cases of neutropenia in the development program. FDA emphasized the importance of establishing adequate dose ranging
- Limited discussion occurred [REDACTED] (b) (4)

### September 15, 2011 – End of Phase 2 (EOP2) meeting

- Agreed that the two proposed pivotal phase 3 trials, in conjunction with an acceptable safety profile, should be adequate to support filing a BLA for sarilumab for the treatment of RA
- Recommended incorporation of tocilizumab into a phase 3 study for use as a benchmark for safety comparison
- Noted that the adequacy of a single study to support a claim of inhibition of structural damage in patients with RA will be a review issue
- Advised to conduct a 12-week study using the autoinjector to obtain pharmacokinetic and actual use data in patients with RA
- Recommended use of an adjudication committee for major cardiovascular events
- Agreement on the clinical pharmacology and nonclinical programs

### October 26, 2011 – CMC EOP2 meeting

- Agreement on expectations for stability data
- Expectations for [REDACTED] (b) (4) human factors evaluation described

### April 10, 2012 – Advice/Information Request to submission dated March 13, 2012 (regarding study EFC11072)

- Agreed with modification of the terminology for the primary objectives and co-primary endpoints while maintaining the previously proposed hierarchical testing procedure
- Advised on handling of missing data
- Provide analysis of HAQ-DI at Week 24 as a secondary analysis
- Reasonable to evaluate statistical significance of the treatment effect on the ACR20 endpoint even in the absence of a significant effect on the other two co-primary endpoints. However, FDA may not consider this sufficient for regulatory purposes and would need to consider this in the context of the overall risk-benefit assessment

### June 14, 2012 – Advice/Information Request to submission dated April 13, 2012 (regarding study MSC12665)

- Agreed with proposed patient population and endpoints in study MSC12665

### November 9, 2012 – Advice/Information Request to submission dated September 25, 2012

- Agreed with proposal to assess relative safety of sarilumab vs. tocilizumab for 24 weeks
- Noted that a trial of 200 patients divided among 3 treatment arms was anticipated to have a relatively large amount of variability and it was not clear whether the number of

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

patients would be adequate to make reliable comparisons between tocilizumab and sarilumab. The sponsor was advised that they could proceed with the proposed trial, but it was noted that additional data could be required.

May 15, 2013 – Advice/Information Request to submission dated November 12, 2012

- Agreed with proposed analyses for the radiographic data and HAQ-DI endpoint
- Agreed with approach to handling missing data for ACR20 and van der Heijde total Sharp score, but did not agree with approach for HAQ-DI. For HAQ-DI, an approach that appropriately estimates the variance of the treatment effect, but does not perpetuate a treatment effect, such as multiple imputation, was requested.

August 21, 2013 – Advice/Information Request to submission dated June 3, 2013 (regarding SAP for Study EFC13752)

- Recommended re-defining primary analysis of HAQ-DI to a time point before many treatment discontinuations have occurred, such as 16 weeks, to minimize the amount of missing data

September 30, 2013 – Advice/Information Request to submission dated May 30, 2013 (regarding study EFC13752)

- Did not agree with proposed design of study EFC13752 [REDACTED] (b) (4)  
[REDACTED] It was noted that an evaluation of sarilumab monotherapy is not a requirement, but is of interest from the perspective of safety and immunogenicity.
- Recommended several potential study designs, noting the study should be 6 months or longer to assess immunogenicity

December 4, 2013 – FDA response regarding carcinogenicity assessment (submission dated August 16, 2011)

- Agreed that no additional nonclinical studies were needed to address the carcinogenic potential of sarilumab

January 10, 2014 – Advice/Information Request to submission dated August 12, 2013

- Agreed with iPSP

August 19, 2014 – Type C meeting (written responses only)

- Agreed with the content, structure, and version of the electronic submission datasets to be included in the BLA
- Agreed with the proposed BIMO listings and provisions for narratives

October 22, 2014 – pre-BLA meeting

- Agreement reached regarding the proposed pooling strategies for the safety analyses
- Recommended additional safety analyses to better characterize sarilumab's safety

CDER Clinical Review Template 2015 Edition

Version date: November 5, 2015 for initial rollout (NME/original BLA reviews)

29

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

profile and to address the complexity in the study design

- Noted that data from study EFC13752 (monotherapy safety study) was not required at the time of BLA submission

December 16, 2014 – CMC pre-BLA meeting

- All facilities should be registered with FDA at the time of the BLA submission and ready for inspection
- Outlined specific microbiology information that should be included in the BLA
- Agreement on comparability between products made with industrial versus the clinical filing lines

*Reviewer Comment: Sanofi was generally responsive to FDA feedback during the development of sarilumab.*

### 3.3. Foreign Regulatory Actions and Marketing History

Sarilumab is not approved for marketing in any country.

## 4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

---

### 4.1. Office of Scientific Investigations (OSI)

Three clinical sites covering study protocols EFC11072 and EFC10832 were selected for inspection. These sites principally enrolled large numbers of patients. In addition, Sanofi-Aventis was inspected. The sites identified for OSI audit are in Table 3.

Clinical Review  
 Reviewer: Suzette Peng, MD  
 NME/BLA 761037  
 Sarilumab/Kevzara

**Table 3. Sites Identified for OSI Audit**

Name of CI, Address	Site #, Protocol #, and # of Subjects
Jacob Aelion, M.D. West Tennessee Research Institute 369 N. Pkwy. Suite 400 Jackson, TN 38305	Site 840025 Study Protocol: EFC11072 (Part B)  15 enrolled subjects
Eric Lee, M.D. Inland Rheumatology Clinical Trials, Inc. 1238 East Arrow Hwy Upland, CA 91786	Site 840049 Study Protocol: EFC10832  7 enrolled subjects
Jeffrey Kaine, M.D. Sarasota Arthritis Center 1945 Versailles St. Suite 101 Sarasota, FL 34239	Site 840060 Study Protocol: EFC10832  7 enrolled subjects
Sanofi-Aventis U.S. LLC 500 Kendall Street Cambridge, MA 02142	Sponsor for: Study Protocol: EFC11072 (Part B) Subjects =1197  Study Protocol: EFC10832 Subjects =546

In each case, inspection findings supported the acceptability of the clinical data submitted.

## 4.2. Product Quality

### Overview

Sarilumab is a recombinant human IgG1 monoclonal antibody consisting of two disulfide-bonded human heavy chains. Each heavy chain is covalently linked through a disulfide bond to a human kappa light chain. Sarilumab binds to both soluble and membrane-bound IL-6R.

### Drug Substance



Clinical Review  
Reviewer: Suzette Peng, MD  
NME/BLA 761037  
Sarilumab/Kevzara

Sarilumab is produced by (b) (4) suspension culture of recombinant Chinese Hamster Ovary (CHO) cells that have been engineered to constitutively express sarilumab heavy and light chains in culture. (b) (4)

The applicant has provided CMC data to support the comparability of the processes.

### Drug Product

Sarilumab solution for injection is a clear, colorless to pale yellow, aqueous (b) (4) sterile solution, pH 6.0. Sarilumab solution for injection is supplied, for subcutaneous (SC) injection, as a single-use prefilled syringe (PFS) drug product (DP) presentation in two strengths, 131.6 mg/mL and 175 mg/mL, providing doses of 150 mg and 200 mg, respectively. (b) (4)  
(Table 4).

**Table 4. Summary of the PFS Components and Presentations for the 150mg and 200mg Dose Forms**

(b) (4)

Source: Module 2.3.P, submitted 10/30/15, table 1, page 8

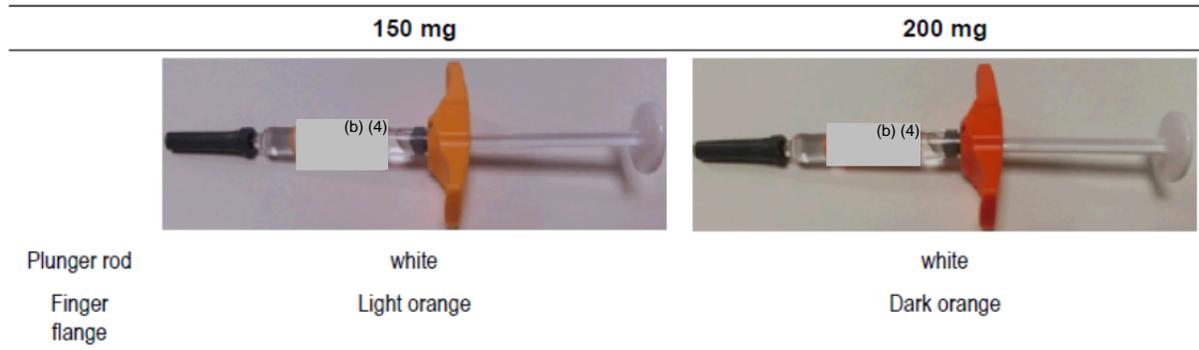
The bulk PFS container closure system is comprised of a (b) (4) 1-mL-long, clear glass (Type I (b) (4)) syringe, equipped with a staked (b) (4) (27 gauge, ½-inch, (b) (4)) needle, and closed with a (b) (4) elastomer (b) (4) soft needle shield and (b) (4) elastomer (b) (4) plunger stopper.

On the PFS, the finger flange and product label are differentially colored for each dose form. The 150 mg dose form contains a light orange finger flange. The 200 mg dose form contains a

Clinical Review  
Reviewer: Suzette Peng, MD  
NME/BLA 761037  
Sarilumab/Kevzara

dark orange finger flange (Figure 1).

**Figure 1. Prefilled Syringes (PFS)**



The labels affixed to the syringes in the figures are mock ups of the actual labels that will be included on the commercial prefilled syringe

Source: Module 2.3.P, submitted 10/30/15, Table 2, page 9

### Facilities Review/Inspection

The site for manufacture of the drug product is Sanofi Winthrop Industrie, LeTrait France. The site was inspected over a period from July 7-19, 2016. Thirteen observations were noted:

1. The firm has repeatedly refused to provide the requested documentation for review (b) (4)  
(b) (4)
2. The firm does not have a thorough understanding of the requirements for submission of NDA Field Alerts.
3. The written complaint record did not include the reason an investigation was found not to be necessary when an investigation into unexplained discrepancies was not conducted.
4. Investigations were found to be inadequate for two media fill failures and there have been 4 deviations opened for bioburden excursions.
5. Aseptic process simulations were found inadequate.
6. Procedures designed to prevent microbiological contamination of drugs products purporting to be sterile are not established.
7. Routine calibration and inspection of electronic equipment is not performed according to a written program designed to assure proper performance.
8. The equipment used in the manufacture, processing, and packaging (b) (4)  
(b) (4) is not adequate construction and design for its intended use.
9. Equipment and utensils are not sanitized at appropriate intervals to prevent contamination that would alter the safety, identity, strength, quality or purity of the drug product.
10. The firm does not have scientific rationale or justification for the placement of their non-viable particle monitors.

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

11. The controlled areas within the manufacturing department are not maintained in a state of control.
12. Qualification/requalification studies were found deficient.
13. Reports of analysis from component suppliers are accepted in lieu of testing each component for conformity with all appropriate written specifications, establishing the reliability of the supplier's analyses through appropriate written specifications, establishing the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals.

Additional details of these deficiencies are listed in the Form 483. Final designation and recommendations from CMC are pending at this time. If CMC recommends withholding approval based on these facilities issues, this would impact the overall approvability of this application.

Please see the CMC review for additional details.

### 4.3. **Clinical Microbiology**

The final microbiology review is pending at the time of this review.

### 4.4. **Nonclinical Pharmacology/Toxicology**

#### **General nonclinical pharmacology/toxicology considerations**

The nonclinical safety program for sarilumab was performed in cynomolgus monkeys, which were established as the most pharmacologically relevant nonclinical species. As determined by surface plasmon resonance (SPR), sarilumab binds human IL-6R and cynomolgus monkey IL-6R with equilibrium dissociation constants (Kd) of 54.4 pM and 123 pM, respectively.

Results from a number of GLP-compliant repeat-dose toxicology studies in cynomolgus monkeys with sarilumab by intravenous (IV) administration for durations up to 6 months and by SC administration for 3 months did not identify any significant dose-limiting toxicity or target organs of toxicity at IV doses up to 50mg/kg/week or SC doses up to 100mg/kg/week (two weekly doses of 50mg/kg). There were no deaths that were attributed to treatment with sarilumab. Microscopic findings were limited to effects at the injection site (minimal to moderate perivascular mixed inflammatory cell infiltrates). The most common effects related to treatment with sarilumab were decreased levels of neutrophils, fibrinogen, and/or C-reactive protein (CRP). These decreases were considered pharmacodynamics (PD) effects of inhibiting IL-6 signaling. In most cases, these effects were not dose-dependent and were generally reversible during the recovery period. The 6-month study revealed slight decreases in primary and secondary IgG responses following antigen challenge.

Clinical Review  
Reviewer: Suzette Peng, MD  
NME/BLA 761037  
Sarilumab/Kevzara

### **Carcinogenicity**

Based on species specificity, a rodent carcinogenicity study with sarilumab was not considered feasible. The Executive Carcinogenicity Assessment Committee (ECAC) concurred that a carcinogenicity study was not feasible. No nonclinical studies were required to evaluate the potential carcinogenicity of sarilumab. A review of the scientific literature related to the role of IL-6/IL-6R pathway in cancer was conducted.

### **Reproductive toxicology**

The reproductive and developmental toxicity of sarilumab was evaluated in an enhanced pre- and postnatal development (ePPND) study in cynomolgus monkeys. Further, a murine surrogate monoclonal antibody to sarilumab that binds mouse IL-6Ra (i.e., REGN844) was developed and used for a fertility study in mice. In the ePPND study, there was no evidence of embryotoxicity or fetal malformations. However, there were concerns about the adequacy of this study based upon the small number of animals per group. Fertility and reproduction were unaffected in male and female mice treated with REGN844 at SC doses up to 100 mg/kg twice per week.

Please see the pharmacology/toxicology review by Dr. Salicru for full details.

## **4.5. Clinical Pharmacology**

### **4.5.1. Mechanism of Action**

Sarilumab is a recombinant human immunoglobulin (IgG)<sub>1</sub> monoclonal antibody that binds specifically to both soluble and membrane-bound interleukin-6 (IL-6) receptors (sIL-6R $\alpha$  and mIL-6R $\alpha$ ) and inhibits IL-6-mediated signaling. Interleukin 6 (IL-6) is a pleiotropic cytokine that stimulates proliferation, differentiation, survival and apoptosis of immune cells (both B cells and T cells) and can activate hepatocytes to release acute-phase proteins, including C-reactive protein (CRP), serum amyloid A (SAA), and fibrinogen. These markers correlate with disease activity in patients with RA (Madhok, et al. 232). Elevated levels of IL-6 are found in the synovial fluid of patients with RA and are thought to play a role in both the pathologic inflammation and joint destruction that are hallmarks of RA.

### **4.5.2. Pharmacodynamics**

Several potential pharmacodynamics markers were assessed in clinical studies, including IL-6, sIL-6R $\alpha$ , and several inflammatory markers (acute phase proteins CRP, SAA, and fibrinogen, and an indirect index of these proteins, the erythrocyte sedimentation rate [ESR]).

Following single or multiple doses of sarilumab, IL-6 levels and sIL-6R $\alpha$  (representing free IL-6R $\alpha$  and sIL-6R $\alpha$  bound to sarilumab) increased and then declined with further treatment in a dose dependent manner.

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

After repeated q2w SC administration of 150 or 200 mg sarilumab, a dose dependent decrease in CRP levels was observed as early as Week 2, reached steady state by Week 24, and was sustained throughout treatment. CRP levels were suppressed within 2 to 2 days after administration of either dose. The 200 mg dose suppressed CRP levels throughout the 2 week interval, while CRP levels had a tendency to rebound towards the end of the dosing interval with the 150 mg dose.

A dose dependent reduction in other acute phase reactants, including SAA, fibrinogen, and ESR was also seen after administration of 150 or 200 mg sarilumab.

### 4.5.3. Pharmacokinetics

Intensive and sparse pharmacokinetic (PK) data from 12 studies (7 phase 1 studies, 1 phase 2 study, 4 phase 3 studies) were pooled for a population PK analysis representing 1,770 patients with RA who received sarilumab SC either as single or repeated once weekly or q2w doses, ranging from 50 to 200 mg, either alone or in combination with MTX or other nonbiologic DMARDs.

Sarilumab exhibits nonlinear PK with target-mediated drug disposition. After SC administration, the time to peak concentration ( $t_{max}$ ) is 2 to 4 days, bioavailability is 80%, and the apparent volume of distribution is 7.31 L, suggesting that sarilumab is distributed primarily in the circulatory system. Sarilumab is eliminated by two parallel linear and non-linear elimination pathways. At higher concentrations, elimination is predominantly through a linear, non-saturable, proteolytic pathway; while at lower concentrations, non-linear saturable target-mediated elimination predominates, leading to an initial half-life of 8 to 10 days and a terminal concentration dependent half-life of 2 to 4 days. After the last steady state doses of 150 and 200 mg sarilumab q2w, the median times to undetectable serum concentrations are 28 and 43 days, respectively.

At steady state, exposure over the dosing interval measured by area under the serum concentration versus time curve at steady state ( $AUC_{0-14 \text{ days}}$ ) increased 2-fold for an increase in SC sarilumab dose from 150 to 200 mg q2w (corresponding to 1.33-fold increase in dose). Steady state was reached in 14 to 16 weeks following repeated q2w SC administration, with a 2- to 3-fold accumulation compared to single dose exposure for  $AUC_{0-14 \text{ days}}$ .

The main source of intrinsic PK variability identified in the population PK analysis was body weight, with decreasing body weight resulting in greater sarilumab exposure. However, body weight was not a meaningful covariate in PK/PD modeling for efficacy and safety endpoints. No significant differences in the pharmacokinetics of sarilumab were observed by age, gender, and race.

Administration of concomitant methotrexate did not impact sarilumab clearance in population PK analyses.

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

Elevated interleukin-6 (IL-6) concentration in patients with RA may down-regulate CYP activity, increasing drug levels compared to subjects without RA. Thus, blockade of IL-6 signaling by IL-6R $\alpha$  antagonists such as sarilumab might reverse the inhibitory effect of IL-6 and restore CYP activity, leading to reduced drug concentrations. An interaction study of the effect of sarilumab on simvastatin, a sensitive CYP3A4 substrate, showed that in 17 patients with RA, exposure of simvastatin and simvastatin acid decreased by 45% and 36%, respectively, following a single 40 mg oral dose of simvastatin one week after a single SC dose of sarilumab 200 mg. The modulation of IL-6 effect on CYP enzymes may be clinically relevant for CYP substrates with a narrow therapeutic index. The sponsor suggests that the therapeutic effect (e.g., warfarin) or drug concentration (e.g., theophylline) should be performed and the dose of the individual drug should be adjusted as needed.

See the clinical pharmacology review by Dr. Jianmeng Chen for full details of the clinical pharmacology review.

### 4.6. Devices and Companion Diagnostic Issues

Not applicable

### 4.7. Consumer Study Reviews

Not applicable

## 5 Sources of Clinical Data and Review Strategy

---

### 5.1. Table of Clinical Studies

Table 5 displays all the trials relevant to the review of this BLA. Thus, it lists the trials utilized to assess efficacy (EFC11072 Part B and EFC10832) as well as all the RA trials the applicant included in the long-term safety population.

Clinical Review  
 Reviewer: Suzette Peng, MD  
 NME/BLA 761037  
 Sarilumab/Kevzara

**Table 5. Clinical Trials Relevant to BLA 761037**

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Primary Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	Study Status
Study Center and Countries							
<b>Phase 2 Studies</b>							
<b>Studies to Support Safety</b>							
<b>EFC11072 Part A (MOBILITY)</b>  101 centers initiated  EU, North America (Canada Mexico, USA), South America, Australia, Republic of Korea, South Africa	Randomized, double- blind, placebo- controlled, dose- ranging study	Sarilumab SC <ul style="list-style-type: none"> <li>• 100mg qw</li> <li>• 150mg qw</li> <li>• 100mg q2w</li> <li>• 150mg q2w</li> <li>• 200mg q2w</li> </ul> Placebo SC qw	<ul style="list-style-type: none"> <li>• % of patients who achieved ACR20 at Week 12</li> </ul>	12 weeks	306 randomized  305 treated  270 completed	Patients with RA receiving MTX	Completed
<b>ACT11575</b>  10 centers  USA	Multicenter, multinational, randomized, double- blind, parallel-group, placebo- and active- calibrator-controlled study	Sarilumab SC <ul style="list-style-type: none"> <li>• 150mg qw</li> <li>• 150mg q2w</li> </ul> Golimumab SC <ul style="list-style-type: none"> <li>• 50 mg q4w</li> </ul> PBO SC qw		12 weeks	16 randomized  16 treated  13 completed	Patients with RA who do not response to $\leq 2$ TNF $\alpha$ blockers	Terminated early due to study delays
<b>Phase 3 Studies</b>							

Clinical Review  
 Reviewer: Suzette Peng, MD  
 NME/BLA 761037  
 Sarilumab/Kevzara

Studies to Support Efficacy and Safety							
<b>EFC11072 Part B (SARIL-RA-MOBILITY)</b>  199 centers  EU, North America (Canada, Mexico, USA), South America, Asia, Australia, New Zealand, South Africa	Multicenter, randomized, double-blind, parallel-group, placebo-controlled study	<b>Cohort 1:</b> Sarilumab SC <ul style="list-style-type: none"> <li>• 100mg qw</li> <li>• 150mg q2w</li> <li>• 100mg q2w</li> <li>• 150mg q2w</li> <li>• 200mg q2w</li> </ul> PBO SC qw  <b>Cohort 2:</b> Sarilumab SC <ul style="list-style-type: none"> <li>• 150mg q2w</li> <li>• 200mg q2w</li> </ul> PBO SC q2w	<ul style="list-style-type: none"> <li>• ACR20 response at Week 24</li> <li>• Change from baseline in HAQ-DI at Week 16</li> <li>• Change in mTSS at Week 52</li> </ul>	52 weeks  Rescue assessment at Week 16	1369 randomized  1366 treated  1020 completed	Patients with RA receiving MTX	Completed
<b>EFC10832 (SARIL-RA-TARGET)</b>  240 centers  “worldwide”	3-arm, multicenter, randomized, double-blind, parallel group, placebo-controlled 24-week study	Sarilumab SC <ul style="list-style-type: none"> <li>• 150mg q2w</li> <li>• 200mg q2w</li> </ul> PBO SC	<ul style="list-style-type: none"> <li>• ACR20 response rate at Week 24</li> <li>• Change from baseline in HAQ-DI at Week 12</li> </ul>	24 weeks  Rescue assessment at Week 12	546 randomized  546 treated  359 completed	Patients with RA who are intolerant of or who response inadequately to TNF- $\alpha$ and who receiving a non-biologic DMARD	Completed
Studies to Support Safety							
<b>LTS11210</b>	Multicenter,	Sarilumab SC	Primary objective:	≤ 5 years	1998 randomized	Patients	Ongoing

Clinical Review  
 Reviewer: Suzette Peng, MD  
 NME/BLA 761037  
 Sarilumab/Kevzara

<p><b>(SARIL-RA-EXTEND)</b></p> <p>334 centers</p> <p>40 countries</p>	<p>multinational, open-label, uncontrolled long-term study</p>	<ul style="list-style-type: none"> <li>• 150mg q2w</li> <li>• 200mg q2w</li> <li>• 150mg qw</li> </ul> <p>All doses adjusted to 200mg q2w after pivotal dose selection</p>	<p>to evaluate longterm safety of sarilumab in patients with RA</p> <p>Secondary objective: to evaluate longterm efficacy</p>	<p>from first treatment in initial study</p>	<p>1998 treated</p> <p>1558 completed</p>	<p>with RA who completed or transferred from 5 other sarilumab trials</p>	
<p><b>SFY13370 (SARIL-RA-ASCERTAIN)</b></p> <p>68 centers</p> <p>North America, South America, Europe (including Russia)</p>	<p>Randomized, double-blind, double-dummy, parallel group, 3-arm, 24-week, active comparator controlled study</p>	<p>Sarilumab SC</p> <ul style="list-style-type: none"> <li>• 150mg q2w</li> <li>• 200mg q2w</li> </ul> <p>PBO SC q2w</p> <p>Tocilizumab IV 20mg/ml q4w</p> <p>PBO IV q4w</p>	<p>Primary objective: to assess safety of sarilumab and tocilizumab in patients with RA</p> <ul style="list-style-type: none"> <li>• AEs, SAEs, etc.</li> <li>• Anti-sarilumab antibodies</li> </ul> <p>Exploratory efficacy assessments:</p> <ul style="list-style-type: none"> <li>• ACR20/50/70 response rates at Wk 24</li> <li>• DAS28-CRP remission rate at Wk 24</li> </ul>	<p>24 weeks</p>	<p>202 randomized</p> <p>202 treated</p> <p>184 completed</p>	<p>Patients with RA who are inadequate responders to or intolerant of TNF<math>\alpha</math> antagonists</p>	<p>Completed</p>
<p><b>EFC13752 (SARIL-RA-ONE)</b></p>	<p>Multicenter, worldwide,</p>	<p>Sarilumab SC</p> <ul style="list-style-type: none"> <li>• 150mg q2w</li> </ul>	<p>Primary objective: immunogenicity</p>	<p>24 weeks</p>	<p>132 randomized</p>	<p>Patients with RA who</p>	<p>Completed</p>

28 centers  Chile, Czech Republic, Estonia, Hungary, Poland, Russia, and USA	randomized, open-label, parallel-group, 2-arm, study	<ul style="list-style-type: none"> <li>200mg q2w</li> </ul>	<p>Secondary objective: safety through Week 24</p> <p>Exploratory Efficacy:</p> <ul style="list-style-type: none"> <li>ACR20/50/70 response rate from baseline at Week 24</li> <li>Change from baseline in DAS28-CRP through Week 24</li> </ul>		132 treated  116 completed	are inadequate responders to or are intolerant of $\geq 1$ nonbiologic DMARD	
<b>EFC11574 (SARIL-RA-COMPARE)</b>  228 centers  31 countries	Three-arm, multicenter, multinational, double-blind, double-dummy, parallel-group, active comparator controlled study	<p>Sarilumab SC</p> <ul style="list-style-type: none"> <li>150mg q2w</li> <li>200mg q2w</li> </ul> <p>PBO SC q2w</p> <p>Etanercept SC 50mg qw</p> <p>PBO SC qw</p>	<ul style="list-style-type: none"> <li>Change from baseline in DAS28-CRP at Week 24 (<i>Not analyzed because of study termination</i>)</li> <li>Safety</li> </ul>	<p>Randomized phase: 24 weeks</p> <p>Substudy phase: 52 weeks</p>	365 randomized  365 treated  328 completed	Patients with RA with an inadequate response to adalimumab 40mg q2w in combination with MTX during a 4-month open-label run-in phase	Early termination due to inability to provide a timely result
<b>MSC12665</b>	Multicenter,	Sarilumab	<ul style="list-style-type: none"> <li>Number of</li> </ul>	12 weeks	217 randomized	Patients	Ongoing

Clinical Review  
 Reviewer: Suzette Peng, MD  
 NME/BLA 761037  
 Sarilumab/Kevzara

<p><b>(SARIL-RA-EASY)</b></p> <p>57 centers</p> <p>Europe, North America, South America, and South Africa</p>	<p>worldwide, randomized, open-label, parallel-group, 4-arm, 12-week study followed by a 1-year open-label extension phase</p>	<p>(autoinjector) SC</p> <ul style="list-style-type: none"> <li>• 150mg q2w</li> <li>• 200mg q2w</li> </ul> <p>Sarilumab (pre-filled syringe) SC</p> <ul style="list-style-type: none"> <li>• 150mg q2w</li> <li>• 200mg q2w</li> </ul>	<p>validated AI-associated product technical failures</p> <p>Secondary device-related endpoints</p> <p>Other efficacy endpoints</p> <ul style="list-style-type: none"> <li>• ACR20/50/70 response at Week 12</li> <li>• Change from baseline in ACR components score at Week 12</li> <li>• DAS28-CRP remission at Week 12</li> <li>• Change from baseline in DAS28-CRP at Week 12</li> </ul>	<p>Extension phase: 52 weeks</p>	<p>217 treated</p> <p>201 completed</p>	<p>with RA who are candidates for anti-IL6R therapy receiving ≥1 nonbiologic DMARD</p>	
---	--	---	--	----------------------------------	---	--	--

## 5.2. Review Strategy

The efficacy data are based on the pivotal trials EFC11072 Part B Cohort 2 and EFC10832. The safety analysis will focus on these studies as well, particularly the pre-rescue period (Weeks 0-16 for study EFC10832 and 0-12 for study EFC11072 Part B). The pre-rescue data are the least affected by potential changes in sarilumab dose that were allowed by the protocols.

For some adverse events, an assessment will be made of the longterm safety population. The longterm safety population includes all subjects who entered the open-label extension. Additionally, it includes subjects from all the tables listed in Table 5.

A more detailed review of SFY13370 will be presented because this study has an active comparator with the only other FDA-approved IL-6 inhibitor, tocilizumab. Although the focus of the comparison will be safety, exploratory efficacy endpoints were also assessed and, thus, will be reviewed.

Major safety events in study EFC13752 will also be reviewed separately, as this is the monotherapy study. It will be important to ensure similar safety in this monotherapy study compared to the safety of the other studies where sarilumab was administered with a DMARD.

For the majority of the review, I will be presenting the applicant's results but will provide my own commentary. For efficacy, I will work with the statistical team to confirm the applicant's analyses.

## 6 Review of Relevant Individual Trials Used to Support Efficacy

---

### 6.1. EFC11072 (MOBILITY) Part A

#### 6.1.1. Study Design

##### Overview and Objective

EFC11072 was a randomized, double-blind, placebo-controlled, multicenter, two-part, dose ranging and confirmatory study with an operationally seamless design, evaluating efficacy and safety of sarilumab on top of MTX in patients with active RA who are inadequate responders to MTX therapy. Although Part A is a phase 2 study, it will be discussed first since it transitions to Part B, one of the pivotal trials. Part A was the randomized, multicenter, double-blind, parallel-group, placebo-controlled, 12-week study of 6 treatment arms of sarilumab (5 active dose regimens and placebo), all with MTX cotherapy, to compare the efficacy and safety of sarilumab

Clinical Review  
Reviewer: Suzette Peng, MD  
NME/BLA 761037  
Sarilumab/Kevzara

with MTX cotherapy in patients with active RA who are inadequate responder to MTX therapy.

The primary objective of Part A was to demonstrate that sarilumab with MTX is effective on reduction of signs and symptoms of RA at 12 weeks and to define the best dose regimen for further development. Secondary objectives included assessment of safety and PK. An exploratory objective was to collect DNA, RNA, and other biomarkers for the purpose of discovery of predictive biomarkers.

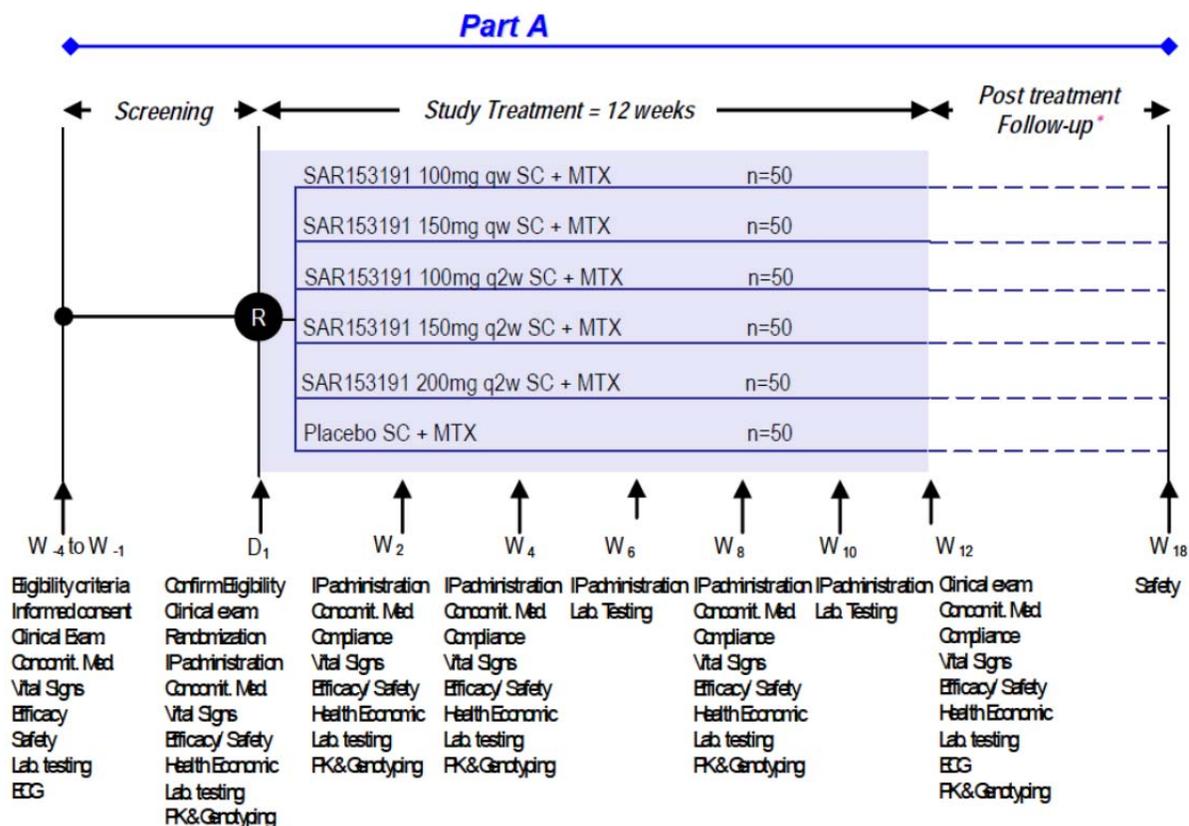
## **Trial Design**

### **Basic Study Design**

Part A was a 12-week, 6-arm, dose-ranging study with the intention to select the 2 best dose regimens based on efficacy (reduction in signs and symptoms) and safety. The maximum duration was 22 weeks (4 weeks for screening, 12 weeks for treatment, and 6 weeks for follow-up). Subjects, who completed Part A and were eligible, could enter the open-label extension study (LTS11210). Patients in Part A did not participate in Part B in the study. Figure 2 shows the study schema of Part A of EFC11072. The schedule of assessments for Part A is presented in Table 139 in the Appendix (Section 13.3).

APPEARS THIS WAY ON ORIGINAL

Figure 2. Study Schema of EFC11072 Part A



\* For patients who are not included in the Long Term Extension Study

Source: EFC11072 Part A Clinical Study Report, dated January 16, 2012, Figure 1, page 25.

*Reviewer Comment: Although EFC11072 is a 2 part study, it is not an adaptive study design. The applicant notes that Part A was a “learning stage” to select the relevant dose regimen, whereas Part B was the confirmatory stage to test the selected doses without interruption of the recruitment process. The lack of interruption of recruitment was likely a major factor of utilizing this particular study design.*

*The study design for Part A is a placebo-controlled, dose-ranging study. Multiple doses (a range of strengths and frequencies) were studied. See below for the applicant’s reasoning for the doses selected. Changes in signs and symptoms in RA can be made as early as Week 12, and, thus, the choice of timing of efficacy endpoints is appropriate. The use of a placebo control group is ethical, appropriate, and recommended. Given that this study is 12 weeks in treatment, there is no formal assessment of treatment failure and no formal opportunity for dose*

Clinical Review  
Reviewer: Suzette Peng, MD  
NME/BLA 761037  
Sarilumab/Kevzara

*modification or rescue. Overall, this is an acceptable, standard study for the purpose of dose-ranging.*

### **Key inclusion/exclusion criteria**

#### **Inclusion criteria**

- Diagnosis of rheumatoid arthritis as defined by the 1987 revised American College of Rheumatology (ACR) criteria with disease duration of no less than 3 months and ACR class I-III

The ACR 1991 revised criteria for classification of global functional status in RA include the following:

- Class I: completely able to perform usual activities of daily living (self-care, vocational, and avocational)
    - Usual self-care activities include dressing, feeding, bathing, grooming, and toileting.
    - Avocational activities are recreational and/or leisure.
    - Vocational activities include work, school, and homemaking activities.
    - Both avocational and vocational activities are patient-desired as well as age- and sex-specific.
  - Class II: able to perform usual self-care and vocational activities, but limited in avocational activities
  - Class III: able to perform usual self-care activities, but limited in vocational and avocational activities
  - Class IV: limited in ability to perform usual self-care, vocational and avocational activities
- Patients were required to be on a stable dose of MTX (10-25 mg/week) for a minimum of 6 weeks prior to the screening visit and intend to continue for the duration of the study
    - Patients within the Asia-Pacific region (Taiwan, South Korea, Malaysia, Philippines, Thailand, and India) were allowed to use a stable dose between 6-25 mg/week for a minimum of 6 weeks prior to the screening visit.
  - Patients were to have been treated with, and tolerated, a minimum of 12 weeks of treatment with MTX prior to the randomization visit
  - Patient with moderate to severe active disease defined as the following
    - At least 8 out of 68 joints assessed as painful or tender on motion at both screening and baseline visits AND
    - At least 6 out of 66 joints assessed as swollen at both screening and baseline visits AND
    - hsCRP >10 mg/L at the screening visit

#### **Exclusion criteria**

CDER Clinical Review Template 2015 Edition  
*Version date: November 5, 2015 for initial rollout (NME/original BLA reviews)*

46

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

- Male or female < 18 years of age or > 75 years of age
- Weight < 50kg for men or < 45kg for women or > 110kg
- Autoimmune disorder other than RA or significant systemic involvement (vasculitis, pulmonary fibrosis, Felty's syndrome)
- History of or current acute inflammatory joint disease other than RA or RA diagnosed before the age of 16
- Treatment with oral prednisone or equivalent > 10mg per day within 4 weeks prior to the Inclusion Visit or use of parenteral or intra-articular glucocorticoids within 4 weeks prior to the screening visit
- Starting treatment or changed dose of current treatment with NSAIDs/COX2 inhibitors or oral corticosteroids for 4 weeks prior to baseline
- Current treatment with DMARDs/immunosuppressive agents other than MTX: cyclosporine, mycophenolate mofetil (MMF), tacrolimus, gold, penicillamine, sulfasalazine or hydrochloroquine within 4 weeks prior to the screening visit or azathioprine, cyclophosphamide within 12 weeks prior to the screening visit, or leflunomide within 12 weeks prior to the screening visit (or 4 weeks after 11 days of standard cholestyramine washout)
- Past history of nonresponse to prior therapy with TNF antagonist or a biologic treatment
- Prior therapy with a TNF antagonist or any other biologic agents within 3 months prior to randomization
- Participation in any clinical research study evaluating another investigational drug or therapy within 60 days or at least 5 half-lives, whichever is longer, of the investigational drug, prior to the screening visit
- History of malignancy other than carcinoma in-situ of the cervix or adequately treated, nonmetastatic squamous or basal cell carcinoma of the skin within 5 years prior to screening visit. History of lymphoproliferative disease or possible current lymphoproliferative disease
- History of alcohol or drug abuse within the 5 years prior to the screening visit
- Have a history or presence of significant other concomitant illness according to the Investigator's judgment such as, but not limited to, cardiovascular (including Stage III or IV cardiac failure according to New York Heart Association [NYHA] classification), renal, neurological, endocrinological, gastrointestinal, hepatic disease, metabolic, pulmonary, or lymphatic disease that would adversely affect the subject's participation in this study
- Conditions/situations such as the following
  - Patients with short life expectancy
  - Patients with conditions/concomitant diseases making them nonevaluable for the primary efficacy endpoint
  - Requirement for concomitant treatment that could bias primary evaluation
  - Impossibility to meet specific protocol requirements (e.g., need for hospitalization)
  - Patient is the Investigator or any subinvestigator, research assistant, pharmacist,

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

study coordinator, other staff, or relative directly involved in the conduct of the protocol

- Uncooperative or any condition that could make the patient potentially noncompliant with the study procedure

### **Exclusion criteria related to the mandatory background therapies**

- Patients not willing to take folic acid with the MTX dose

### **Exclusion criteria related to the current knowledge of sarilumab**

- Pregnant or breast-feeding women
- Previous exposure to sarilumab
- For women of childbearing potential, unwillingness to utilize adequate contraception or not become pregnant during the full course of the study. The applicant defines “adequate contraceptive measures” as oral contraceptives (stable use for 2 or more cycles prior to screening) or other prescription pharmaceutical contraceptives, IUD, bilateral tubal ligation, vasectomy, condom or diaphragm plus either contraceptive sponge, foam, or jelly
- Any subject who had surgery within 4 weeks prior to the screening visit or with planned elective surgery
- Patients with a latent or active tuberculosis (TB) defined as the following
  - Any signs or symptoms suggestive of active TB upon medical history or clinical examination
  - Subjects with a positive QuantiFERON®-TB Gold test or tuberculin (PPD) skin test ( $\geq 10\text{mm}$ ) at Screening
  - Chest radiograph within 3 months prior to the randomization visit consistent with prior tuberculosis infection including, but not limited to, apical scarring, apical fibrosis, or multiple calcified granulomata. This did not include noncaseating granulomata.
  - Subjects with close contact with a person with active TB
  - The applicant emphasized that RA patients are more likely to have a false negative skin test because of immunosuppression. Therefore, a negative skin test alone was not enough to exclude tuberculosis.
- Patients with a history of resolved Listeria or tuberculosis, unless documented as adequately treated
- Fever ( $\geq 38^{\circ}\text{C}$ ) or persistent chronic or active recurring infection that required treatment with antibiotics, antivirals, or antifungals within 4 weeks prior to the screening visit or history of frequent, recurrent infections deemed unacceptable per Investigator judgment
- Nonhealed infected skin ulcers
- Received any live (attenuated) vaccine within 3 months prior to the randomization visit (e.g., varicella-zoster vaccine, oral polio, rabies)
- Received vaccination of BCG within 12 months prior to screening
- Known history of human immunodeficiency virus (HIV) antibody and/or positive hepatitis B surface antigen (HBsAg) and/or positive total hepatitis B core antibody and/or positive

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

hepatitis C antibody (HCV) at the screening visit

- History of recurrent herpes zoster or active herpes zoster infection
- History of prior articular or prosthetic joint infection
- History of a systemic hypersensitivity reaction, other than localized injection site reaction, to any biological molecule
- History of a hypersensitivity reaction to doxycycline, tetracycline, or related compounds (until absence of traces is demonstrated in IMP)
- Uncontrolled diabetes defined as HbA1c  $\geq$  9.0% at the screening visit
- History of demyelinating disease
- Patients on dialysis
- Presence of any of the following laboratory abnormalities (for the central laboratory conducting the test) at the screening visit
  - Hemoglobin (Hgb) < 8.5 g/dL
  - WBC < 3000/ $\mu$ L
  - Platelet count < 100,000/ $\mu$ L
  - Neutrophils < 2000/ $\mu$ L
  - AST or ALT > 1.5 x ULN
  - Bilirubin > 1.5 x ULN unless the patient had been diagnosed and documented with Gilbert disease by genetic testing
  - Creatinine clearance < 30 mL/min (< 0.5 mL/s), according to the Cockcroft formula
- For men who are unwilling to utilize 2 forms of contraception, a condom and a spermicidal agent

*Reviewer Comment: The inclusion and exclusion criteria were appropriate to select for patients with active rheumatoid arthritis but without major extra-articular manifestations of the disease. In addition, these patients needed to be on stable doses of concomitant MTX. No other DMARDs were allowed. Subjects could have had previous treatment with TNF $\alpha$  inhibitors or other biologics; however, the biologic therapy needed to precede randomization by 3 months. In order to enter the study, subjects could not be "non-responders" to these biologics. Overall, these inclusion and exclusion criteria are similar to those from other studies with biologics for RA.*

### Dose selection

The doses selected for phase 2 development was based on the efficacy and safety results obtained in 89 active and nonactive RA patients exposed to either single or multiple doses (up to 5 sequential injections) of sarilumab during phase 1. The applicant gives the following rationale for the 5 doses of sarilumab studied in Part A.

- **150 mg qw:** This dose provided maximum effect on CRP. Thus, this dose was studied to test the hypothesis that full suppression of CRP throughout the dosing interval may provide the highest efficacy. No increase in ALT > 3x ULN had been observed at this dose level.

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

- **100 mg qw:** This dose provided strong suppression of CRP but not quite as effective as 150 mg weekly. Shorter time to clear functional sarilumab concentrations following cessation of dosing (~3 weeks versus ~5 weeks for 100 mg weekly versus 150 mg weekly, respectively) could be advantageous for safety if 100 mg weekly achieved comparable clinical benefits.
- **200 mg q2w:** On this dose, most patients (but not all patients) displayed strong continuous suppression of CRP.
- **150 mg q2w:** Most patients showed a sawtooth pattern of suppression of CRP with partial or complete return to baseline during the dosing interval. The applicant notes that this same sawtooth pattern had also been observed with monthly IV tocilizumab (4mg/kg) but was associated with significant clinical efficacy on clinical symptoms in RA patients. Moreover, there was a suggestion of accumulation in  $C_{min}$  following the third dose of sarilumab, raising the possibility that this dose could be fully effective in patients given a longer treatment period.
- **100 mg q2w:** On this dose, most patients showed a sawtooth pattern of CRP suppression. This dose was to be active in some patients and was expected to provide an anchor to the lower end of the dose response.

*Reviewer Comment: Sanofi's explanations for the doses studied are based mostly on PD markers but were reasonable. A range of doses were investigated in Part A.*

### Concomitant medications

Methotrexate (MTX) was the only traditional DMARD allowed during the study. Additionally, oral corticosteroids, NSAIDs, acetaminophen, and statins were permitted with strict limitations. Other medications that were prohibited are described in the Exclusion Criteria above. These include but are not limited to parenteral and intra-articular glucocorticoids, biologics, and traditional DMARDs (other than MTX).

All medications taken during the study were to be recorded on the corresponding pages of the eCRF.

### Study treatments

The pharmaceutical form of sarilumab was provided in amber glass vials in the following strengths: 50 mg/mL, 75 mg/mL, or 100 mg/mL in a 2-mL volume. Matching placebo was also provided in a 2-mL volume. Therefore, depending on randomization, all subjects receive one of the following products:

- Glass vials of 100 mg or 150 mg of sarilumab or matching placebo 2 mL once a week
- Glass vials of 100 mg every other week alternating with placebo 2 mL, 150 mg every other week alternating with placebo 2 mL, 200 mg every other week alternating with placebo 2 mL, or placebo 2 mL every other week

The IMP was administered subcutaneously. The study coordinator or designee administered  
CDER Clinical Review Template 2015 Edition  
*Version date: November 5, 2015 for initial rollout (NME/original BLA reviews)*

Clinical Review  
Reviewer: Suzette Peng, MD  
NME/BLA 761037  
Sarilumab/Kevzara

the first injection comprising the initial dose as part of the training procedure on Day 1 (Visit 2). For doses not given at the study site, diaries were to be provided to record information pertaining to these injections. If the patient was unable or unwilling to administer the IMP, arrangements had to be made for qualified site personnel and/or caregiver(s) to administer the IMP for the doses that were not scheduled to be given at the study site.

In addition to the IMP, all subjects also received background MTX of which the dose needed to be stable for at least 6 weeks prior to the screening visit. All patients also needed to receive the same dose for the duration of the study.

### **Assignment to treatment**

Patients were randomized to one of the treatment arms via interactive voice response system (IVRS). At the screening visit (Visit 1), the Site Coordinator contacted the IVRS to obtain a patient number for each patient who had given informed consent. Each patient was allocated a patient number associated with the center in the chronological order of his/her enrollment in the study. At Visit 2, after confirming that the patient was eligible for entry into the double-blind period, the Site Coordinator contacted the IVRS via telephone or web to provide the patients a unique patient number in order to receive the treatment assignment. Patients were randomized to receive either placebo or one of the 5 treatment arms of sarilumab. The randomization ratio was 1:1:1:1:1. The treatment assignment was allocated to the patient according to the central randomization list via the IVRS. Randomization in Part A was stratified according to prior biologic use. The applicant reasoned that it has been observed that patients respond differently to a biologic if they had previous exposure. Randomization in Part A was also stratified by region (South America, Western countries, and rest of the world) to take into account differences in treatment effects across these regions.

A randomized patient was defined as a patient who signed informed consent and was assigned a treatment kit number allocated and recorded in the IVRS, regardless of whether the treatment kit was used or not. Study drug was also recorded and tracked in the center investigational medicinal product (IMP) inventory forms.

### **Blinding**

Sarilumab and matching placebo were provided in identically matched amber glass vials. Each vial contained 2.55 mL of sarilumab or matching placebo solution with 2.0 mL minimum withdrawal volume.

Sanofi generated 2 lists of treatment kit numbers – one list for Part A and Part B Cohort 1 and another for Part B Cohort 2. The IVRS also generated 3 patient randomization lists corresponding to each study part as well. Both the randomization and treatment kit lists were loaded into the IVR. The Investigator then obtained the treatment kit numbers via the IVRS at the time of patient randomization and subsequent patient scheduled visits.

Clinical Review  
Reviewer: Suzette Peng, MD  
NME/BLA 761037  
Sarilumab/Kevzara

### **Administrative structure**

Dr. Roy Fleischmann was the Principal Investigator for this study. The study employed (b) (4) as a central ECG reader, (b) (4) as a central laboratory, and (b) (4) as an IVRS provider.

The study employed an independent data monitoring committee (DMC) to be in charge of monitoring the safety of patients in this trial. The DMC's role included giving appropriate recommendations to the applicant on safety aspects during the conduct of the study. The DMC consisted of at least 4 members with expertise in areas including rheumatology, hepatology, infectious diseases, and medical statistics. Members of the DMC were independent of those performing the study (i.e., neither investigators nor employees of Sanofi) and, therefore, without conflict of interest regarding the study outcome.

### **Treatment compliance**

Measures were taken to ensure and document treatment compliance and IMP accountability.

- Proper recording of medication treatment pack number on the appropriate e-CRF page for accounting purposes.
- All medication treatment kits were returned by the patient at each visit.
- The study coordinator tracked treatment accountability/compliance and filled in the appropriate page of the patient treatment log.
- The monitor in charge of the study then checked the data entered on the IMP administration page by comparing them with the IMP that had been retrieved and the patient treatment log form.

### **Subject completion, discontinuation, or withdrawal**

Patients were allowed to withdraw from treatment with the IMP at any time, irrespective of the reason (either of the patient or of the Investigator). All efforts were to be made to document the reasons for treatment discontinuation on the e-CRF.

Temporary treatment discontinuation was to be considered by the Investigator because of suspected adverse events (AEs) or because of abnormal laboratory values (such as neutrophil counts <1000/ $\mu$ L). Reinitiation of treatment with the IMP was to be done under close and appropriate clinical and/or laboratory monitoring once the Investigator (using best medical judgment) determined that the event was unlikely related to the IMP and that the selection criteria for the study were still being met. If temporary discontinuation for a safety reason was  $\geq$  28 days (i.e., the interval between 2 injections), discontinuation was considered to be permanent. For all temporary treatment discontinuations, the Investigator needed to record the duration on the appropriate pages in the eCRF after confirmation.

Study treatment was to be permanently discontinued in case of the following events:

CDER Clinical Review Template 2015 Edition

*Version date: November 5, 2015 for initial rollout (NME/original BLA reviews)*

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

- Opportunistic infections including, but not limited to, active TB
- Symptoms of systemic hypersensitivity or anaphylactic reactions
- Severe neurologic disease, such as demyelinating disease or progressive multifocal leukoencephalopathy (PML)
- Significant laboratory abnormalities: ALT/bilirubin abnormalities, neutrophil count <500/ $\mu$ L, or platelet count <50,000/ $\mu$ L
- Pregnancy
- Use of any biologics
- Any unblinding by the Investigator

Patients who withdrew from the study could not be re-randomized in the same study. Additionally, their inclusion and treatment numbers could not be re-used. The Investigator recorded all withdrawals in the appropriate pages of the eCRF after confirmation. If possible, the patients were assessed using the procedure normally planned for the end of treatment (EOT) and post-treatment safety follow-up visits (see the Schedule of Assessments table in the Appendix section 13.3) The Investigator was to make the best effort to contact the patients who were lost to follow-up to identify the reasons why they had failed to attend the visit and determine their health status.

## Study Endpoints

### Primary Endpoint

The percentage of patients who achieved ACR20 at Week 12 was the primary endpoint in Part A.

The ACR (American College of Rheumatology) score is a composite rating scale that includes 7 variables.

#### 1. Tender joint counts

- Sixty-eight joints were assessed for tenderness, and sixty-six for swelling at screening, at baseline prior to dosing, and at each site study visit until the end of treatment visit. The 68 joints to be examined for tenderness were temporomandibular (n=2), sternoclavicular (n=2), acromioclavicular (n=2), shoulder (n=2), elbow (n=2), wrist (n=2), metacarpophalangeal (n=10), interphalangeal of thumb (n=2), distal interphalangeal (n=8), proximal interphalangeal (n=8), hip (n=2), knee (n=2), ankle mortise (n=2), ankle tarsus (n=2), metatarsophalangeal (n=10), interphalangeal of great toe (n=2), and proximal/distal interphalangeal of the toes (n=8). The 66 joints examined for swelling were the same as those for tenderness, excluding the hips. A formal count of the joints will be performed by a trained, independent assessor. Each

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

study center designated an independent assessor at each study center, and this assessor had no access to any patient data (including previous joint assessments during the study). This assessor was not the patient's treating physician.

2. Swollen joint counts
  - See definition above under "tender joint counts."
3. Levels of acute phase reactant (CRP)
  - hs-CRP was checked at screening, baseline before dosing, and at every site visit. Since CRP levels are directly correlated with IL-6R activity, it was expected that active dose regimens would have a dramatic lowering effect on CRP levels. In order to maintain the blind, hs-CRP was assessed centrally, and the results remained blinded to the Investigator, Sanofi, and the patient for post-dosing assessments. If the Investigator needed to know the patient's CRP levels (e.g., for safety reasons), a local test could be performed and needed to be noted on the CRF.
4. Patient's assessment of pain
  - Patients indicated their pain intensity due to RA in the previous week, using a 100 mm visual analog scale (VAS) at screening, at baseline prior to dosing, and at every site visit until the end of treatment. On the VAS, 0 is considered "no pain" and 100 "the most severe pain you can imagine."
5. Patient's global assessment of disease activity
  - Patient's global assessment of disease activity was performed at screening, at baseline prior to dosing, and at each site visit until the end of treatment visit. The patient rated his/her disease activity on an anchored 100 mm horizontal VAS where 0 was considered the best disease activity and 100 the worst.
6. Physician's global assessment of disease activity
  - Physician's global assessment of disease activity was performed at screening, at baseline prior to dosing, and at each site visit until the end of treatment visit. Like the patient's global assessment, described above, the investigator rated the patient's disease activity on an anchored 100 mm VAS where 0 was considered the best disease activity and 100 the worst.
7. Patient's assessment of physical function
  - Patients completed the Health Assessment of Questionnaire-Disability Index (HAQ-DI) at screening, at baseline prior to dosing, and at every site visit until the end of treatment visit. The HAQ-DI is a standardized questionnaire developed for use in RA with a scoring range between 0 and 3. A high HAQ score has been found to be a strong predictor of morbidity and mortality in RA. A 0.22 unit difference is considered clinically meaningful.

Specifically, ACR20 is defined as the percentage of patients who achieve at least 20% improvement in both tender joint count and swollen joint count and, at least 20% improvement in at least 3 of the 5 other assessments of the ACR.

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

*Reviewer Comment: ACR20 is a composite endpoint that is essentially the standard endpoint to assess improvement in signs and symptoms in patients with RA. Therefore, Sanofi's choice to assess ACR20 was reasonable. Additionally, an assessment at Week 12 would be appropriate.*

### Secondary Endpoints

- ACR50, ACR70
  - ACR50 is defined as the achievement of at least 50% improvement in both tender joint count and swollen joint count and at least 50% improvement in at least 3 of the 5 other assessments of the ACR. It was assessed at Week 12.
  - ACR70 is defined as the achievement of at least 70% improvement in both tender joint count and swollen joint count and at least 70% improvement in at least 3 of the 5 other assessments of the ACR. It was assessed at Week 12 in Part A.
- Disease activity state
  - Disease activity was measured using the DAS28 (Disease Activity Score 28). DAS28 is a composite score that includes 4 variables.
    - Tender joint count (28 joints)
    - Swollen joint count (28 joints)
    - General health assessment, defined as the patient's global assessment of disease activity
    - Marker of inflammation, assessed by hs-CRP
  - The DAS28 score is calculated from a formula utilizing the above variables:  
$$\text{DAS28} = 0.56 \times \sqrt{28\text{TJC}} + 0.28 \times \sqrt{28\text{SJC}} + 0.36 \times \text{Log}(\text{CRP}+1) + 0.014 \times \text{GH} + 0.96$$
  - DAS28 is a continuous measure allowing for measurement of absolute change in disease burden and percentage improvement. The DAS28 provides a number indicating the current activity of RA. A DAS28 above 5.1 means high activity, whereas a DAS28 below 3.2 indicates low disease activity.
  - The disease activity response was also presented using the European League Against Rheumatism (EULAR) response criteria.
    - Good response = improvement of > 1.2 and a present DAS score of  $\leq 3.2$
    - Moderate response = either improvement of > 0.6 to  $\leq 1.2$  and a present score  $\leq 5.1$ , OR improvement > 1.2 and a present score > 3.2
    - Nonresponse = either an improvement of  $\leq 0.6$  OR an improvement  $\geq 0.6$  to  $\leq 1.2$  and a present score > 5.1
- DAS28 remission
  - DAS28 remission is defined as a DAS28 score < 2.6.
- ACR components
  - Each component of the ACR was analyzed at Week 12.
- Time to onset of benefit
  - ACR20, ACR50, ACR70, and each ACR component were analyzed at every visit and, thus, the time to onset of benefit could be described.

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

*Reviewer Comment: The secondary endpoints are all endpoints that have been evaluated in other RA studies. Some of the endpoints have also been included in the labels of recently approved DMARDs. Thus, these are acceptable to evaluate as supportive of the primary endpoint.*

### **Safety Assessments**

The safety variables included adverse events (AEs), clinical laboratory parameters, vital signs, and ECGs. The baseline values are defined as the Visit 2 assessments prior to the first dose of the randomized study medication. The observation of safety data was divided into the screening observation period and the treatment-emergent adverse event (TEAE) observation period. The screening observation period was defined as the time from the signed informed consent to randomization, whereas the TEAE observation period was defined as the time from the first dose of the IMP up to the end of the follow-up period.

Patients were questioned about how they felt since the last study visit in order to collect adverse event (AE) information. All AEs, regardless of seriousness or relationship to the IMP, were recorded from the informed consent form (ICF) until the end of the study.

- Adverse events (AEs) were defined as any untoward medical occurrence in a patient or clinical investigation. The AE did not have to have a causal relationship with this treatment.
- Serious adverse events (SAEs) were any untoward medical occurrence that, at any dose, resulted in the following:
  - Death
  - Life-threatening
  - Inpatient hospitalization or prolongation of existing hospitalization
  - Persistent or significant disability/incapacity
  - Congenital anomaly/birth defect
  - Medically important event – i.e., medical and scientific judgment were exercised in deciding whether expedited reporting was appropriate in situations other than what has already been listed but may still have jeopardized the patients or may have required intervention to prevent any of the outcomes listed above. Medically important events could include the following:
    - Intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, convulsions, seizures, epilepsy, and epileptic seizure
    - Development of drug-dependency or drug abuse
    - ALT > 3x ULN + total bilirubin > 2x ULN or asymptomatic ALT increase >10x ULN
    - Suicide attempt or any event suggestive of suicidality
    - Syncope, loss of consciousness
    - Bullous cutaneous eruptions

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

- Cancers diagnosed during the study
- Chronic neurodegenerative diseases (newly diagnosed) or aggravated during the study
- Adverse events with prespecified monitoring (AEPMs) were adverse events (serious or nonserious) that needed to be monitored, documented, and managed in a prespecified manner. The AEPMs were reported by the Investigator in the eCRF. Adverse events that should have been reported as AEPMs were identified through searches that were based on Standard MedDRA Query (SMQ) or modified SMQ and/or prespecified event terms.

The AESIs included the following:

- Opportunistic infections such as herpes zoster infection
- Gastrointestinal ulcerations or confirmed diverticulitis. Any perforation was considered to be serious.
- Hypersensitivity reactions or anaphylaxis
- Autoimmune or lupus-like syndrome
- Drug-induced liver injury (DILI)
- Neutropenia
- Thrombocytopenia
- Neurologic disorders such as central or peripheral demyelination or abnormal MRI evaluation and suspicion for progressive multifocal leukoencephalopathy (PML) and unexplained neurological symptoms. These patients were referred to a neurologist for evaluation.
- Pregnancy
  - Pregnancy that occurred in a female patient was recorded as a prespecified adverse event with immediate notification in all cases. It qualified as an SAE only if it fulfilled the SAE criteria.
  - In the event of pregnancy, the IMP was discontinued.
  - Follow-up of the pregnancy was mandatory until the outcome was determined.
- Overdose was an event that was suspected by the Investigator or spontaneously notified by the patient and defined as administration of at least twice the dose during fewer than 6 days.
- Laboratory safety parameters
  - Hematology (all visits)
    - Hemoglobin, hematocrit, RBC morphology if abnormal blood cell count, WBC count with differential, and platelet count
  - Liver Function Tests (all visits)
    - PT, albumin, AST, ALT, alkaline phosphatase (ALP), total bilirubin, and conjugated and unconjugated bilirubin
  - Lipid profiles (Visits 1, 2, 4, 6, 8)
    - Total cholesterol, HDL, LDL

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

- Triglycerides, apolipoprotein A, and apolipoprotein B (baseline, EOT visits only)
  - Clinical chemistry (Visits 1, 2, 4, 6, 8)
    - Fasting glucose, total protein, calcium, sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN), lactate dehydrogenase (LDH), creatinine (Visit 1 only), uric acid
  - Pregnancy tests for women of childbearing potential (prior to any x-ray procedures): serum  $\beta$ -HCG test (Visit 1) and urine tests (Visits 2, 4, 6, 8 in Part A)
  - Urine dipstick (Visits 1, 2, 4, 6, 8)
    - Glucose, protein, bilirubin, urobilinogen, pH, specific gravity, blood, ketones, nitrites, and leukocytes
    - If the urine dipstick was abnormal, a central urinalysis was performed.
  - Hepatitis B and C serology (Visit 1 only per exclusion criterion or in case of liver injury)
  - CK and HbA1c (Visit 1 only and later if clinically indicated)
- Vital signs
    - Heart rate, blood pressure, and temperature measurements were to be obtained at every visit, except for home visits, prior to dosing
      - Body temperature was measured using the same method for a given patient. Temperature  $\geq 38^{\circ}\text{C}$  was to be recorded as an AE, and the Investigator was responsible for performing all investigations necessary to rule out an infection.
      - Blood pressure was measured in agreement with the Committee for Proprietary Medicinal Products (CPMP) guidelines, under standardization conditions, using the same well-calibrated apparatus and the same arm throughout the study. Supine blood pressure (BP) was checked after 2 minutes of rest. Standing BP was obtained 1 minute after the patient had stood up.
    - Body weight was to be taken on a regular basis at screening and at every site visit with the patient wearing undergarments or very light clothing and no shoes. The same scale was used throughout the study.
  - Electrocardiogram (ECG)
    - A standard 12-lead ECG was recorded at screening and at the EOT visit at Week 12 (Visit 8). HR, QRS duration, PR interval, QT interval, ST deviation, T-wave morphology, and U wave presence or absence were determined using centralized automatic and manual readings of all ECGs.
  - Physical examination
    - A complete physical examination, including a neurological examination, was to be performed at the screening visit (Visit 1), at baseline (Visit 2), and at the EOT or early termination visit (Visit 8). Any clinically significant abnormalities were to be

reported in the patient's e-CRF as medical history when observed at Visit 1 or Visit 2 or as an AE if observed during subsequent visits.

### Pharmacokinetics and Immunogenicity Assessments

See the study flowchart (Table 139) for timing of blood sample collections. Serum samples for functional sarilumab (with either one or two available binding sites) and bound sarilumab (serum sarilumab + soluble interleukin 6  $\alpha$ -receptor [sIL-6R $\alpha$ ] complex) were collected for each patient before dosing at Weeks 0, 2, 4, 8, and 12. Serum IL-6 and serum sIL-6R $\alpha$  were collected for each patient at baseline (Week 0) and Weeks 2, 4, 8, and 12. Serum anti-sarilumab antibody samples were collected for each patient at pre-dose at Week 0 and at Weeks 4, 8, and 12. If an SAE occurred in a patient, blood samples had to be collected to determine serum sarilumab concentrations at or near the completion of the occurrence of the event.

- PK Variables
  - Observed serum functional and bound sarilumab trough concentrations were reported. An exploratory population pharmacokinetic (PopPK) model was developed using subset data from the current study and DRI11073 and 68 patients from four phase 1 studies (TDU10808, TDU10809, TDR10805, and ACT10804). Subsequently, PopPK analysis was performed using Nonmem 7.1.2 software running on a Linux cluster. The exploratory PopPK model was used to predict individual drug exposure, including C<sub>max</sub> (maximum concentration), AUC (area of under the concentration curve), and C<sub>ss</sub> (steady state concentration at Week 12).
- Immunogenicity Variables
  - Serum anti-sarilumab antibody status at baseline and post-dose were reported.
- Pharmacodynamic Variables
  - Serum concentrations of IL-6, sIL-6R $\alpha$ , and CRP were summarized using arithmetic and geometric means, standard deviation (SD), standard error of the mean (SEM), coefficient of variation (CV%), minimum, median, and maximum by dose and visit. Serum IL-6 and sIL-6R $\alpha$  concentrations at baseline and post-dose were reported.

### Statistical Analysis Plan

**Sample size determination:** It was assumed that the response rates were 40% in the placebo group and 75% in at least 1 active sarilumab group. With 50 patients per group, the study had approximately 80% power to detect a difference of 35% between any dose of sarilumab and placebo using a 2-sided test with alpha = 0.01.

**Analysis population:** The efficacy analyses were based on the intent-to-treat (ITT) patient population consisting of all patients who had given their informed consent and for whom there was confirmation of successful allocation of a randomization number through the IVRS. The

Clinical Review  
Reviewer: Suzette Peng, MD  
NME/BLA 761037  
Sarilumab/Kevzara

safety analysis was performed on the safety population. The safety population consisted of all randomized patients who received at least one dose of the investigational medicinal product.

### **Primary Analysis**

Each dose regimen of sarilumab was tested versus placebo. Each individual null hypothesis was that there was no difference from placebo in terms of the primary efficacy endpoint. The primary efficacy variable was analyzed as the proportion of patients at Week 12 who achieved ACR20.

### **Handling of dropouts or missing data**

In the primary method of missing data handling, a last observation carried forward (LOCF) procedure from the point of treatment discontinuation or rescue was applied to impute missing data for all 7 ACR components for all visits after that point. Responder status was determined using the imputed components. However, patients who discontinued the treatment because of lack of efficacy were considered as nonresponders for all time points beyond the time they discontinued.

### **Main statistical model and adjustment of covariates**

The primary efficacy variable (ACR20 at Week 12) was analyzed using the 2-sided CochranMantel-Haenszel (CMH) test stratified by prior biologic use and region. Pairwise comparisons of the response rates between each dose of sarilumab and placebo were derived by testing each active dose group versus placebo separately. The Mantel-Haenszel (MH) estimate of the odds ratio and the corresponding 95% CI was derived by testing each active dose group versus placebo separately. In addition, the ACR20 response rate at each visit during the double-blind treatment period was summarized and plotted by treatment groups.

### **Multiple comparison/multiplicity**

The multiplicity issues for testing multiple doses of sarilumab against placebo for the primary efficacy variable were addressed by using the Hommel procedure. The Hommel procedure was based on the Simes' test and was valid under independence or positively dependent p-values. As the 5 comparisons of sarilumab versus placebo in this protocol had positively dependent p-value structures, the application of the Hommel procedure effectively preserved the familywise error rate. In addition, the Hommel procedure was uniformly more powerful than the Hochberg procedure.

### **Analysis of Secondary Endpoints**

A 2-sided CMH test stratified by prior biologic use and region was used to assess treatment differences in the following binary efficacy variables:

- ACR50, ACR70 at Week 12
- DAS28 remission at Week 12
- EULAR response at Week 12

Clinical Review  
Reviewer: Suzette Peng, MD  
NME/BLA 761037  
Sarilumab/Kevzara

Pairwise comparisons of the response rates between each dose of sarilumab and placebo were derived by testing each active dose group versus placebo separately.

An ANCOVA model, including terms for baseline, treatment, prior biologic use, and region was used to assess treatment differences in the change from baseline for each of the following continuous efficacy variables.

- Change from baseline in DAS28 at Week 12
- Change from baseline in each of the seven ACR components at Week 12

Descriptive statistics including number of subjects, mean, standard error, and least-squares means (LS means) are provided. In addition, difference in LS means, the corresponding 95% CI and the p-value are provided for comparisons of each sarilumab dose against placebo. A review of the residuals was done to determine whether the model assumptions were met. If not, a rank based ANCOVA was done to corroborate the ANCOVA result. Change from baseline in each of the ACR components and DAS28 at each visit during the double-blind treatment period was summarized and plotted by treatment groups. Descriptive statistics including number of subjects, mean, standard error, and LS means are provided. In addition, difference in LS means between each dose of sarilumab and placebo and the corresponding 95% CI are provided.

ACRn: An ANOVA model, including terms for treatment, prior biologic use and region, was used to assess treatment differences in ACRn at Week 12.

Descriptive statistics including number of subjects, mean, standard error, and least-squares means (LS means) are provided. In addition, difference in LS means, the corresponding 95% CI and the p-value are provided for comparisons of each sarilumab dose against placebo. A review of the residuals was done to determine whether the model assumptions are met. If not, an ANOVA with rank transformation was done to corroborate the ANOVA result. ACRn at each visit during the double-blind treatment period was summarized and plotted by treatment groups. Descriptive statistics including number of subjects, mean, standard error, and LS means are provided. In addition, difference in LS means between each dose of sarilumab and placebo and the corresponding 95% CI are provided.

### **Analyses of Safety Data**

The time interval to detect any treatment-emergent event or abnormality was defined as the time from the first dose injection of the double-blind IMP to the end of the follow-up period, often after the last dose injection of the double-blind IMP.

The following definitions are applied to laboratory parameters, vital signs, and ECG.

- The potentially clinically significant abnormality (PCSA) values are defined as abnormal values considered medically important by Sanofi according to predefined criteria/thresholds

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

based on literature review and defined by the Sanofi for clinical laboratory tests, vital signs, and ECGs. The PCSA values used for the clinical study report (CSR) are those consistently used for sarilumab.

- PCSA criteria determine which patients had at least 1 PCSA during the on-treatment period, taking into account all evaluations performed during the on-treatment period, including non-scheduled or repeated evaluations. The number of all such patients is the numerator for the on-treatment PCSA percentage.

### Drug-induced liver injury

Time to onset of the initial ALT elevation (>3x ULN), the initial AST elevation (>3x ULN), the initial total bilirubin elevation (>2x ULN), and the first observation of ALT >3x ULN or total bilirubin >2x ULN (whichever came first) was analyzed using Kaplan-Meier estimates, using the midpoint of the time interval between the first assessment showing the elevation and the previous assessment, presented by treatment group. A graph of distribution of peak values of ALT versus peak values of total bilirubin is also presented. The graph was divided into 4 quadrants with a vertical line corresponding to 3x ULN for ALT and a horizontal line corresponding to 2x ULN for total bilirubin.

The normalization to  $\leq 1x$  ULN or return to baseline of elevated LFTs was also summarized by categories of elevation (>3x ULN, >5x ULN, >10x ULN, >20x ULN for ALT and AST; >1.5x ULN for alkaline phosphatase; and >1.5x ULN and >2x ULN for total bilirubin) with the following categories of normalization: never normalized and normalized after permanent discontinuation of study drug.

### Adverse events (AEs)

Adverse events reported in this study were coded using the Medical Dictionary for Regulatory Activities (MedDRA, Version 14.0). AEs were classified according to chronological criteria into pretreatment AEs and TEAEs. The analyses of AEs focus on the TEAEs.

Pretreatment AEs were defined as AEs that developed or worsened during the pretreatment period. TEAEs are defined as AEs that developed or worsened during the on-treatment period, which is defined as the time from the first dose injection of the double-blind study drug to the end of the TEAE period.

TEAE incidence tables were presented by system organ system (SOC) and preferred term (PT) sorted in alphabetical order for each treatment group, the number (n) and percentage (%) of patients experiencing a TEAE. Multiple occurrences of the same event in the same patient were counted only once in the tables within the treatment phase. The denominator for computation of percentages was the safety population within each treatment group.

The table of all TEAEs were presented by SOC, high-level group term (HLGT), high-level term

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

(HLT), and PT, sorted by the internationally agreed order of SOCs and decreasing frequency of PT within the SOC. Sorting was based on the treatment arm given with the highest dose/intensity.

## Deaths

The following summaries of deaths were generated if the number of patients concerned was greater than 3.

- Number (%) of patients who died, by study period (TEAE, on study) summarized on the safety population by treatment received
- All AEs leading to death (death as an outcome on the AE CRF page as reported by the Investigator) by primary SOC, HLGT, HLT, and PT, showing number (%) of patients sorted by internationally agreed order of SOC and alphabetic order of HLGT, HLT, and PT
- TEAE leading to death (death as an outcome on the AE CRF page as reported by the Investigator) by primary SOC, HLGT, HLT, and PT showing number (%) of patients sorted by internationally agreed order of SOC and alphabetic order of HLGT, HLT, and PT

## Serious Adverse Events (SAEs)

The number and percentage of patients with SAEs were summarized by treatment group and by primary SOC, HLGT, HLT, and PT if the number of patients concerned was greater than 3

## AEs leading to treatment discontinuation

The number and percentage of patients with AEs leading to permanent treatment discontinuation were summarized by treatment group and primary SOC, HLGT, HLT, and PT if the number of patients concerned was greater than 3.

## Clinical laboratory evaluations

The number and percentage of patients with at least one PCSA during the time from the first dose injection of the double-blind study drug to the end of the follow-up period after the last dose injection of double-blind IMP were summarized by treatment group for each laboratory parameter. Descriptive statistics were also used to summarize baseline, raw values, and changes from baseline for each treatment group at each visit. The baseline value for each laboratory visit was the Visit 2 assessment. Shift tables showing changes with respect to the normal range between baseline and post-baseline were provided.

## Vital Signs

Vital signs, including BP and HR, were measured at Visits 1, 2, 3, 4, 6, and 8. Descriptive statistics were provided for the baseline, absolute raw values, and changes from baseline for each treatment group at each visit. Baseline was defined as the predose value at Visit 2. The number and percentage of patients with at least one PCSA during the time from the first dose injection of the double-blind study drug to the end of the follow-up period were summarized by treatment group.

Clinical Review  
Reviewer: Suzette Peng, MD  
NME/BLA 761037  
Sarilumab/Kevzara

#### Electrocardiogram

Standard 12-lead ECG data were collected at screening (Visit 1) and during Visit 8. Descriptive statistics were provided for baseline absolute values and changes from baseline for each treatment group per visit. Baseline was defined as the Visit 2 assessment. The number and percentage of patients with at least one PCSA during the time from the first dose injection of the double-blind study drug to the end of the follow-up period were summarized by treatment group for each ECG parameter (i.e., HR, QRS duration, PR interval, QT interval, ST deviation, T-wave morphology, and U wave presence or absence).

#### **Analyses of PK, PD, and immunogenicity variables**

##### PK Variables

Serum concentrations of functional and bound sarilumab were summarized by treatment group as well as immunogenicity status (negative or positive) for each visit using descriptive statistics, including number, arithmetic mean, geometric mean, standard deviation, standard error of the mean (SEM), coefficient of variation (CV%), minimum, median, and maximum.

##### PD Variables

Serum concentrations of IL-6, sIL-6R $\alpha$ , and CRP were summarized by treatment group for each visit using descriptive statistics including number, arithmetic and geometric means, standard deviation, standard error of the mean (SEM), coefficient of variation (CV%), minimum, median, and maximum.

##### PK/PD analyses

A linear regression model was applied to check the correlation between neutrophil counts and drug exposure (PK concentration [log scale], area under the drug concentration curve [AUC], and maximum concentration [C<sub>max</sub>]) at each visit. PK concentration was the trough concentration from the observed data. AUC and C<sub>max</sub> were estimated from an exploratory population PK model. AUC for q2w dosing was AUC <sub>$\tau$</sub>  (area under the concentration curve for dosing interval) and AUC for qw dosing was actually sum of AUC <sub>$\tau$</sub>  for 2 weeks. C<sub>max</sub> for q2w dosing was the maximum concentration after the previous dose, and C<sub>max</sub> for qw dosing was the maximum concentration after the previous dose and nearest to the efficacy/PD or safety measurements.

The independent variables in the models included the following

- Model 1: Baseline, log (PK concentration), anti-sarilumab neutralizing antibody
- Model 2: Baseline, AUC, anti-sarilumab antibody
- Model 3: Baseline, C<sub>max</sub>, anti-sarilumab antibody

The p-values and the point estimators were provided for the coefficients of the exposure and anti-sarilumab neutralizing antibody. The p-value from an F test was provided to show the

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

goodness of fit of the model. There was no imputation for any missing exposure. In addition, scatter plots for neutrophil counts against log (PK concentration) were provided at each visit.

A linear regression model was applied to check the correlation between the change of CRP level, DAS28, and drug exposure at each visit using the same procedure described above. In addition, scatter plots for change of CRP levels and DAS28 against log (PK concentration) were provided at each visit.

A logistic regression model was applied to explore the linear relationship between logit ACR20 response and drug exposure (PK concentration [log scale] at each visit, concentration at steady state [C<sub>ss</sub>] at Week 12). PK concentration was the trough concentration from the observed data and C<sub>ss</sub> at Week 12 was estimated from an exploratory population PK model using the equation  $AUC_{\tau}/\text{dosing interval}$ .

The independent variables in the models were the following:

- Model 1: log (PK concentration), anti-sarilumab antibody
- Model 2: C<sub>ss</sub> (Week 12), anti-sarilumab antibody

The p-value and the point estimator were provided for the coefficient of the drug exposure and anti-sarilumab antibody. The p-value from a chi-square test was provided to show the goodness of fit of the model. In addition, a box plot of ACR20 response at Week 12 against log (PK concentration) was provided. There was no imputation for any missing exposure.

A logistic regression model was applied to explore the linear relationship between logit ACR50, logit ACR70 responses, and drug exposure at each visit using the models described above. In addition, box plots of ACR50 and ACR70 responses at Week 12 against log (PK concentration) were provided.

In case of a nonlinear relationship between drug exposure and effects were found, nonlinear PD models were to be employed.

### Immunogenicity variables

Anti-sarilumab antibody results were described categorically as negative (below the assay cutpoint or not drug-specific) or positive (drug-specific signal above the assay cutpoint) by dose and visit.

### **Analyses of quality of life/health economics variables**

#### Quality of life variables

Change from baseline in FACIT-Fatigue and the sleep questionnaire scale at Week 12 were analyzed using an ANCOVA model with factors for baseline, treatment, prior biologic use, and region as covariates. The summary statistics were provided for FACIT-Fatigue and the sleep

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

questionnaire scales (raw value and change from baseline) at each visit or study assessment (baseline, endpoint) by treatment group. Descriptive statistics, including number of subjects, mean, standard error, and LS means were provided. In addition, difference in LS means between each dose of sarilumab and placebo and the corresponding 95% CI were provided.

### Health economics variables

Change from baseline in the four WPAI scores at Week 12 were analyzed using an ANCOVA model with factors for baseline, treatment, prior biologic use, and region as covariates. The summary statistics were provided for the four WPAI scores (raw value and change from baseline) at each visit or study assessment (baseline, endpoint) by treatment group. Descriptive statistics including number of subjects, mean, standard error, and LS means were provided. In addition, difference in LS means between each dose of sarilumab and placebo and the corresponding 95% CI were provided.

## Protocol Amendments

Amendment 1 was dated February 9, 2010, and was implemented prior to enrollment of the first patient.

Amendment 2 was dated June 1, 2010, and was implemented after the first patient was randomized.

In regards to Part A, the reasons for these 2 amendments included the following:

- To indicate that, in selected countries, patients were randomized to participate in EFC11072 Part A
- To correct the hemoglobin unit of measure from g/l to g/dL
- To add a CK sampling timepoint at the EOT visit for Part A (Visit 8/Week 12)
- To add a lipids sampling timepoint at Visit 6/Week 8 for Part A
- To clarify that all patients were scheduled for the post-treatment follow-up visit prior to entry into the sarilumab long-term extension study LTS11210
- To clarify that hypersensitivity reactions referred to throughout the protocol were systemic hypersensitivity reactions rather than local reactions
- To clarify that, in the event of a medically indicated joint replacement treatment/procedure, the patient could continue to participate in the trial unless study treatment had been discontinued for  $\geq 28$  days

*Reviewer Comment: These amendments were not significant changes to the originally proposed protocol. I do not suspect these amendments would have changed the conduct of the study to any major extent.*

## Data Quality and Integrity: Sponsor's Assurance

CDER Clinical Review Template 2015 Edition

Version date: November 5, 2015 for initial rollout (NME/original BLA reviews)

66

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

Sanofi noted that regular site monitoring ensured the quality of trial conduct. Management of clinical trial data was performed according to the following rules and procedures:

- Data entry, verification, and validation were carried out using standard computer software (Oracle Clinical version 4.5.3); data were stored in an Oracle database on a Digital VMS computer.
- A double-entry method was used to ensure that the data (except comments) were transferred accurately from the CRFs to the database.
- Every modification in the database could be traced following an audit trail.
- A data checking plan was established to define all automatic validation checks, as well as supplemental manual checks, to ensure data quality.
- All discrepancies were researched until resolved.

Lastly, Sanofi-aventis conducted investigator meetings to ensure that there was a common understanding of the clinical study protocol, CRF, and study procedures, as well as the individual site initiation meetings.

### 6.1.2. Study Results

#### Compliance with Good Clinical Practices

The protocol and its 2 amendments were submitted to independent ethics committees and/or institutional review boards for review and written approval. The protocol complied with recommendations of the 18<sup>th</sup> World Health Congress (Helsinki, 1964) and all applicable amendments. The protocol also complied with the laws and regulations, as well as any applicable guidelines, of the countries where the study was conducted. Informed consent was to be obtained prior to the conduct of any study-related procedures. The patient informed consent form (ICF) was modified according to local regulations and requirements.

#### Financial Disclosure

Sanofi has adequately disclosed financial interests/arrangements with clinical investigators for this study. See Table 138 in Appendix Section 13.2 for a full review of Sanofi's financial disclosure.

#### Patient Disposition

A total of 737 patients were screened for entry into the study, but 431 (58.5%) were screen failures. Therefore, a total of 306 patients were randomly assigned to one of 6 treatment groups.

- Placebo: 52 subjects
- 100mg q2w: 51 subjects
- 150mg q2w: 51 subjects

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

- 100mg qw: 50 subjects
- 200mg q2w: 52 subjects
- 150mg qw: 50 subjects

It should be noted that there were no randomization errors, and no treatment codes were broken prior to database lock. However, incorrect study drug kits were dispensed to 2 patients in error. From Days 57-78, one patient in the placebo group received sarilumab 150mg q2w kit, and one patient in the 150mg q2w group received a placebo kit. As a result, the placebo patient was considered to be in the placebo group for ITT analyses but was considered to be in the 150mg q2w group for safety and PK analyses.

Table 6 describes the disposition of all the randomized patients. Thirty-five subjects (32 in sarilumab and 3 in placebo) did not complete the study treatment period because of adverse events, lack of efficacy, and other reasons. A majority of subjects (79.4% total) who completed EFC11072 Part A entered the open-label extension study, LTS11210.

APPEARS THIS WAY ON ORIGINAL

**Table 6. EFC11072 Part A Patient Disposition**

	Placebo (N=52)	Sarilumab				
		100mg q2w (N=51)	150mg q2w (N=51)	100mg qw (N=50)	200mg q2w (N=52)	150mg qw (N=50)
Randomized and not treated	0	0	0	0	1 (1.9%)	0
Randomized and treated	52 (100%)	51 (100%)	51 (100%)	50 (100%)	51 (98.1%)	50 (100%)
Did not complete the study treatment period	3 (5.8%)	6 (11.8%)	3 (5.9%)	13 (26.0%)	6 (11.5%)	4 (8.0%)
Subject's request for treatment discontinuation	1 (1.9%)	3 (5.9%)	2 (3.9%)	4 (8.0%)	2 (3.8%)	1 (2.0%)
Reason for treatment discontinuation						
Adverse event	1 (1.9%)	3 (5.9%)	2 (3.9%)	13 (26.0%)	4 (7.7%)	1 (2.0%)
Lack of efficacy	2 (3.8%)	1 (2.0%)	1 (2.0%)	0	1 (1.9%)	2 (4.0%)
Poor compliance to protocol	0	0	0	0	0	0
Other reasons	0	2 (3.9%)	0	0	1 (1.9%)	1 (2.0%)
Status at last study contact						
Alive	52 (100%)	50 (98.0%)	51 (100%)	50 (100%)	52 (100%)	50 (100%)
Dead	0	1 (2.0%)	0	0	0	0
Rolled over to LTS study						
Yes	46 (88.5%)	42 (82.4%)	39 (76.5%)	36 (72.0%)	39 (75.0%)	41 (82.0%)
No	6 (11.5%)	9 (17.6%)	12 (23.5%)	14 (28.0%)	13 (25.0%)	9 (18.0%)

Source: EFC11072 Part A Clinical Study Report, dated January 16, 2012, Table 4, page 63.

*Reviewer Comment: All the randomized subjects who signed informed consent made up the ITT population for the primary efficacy analysis. The PK and safety populations were slightly different because of the error in study kits dispense as described above. Additionally, one subject in the 200mg q2w group did not receive treatment, so this subject was not included in the 200mg arm for safety and PK analyses.*

Clinical Review  
Reviewer: Suzette Peng, MD  
NME/BLA 761037  
Sarilumab/Kevzara

### **Protocol Violations/Deviations**

There were 13 patients with important protocol deviations that, per Sanofi, had a potential to affect the efficacy analyses of the ITT population. One deviation was in the placebo group, and 12 deviations were in the sarilumab group.

- Four subjects had patient compliance <80%.
- One of the protocol requirements was to be on a stable dose of MTX for a minimum of 6 weeks prior to the screening visit and then continue the same dose for the duration of the study. A total of 5 patients in the study had an increase in MTX dose during the 6 weeks prior to the screening visit; 2 patients had an increase in MTX dose during the study.
- Another protocol requirement was that patients must have been treated with and tolerated a minimum of 12 weeks of treatment of MTX prior to randomization. Only 1 patient in the sarilumab 100mg q2w arm did not meet this requirement.
- Three patients did not meet the requirement of having moderate to severe active disease. One of these patients was the subject in the placebo arm who had a protocol deviation.

*Reviewer Comment: The vast majority of the protocol deviations occurred in the sarilumab treatment arms. Most of these deviations may have variable (that is, possibly positive or negative) effect on the data. It should be noted, though, that the increase in MTX in the sarilumab arms would likely be favorable toward sarilumab. Also, if the subjects, who did not meet the requirement for moderate to severe disease, had milder disease, those in the sarilumab arms may also be more likely to have a positive response to treatment.*

*It is unclear how Sanofi handled these deviations. However, overall, the number of deviations is low and should not have a large impact on the efficacy and safety results.*

### **Table of Demographic Characteristics**

Table 7 describes the baseline demographics and patient characteristics of the subjects in study EFC11072 Part A. Overall, the patient characteristics and demographics at baseline are similar across treatment arms. The majority of subjects were less than 65 years old, female, and Caucasian; these features are representative of the general RA population, particularly, here in the United States. It is notable, however, that the majority of subjects were recruited outside of Western countries. As Part A was a phase 2 study, the demographics are reasonable and acceptable.

Clinical Review  
 Reviewer: Suzette Peng, MD  
 NME/BLA 761037  
 Sarilumab/Kevzara

**Table 7. Demographics and Patient Characteristics at Baseline in Study EFC11072 Part A**

	Placebo (N=52)	Sarilumab				
		100mg q2w (N=51)	150mg q2w (N=51)	100mg qw (N=50)	200mg q2w (N=52)	150mg qw (N=50)
<b>Age (years)</b>						
Number	52	51	51	50	52	50
Mean (SD)	55.2 (12.5)	53.5 (11.8)	51.2 (12.9)	53.9 (12.3)	48.7 (12.4)	50.9 (11.1)
Median	58.5	57.0	53.0	56.0	50.5	51.0
Min: Max	23: 74	19: 68	23: 73	22: 73	21: 71	24: 71
<b>Age Group [n(%)]</b>						
Number	52	51	51	50	52	50
<65 years	40 (76.9%)	42 (82.4%)	43 (84.3%)	38 (76.0%)	47 (90.4%)	45 (90.0%)
≥65-75 years	12 (23.1%)	9 (17.6%)	8 (15.7%)	12 (24.0%)	5 (9.6%)	5 (10.0%)
≥ 75 years	0	0	0	0	0	0
<b>Sex [n(%)]</b>						
Number	52	51	51	50	52	50
Male	14 (26.9%)	13 (25.5%)	9 (17.6%)	9 (18.0%)	10 (19.2%)	8 (16.0%)
Female	38 (73.1%)	38 (74.5%)	42 (82.4%)	41 (82.0%)	42 (80.8%)	42 (84.0%)
<b>Race [n(%)]</b>						
Number	52	51	51	50	52	50
Caucasian	49 (94.2%)	49 (96.1%)	49 (96.1%)	47 (94.0%)	47 (90.4%)	46 (92.0%)
Black	0	1 (2.0%)	2 (3.9%)	1 (2.0%)	3 (5.8%)	1 (2.0%)
Asian	2 (3.8%)	0	0	1 (2.0%)	2 (3.8%)	1 (2.0%)
Other	1 (1.9%)	1 (2.0%)	0	1 (2.0%)	0	2 (4.0%)
<b>Ethnicity [n(%)]</b>						
Number	52	51	51	50	52	50
Hispanic	14 (26.9%)	16 (31.4%)	16 (31.4%)	14 (28.0%)	15 (28.8%)	14 (28.0%)
Non-Hispanic	38 (73.1%)	35 (68.6%)	35 (68.6%)	36 (72.0%)	37 (71.2%)	36 (72.0%)
<b>Weight (kg)</b>						
Number	52	51	51	50	51	50

Clinical Review  
 Reviewer: Suzette Peng, MD  
 NME/BLA 761037  
 Sarilumab/Kevzara

Mean (SD)	75.37 (15.49)	75.86 (15.55)	73.90 (15.25)	74.08 (16.28)	77.49 (16.28)	72.37 (13.78)
Median	77.90	77.60	73.00	71.50	77.00	69.65
Min: Max	46.0: 108.4	46.5: 109.0	46.0: 108.0	50.5: 107.0	46.2: 109.1	48.5: 109.1
<b>BMI (kg/m<sup>2</sup>)</b>						
Number	52	51	51	50	50	49
Mean (SD)	28.32 (6.53)	28.51 (5.41)	27.82 (5.35)	28.20 (6.19)	29.13 (5.52)	27.69 (4.81)
<25	16 (30.8%)	17 (33.3%)	14 (27.5%)	16 (32.0%)	13 (26.0%)	17 (34.7%)
≥25-30	20 (38.5%)	14 (27.5%)	23 (45.1%)	17 (34.0%)	13 (26.0%)	16 (32.7%)
≥30	16 (30.8%)	20 (39.2%)	14 (27.5%)	17 (34.0%)	24 (48.0%)	16 (32.7%)
<b>Region [n(%)]</b>						
Number	52	51	51	50	52	50
Western countries	16 (30.8%)	15 (29.4%)	16 (31.4%)	14 (28.0%)	16 (30.8%)	17 (34.0%)
South America	13 (25.0%)	14 (27.5%)	13 (25.5%)	13 (26.0%)	14 (26.9%)	13 (26.0%)
Rest of the world	23 (44.2%)	22 (43.1%)	22 (43.1%)	23 (46.0%)	22 (42.3%)	20 (40.0%)

Number = Number of patients assessed. This served as the denominator in the % calculated.  
 Source: EFC11072 Part A Clinical Study Report, dated January 16, 2012, Table 8, page 71-73.

APPEARS THIS WAY ON ORIGINAL

Clinical Review  
Reviewer: Suzette Peng, MD  
NME/BLA 761037  
Sarilumab/Kevzara

**Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)**

As with the baseline patient characteristics, the baseline disease characteristics were consistent across treatment arms. The mean duration of RA for all subjects was 7.81 years. The majority of subjects were seropositive (rheumatoid factor and anti-CCP antibody) with 15-20 swollen joints and 25-30 tender joints, thus, moderate to severe disease. Table 8 describes the baseline disease characteristics of subjects in this study.

APPEARS THIS WAY ON ORIGINAL

**Table 8. Disease Characteristics at Baseline in Study EFC11072 Part A**

	Placebo (N=52)	Sarilumab				
		100mg q2w (N=51)	150mg q2w (N=51)	100mg qw (N=50)	200mg q2w (N=52)	150mg qw (N=50)
<b>Duration of RA (years)</b>						
Number	52	51	51	50	52	50
Mean (SD)	8.07 (8.62)	9.76 (9.08)	7.74 (7.20)	8.07 (8.68)	5.95 (6.18)	7.30 (6.18)
Median	4.92	7.36	5.50	5.36	4.10	4.29
Min: Max	0.4: 43.3	0.6: 36.9	0.4: 28.9	0.3: 38.1	0.4: 33.1	0.5: 38.7
<b>RA functional class [n(%)]</b>						
Number	52	51	51	50	52	50
I	3 (5.8%)	2 (3.9%)	4 (7.8%)	2 (4.0%)	8 (15.4%)	0
II	37 (71.2%)	35 (68.6%)	36 (70.6%)	31 (62.0%)	34 (65.4%)	42 (84.0%)
III	12 (23.1%)	14 (27.5%)	11 (21.6%)	17 (34.0%)	10 (19.2%)	8 (16.0%)
IV	0	0	0	0	0	0
<b>Prior biologic use [n(%)]</b>						
Number	52	51	51	50	52	50
Yes	12 (23.1%)	13 (25.5%)	12 (23.5%)	12 (24.0%)	14 (26.9%)	12 (24.0%)
No	40 (76.9%)	38 (74.5%)	39 (76.5%)	38 (76.0%)	38 (73.1%)	38 (76.0%)
<b>Rheumatoid factor [n(%)]</b>						
Number	52	51	51	50	52	50
Positive	35 (67.3%)	52 (82.4%)	44 (86.3%)	35 (70.0%)	44 (86.3%)	43 (86.0%)
Negative	17 (32.7%)	9 (17.6%)	7 (13.7%)	15 (30.0%)	7 (13.7%)	7 (14.0%)
<b>Anti-CCP antibody [n(%)]</b>						
Number	22	20	22	20	23	21
Positive	16 (72.7%)	16 (80.0%)	21 (95.5%)	14 (70.0%)	20 (87.0%)	18 (85.7%)
Negative	6 (27.3%)	4 (20.0%)	1 (4.5%)	6 (30.0%)	3 (13.0%)	3 (14.3%)
<b>Number of prior DMARD [n(%)]</b>						
Number	52	51	51	50	52	50
None	51 (98.1%)	49 (96.1%)	45 (88.2%)	45 (90.0%)	48 (92.3%)	46 (92.0%)

Clinical Review  
 Reviewer: Suzette Peng, MD  
 NME/BLA 761037  
 Sarilumab/Kevzara

1	0	1 (2.0%)	3 (5.9%)	4 (8.0%)	4 (7.7%)	3 (6.0%)
2	1 (1.9%)	1 (2.0%)	3 (5.9%)	1 (2.0%)	0	1 (2.0%)
≥ 3	0	0	0	0	0	0
<b>Smoking history [n(%)]</b>						
Number	52	51	51	52	50	49
Yes	14 (26.9%)	14 (27.5%)	16 (31.4%)	18 (36.0%)	17 (32.7%)	17 (34.0%)
No	38 (73.1%)	37 (72.5%)	35 (68.6%)	32 (64.0%)	35 (67.3%)	33 (66.0%)
<b>Alcohol use [n(%)]</b>						
Number	52	50	51	49	52	49
Yes	9 (17.3%)	12 (24.0%)	15 (29.4%)	13 (26.5%)	8 (15.4%)	11 (22.4%)
No	43 (82.7%)	38 (76.0%)	36 (70.6%)	36 (73.5%)	44 (84.6%)	38 (77.6%)
<b>Tender joint count (0-68)</b>						
Number	52	51	51	50	52	50
Mean (SD)	27.09 (16.12)	30.31 (14.68)	26.94 (16.79)	29.12 (15.36)	25.52 (14.21)	25.36 (11.97)
Median	21.50	28.00	21.00	26.50	20.50	23.50
Min: Max	6.0: 64.0	10.0: 66.0	8.0: 68.0	5.0: 68.0	8.0: 62.0	8.0: 50.0
<b>Swollen joint count (0-66)</b>						
Number	52	51	51	50	52	50
Mean (SD)	17.45 (11.68)	19.53 (9.46)	17.59 (10.60)	16.76 (9.05)	16.63 (8.94)	16.29 (8.33)
Median	14.00	18.00	14.00	14.50	12.50	13.50
Min: Max	6.0: 56.0	6.0: 39.0	6.0: 54.0	5.0: 45.0	6.0: 41.0	7.0: 44.0
<b>Patient global VAS (0-100)</b>						
Number	52	51	51	50	52	50
Mean (SD)	66.23 (19.51)	69.18 (20.65)	66.10 (19.41)	68.26 (18.76)	66.92 (19.49)	68.54 (19.14)
Median	67.50	74.00	70.00	68.50	66.50	70.00
Min: Max	7.0: 98.0	24.0: 100.0	12.0: 98.0	15.0: 100.0	10.0: 100.0	26.0: 100.0
<b>Physician global VAS (0-100)</b>						
Number	52	51	51	50	52	50
Mean (SD)	62.73 (17.24)	68.57 (17.85)	63.25 (19.86)	61.78 (16.48)	63.31 (14.71)	67.30 (14.80)
Median	63.00	71.00	64.00	61.50	64.00	66.50

Clinical Review  
 Reviewer: Suzette Peng, MD  
 NME/BLA 761037  
 Sarilumab/Kevzara

Min: Max	27.0: 94.0	25.0: 95.0	8.0: 100.0	24.0: 98.0	20.0: 92.0	35.0: 96.0
<b>Pain VAS (0-100)</b>						
Number	52	51	51	50	52	50
Mean (SD)	64.92 (21.78)	68.45 (21.90)	67.86 (19.83)	69.12 (20.54)	66.56 (19.86)	67.58 (21.33)
Median	70.00	70.00	71.00	72.00	67.50	72.00
Min: Max	4.0: 99.0	18.0: 100.0	12.0: 98.0	6.0: 100.0	10.0: 100.0	21.0: 98.0
<b>CRP (mg/dL)</b>						
Number	52	51	51	50	52	50
Mean (SD)	2.97 (2.78)	2.69 (2.62)	2.75 (2.79)	2.57 (3.00)	3.23 (4.15)	2.47 (2.09)
Median	2.18	1.98	1.76	1.70	1.90	1.71
Min: Max	0.2: 14.4	0.1: 13.9	0.0: 13.0	0.1: 17.3	0.0: 21.8	0.1: 8.7
<b>CRP group [n(%)]</b>						
Number	52	51	51	50	52	50
≤ 1.5 mg/dL	18 (34.6%)	20 (39.2%)	22 (43.1%)	20 (40.0%)	18 (34.6%)	20 (40.0%)
> 1.5 mg/dL	34 (65.4%)	31 (60.8%)	29 (56.9%)	30 (60.0%)	34 (65.4%)	30 (60.0%)
<b>HAQ-DI</b>						
Number	52	51	51	50	52	50
Mean (SD)	1.57 (0.57)	1.67 (0.60)	1.54 (0.73)	1.69 (0.58)	1.50 (0.57)	1.59 (0.62)
Median	1.50	1.50	1.63	1.56	1.50	1.63
Min: Max	0.5: 2.9	0.6: 2.9	0.0: 3.0	0.4: 3.0	0.0: 2.8	0.1: 2.9
<b>DAS28</b>						
Number	52	51	51	50	52	50
Mean (SD)	6.08 (0.86)	6.28 (0.92)	6.11 (0.91)	6.05 (0.79)	6.06 (0.90)	6.07 (0.65)
Median	5.99	6.25	6.03	6.10	5.85	6.07
Min: Max	4.1: 7.9	4.8: 8.0	4.4: 8.1	4.0: 8.0	4.4: 8.1	4.8: 8.1

Number = Number of patients assessed. This served as the denominator in the % calculated.  
 Source: EFC11072 Part A Clinical Study Report, dated January 16, 2012, Table 9, page 75-80.

### **Treatment Compliance, Concomitant Medications, and Rescue Medication Use**

Study treatment compliance was ascertained from records of medication treatment packs and/or diaries. The mean compliance for the safety population was high and ranged from 96.59% for the 100mg qw group to 99.7% for the 100mg q2w group. As previously noted, five subjects (all in sarilumab arms: 150mg q2w [n=1], 100mg qw [n=3], 150mg qw [n=1]) were <80% compliant; all of these subjects suffered adverse events (mostly, neutropenia), which resulted in the decreased compliance.

Subjects did receive concomitant therapy for their arthritis. As required in the protocol, all subjects received methotrexate. With the MTX use, 94-100% of subjects also took folic acid, as it was required “according to local regulations.” The most common corticosteroids used were prednisone and methylprednisolone. The range of use of prednisone was 15.4% in the placebo group up to 32.0% in the 100mg q2 group; methylprednisolone use ranged from 11.8% in the 100mg q2w group to 31.4% in the 150mg q2w group. The other types of steroids were used much less frequently. One subject in the placebo group did receive “concomitant” infliximab, as it was administered 2 weeks after the last dose of IMP.

Other concomitant medications are not reviewed here. A discussion of statin use/initiation is found in the safety section on lipid elevations (Section 8.5.2).

APPEARS THIS WAY ON ORIGINAL

Clinical Review  
Reviewer: Suzette Peng, MD  
NME/BLA 761037  
Sarilumab/Kevzara

### **Efficacy Results – Primary Endpoint**

*Reviewer Comment: The efficacy discussion for study EFC11072 Part A is limited, as this is a phase 2 study. My intention is to present the primary efficacy endpoint and a few secondary endpoints. However, the purpose of the efficacy presentation is to reflect on how Sanofi utilized this data to choose the doses that were carried forward in the pivotal studies (EFC11072 Part B and EFC10832).*

The primary objective of this study was to demonstrate that sarilumab with concomitant MTX is effective for the reduction of signs and symptoms of RA at 12 weeks. Therefore, the primary efficacy endpoint was the proportion of subjects who achieved ACR20 at 12 weeks.

Table 9 presents the incidence of ACR20 response after 12 weeks. The proportion of responders was numerically higher in all the sarilumab groups compared to placebo: 46.2% in placebo vs. 49.0% in 100mg q2w group, 66.7% in 150mg q2w group, 62.0% in 100mg q2 group, 65.4% in 200mg q2w group, and 72.0% in 150mg q2 group. However, the difference was not statistically significant for the 100mg q2w group. Utilizing the Hommel-adjusted p-value, only the 150mg q2 group had a statistically higher proportion of responders.

APPEARS THIS WAY ON ORIGINAL

Clinical Review  
 Reviewer: Suzette Peng, MD  
 NME/BLA 761037  
 Sarilumab/Kevzara

**Table 9. ACR20 Response at Week 12 in Study EFC11072 Part A**

ACR20 at Week 12 n (%)	Placebo (N=52)	Sarilumab				
		100mg q2w (N=51)	150mg q2w (N=51)	100mg qw (N=50)	200mg q2w (N=52)	150mg qw (N=50)
Responders	24 (46.2%)	25 (49.0%)	34 (66.7%)	31 (62.0%)	34 (65.4%)	36 (72.0%)
Non-responders	28 (53.8%)	26 (51.0%)	17 (33.3%)	19 (38.0%)	18 (34.6%)	14 (28.0%)
P-value vs. placebo [1]	-	0.7119	0.0363	0.1155	0.0426	0.0041
OR, CI vs. placebo [2]	-	1.17 (0.52, 2.61)	2.38 (1.06, 5.35)	1.99 (0.85, 4.64)	2.34 (1.03, 5.29)	3.84 (1.53, 9.63)
Hommel-adjusted p-value	-	0.7119	0.1090	0.2311	0.1277	0.0203

LOCF used for all seven ACR components.

Patients are considered non-responders from the time they discontinued study medication due to lack of efficacy.

Note: % calculated using the number of ITT patients in the corresponding treatment group as the denominator.

[1] CMH test stratified by prior biologic use and region

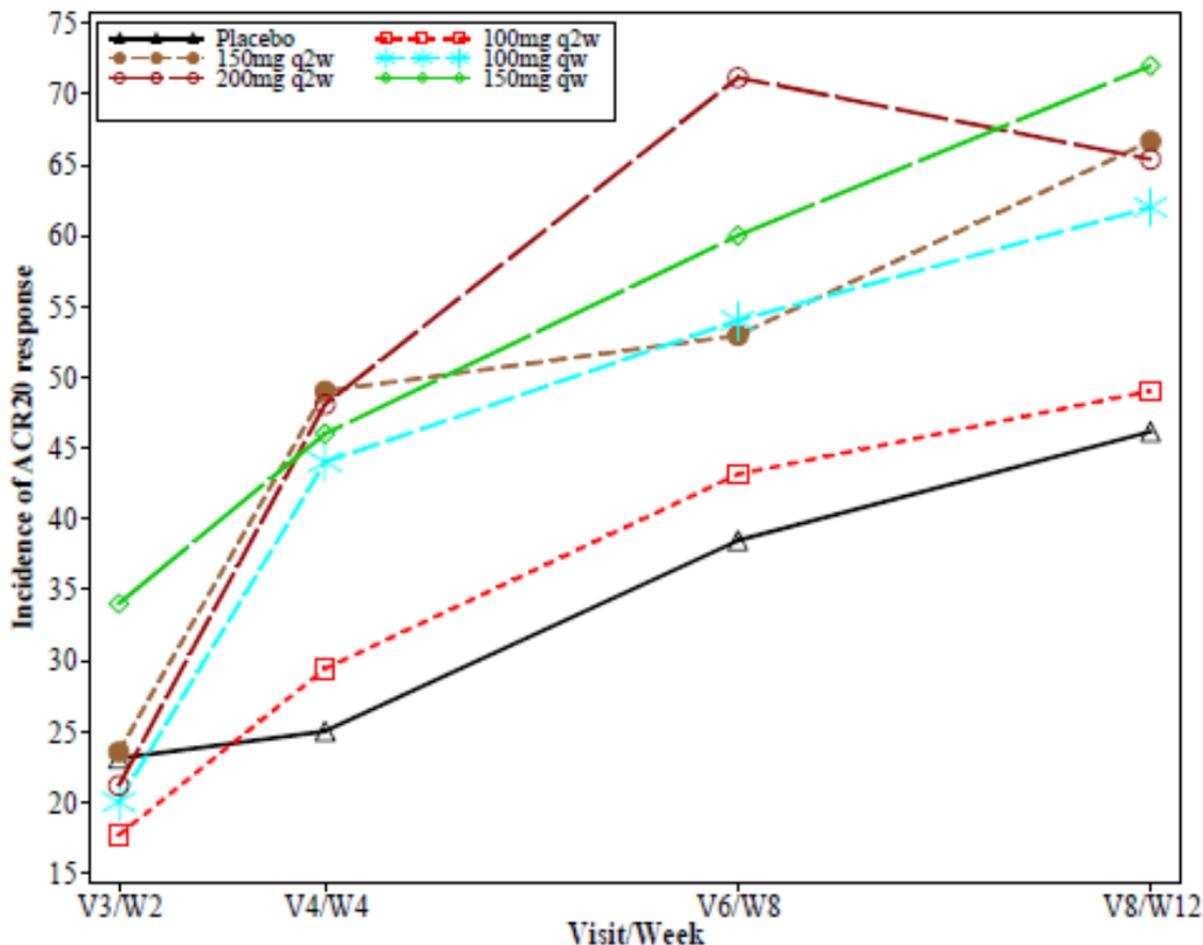
[2] Mantel-Haenszel estimate

Source: EFC11072 Part A Clinical Study Report, dated January 16, 2012, Table 16, page 91.

APPEARS THIS WAY ON ORIGINAL

It was also noted that the incidence of ACR20 response increased at each visit, as displayed in Figure 3. All treatment arms, including placebo, had a greater proportion of responders at each visit. It should be noted, however, that the proportion of responders in the 200mg q2w arm did decrease between Weeks 8 and 12.

**Figure 3. Incidence of ACR20 Response at Each Visit (EFC11072 Part A)**



Source: EFC11072 Part A Clinical Study Report, dated January 16, 2012, Figure 2, page 97.

In conclusion, with regards to the primary endpoint, all doses, except for the lowest studied dose (100mg q2w) appeared to show efficacy in comparison to placebo.

#### **Data Quality and Integrity – Reviewers’ Assessment**

No audits were performed on the case report forms or clinical source data. There were no significant OSI findings that would affect the data or require exclusion of data from any sites. Therefore, the data were felt to be adequate.

Clinical Review  
Reviewer: Suzette Peng, MD  
NME/BLA 761037  
Sarilumab/Kevzara

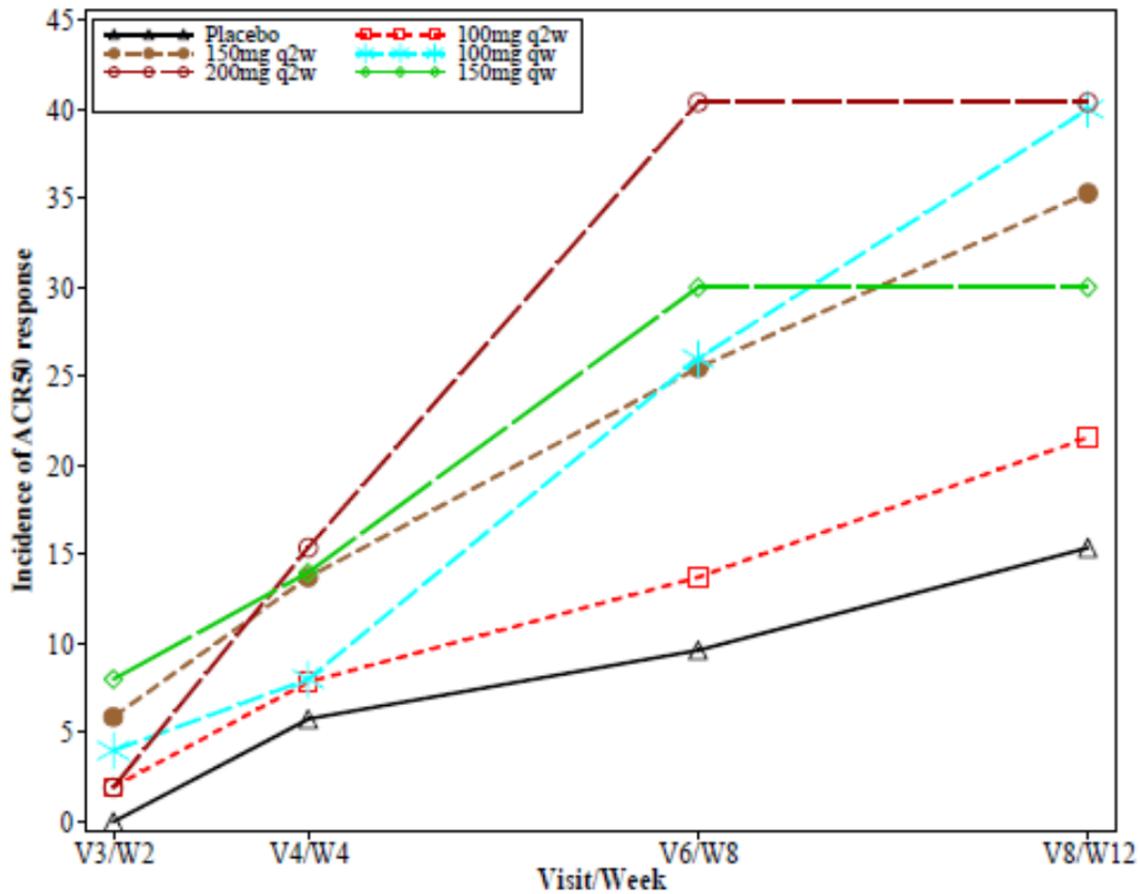
### **Efficacy Results – Secondary and other relevant endpoints**

Multiple secondary endpoints were evaluated at Week 12 to support the primary endpoint. As already described in the study design, the endpoints included ACR50, ACR70, change from baseline in each of the 7 ACR components, change from baseline in DAS28, DAS28 remission, EULAR response (nonresponders vs. responders), and ACRn. As previously noted, the efficacy presentation for this particular study will be brief, as Part A is not one of the studies utilized to support approval. Overall, the secondary endpoints supported the findings of the primary endpoint. Only ACR50 will be presented here.

The placebo group (15.4%) had the smallest proportion of responders at Week 12 in comparison with the other treatment groups: 100mg q2w (21.6%), 150mg q2w (35.3%), 100mg qw (40.0%), 200 mg q2w (40.4%), and 150mg q2 (30.0%). Of these, the results for 100 mg qw ( $p=0.0062$ ) and 200 mg q2w ( $p=0.0038$ ) were considered to be statistically significant with  $p<0.01$  considered statistically significant versus placebo after post-hoc adjustment for multiplicity. As with ACR20, the proportion of ACR50 responders increased with time (Figure 4).

APPEARS THIS WAY ON ORIGINAL

**Figure 4. Incidence of ACR50 Response at Each Visit (Study EFC11072 Part A)**



Source: EFC11072 Part A Clinical Study Report, dated January 16, 2012, Figure 3, page 105.

### Dose/Dose Response

Please see Section 7.1.4 for an overall discussion of dose and dose-response in the sarilumab clinical development program.

### Durability of Response

Durability of response is not discussed for this phase 2 study.

### Persistence of Effect

Persistence of effect is not discussed for this phase 2 study.

### Additional Analyses Conducted on the Individual Trial

Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

No further FDA analyses or Applicant analyses were conducted on this phase 2 study results.

Although the majority of the safety findings are presented in Section 8, which include safety findings from this phase 2 study, a brief summary of the safety findings are presented here, as it is the data from EFC11072 Part A (safety, PK, and efficacy) that led to dose selection.

An overview of adverse events is presented in Table 10. What is notable is that 26 of 28 subjects prematurely discontinued the treatment because of an adverse event in all of the sarilumab treatment arms. The most frequent adverse event leading to discontinuation was neutropenia. Neutropenia was also the most common adverse event reported in the sarilumab arms. Table 11 lists the 3 most common SOCs and PTs in the study. Neutropenia did not occur in the placebo groups, whereas it occurred in all the sarilumab arms. The incidence was higher in the 3 highest dose sarilumab groups compared with the 2 lower dose sarilumab groups.

APPEARS THIS WAY ON ORIGINAL

**Table 10. Overview of Adverse Events in Study EFC11072 Part A**

n (%)	Placebo (N=51)	Sarilumab				
		100mg q2w (N=51)	150mg q2w (N=52)	100mg qw (N=50)	200mg q2w (N=51)	150mg qw (N=50)
Patients with any TEAE	24 (47.1%)	22 (43.1%)	28 (53.8%)	36 (72.0%)	33 (64.7%)	27 (54.0%)
Patients with any SAE	2 (3.9%)	3 (5.9%)	0	3 (6.0%)	0	0
Patients with any TEAE leading to death	0	1 (2.0%)	0	0	0	0
Patients with any TEAE leading to permanent treatment discontinuation	2 (3.9%)	4 (7.8%)	2 (3.8%)	13 (26.0%)	4 (7.8%)	3 (6.0%)

Source: EFC11072 Part A Clinical Study Report, dated January 16, 2012, Table 41, page 159.

**Table 11. Most Common Adverse Events in Study EFC11072 Part A**

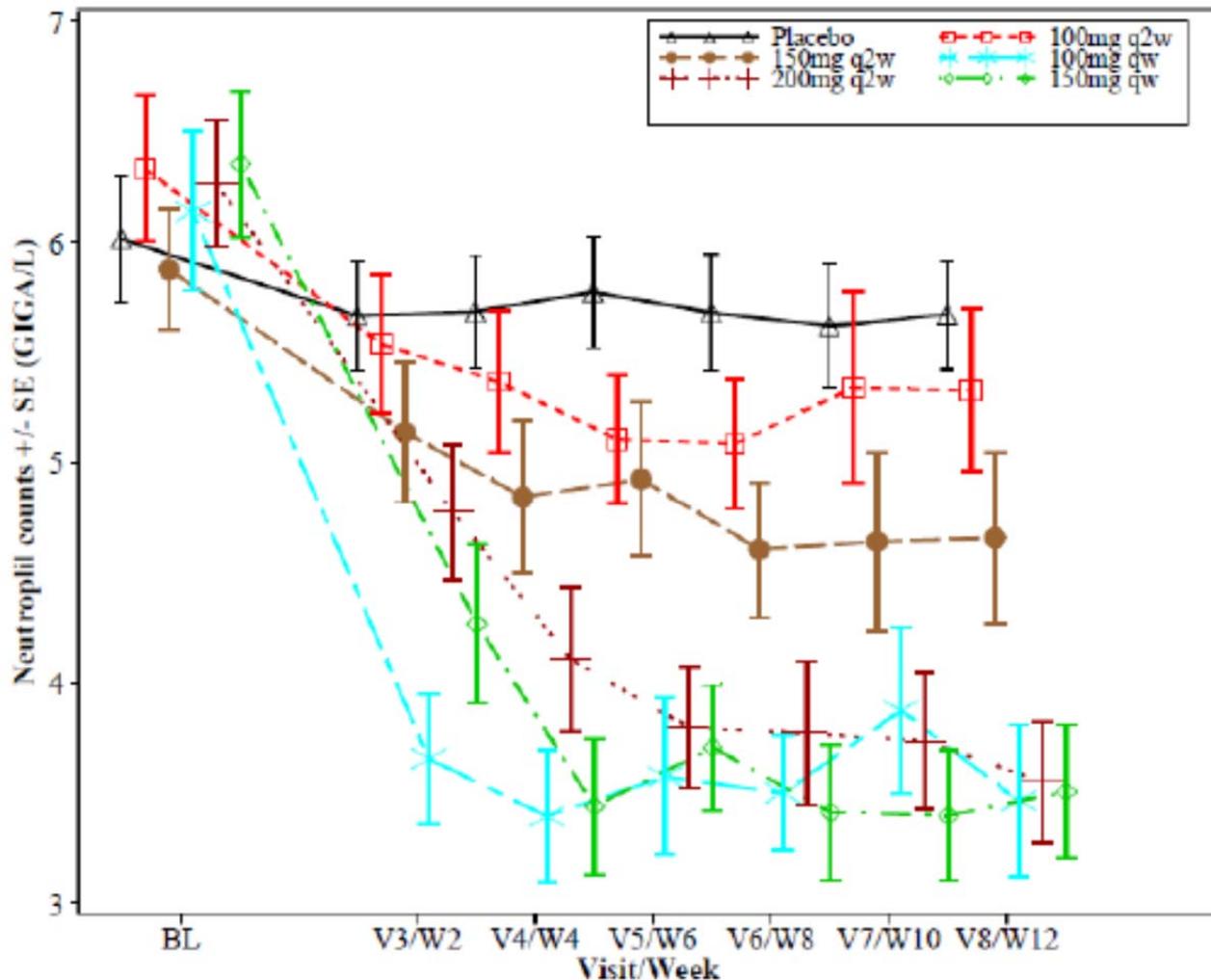
Primary System Organ Class Preferred Term n (%)	Placebo (N=51)	Sarilumab				
		100mg q2w (N=51)	150mg q2w (N=52)	100mg qw (N=50)	200mg q2w (N=51)	150mg qw (N=50)
<b>Infections and infestations</b>	7 (13.7%)	6 (11.8%)	12 (23.1%)	13 (26.0%)	12 (23.5%)	10 (20.0%)
Nasopharyngitis	3 (5.9%)	2 (3.9%)	2 (3.8%)	2 (4.0%)	2 (3.9%)	1 (2.0%)
Upper respiratory tract infection	2 (3.9%)	0	2 (3.8%)	1 (2.0%)	3 (5.9%)	2 (4.0%)
Urinary tract infection	1 (2.0%)	1 (2.0%)	1 (1.9%)	3 (6.0%)	1 (2.0%)	0
<b>Blood and lymphatic system disorders</b>	0	1 (2.0%)	1 (1.9%)	9 (18.0%)	11 (21.6%)	6 (12.0%)
Neutropenia	0	0	1 (1.9%)	7 (14.0%)	10 (19.6%)	5 (10.0%)
<b>Injury, poisoning, and procedural complications</b>	6 (11.8%)	1 (2.0%)	5 (9.6%)	2 (4.0%)	6 (11.8%)	3 (6.0%)
Accidental overdose	5 (9.8%)	1 (2.0%)	3 (5.8%)	2 (4.0%)	2 (3.9%)	3 (6.0%)

n (%) = number and percentage of patients with at least one TEAE

Source: EFC11072 Part A Clinical Study Report, dated January 16, 2012, Table 42, page 161.

To look at neutropenia a little more closely, Figure 5 trends the absolute neutrophil count over time for each treatment arm. Neutrophils decreased in all treatment arms around Week 2. The reduction was greatest in the higher doses of sarilumab (150mg qw > 200mg q2w > 100mg qw > 150mg q2w > 100mg q2w > placebo).

Figure 5. ANC at Each Visit in Study EFC11072 Part A



ANC = absolute neutrophil count  
Source: EFC11072 Part A Clinical Study Report, dated January 16, 2012, Figure 14, page 182.

The applicant utilized the efficacy and safety data in combination with PK and PD data to select the doses. Please see the primary review of the clinical pharmacology team for a full review of the PK/PD data. Briefly, the effect on PD markers (free sIL6R $\alpha$  and CRP levels) and efficacy endpoints (ACR20, ACR50, ACR70, and DAS28-CRP) was evident only at concentrations achieved with doses of 150mg q2w or above. Sanofi noted that a plateau was reached for all endpoints at the sarilumab concentrations for the 200mg q2w dose with higher doses (higher exposures)

Clinical Review  
Reviewer: Suzette Peng, MD  
NME/BLA 761037  
Sarilumab/Kevzara

with a marginal change in response. In evaluating safety, Sanofi noted greater reduction in ANC with increase in sarilumab trough concentration over the doses studied, but this trend toward ANC reduction appeared to plateau at the trough concentration for 200mg q2w. Thus, with analyses of the PK/PD, safety, and efficacy data, Sanofi decided to move forward with 150mg q2w and 200mg q2w in the pivotal trials.

## 6.2. EFC11072 (MOBILITY) Part B

### 6.2.1. Study Design

#### Overview and Objective

Part B was a 52-week, 6-arm study with 2 cohorts, intended to confirm the efficacy and safety of the 2 dose regimens (150mg q2w and 200mg q2w) selected from Part A. It was one of the 2 pivotal trial used to support efficacy of sarilumab for RA.

The primary objective in Part B was to demonstrate that sarilumab added to MTX was effective in reduction of signs and symptoms of RA at Week 24, inhibition of progression of structural damage at Week 52, and improvement in physical function at Week 16. The main secondary objectives in Part B were to demonstrate that sarilumab added to MTX is effective in induction of a major clinical response at Week 52, to assess the safety of sarilumab added to MTX, and to document the PK profile of sarilumab added to MTX in patients with active RA who are inadequate responded to MTX therapy. An exploratory objective was to collect DNA, RNA, and other biomarkers for future use for the purpose of discovery of predictive biomarkers.

#### Trial Design

##### Basic Study Design

As described above, EFC11072 Part B was a 52-week study to confirm the efficacy and safety of the 2 dose regimens selected from Part A. Patients in Part B Cohort 1 were randomly assigned to receive either placebo qw, sarilumab 100mg q2, sarilumab 150mg qw, sarilumab 100mg q2w, sarilumab 150mg q2w, or sarilumab 200mg q2w in a ratio of 1:1:1:1:1:1. Essentially, the dose cohorts were the same as those for Part A. Once the results from Part A were known and the doses for further evaluation in Part B were selected, patients in Cohort 1, who were taking the selected doses of sarilumab (150mg q2w or 200mg q2w) or placebo, continued in the study. After dose selection, blinding in the patients in Cohort 1 who were receiving the selected doses and placebo was maintained. Patients in the “non-selected” sarilumab dose groups in Cohort 1 were discontinued from study EFC11072 and were eligible to enter study LTS11210. Figure 6 illustrates the study design of Part B Cohort 1.

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

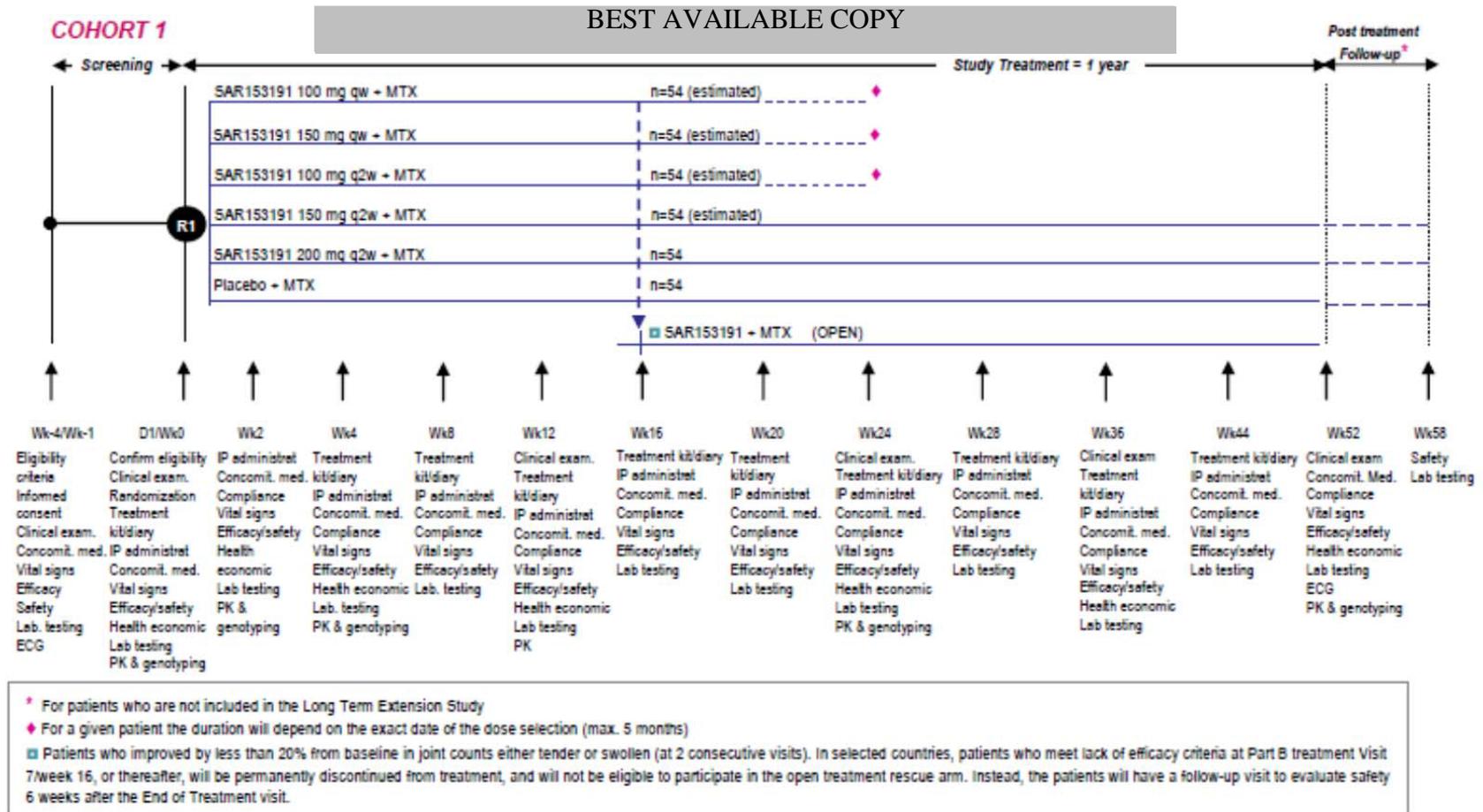
Patients for Part B Cohort 2 were recruited after dose selection from Part A and were randomly assigned to receive either placebo q2w, sarilumab 150mg q2w, or sarilumab 200mg q2w in a ratio of 1:1:1. Patients in Cohort 1 selected doses started receiving injections every other week after IRB/IEC approval was obtained. Starting at Week 16, patients with a lack of efficacy, which was defined as less than 20% improvement compared to baseline in swollen joint counts (SJC) or tender joint count (TJC) for 2 consecutive visits or any other clear lack of efficacy (based on Investigator judgment) could be “rescued” by permitted the patient to take open-label sarilumab at the highest available dose at the time. Thus, open-label sarilumab was administered at 150mg qw until the site was approved to enroll patients in Cohort 2. Once approval was received, subjects were switched to sarilumab 200mg q2w. Rescued patients continued in the study according to their planned visit schedule. Patients with a lack of efficacy, who were not rescued, were discontinued from the study. The maximum duration of the study per patient was 62 weeks (up to 4 weeks for screening, 52 weeks for treatment, and 6 weeks for follow-up). All patients who completed Part B and who were eligible had the opportunity to enter the open-label study LTS11210. Figure 7 illustrates the study design for Part B Cohort 2.

The schedule of assessments for Part B is displayed in Table 140 in the Appendix (Section 13.3).

*Reviewer Comment: EFC11072 is a 2-part study, and then Part B is further divided into 2 cohorts. The applicant has assured that the transition between different parts and different cohorts was “seamless” with maintaining the blind, etc. However, to ensure any introduction of bias, only subjects from Part B Cohort 2 are included in the efficacy analysis.*

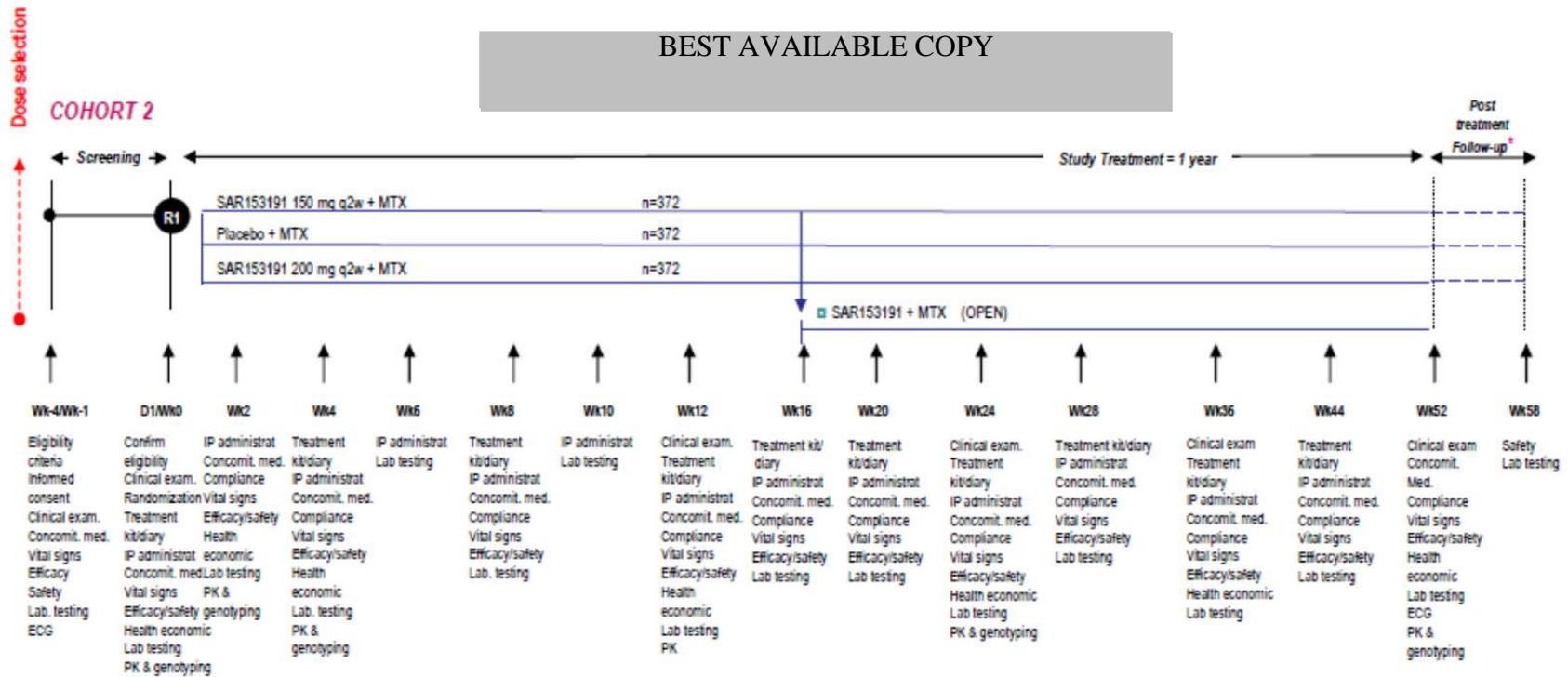
*The focus of my comments here is on Part B. In general, the study design is consistent with that of clinical trials for the RA indication. There is an assessment of signs and symptoms at Week 24, and this is appropriate. However, subjects do have an opportunity to be rescued into open-label sarilumab after Week 16 – which precedes the efficacy assessments at Week 24 and 52. These dosing changes will complicate the analyses both for efficacy and for safety but were agreed upon by the Agency. What is most notable about Part B, however, is that it is a 52-week placebo-controlled study. While patients had the option for rescue therapy for disease activity, they could remain on placebo for up to 52 weeks. Sanofi notes that they chose to use placebo as control given that the RA population has demonstrated a “large and quite variable” placebo response for the primary endpoint (ACR20). Most recent RA studies, however, are only placebo-controlled for 12-24 weeks. Fifty-two weeks of placebo-controlled data will be very informative for both safety and efficacy analyses.*

Figure 6. Study Schema of EFC11072 Part B Cohort 1



Source: EFC11072 Part B Clinical Study Report, Figure 1, page 24.

Figure 7. Study Schema of EFC11072 Part B Cohort 2



Source: EFC11072 Part B Clinical Study Report, Figure 2, page 25.

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

### Key inclusion/exclusion criteria

Overall, the inclusion and exclusion criteria for Part B were the same as those for Part A. There are some additional disease severity criteria for Part B, noted below:

- At least 1 locally documented bone erosion (on x-ray) prior to the first IMP administration  
OR
- Anti-CCP antibody positive according to screening laboratory tests  
OR
- Positive rheumatoid factor according to screening laboratory tests

### Dose selection

The dose regimens selected for Part B were 150mg q2w and 200mg q2w. The doses were selected based on the results from the phase 1 studies and from Part A of this study. As discussed in Section 6.1.2, clinical assessment of the results from Part A concluded that 4 doses (150mg q2w, 200mg q2w, 100mg qw, and 150mg qw) showed efficacy in the RA population. As the frequency of AEs and SAEs was low, there was no clear dose relationship. For some safety analyses (discontinuations due to AEs and reduction in ANC), there did appear to be more events at higher doses. Therefore, based on analysis of the benefit-risk ratio, the lowest dose with efficacy (150mg q2w) and a second dose regimen (200mg q2w) were chosen for evaluation in the pivotal phase 3 studies, which would include this study and EFC10832. In addition, from the perspective of patient convenience, a less frequent injection schedule seemed preferable.

*Reviewer Comment: The results of Part A were previously presented. It was from this data that Sanofi selected the doses for Part B. Sanofi's justification for the doses used is reasonable.*

### Concurrent medications

As noted in the Inclusion Criteria, all subjects were then required to be on a stable dose (10-25 mg/wk) for a minimum of 6 weeks prior to the screening visit and then to continue the stable dose for the duration of the study.

Prohibited medications, such as all conventional DMARDs except for MTX and all other biologics, were the same as those identified in the Exclusion Criteria for Part A (Section 6.1.1). In addition, for Part B, the following prohibited medications/interventions were listed:

- The use of acetaminophen was limited to 4g per 24 hours with even more caution when used with hepatotoxic drugs. The use of acetaminophen was to be avoided within 6 hours prior to assessment of efficacy.
- IL-6 has been shown to reduce CYP1A2, CYP2C9, CYP2C19, and CYP3A4 enzyme expression in in vitro studies, and IL-6 blockade might increase enzyme expression. Therefore, as a precautionary measure, drugs, which are metabolized via these cytochromes and which have a narrow therapeutic index, were adjusted accordingly. The dose of drug was

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

increased to maintain efficacy after sarilumab was initiated and then decreased after sarilumab was stopped.

- Joint replacement was discouraged during the study. However, in the event of medically indicated joint replacement, the patient could continue to participate in the trial unless study treatment was discontinued for >31 days.

### Study treatments

Sanofi provided two pharmaceutical forms of sarilumab in EFC11072 Part B.

- Cohort 1 essentially received the same form of sarilumab as Part A. Sarilumab was provided in amber glass vials in the following strengths: 50 mg/mL, 75 mg/mL, or 100 mg/mL in a 2 mL volume. Cohort 1 used the glass vials until prefilled syringes were available.
- Sarilumab was also provided in prefilled glass syringes with a transparent orange overlay, for both Cohorts 1 and 2, in the following strengths: 131.6 mg/mL or 175 mg/mL in a 1.14 mL volume.

Matching placebo was provided in a 2mL volume when glass vials were used and in a 1.14 mL volume when prefilled syringes were used.

The IMP was administered subcutaneously. As with Part A, the study coordinator or designee administered the first injection comprising the initial dose as part of the training procedure on Day 1 (Visit 2). For doses not given at the study site, diaries were kept as a source data in the patient's study file.

- For patients in Cohort 1, the IMP was to be taken every 7 days. Thus, patients who were randomized to receive sarilumab q2w received alternating injections of sarilumab and placebo. After dose selection from Part A, patients in Cohort 1, who were in the selected treatment groups, were able to take IMP once every 14 days.
- For patients in Cohort 2, the IMP was to be taken every 14 days. However, a time window of  $\pm 3$  days was permitted in exceptional circumstances (e.g., results from repeat labwork or ongoing adverse event). For subsequent IMP administrations, however, the patient needed to return to the schedule set from the initial IMP administration.

### Assignment to treatment

In much of the same way as Part A, all subjects were randomized to one of the treatment group via IVRS. Once IVRS provided a treatment number for a subject, that subject was considered to be officially randomized.

The method of obtaining the patient number through IVRS was the same as that for Part A. Also, similar to Part A, patients in Cohort 1 were randomized 1:1:1:1:1:1 to either placebo or 1 of the 5 treatment arms. Cohort 2 subjects were randomized after dose selection from Part A was completed. Patients in Cohort 2 were randomized 1:1:1 to the 2 active dose regimens of sarilumab and placebo.

Clinical Review  
Reviewer: Suzette Peng, MD  
NME/BLA 761037  
Sarilumab/Kevzara

The treatment assignment was allocated to the patient according to the central randomization list via the IVRS, stratified according to prior biologic use and region. A confirmation fax/e-mail was sent to the site following each assignment. Study drug was recorded and tracked in the center IMP inventory forms. The treatment kit lists were generated by the Biostatistics department of Sanofi-Avenits.

### **Blinding**

The IMPs were supplied in treatment kit boxes that were labeled in accordance with the local regulatory specifications, requirements, content information, dosing instructions, and the precautionary statement for “clinical use only.” The number of treatment kits allocated to the provided sufficient medication until the following clinical visit. The Investigator, hospital pharmacist, or other personnel allowed to store/dispense IMP were responsible for ensuring that the IMP was securely maintained as specified by Sanofi and in accordance with applicable regulatory requirements.

Since CRP and IL-6 levels can be correlated to the dose of sarilumab and served as efficacy variables, the Investigator, Sponsor, and patient were blinded to CRP and IL-6 levels, except for the screening and baseline values. In addition, the complete joint exam (tender and swollen joint counts) was performed by an independent assessor from the Investigator and the patient’s data. Radiographs similarly were de-identified of any patient information and were sent to central readers for calculation of the van de Heijde modified Sharp score (described below).

### **Dose modification/Rescue medication**

As described above, subjects were assessed for lack of efficacy starting at Week 16. Subjects who meet criteria for lack of efficacy could be “rescued” to open-label sarilumab at the highest available dose at the time. Open-label sarilumab was initially administered at 150mg weekly until the doses were selected for phase 3 development. Once the doses were selected and the study site was approved to enroll patients in Cohort 2, patients were switched to sarilumab 200mg q2w.

### **Administrative structure**

Dr. Mark C. Genovese was the Coordinating Investigator for this study. There were a total of 199 sites located in Europe, North America, South America, Asia, Australia, New Zealand, and South Africa. The study employed (b) (4) as a central ECG reader, (b) (4) as a central laboratory and for analysis of serum total sIL-6R $\alpha$ , (b) (4) as a central x-ray reader, (b) (4) as a central laboratory for immunogenicity analyses, and (b) (4) as an interactive voice response system (IVRS) provider.

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

Lastly, the study employed an independent data monitoring committee (DMC) to be in charge of monitoring the safety of patients in this trial. The DMC's role included giving appropriate recommendations to the applicant on safety aspects during the conduct of the study. The DMC consisted of at least 4 members with expertise in areas including rheumatology, hepatology, infectious diseases, and medical statistics. Members of the DMC were independent of those performing the study (i.e., neither investigators nor employees of Sanofi) and, therefore, without conflict of interest regarding the study outcome.

One major change was that, based on the Agency's advice during the EOP2 meeting, Sanofi established an independent Cardiovascular Adjudication Committee (CAC). The CAC was established in protocol amendment 4. The role of the CAC was to apply uniform criteria for the evaluation of cardiovascular events and to adjudicate these events in a consistent and unbiased manner throughout the course of the study. The goal of the CAC was to ensure that all cardiovascular events reported by the site are judged uniformly, using the same criteria by a single group independent of the applicant. The CAC were blinded to treatment allocation.

### **Treatment compliance**

The same measures were taken to ensure treatment compliance in Part B as described in Part A. Additionally, the completed patient injection diary (returned to the site at each visit), returned treatment kit boxes, and any unused prefilled syringes were used for drug accountability purposes.

### **Subject completion, discontinuation, or withdrawal**

Subjects could withdraw and be discontinued from therapy for many of the same reasons as presented in Part A in Section 6.1.1. However, there were some additional criteria and some slight differences.

#### Temporary discontinuation

- In Part A, if temporary discontinuation was  $\geq 28$  days, then the discontinuation was considered to be permanent. However, in Part B, discontinuation for a safety reason was continued to be permanent after  $\geq 31$  days.
- These additional criteria for temporary discontinuation were provided in Part B. Also, temporary discontinuation could occur for any other reason based on Investigator judgment.
  - Increase in ALT  $\geq 3x$  ULN to  $\leq 5x$  ULN and bilirubin  $\leq 2x$  ULN (unless the subject had document Gilbert's disease)
  - Decrease in neutrophil count to a level between  $500/mm^3$  to  $<1000/mm^3$  without signs and symptoms of a potential infection
  - Decrease in platelet count to between  $50,000$  cells/ $mm^3$  to  $<100,000$  cells/ $mm^3$  without spontaneous bleeding

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

- Intercurrent infections requiring oral or parenteral treatment with antibacterial, antiviral, and/or antifungal agents

### Permanent discontinuation

- Criteria for permanent discontinuation were essentially the same as those for Part A. Part B did provide more detailed laboratory criteria.
  - ALT/bilirubin abnormalities
  - Neutrophil  $<500/\text{mm}^3$
  - Neutrophil  $<1000/\text{mm}^3$  with evidence of infection
  - Platelet count  $<50,000/\text{mm}^3$
  - Platelet count  $<100,000/\text{mm}^3$  with evidence of bleeding
  - Acute renal failure
  - Visit 2 labs consistent with any of the exclusion criteria

### **Study Endpoints**

*Reviewer Comment: Efficacy endpoints are listed below. If they were already described in Part A (Section 6.1.1), they will not be described again here.*

#### **Primary Endpoint**

- ACR20 at Week 24
- HAQ-DI at Week 16

*Reviewer Comment: ACR20 is a measure of signs and symptoms, and HAQ-DI is a measure of physical function. Both endpoints have been used in recent RA studies. A measure of ACR20 at Week 24 is appropriate to determine efficacy of a product. However, as noted earlier, the study design does offer an opportunity to escape at Week 16 for subjects who meet criteria for lack of efficacy. This change in dose prior to the primary endpoint complicates analysis. However, for the purpose of statistical analysis, subjects who were rescued were considered non-responders. HAQ-DI assessment at Week 16 is also appropriate and precedes any formal rescue criteria.*

- van der Heijde modified total Sharp score (mTSS) at Week 52

The Sharp method is a composite x-ray scoring system used to quantify structural (joint) disease progression in RA. The method evaluates both joint erosion and joint space narrowing (JSN) in bilateral hand and foot joints with a score ranging from 0 to 448. Thirty-two joints in the hands and 12 joints in the feet are scored for erosions with a maximum score of 5 per joint in the hands and 10 per joint in the feet. Joint space narrowing is graded from 0 to 4 in 30 joints in the hands and in 12 joints in the feet. The principal score used in the analyses is the total score, which is the sum of the erosion score and the joint space narrowing score.

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

Radiographic assessment of joint destruction of the hands and feet was performed using a standard technique. Appropriate positioning of the hand and joints was needed to ensure reproducible projection of the joints with a posteroanterior view for hand radiographs and anteroposterior view for foot radiographs. The left and right sides were clearly identified on the images. Methods were used to avoid over exposure of the film, and high resolution was essential to detect early erosive disease.

All images, either analog or digitalized, had personal patient information removed prior to being shipped to central readers. Analog images were shipped by courier to the central readers where they were digitalized prior to data entry and reading. If a radiograph was not readable, the patient could be requested to return for another image. All x-rays for a given patient were analyzed at the same time. Examination order was randomized to maintain chronological blinding. At least 2 well-trained readers analyzed each electronic image independently and quantified each joint for erosion and JSN. The average of the 2 scores was used for analysis.

Radiographs of both hands and feet were performed at Week 0 (Visit 2) for baseline value. For patients who required central confirmation of erosion at screening, the first evaluation at screening was used as the baseline assessment, replacing the scheduled x-ray at Visit 2. Radiographs were then taken at Week 24 and the EOT visit (i.e., Week 52 or withdrawal) or at time of rescue. Best efforts were made to perform x-ray assessments at the scheduled time points for all patients, including patients who discontinued early from the study. There was to be a window of at least 3 months between x-ray assessments. The primary endpoint was the assessment at Week 52.

*Reviewer Comment: The mTSS score is a radiographic assessment for joint damage. It is an accepted endpoint and has been utilized as support for the labeling claim of inhibition of structural progression. The evaluation of mTSS score at Week 52 against placebo should be an appropriate and informative assessment. As noted earlier, 52-week placebo-controlled data have not been pursued for many recent RA clinical trials.*

## Secondary Endpoints

### • Major Secondary Endpoints

- Maintenance of ACR70 for at least 24 consecutive weeks during the 52-week period

*Reviewer Comment: This endpoint is referred to as “major clinical response” in previous trials for other biologics. It has been included in the label for infliximab, etanercept, adalimumab, abatacept, certolizumab pegol, and tocilizumab.*

### • Other Secondary Efficacy Endpoints

- ACR50 and ACR70 at each visit
- DAS28-CRP at each visit

CDER Clinical Review Template 2015 Edition

Version date: November 5, 2015 for initial rollout (NME/original BLA reviews)

95

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

- EULAR response at Weeks 24 and 52
- DAS28-CRP remission at Weeks 24 and 52
- Time to onset of benefit
  - Time to onset of benefit was defined as the first visit to achieve ACR20, ACR50, or ACR70
- ACRn
  - ACRn was defined as each patient's lowest percent improvement from baseline using 3 measures:
    - TJC
    - SJC
    - Median improved score of the 5 remaining ACR components (physician global VAS, patient global VAS, pain VAS, HAQ-DI, CRP)
- HAQ-DI response over 52 weeks
  - Two definitions were utilized for this assessment.
    - Average of the change in score in HAQ-DI from Week 8 to Week 52 < -0.3 (i.e., achieving an improvement of >0.3 units in the average from change from baseline)
    - Average of the change in score in HAQ-DI from Week 8 to Week 52 < -0.22 (i.e., achieving an improvement of >0.22 units in the average change from baseline)
- Simplified Disease Activity Index (SDAI)
  - The SDAI is an assessment comprised of 5 components.
    - TJC (based on 28 joints)
    - SJC (based on 28 joints)
    - Patient's global disease activity (based on a scale from 0-100mm)
    - Physician's global disease activity (based on a scale from 0-100mm)
    - CRP (mg/dL)
  - The SDAI is a simple numerical summation of these 5 components. The score ranges from 0.1 to 86 with a higher score representing higher disease activity.
  - SDAI remission is defined as SDAI score  $\leq 3.3$
- Clinical Disease Activity Index (CDAI)
  - The CDAI is a composite index comprised of 4 of the 5 SDAI components. The CDAI does not include the laboratory test.
  - The CDAI scores range from 0 to 76, and, similar to the SDAI, a higher score represents greater disease activity.
  - CDAI remission is defined as a CDAI score  $\leq 2.8$ .
- Radiographic progression
  - Radiographic progression of mTSS
    - Radiographic progression of mTSS is defined as a change from baseline in the mTSS > 0. A change from baseline in the mTSS of  $\leq 0$  is

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

considered to be “no progression.” The event of missing a change from baseline value in the mTSS was considered to be progression.

- Radiographic progression of the erosion score (ES)
  - Radiographic progression of the ES is defined as a change from baseline in the ES > 0. Therefore, a change from baseline in the ES of ≤ 0 is considered to be “no progression.” As above, the event of missing a change from baseline value in the ES was considered to be progression.
- Radiographic progression of the joint space narrowing score (JSN)
  - Radiographic progression of JSN score is defined as a change from baseline in the JSN score > 0. A change from baseline in the JSN score of ≤ 0 is considered to be “no progression.” The event of missing a change from baseline value in the JSN score was considered to be progression.

### • Safety Assessments

In general, the safety assessments are similar to those described in Part A, except for the timing of assessment. Table 140 in the Appendix Section 13.3 shows the timing of safety assessment for Part B.

There were, however, a few differences in the adverse events of special interest (AESIs) in Part B. In Part A, AESIs were called AEPs. The following were considered as AESIs in Part B:

- Clinically significant infections
  - Opportunistic infections (systemic opportunistic infections were considered SAEs), including Herpes Zoster infection
  - Infections requiring prolonged (> 14 days) medications, parenteral antibiotics, parenteral antifungals, or parenteral antivirals
  - Tuberculosis or use of anti-tuberculosis medication
  - Parasitic and fungal infections not considered opportunistic infections. For fungal infections, this applied only to systemic and extensive cutaneous cases.
- Anaphylaxis was to be reported as an SAE
- Increased ALT
- Neutropenia (Grade 4 neutropenia lasting more than 5 days was to be reported as an SAE)
- Thrombocytopenia
- Autoimmune or drug-induced lupus-like syndrome
- Demyelinating events (including suspicion of PML) or significant, unexplained neurological symptoms. These patients were to be referred to a neurologist for evaluation. Demyelinating events were to be reported as an SAE.

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

- Gastrointestinal (GI) perforation or ulceration or confirmed diverticulitis. Any perforation was considered serious.
- Specific cardiovascular events and deaths (in addition be reported as SAEs)
  - Myocardial infarction
  - Stroke
  - Hospitalization due to unstable angina
  - Hospitalization due to heart failure
  - Hospitalization due to transient ischemic attack
  - Death (CV and non-CV)

Cardiovascular events were to be evaluated by an independent CAC to adjudicate the events in an unbiased manner.

- Pregnancy
  - Pregnancy that occurred in a female patient was to be recorded as a prespecified adverse event with immediate notification in all cases. It qualified as an SAE only if it fulfilled the SAE criteria.
  - In the event of pregnancy, the IMP was to be discontinued
  - Follow-up of the pregnancy was mandatory until the outcome was determined
- Overdose
  - Per Amendment 4, an overdose with the IMP was an event that was suspected by the Investigator or spontaneously notified by the patient had defined as administration of at least twice the dose during an interval of < 11 days. Prior to Amendment 4, for Cohort 1 patients, an interval of < 6 days was used.
  - An overdose with the non-investigational medicinal product was an event that was suspected by the Investigator or spontaneously notified by the patient and defined as administration of at least twice the intended dose within the intended therapeutic interval.

Lastly, there were a few additional laboratory assessments as listed here:

- Glycosylated hemoglobin (HbA1c) at screening only per exclusion criterion or if clinically indicating during the study
- Anti-nuclear antibody (ANA) at Weeks 0, 24, and the EOT visit

### • **PK, PD, and Immunogenicity Assessments**

Overall, the PK, PD, and immunogenicity variables are the same as the ones detailed for Part A. Again, see Table 140 which charts the schedule of assessments for EFC11072 Part B.

### • **Other Assessments**

- Genotyping and biomarkers

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

Blood and urine samples were collected and stored for the purpose of discovery of biomarkers. For patients who provided consent to participate in the DNA and RNA sequencing that part of the sarilumab predictive medicine program, blood samples were collected according to the schedule in Table 140.

- Quality of life and health economic variables
  - Short Form-36 (SF-36)

The SF-36 score is a generic questionnaire measuring general health status (quality of life) in the last 4 weeks before completing the questionnaire. Per Sanofi, it is one of the most frequently used and has been extensively validated in rheumatologic disease. The SF-36 is a 36 item questionnaire that measures 8 multi-item dimensions of health: physical functioning (10 items), social functioning (2 items), role limitations due to physical problems (4 items), role limitations due to emotional problems (3 items), mental health (5 items), energy/vitality (4 items), pain (2 items), and general health perception (5 items). For each dimension, item scores are coded, summed, and transformed on to a scale from 0 (worst possible health state measured by the questionnaire) to 100 (best possible health state). Two standardized summary scores can also be calculated from the SF-36: the physical component summary (PCS) and the mental health component summary (MCS).
  - Assessment of fatigue

The Functional Assessment of Chronic Illness Therapy Fatigue scale (FACIT-Fatigue) and sleep questionnaire were assessed at baseline and Weeks 2, 4, 12, 24, 36, and 52. The FACIT-Fatigue is a 13-item questionnaire that is rated from 0 to 4. It was developed to measure fatigue in patients with cancer and has also been used for patients with RA. The sleep questionnaire is based on a VAS that assesses pain, as sleep disturbances are linked to pain, mood, and disease activity.
  - Work productivity and activity impairment (WPAI)

The WPAI is assessed by administering a 6-item questionnaire at baseline and Weeks 12 and 52. It measures the percent of work time missed, the percent of impairment while working, overall percent of work impairment, and percent activity impairment due to RA. The scores from the questionnaire are expressed as an impairment percentage with higher numbers indicating greater impairment and decreased productivity.

## Statistical Analysis Plan

**Sample size:** The study power was based on the change in mTSS. The estimate was calculated based on the Wilcoxon/Mann Whitney rank-sum test in the nQuery Advisor 6.01 software.

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

Computations were based on the main scenario of 2 dose regimens selected for Part B Cohort 2. Assuming an  $\alpha$  of 0.025 to address the multiplicity across the 2 active dose regimens, 90% power, a Week 52 mean change of 1.10 and 0.35 in the placebo and active groups, respectively, with an associated standard deviation (SD) of 2.6 and a missing data rate of 15% resulted in a requirement of 372 patients per group. The assumed mean changes and SD were based on results from the tocilizumab program (Tocilizumab safety and THE prevention of structural joint damage, aka, the LITHE study). The tocilizumab program utilized the Genant scores rather than the van der Heijde Sharp scores. Despite the difference in radiographic scoring systems, Sanofi noted that the effect size was generally similar between the scales, so the total sample size remained unchanged.

- The sample size of 372 per group provided >99% power for ACR20.
- The sample size of 372 per group provides 98% power for the change in HAQ-DI.
- The sample size of 372 per group provides a 76% and 97% for major clinical response (ACR70 for at least 24 consecutive weeks) based on the 4% and 8% major response rates in the tocilizumab 4mg and 8mg doses, respectively, from the LITHE study.

### **Analysis populations:**

- The randomized population included any patient who had signed informed consent for Part B and had been allocated to a randomized treatment for Part B regardless of whether the treatment kit was used or not.
- The ITT population consisted of patients in the randomized population who were analyzed according to the treatment group to which they were allocated by randomization.
  - Part B Cohort 1 ITT included all randomized patients in Part B Cohort 1.
  - Part B Cohort 2 ITT included all randomized patients in Part B Cohort 2.
  - Part B Cohort 2 + 1 selected doses ITT included patients randomized to the selected Phase 3 dose regimens in Part B Cohort 1 and all randomized patients in Part B Cohort 2.
- The safety population consisted of patients in the randomized population who received at least 1 dose or a partial dose of IMP, analyzed according to the treatment actually received. For patients who received IMP from more than 1 treatment group during the study, the treatment group allocation for the as-treated analysis was the lowest dose of the active treatment group taken.
  - Part B Cohort 1 safety population included all randomized patients in Part B Cohort 1 who were exposed to IMP.
  - Part B Cohort 2 safety population included all randomized patients in Part B Cohort 2 who were exposed to IMP.
  - Part B Cohort 2 + Cohort 1 selected doses safety population included patients randomized to the selected Phase 3 dose regimens in Part B Cohort 1 and all randomized patients in Part B Cohort 2 who were exposed to IMP.
- The PK population of Part B Cohort 1, Part B Cohort 2, and Part B Cohort 2 + Cohort 1 selected doses consisted of all patients in the corresponding safety population who had at

Clinical Review  
Reviewer: Suzette Peng, MD  
NME/BLA 761037  
Sarilumab/Kevzara

least 1 post-dose, non-missing serum concentration value. Patients were analyzed according to the treatment actually received

**Demographics and baseline characteristics:** Patient characteristics, including demographics, medical history, and subject accountability were summarized by treatment and overall for the ITT population. The summaries were done using descriptive statistics, such as mean, SD, median, etc. The safety and PK populations were based on the treatment received, and the ITT population was based on randomized treatment group.

**Prior and concomitant medications:** The prior and concomitant medications were presented based on randomized population. Medications were summarized by treatment group according to the World Health Organization-Drug Dictionary (WHO-DD). The Anatomical Therapeutic Chemical (ATC) classification is an integral part of the WHO-DD. All ATC codes corresponding to a medication were summarized. In addition, previous medications for the treatment of RA were summarized for the ITT population for each treatment group.

**Extent of investigational medicinal product (IMP) exposure and compliance:**

The extent of IMP exposure and compliance were assessed and were summarized by the duration of IMP exposure and actual dose information.

- For Part B Cohort 1 patients, if the treatment regimen of the last dose was every week, the duration of exposure was defined as the following:  $[Last\ dose\ date] - [First\ dose\ date] + 7\ days$
- For Part B Cohort 1 patients, if the treatment regimen of the last dose was every other week, the duration of exposure was defined as the following:  $[Last\ dose\ date] - [First\ dose\ date] + 14\ days$
- Duration of exposure for Part B Cohort 2 patients was defined the same as Part B Cohort 1 patients who was dosed every other week.

Temporary IMP discontinuation was ignored in the above calculations. The duration of exposure was summarized for each treatment group using descriptive statistics. Additionally, the number and percentage of patients randomized and exposed to the double-blind IMP were presented by specific time period for each treatment group.

In regards to compliance, a given administration was considered to be non-compliant if the patient did not take the planned dose of IMP as required in the protocol. No imputation was made for patients with missing or incomplete data. Percentage of compliance for a patient was defined as the number of administrations the patient was compliant divided by the total number of administrations the patient was planned to take on or before the last dose date during the double-blind treatment period. Treatment compliance percentages were summarized descriptively as quantitative variables. The percentage of patients whose compliance was <80% were summarized.

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

Overdose was defined for each of the treatment populations. For Part B Cohort 1 patients on non-selected doses, overdose was administration of 2 or more doses in less than 6 calendar days for every week dose regimen. For Part B Cohort 1 patients who continued the study (that is, switching to every other week dosing), overdose was administration of 2 or more doses in less than 11 calendar days for every other week dose regimen. The definition of overdose was the same for Part B Cohort 2 patients.

**Analysis of efficacy endpoints:** Each dose of sarilumab (150mg q2w and 200mg q2w) was tested versus placebo; thus, each individual null hypothesis was that there was no difference from placebo in terms of the co-primary efficacy or the main secondary endpoints. The co-primary efficacy variables were ACR20 response at Week 24, change from baseline in HAQ-DI at Week 16, and change from baseline in the mTSS at Week 52. The main secondary variable was the event of achieving major clinical response during the 52-week period.

*Reviewer Comment: In actuality, given the analyses, ACR20 response at Week 24 was the primary endpoint. Change from baseline in HAQ-DI at Week 16 and change from baseline in mTSS at Week 52 should be considered key secondary endpoints. This was based on the statistical analysis, particularly, a hierarchal testing procedure for these endpoints. The hierarchy will be discussed in more detail below.*

*An overview of the SAP for the primary and key secondary endpoints will be presented below. This overview is based on the review by Dr. Yongman Kim (primary reviewer for the statistical team).*

### 1. ACR20 response at Week 24

The binary ACR20 response at Week 24 was analyzed with a 2-sided Cochran-Mantel-Haenszel (CMH) test stratified by prior biologic use and region. Separate pairwise comparisons of the response rates between each dose regimen of sarilumab and placebo were derived. The Mantel-Haenszel (MH) estimate of the odds ratio and the corresponding 95% confidence interval (CI) were derived by testing each active dose group versus placebo separately.

In the primary approach, data collected after treatment discontinuation or rescue was set to missing. No imputation of missing post-baseline values was performed. Responder status was determined if possible. With these rules, patients automatically became non-responders for all time points beyond the time point they started rescue treatment or discontinued study treatment. Rescue medications included open-label sarilumab (200mg q2w) or any other non-study rescue medication such as glucocorticoids (intra-articular, intramuscular, >10 mg of oral prednisone), new biologic, or new DMARD (other than MTX).

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

*Reviewer Comment: The statistical team noted that this primary endpoint should really be considered a composite endpoint defined by the following: (1) not receiving rescue (generally by achieving at least 20% improvement in swollen and tender joint counts at Week 16), (2) remaining on treatment and in the study through the time point of interest (Week 24), and (3) achieving a response in the outcome of interest at the timepoint of interest (ACR20 at Week 24).*

**Sensitivity analysis:** The data collected after treatment discontinuation or rescue were set to missing. Then, a last observation carried forward (LOCF) procedure from the point of treatment discontinuation or rescue was applied to impute missing data for all seven ACR components for all visits post that point. Responder status was determined using the imputed data.

*Reviewer Comment: The statistical team did not agree with this approach. The LOCF analysis was considered inappropriate since it is based on strong and unverifiable assumptions about the missing data mechanism. Also, as a single imputation approach, it does not take into account the uncertainty in the imputation process. Therefore, Dr. Kim conducted an intent-to-treat analysis with post-escape observed data and non-responder imputation for dropouts to evaluate an ITT or de facto estimand, i.e., the difference in outcomes in all randomized patients regardless of adherence or use of ancillary therapies. Of note, Dr. Kim performed similar sensitivity analyses incorporating observed post-escape data for secondary endpoints. Additionally, the statistical team had some concerns about the handling of non-responders at Week 16 and requested additional sensitivity analyses including tipping point analyses for the primary endpoint. These analyses were submitted by Sanofi as a response to the statistical team's IR.*

**Subgroup analyses:** Subgroup analyses were conducted with respect to the following subgroups in the ITT population: gender (male vs. female), race (Caucasian vs. other), region (Western countries, South America, rest of the world), age (<65, ≥65 and <75, ≥75 years), baseline weight (<50, ≥50 and <100, ≥100 kg), BMI (<25, ≥25 and <30, ≥30 kg/m<sup>2</sup>), prior biologic use (yes vs. no), rheumatoid factor (positive, negative), anti-CCP antibody (positive, negative), baseline CRP (≤1.5 mg/dL, >1.5 mg/dL), duration of RA (≤median, >median in years), duration of RA (≤3 years, >3 years), number of prior DMARDs (none, 1, 2, ≥3), smoking history (yes, no). Descriptive statistics including number (n) and incidence of response by subgroup were provided for each treatment group.

### 2. Change from baseline in HAQ-DI at Week 16

The continuous HAQ-DI change from baseline at Week 16 was analyzed with a mixed model for repeated measures (MMRM). The repeated-measure analysis was based on the restricted maximum likelihood method assuming an unstructured covariance structure to model the within-subject errors. The model, including treatment, region, prior biologic use, visit (Weeks 2-16), and treatment-by-visit interaction as fixed effects and baseline as covariate, was used to test the difference between each active treatment group versus

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

placebo in the change from baseline in HAQ-DI at Week 16. The data collected after treatment discontinuation or rescue were set to missing. Therefore, the MMRM analysis assumed a missing-at-random (MAR) mechanism for missing data due to dropout and post-rescue data.

Sensitivity analysis: Data collected after treatment discontinuation or rescue were set to missing, and an LOCF procedure from the point of treatment discontinuation or rescue was used to impute any missing HAQ-DI values for all visits after that point. The change from baseline in HAQ-DI at Week 16 was assessed by fitting an ANCOVA model with the baseline covariate and factors for treatment, region, and prior biologic use.

*Reviewer Comment: Since the statistical team did not consider the LOCF analysis to be useful, Dr.Kim conducted continuous responder analysis using available post-rescue data with missing data due to dropout considered as worst outcomes.*

Subgroup analysis: Under the MMRM approach, descriptive statistics, including number of subjects, mean, standard error, and LS means for the change from baseline in HAQ-DI at Week 16 are provided by subgroup for each treatment group.

### 3. Change from baseline in the mTSS at Week 52

The van der Heijde modified Total Sharp Score (mTSS) change from baseline at Week 52 was analyzed with a 2-sided rank-based analysis of covariance (rank ANCOVA) model adjusted for baseline, prior biologic use, and region. The linear extrapolation method was the primary method used to impute missing or post-rescue Week 52 mTSS, erosion score, or joint space narrowing score. The data collected after treatment discontinuation + 14 days or rescue + 14 days were set to missing before linear extrapolation.

Sensitivity analysis: The sensitivity approaches to handle the missing or post-rescue Week 52 mTSS included the following approaches.

- Approach 1 – Mean rank imputation
- Approach 2 – LOCF with data post-treatment discontinuation or rescue + 14 days set to missing and imputed by LOCF
- Approach 3 – As observed cases (excluding post-treatment discontinuation or rescue data)
- Approach 4 – Observed cases (including post-treatment discontinuation or rescue data)
- Approach 5 – Linear extrapolation including both post-treatment discontinuation and rescue data

*Reviewer Comment: In addition to the above sensitivity analyses, Dr.Kim conducted an analysis using all observed data, including available post-rescue data, to evaluate at mTSS at Week 24 rather than Week 52. The statistical team noted that there were less missing data and rescue at*

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

*this earlier time point, and 24 weeks still might be a sufficient treatment duration to assess radiographic progression of structural damage.*

**Subgroup analysis:** Subgroup analyses of the change from baseline in the mTSS at Week 52 were also conducted. For each subgroup, the change from baseline in mTSS at Week 52 was analyzed by fitting a 2-sided rank ANCOVA model adjusted for baseline. Descriptive statistics were provided for each treatment group. In addition, pairwise comparisons of the residuals between each dose of sarilumab and placebo were derived by testing each active dose group versus placebo separately.

#### 4. Incidence of major clinical response during the 52-week period

Major clinical response was defined as the event of achieving ACR70 for at least 24 consecutive weeks during the 52-week period. A 2-sided CMH test stratified by prior biologic use and region was used to assess treatment differences in major clinical response. A patient that did not achieve a major clinical response was considered a non-responder. Pairwise comparisons of the response rates between each dose of sarilumab and placebo were derived by testing each active dose group versus placebo separately. The MH estimate of the odds ratio and the corresponding 95% CI were derived by testing each active dose group versus placebo separately.

**Sensitivity analysis:** The sensitivity analysis of the major clinical response was similar to the primary analysis, except that a 2-sided CMH test without stratification was used to assess treatment differences.

The other secondary endpoints are described above under “Efficacy Assessments.” The SAP for these variables will not be described in detail here.

The primary and key secondary efficacy endpoints were tested for each sarilumab dose versus placebo in a testing strategy designed to protect the family-wise type I error rate at  $\alpha=5\%$  (two-sided). The applicant proposed a hierarchal testing procedure with a Bonferroni correction to adjust for the multiple doses and endpoints. Thus, a hierarchical testing procedure was used for the multiple endpoints at  $\alpha=0.025$  for each dose regimen separately. The testing hierarchy was the following:

1. Incidence of ACR20 response at Week 24
2. Change from baseline in HAQ-DI at Week 16
3. Change from baseline in the mTSS at Week 52
4. Incidence of achieving major clinical response during the 52-week period

**Analyses of safety data:** Safety analyses were based on the reported AEs, clinical laboratory evaluations, vital signs, and 12-lead ECGs. A more detailed description of the analyses of safety is located in Section 8. Additionally, many of the analyses were the same as that for Part A in Section 6.1.1 above. However, a brief overview is presented here.

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

Adverse events (AEs) were coded using MedDRA, Version 16.0. AEs were classified according to chronological criteria into pretreatment adverse events and “treatment emergent” AEs (TEAEs). The analyses of AEs focused on the TEAEs. In my review, these terms are used interchangeably. The table of incidence of TEAEs was presented by SOC and PT sorted in alphabetical order for each treatment group, the number (n) and percentage (%) of patients experiencing a TEAE. The denominator for computing percentages was the safety population within each treatment group. In addition, the number of TEAEs per 100 patient-years (i.e., number of events adjusted for total duration of exposure) were summarized. For each type of AESI, the number of patients with the AESI per 100 patient-years (number of patients adjusted for the exposure up to the first event or up to the end of duration of exposure for subjects with no event) were also summarized.

Deaths were described by the number (%) of patients who died by study period (on study, on treatment, or post-rescue). Additionally, deaths were summarized by TEAEs and Post-Rescue AEs leading to death, by primary SOC, HLGT, HLT, and PT. SAEs and AEs leading to permanent discontinuation were also summarized by treatment group and primary SOC, HLGT, HLT, and PT. The AEs of special interest (AESI) were flagged using specific search criteria. These search criteria are described in the safety section of this review (Section 8.3.2).

For laboratory, vital signs, and ECG evaluations, Sanofi utilized the term “potentially clinically significant abnormalities” (PCSAs) to define abnormal values considered medically important according to predefined criteria/thresholds based on literature review. The same PCSA values were used consistently for the sarilumab clinical program. Therefore, the number and percentage of patients with at least 1 PCSA during the time from the first dose injection of the double-blind study drug to the end of the follow-up period after the last dose injection of double-blind IMP were summarized by treatment group for laboratory, vital sign, and ECG parameters.

In regards to laboratory values, specific attention was given to neutropenia and drug-induced liver injury.

Neutropenia: The incidence of neutropenia by maximal grade (lowest ANC reported) during the TEAE period was summarized. The 4 grades were defined as the following:

- Grade 1:  $\geq 1500/\text{mm}^3$  to lower limit of normal (LLN)
- Grade 2:  $\geq 1000$  to  $1500/\text{mm}^3$
- Grade 3:  $\geq 500$  to  $1000/\text{mm}^3$
- Grade 4:  $< 500/\text{mm}^3$

For patients with Grade 3 or 4 neutropenia, a listing with the individual neutrophil counts, WBC, platelet counts, lymphocytes, and hemoglobin at each visit were provided. In addition, the

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

neutropenia counts at each scheduled visit during the study were plotted by treatment group. The total incidence of neutropenia from placebo, sarilumab 150mg q2w, and sarilumab 200mg q2w by maximal grade (lowest neutrophil value reported) during the rescue period were summarized.

**Drug-induced Liver Injury:** In order to assess possible drug-induced liver toxicity, ALT, AST, ALP, and conjugated bilirubin values were evaluated. The proportion of patients with PCSA values at any post-baseline visit by baseline status was displayed by treatment group for each parameter. See the description of drug-induced liver injury assessment under the SAP for Part A of this study (Section 6.1.1).

**Analysis of PK data:** Overall, analyses of PK and PD data were similar to that for Part A. Please refer to Section 6.1.1.

For analyses of immunogenicity data, please see Section 8.3.2 for definitions of patients with a positive anti-drug antibody (ADA), persistent positive response, transient positive response, and neutralizing and non-neutralizing response. Immunogenicity was evaluated using the safety population. Selected efficacy/safety endpoints were analyzed for the subgroup of patients with any treatment induced positive ADA assay response during the TEAE period versus other.

**Other analyses:** The analyses of quality of life data and health economic data were the same as described for Part A. See details in Section 6.1.1.

## Protocol Amendments

There were a total of 7 amendments to study EFC11072 Part B. Amendments #1 and 2 were implemented prior to enrollment of the first patient in Cohort 1. Amendment #3 was implemented prior to the enrollment of the first patient in Cohort 2. Amendments #3-7 are summarized briefly below.

- Amendment #3 (April 4, 2011):
  - MTX dose in the Inclusion Criteria was changed from 10-25mg/wk to 6-25mg/wk in order to accommodate dosing recommendations and practices worldwide, particularly the Asian-Pacific region.
  - The hs-CRP requirement in the Inclusion Criteria was changed from >10mg/L at the screening visit to >6mg/L at the screening visit. Sanofi felt that this change plus the required swollen/tender joints would still be consistent with a definition of moderate to severe active RA.
  - Exclusion criterion for lower weight subjects (<50 kg for men and <45kg for women) was deleted after PK data showed that weight did not significantly affect certain PK parameters such as AUC and Cmax
  - ANC <500/mm<sup>3</sup> lasting more than 5 days must be reported as an SAE.

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

- Subjects with latex hypersensitivity were added to the exclusion criteria.
- Amendment #4 (November 4, 2011):
  - CAC was established to ensure that cardiovascular events were evaluated with a set of consistent criteria and in an unbiased manner.
  - Exclusion criterion of “platelet count <100,000/μL” was changed to “platelet count <150,000/μL” to be consistent with the platelet cut-off for the other phase 3 study.
  - Exclusion criteria were also added to be consistent with the other phase 3 study protocols, specifically, the exclusion of patients with hepatobiliary disease, severe uncontrolled hypercholesterolemia (>350 mg/dL) or hypertriglyceridemia (>500 mg/dL) at baseline, and history of inflammatory bowel disease/severe diverticulitis/previous GI perforation.
  - A list of CYP450 substrates were added for possible dose adjustment following the initiation of sarilumab.
  - A set of clinical criteria for diagnosing anaphylaxis was provided to investigators so that uniform criteria would be used.
- Amendment #5 (August 8, 2012)
  - New safety measures were added to prevent the administration of sarilumab to subjects at risk for thrombocytopenia <100,000/μL and/or grade 3/4 neutropenia.
    - The CBC results from Visit 3 (Week 2) had to be available prior to secondary administration of IMP.
    - Whenever neutrophil or platelet counts were <LLN, the CBC test had to be reported before next IMP administration.
- Amendment #6 (October 29, 2012)
  - The EMA recommended that the 2 main secondary endpoints related to mTSS and HAQ-DI be converted to primary endpoints. The FDA was in agreement with these changes as described in the Regulatory Background (Section 3).
- Amendment #7 (October 8, 2013)
  - For the HAQ-DI endpoint, Sanofi revised the calculation to change from baseline in HAQ-DI at Week 16. This was changed from the average change from baseline in HAQ-DI from Week 8 to Week 52. The changes were made based on FDA recommendations to minimize missing data.
  - The order of testing of the primary endpoints was modified so that the priority of the HAQ-DI endpoint was increased.
  - New secondary efficacy endpoints were added, namely, the “Boolean-based ACR/EULAR remission at Week 24 and 52.”

In addition to the above protocol changes, these amendments also change aspects of the SAP. These changes in the SAP are summarized in detail in Dr. Yongman Kim’s review (primary

Clinical Review  
Reviewer: Suzette Peng, MD  
NME/BLA 761037  
Sarilumab/Kevzara

statistical review). Most of these changes were related to the Agency's recommendations to the handling of missing data.

- Instead of LOCF imputation for treatment discontinuation or rescue, the data collected after treatment discontinuation or rescue was set to missing. Subjects automatically became non-responders.
- Change from baseline in HAQ-DI was analyzed with MMRM, instead of initially proposed ANCOVA model.
- Modifications were also made to the handling of missing data in the sensitivity approaches for the mTSS.
- As a potential sensitivity analysis for missing data handling, the data collected after treatment discontinuation or rescue was set to missing; then an LOCF procedure from the point of treatment discontinuation/rescue was applied to impute missing data for each continuous secondary efficacy variable for all visits after that point.

#### **Data Quality and Integrity: Sponsor's Assurance**

Sanofi provided the same assurance of data quality and integrity as described for Part A of this study.

#### **6.2.2. Study Results**

##### **Compliance with Good Clinical Practices**

As with Part A, Sanofi noted that the protocol complied with recommendations of the 18<sup>th</sup> World Health Congress (Helsinki, 1964) and all applicable amendments. The protocol also complied with the laws, regulations, and any applicable guidelines of the countries where the study was conducted. Informed consent was obtained prior to the conduct of any study-related procedures. The patient informed consent form (ICF) was modified according to local regulations and requirements.

##### **Financial Disclosure**

Sanofi has adequately disclosed financial interests/arrangements with clinical investigators for this study. See Table 138 in Appendix Section 13.2 for a full review of Sanofi's financial disclosure.

##### **Patient Disposition**

Two thousand nine hundred patients were screened, but 1609 subjects (54.0%) were screen failures. Screen failures were mainly due to failure to meet the inclusion criterion for severity of disease (22.6%) and due to meeting the exclusion criterion related to TB (19.3%). Therefore,

Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

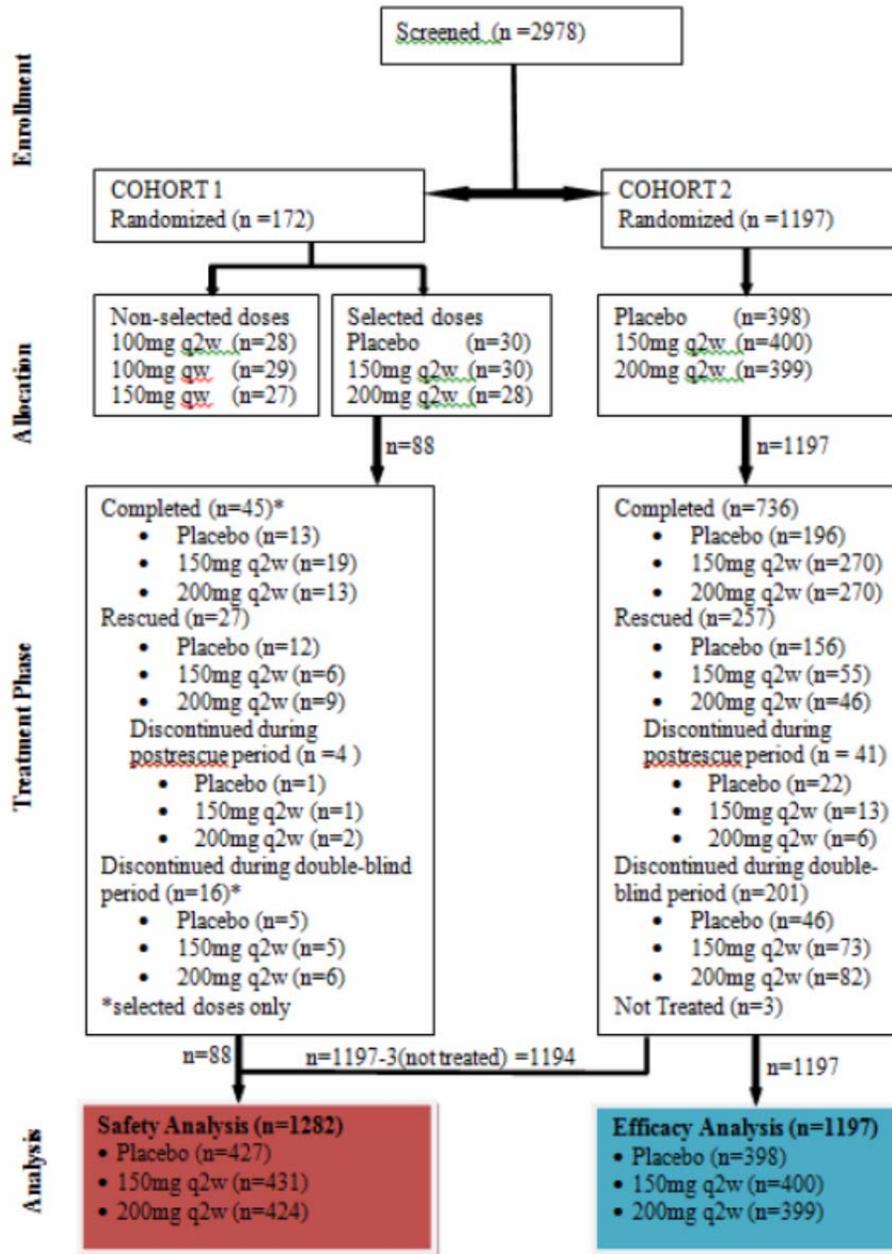
a total of 1369 patients were randomized in study EFC11072 with 172 subjects in Cohort 1 and 1197 subjects in Cohort 2.

Figure 8 is a diagram presenting the patient disposition of subjects in study EFC11072 Part B.

- Cohort 1: Of the 172 randomized patients, 88 were in the selected dose groups and, thus, continued in study EFC11072. Of these 88 subjects, 27 subjects switched to rescue treatment; 45 completed the study; and 16 subjects discontinued treatment during the double-blind period.
- Cohort 2: Of the 1197 randomized patients, 3 patients did not receive treatment. Seven hundred thirty-six subjects (61.5%) completed double-blind treatment without rescue. Two hundred one subjects (16.8%) discontinued study treatment and were not rescued. A greater proportion of subjects on sarilumab (18.3% on the lower dose and 20.6% on the higher dose) discontinued compared to placebo subjects (11.6%). Overall, 16.8% of subjects in Cohort 2 discontinued therapy, and 10.7% of these subjects discontinued due to adverse events. A total of 257 subjects (21.5%) switched to open-label rescue therapy between Weeks 16 and 52; most of these subjects (156, 13%) came from the placebo arm.

APPEARS THIS WAY ON ORIGINAL

**Figure 8. Patient Disposition for EFC11072 Part B**



Source: EFC11072 CSR, Figure 3, dated August 20, 2015; page 85.

*Reviewer Comment: During the review, the statistical review team noted that there was considerably greater rescue on placebo than the 2 sarilumab arms at Week 16, 24, and 52. It came to the attention of Dr. Yongman Kim (primary statistical reviewer) that, at Week 16, among those who met the rescue criteria based on swollen and tender joint counts, a greater proportion of subjects were rescued on the placebo group compared to the sarilumab groups.*

Clinical Review  
Reviewer: Suzette Peng, MD  
NME/BLA 761037  
Sarilumab/Kevzara

*Noticing this imbalance, Dr. Kim requested that the applicant clarify the reason for this imbalance. The applicant argued that Investigators implemented rescue therapy based not only on changes in tender/swollen joint counts but also on their clinical assessments of changes in patient reported outcomes evident during the weeks prior to rescue. Thus, more patients on placebo showed worsening in these outcomes. Also, the applicant explained that subjects may have met protocol-specified rescue criteria but reported greater improvements in self-assessments as well as reductions in active joint counts. These subjects were not rescued. Sanofi's explanation for this imbalance in rescue appeared appropriate. Please see Dr. Kim's review for my details.*

### **Protocol Violations/Deviations**

Major or critical efficacy/PD deviations related to the primary efficacy/PD endpoints:  
In Cohort 2, 35 subjects were identified as having important protocol deviations that had a potential impact on efficacy analyses. Fifteen subjects on placebo and 20 subjects on sarilumab (8 on 150mg q2w and 12 on 200mg q2w) experienced these protocol deviations. The most common deviation was not meeting Sanofi's definition of "active" RA (6 of 68 tender joints, 6 of 66 swollen joints, and hsCRP>6 or >10mg/L), noted in 6 subjects on placebo, 4 subjects on sarilumab 150mg q2w, and 6 subjects on 200mg q2w. Other examples of inclusion/exclusion criteria from which there were deviations included history of or current inflammatory joint disease other than RA, at 1 documented bone erosion (on x-ray), and treatment with prednisone of >10mg/day within 4 weeks prior to randomization.

Randomization and dosing irregularities:

Randomization and dosing irregularities were defined prior to database lock. A total of 29 subjects were identified from Cohort 2 and Cohort 1 selected doses, compared to 23 from Cohort 2 alone. Three subjects were randomized but were not treated (1 in the 200mg group and 2 in the 150mg group); these subjects were, thus, included in the efficacy population but not in the safety population. The common randomization and dosing irregularities included erroneous kit dispensation and stratification error (due to incorrect information provided by the sites during the IVRS call).

Other major or critical deviations:

Forty-seven subjects were noted to have "other important protocol deviations." These included 15 subjects on placebo, 14 subjects on sarilumab 150mg q2w, and 18 subjects on sarilumab 200mg q2w. Examples of protocol deviations that occurred prior to randomization included PPD test performed prior to signing ICF or having a medical history/screening laboratory test that was amongst the exclusion criteria. Other examples of protocol deviations included (but were not limited to) testing positive for hepatitis B core antibody or hepatitis B surface antigen, inadequate contraception at screening, and treatment with excluded medications (a DMARD other than MTX, a new DMARD during the study for the purpose of

Clinical Review  
Reviewer: Suzette Peng, MD  
NME/BLA 761037  
Sarilumab/Kevzara

“rescue”, corticosteroids  $\geq 10$ mg/day). Thirteen subjects also experienced laboratory abnormalities but did not have the proper follow up.

*Reviewer Comment: I agree with the applicant that these deviations have the potential to affect data analyses. These deviations occurred in all treatment arms equally. Therefore, the true effect on efficacy and safety assessments is unclear.*

#### Qualitative issues:

Sanofi noted 77 important qualitative deviations. These will not be described in detail. The majority (39) were related to IMP supply issues which led to IMP dose interruption. None of the IMP supply issues led to permanent treatment discontinuation. Twenty-eight of the total 77 qualitative deviations were related to informed consent procedure such as the IFC amendment with a late or missing signature.

#### Study conduct issues not included in deviations:

The central laboratory vendor (b) (4) incorrectly programmed the blinding definition for CRP for certain study visits. Because of this, 14 unblinded, post-randomization CRP results were mistakenly sent to the study sites. Eleven of the 14 results were sent to the sites 1 or more days after the end of treatment visit. However, 3 subjects were still in the treatment phase. One of these subjects ended up being withdrawn from the study within a month because it was identified that he was originally randomized to one of the non-selected doses of sarilumab. Therefore, it was essentially 2 subjects for whom their CRP results were unblinded. Sanofi noted that, for these subjects, the ACR status remained unchanged after unblinding.

*Reviewer Comment: Revelation of CRP results to the Investigator could certainly lead to breaking of the blind. However, given that only 3 subjects were still in the treatment phase at the time the CRP results were sent to the study sites, I would agree with Sanofi's assessment that this event should not have affected the efficacy assessment.*

#### Breaking of the blind:

In addition to the potential unblinding with the CRP results, there were 2 patients (in the placebo arm) for whom the blind was unintentionally broken by the Investigator. Both subjects were discontinued from the protocol, but their data were analyzed for safety and efficacy. There were also 32 subjects (4 in the placebo arm, 13 on sarilumab 150mg q2w, and 15 on sarilumab 200mg q2w) who had SAEs, and, thus, the blind was broken for regulatory purposes. These 32 subjects continued in the study and were included in all analyses.

#### Table of Demographic Characteristics

Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

The ITT population for efficacy analyses consisted of all 1197 patients who were randomized to Part B Cohort 2. This was the same population that was included in Pool 1a in the integrated safety evaluation in Section 8 of this review. Subjects randomized to Part B Cohort 2 and Cohort 1 selected doses (total 1285 but 1282 treated) were included in the safety evaluation of Pool 1. See Section 8 for a full description of the safety pools. For the baseline patient and disease characteristics described in the next 2 tables, the patients randomized to Part B Cohort 2 and Cohort 1 selected doses will be described.

Table 12 displays the patient demographics and characteristics of subjects randomized to EFC11072 Part B (Cohort 2 and Cohort 1 selected doses). The majority of subjects are less than 65 years-old, female, and Caucasian. The mean weight was 74.39 kg. These baseline patient characteristics were represented similarly across treatment arms.

APPEARS THIS WAY ON ORIGINAL

**Table 12. Baseline Demographics and Patient Characteristics of EFC11072 Part B Cohort 2 and Cohort 1 Selected Doses**

	Placebo + MTX (N=428)	Sarilumab	
		150mg q2w + MTX (N=430)	200mg q2w + MTX (N=427)
<b>Age (years)</b>			
Number	428	430	427
Mean (SD)	51.1 (11.2)	50.3 (11.9)	50.8 (12.0)
Median	52.0	52.0	52.0
Min: Max	19:75	18:74	19:75
<b>Age Group [n(%)]</b>			
Number	428	430	427
<65 years	381 (89.0%)	383 (89.1%)	370 (86.7%)
≥65-75 years	46 (10.7%)	47 (10.9%)	56 (13.1%)
≥ 75 years	1 (0.2%)	0	1 (0.2%)
<b>Sex [n(%)]</b>			
Number	428	430	427
Male	82 (19.2%)	85 (19.8%)	68 (15.9%)
Female	346 (80.8%)	345 (80.2%)	359 (84.1%)
<b>Race [n(%)]</b>			
Number	428	430	427
Caucasian	370 (86.4%)	371 (86.3%)	369 (86.4%)
Black	10 (2.3%)	11 (2.6%)	10 (2.3%)
Asian	35 (8.2%)	35 (8.1%)	33 (7.7%)
Other	13 (3.0%)	13 (3.0%)	15 (3.5%)
<b>Ethnicity [n(%)]</b>			
Number	428	430	427
Hispanic	147 (34.3%)	162 (37.7%)	161 (37.7%)
Non-Hispanic	281 (65.7%)	268 (62.3%)	266 (62.3%)
<b>Weight (kg)</b>			
Number	428	428	426
Mean (SD)	74.31 (17.25)	73.91 (18.27)	74.94 (19.98)
Median	72.00	70.20	72.00
Min: Max	42.0: 164.8	31.5: 151.0	36.7: 173.1
<b>BMI (kg/m<sup>2</sup>)</b>			
Number	427	426	426
Mean (SD)	28.19 (5.81)	27.98 (6.51)	28.61 (6.68)
<25	132 (30.9%)	156 (36.6%)	135 (31.7%)
≥25 and <30	161 (37.7%)	143 (33.6%)	136 (31.9%)
≥30	134 (31.4%)	127 (29.8%)	416 (32.5%)
<b>Region [n(%)]</b>			
Number	428	430	427
Region 1	81 (18.9%)	82 (19.1%)	82 (19.2%)

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

Region 2	162 (37.9%)	163 (37.9%)	162 (37.9%)
Region 3	185 (43.2%)	185 (43.0%)	183 (42.9%)

Number = number of patients assessed. Percentages are calculated using number of patients assessed as denominator.

Region 1: Austria, Australia, Belgium, Canada, Finland, Germany, Greece, Hungary, New Zealand, Norway, Portugal, Spain, USA

Region 2: Argentina, Brazil, Chile, Colombia, Mexico

Region 3: Belarus, Estonia, India, Malaysia, Philippines, Poland, Romania, Russia, South Africa, South Korea, Ukraine, Taiwan, Thailand

Source: EFC11072 CSR, Table 14, dated August 20, 2015; page 95-96.

*Reviewer Comment: Notably, Region 3 (Eastern Europe and Asia) had the higher proportions of representation in all 3 treatment arms. Despite this, the patient baseline characteristics are consistent with that of the general RA population in the United States – ages 40-60 years, female, and Caucasian. Additionally, there is more representation of other races in Part B compared to Part A, which is also more consistent with the general RA population.*

### **Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)**

At baseline, the disease characteristics were also comparable across treatment arms. The mean duration of all 1285 subjects was 9.03 years (range 0.3 to 44.7 years). The majority of subjects in each arm had class II, seropositive (RF/anti-CCP antibody positive) disease. Most subjects had not been previously treated with biologics with approximately 27-28% of subjects in each arm with previous biologic use. Lastly, the mean DAS28-CRP in each arm was between 5.9 and 6.00, consistent with high disease activity.

APPEARS THIS WAY ON ORIGINAL

**Table 13. Baseline Disease Characteristics for EFC11072 Part B Cohort 2 + Cohort 1 Selected Doses**

	Placebo + MTX (N=428)	Sarilumab	
		150mg q2w + MTX (N=430)	200mg q2w + MTX (N=427)
<b>Duration of RA since diagnosis (Years)</b>			
Number	428	430	427
Mean (SD)	9.02 (8.10)	9.41 (8.40)	8.66 (6.98)
Median	6.65	6.91	7.36
Min: Max	0.3: 44.0	0.3: 44.7	0.3: 34.2
<b>RA functional class [n(%)]</b>			
Number	428	430	427
I	52 (12.1%)	53 (12.3%)	45 (10.5%)
II	293 (68.5%)	275 (64.0%)	295 (69.1%)
III	83 (19.4%)	102 (23.7%)	87 (20.4%)
IV	0	0	0
<b>Prior biologic use [n(%)]</b>			
Number	428	430	427
Yes	120 (28.0%)	119 (27.7%)	119 (27.9%)
No	308 (72.0%)	311 (72.3%)	308 (72.1%)
<b>Rheumatoid factor [n(%)]</b>			
Number	428	430	427
Positive	359 (83.9%)	373 (87.6%)	354 (83.3%)
Negative	69 (16.1%)	53 (12.4%)	71 (16.7%)
<b>Anti CCP antibody [n(%)]</b>			
Number	428	430	427
Positive	366 (85.5%)	386 (90.2%)	361 (84.9%)
Negative	62 (14.5%)	42 (9.8%)	64 (15.1%)
<b>Tender joint count (0-68)</b>			
Number	428	430	427
Mean (SD)	26.41 (13.72)	27.49 (14.12)	26.64 (14.39)
Median	23.00	25.00	23.00
Min: Max	5.0: 68.0	8.0: 68.0	3.0: 68.0
<b>Swollen joint count (0-66)</b>			
Number	428	430	427
Mean (SD)	16.51 (9.33)	17.02 (9.42)	16.92 (9.73)
Median	14.00	14.00	14.00
Min: Max	3.0: 56.0	2.0: 64.0	3.0: 66.0
<b>CRP (mg/L)</b>			
Number	428	430	427
Mean (SD)	20.72 (22.82)	23.59 (24.69)	22.38 (23.49)
Median	13.15	14.85	15.60

Clinical Review  
 Reviewer: Suzette Peng, MD  
 NME/BLA 761037  
 Sarilumab/Kevzara

Min: Max	0.3: 169.0	0.2: 209.0	0.2: 203.0
<b>HAQ-DI (0-3)</b>			
Number	428	430	427
Mean (SD)	1.59 (0.66)	1.64 (0.62)	1.70 (0.64)
Median	1.63	1.75	1.75
Min: Max	0.0: 3.0	0.0: 3.0	0.3: 3.0
<b>DAS28-CRP</b>			
Number	428	430	427
Mean (SD)	5.90 (0.90)	5.98 (0.92)	6.00 (0.87)
Median	5.90	5.94	5.97
Min: Max	3.1: 8.1	2.8: 8.5	3.4:8.0

Number = number of patients assessed. Percentages are calculated using number of patients assessed as denominator.

DAS28-CRP>5.1 = high disease activity

Source: EFC11072 CSR, Table 15, dated August 20, 2015; page 98-99.

### Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment compliance was ascertained from records of medication treatment packs and/or diaries. The majority of subjects were >80% compliant with treatment. However, 3.3% in the placebo arm, 5.1% in the sarilumab 150mg q2w arm, and 2.4% in the sarilumab 200mg q2w arm were <80% compliance. Some of the compliance issues related to protocol-specified treatment discontinuations for TEAEs (e.g., neutropenia, elevated liver enzymes, etc.). An overdose was defined as administration of at least twice the randomized dose in less than 6 days during a weekly dosing schedule or in less than 11 days during a q2w dosing schedule. Similar proportion of subjects (5.4%-6.8%) in each treatment experienced an overdose.

In general, the concomitant medications for treatment of RA were similar across treatment arms. Per protocol, all subjects were treated with a stable dose of MTX and folic acid. At baseline, 99.8% of subjects on placebo, 99.5% of subjects on sarilumab 150mg q2w, and 99.8% of subjects on sarilumab 200mg q2w were taking MTX at a mean dose of 15.28-15.60 mg/week. A similar proportion of subjects in each treatment arm used corticosteroids and NSAIDs at baseline and during the study. At baseline, 61.91% of subjects on placebo, 65.34% of subjects on sarilumab 150mg q2w, and 64.63% on sarilumab were taking systemic corticosteroids, and this increased to 62.1% on placebo, 67.0% on sarilumab 150mg q2w, and 64.2% on sarilumab 200mg q2w during the study. Similarly, 68% of subjects on placebo, 67.0% of subjects on sarilumab 150mg q2w, and 67.2% of subjects on sarilumab 200mg q2w took NSAIDs at baseline. These proportions increased in all treatment arms, perhaps, slightly more on the placebo arm during the study: 71.7% of subjects on placebo, 70.5% of subjects on sarilumab 150mg q2w, and 69.6% of subjects on sarilumab 200mg q2w. Other concomitant medications not related to the treatment of RA will not be summarized as part of this review.

As described in the trial design, rescue therapy was open-label sarilumab for all treatment arms. However, 3 subjects were rescued with other medication while continue to receive

Clinical Review  
Reviewer: Suzette Peng, MD  
NME/BLA 761037  
Sarilumab/Kevzara

double-blind IMP. These 3 subjects received hydroxychloroquine, oral steroids  $\geq 10\text{mg/day}$ , and prednisolone  $10\text{mg/day}$ .

### **Efficacy Results - Primary Endpoint**

The co-primary endpoints and major secondary endpoints will be presented from both pivotal studies (EFC11072 Part B Cohort 2 and EFC10832) in Section 7. These endpoints include the co-primary endpoints: ACR20 at Week 24, change from baseline in HAQ-DI at Week 16, change from baseline in mTSS at Week 52. Other secondary endpoints in Section 7 include ACR20 reponse over time, major clinical response, change in baseline in DAS28-CRP, ACR50/70, DAS28-CRP  $< 2.6$ , and SF-36 (physical and mental components).

The dose response, durability of response, and persistence of effect will also be reviewed in the Integrated Review of Efficacy in Section 7.

### **Data Quality and Integrity - Reviewers' Assessment**

There are no issues with data quality and integrity. No audits were performed on the case report forms or clinical source data. There were no significant OSI findings that would affect the data or require exclusion of data from any sites. As will be discussed in Section 7, the major efficacy assessments were supported by various sensitivity analyses and confirmed by the Agency's statistical team.

### **Efficacy Results - Secondary and other relevant endpoints**

The results for SDAI remission, CDAI remission, and the ACR/EULAR Boolean-based definition of remission will be presented here. In the ACR 2015 RA guidelines, use of a "treat-to-target" strategy is recommended rather than a non-targeted approach (Singh et al. 11). The target, thus, should be remission or low disease activity if remission cannot be achieved. The guidelines supported the use of the joint ACR/EULAR definition of remission which was SDAI  $\leq 3.3$  or the Boolean-based definition (i.e., tender joint count, swollen joint count, CRP, and patient global  $\leq 1$ ). The 2013 FDA draft "Guidance for Industry Rheumatoid Arthritis: Developing Drug Products for Treatment" also mentioned the use of the ACR/EULAR definition of remission as a potential clinical endpoint. CDAI is also mentioned in the ACR 2015 guidelines as one of the accepted instruments to measure RA disease activity and to define remission. Therefore, in this review, these endpoints will be presented for each individual trial (EFC11072 and EFC10832). It is important to note that, for EFC11072, these endpoints do not appear on the hierarchy for statistical analyses.

The definition of remission utilizing SDAI is SDAI  $\leq 3.3$ . The proportion of subjects who achieved SDAI remission was numerically higher in subjects on sarilumab at Weeks 24 and 52 compared with placebo. At Week 24, 4.8% of subjects on placebo, 10.3% of subjects on sarilumab 150mg

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

q2w, and 13.0% of subjects on sarilumab 200mg q2w achieved SDAI remission. The nominal p-value vs. placebo was 0.003 for the sarilumab 150mg q2w arm and <0.0001 for the 200mg q2w arm. At Week 52, 4.0% of subjects on placebo, 15.0% of subjects on sarilumab 150mg q2w, and 18.5% of subjects on sarilumab 200mg q2w achieved SDAI remission. The nominal p-value vs. placebo was <0.0001 for both doses of sarilumab.

The definition of remission utilizing CDAI is  $CDAI \leq 2.8$ . The proportion of subjects who achieved CDAI remission was higher in the sarilumab group at both Weeks 24 and 52. The proportions of subjects who achieved CDAI remission were 5.0% for placebo, 10.3% for sarilumab 150mg q2w, and 13.8% for sarilumab 200mg q2w at Week 24 and 4.8% for placebo, 14.8% for sarilumab 150mg q2w, and 18.0% for sarilumab 200mg q2w at Week 52. At Week 24, the nominal p-value vs. placebo was 0.0053 for sarilumab 150mg q2w and <0.0001 for sarilumab 200mg q2w. At Week 52, the nominal p-value vs. placebo was <0.0001 for both doses.

As with SDAI and CDAI, the proportion of subjects achieving the Boolean-based ACR/EULAR definition of remission was numerically higher for subjects on sarilumab compared to placebo. At Week 24, the proportion of subjects achieving remission was 3.8% of subjects on placebo, 6.5% of subjects on sarilumab 150mg q2w, and 10.5% of subjects on sarilumab 200mg q2w. The nominal p-value vs. placebo was 0.0810 for sarilumab 150mg q2w and 0.0002 for sarilumab 200mg q2w. At Week 52, 3% in the placebo arm, 10.5% in the sarilumab 150mg q2w arm, and 14.0% in the sarilumab 200mg q2w arm achieved this definition of remission. The nominal p-value was <0.0001 for both doses.

In summary, for these 3 definitions of remission, more subjects on sarilumab in study EFC11072 Part B achieved remission than subjects on placebo. At Week 24, the difference seemed more prominent in the 200mg dose. At Week 52, subjects on both doses of sarilumab had a difference with a nominal p-value <0.0001 for all 3 definitions of remission.

### **Additional Analyses Conducted on the Individual Trial**

Safety analyses of the pivotal study EFC11072 Part B will not be presented separately as part of this review. It will be reviewed as part of the integrated safety assessment with the other studies from the sarilumab clinical development program in Section 8.

## **6.3. EFC10832 (SARIL-RA-TARGET)**

### **6.3.1. Study Design**

#### **Overview and Objective**

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

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 $\alpha$  antagonists. The primary objective was to demonstrate that sarilumab added to non-biologic DMARDs is effective in reducing the signs and symptoms at Week 24 and improving physical function at Week 12 in patients with active RA who are inadequate responders to or intolerant of TNF $\alpha$  antagonists.

### Secondary Objectives

- To demonstrate that sarilumab added to non-biologic DMARD therapy in patients with active RA, who are inadequate responders or intolerant to TNF $\alpha$  antagonists, is effective in the following:
  - Reduction of signs and symptoms at Week 12
  - Improvement in physical function at Week 24
  - Improvement of disease activity score at Weeks 12 and 24
  - Improvement of quality of life as measured by patient-reported outcomes (PROs) at intermediate visits and at Week 24
- To assess the exposure to sarilumab added to non-biologic DMARD therapy in this population
- To assess the safety of sarilumab in this population

### Exploratory Objectives

- To collect DNA, RNA, and other biomarkers for future use for the purpose of discovery of predictive biomarker

## Trial Design

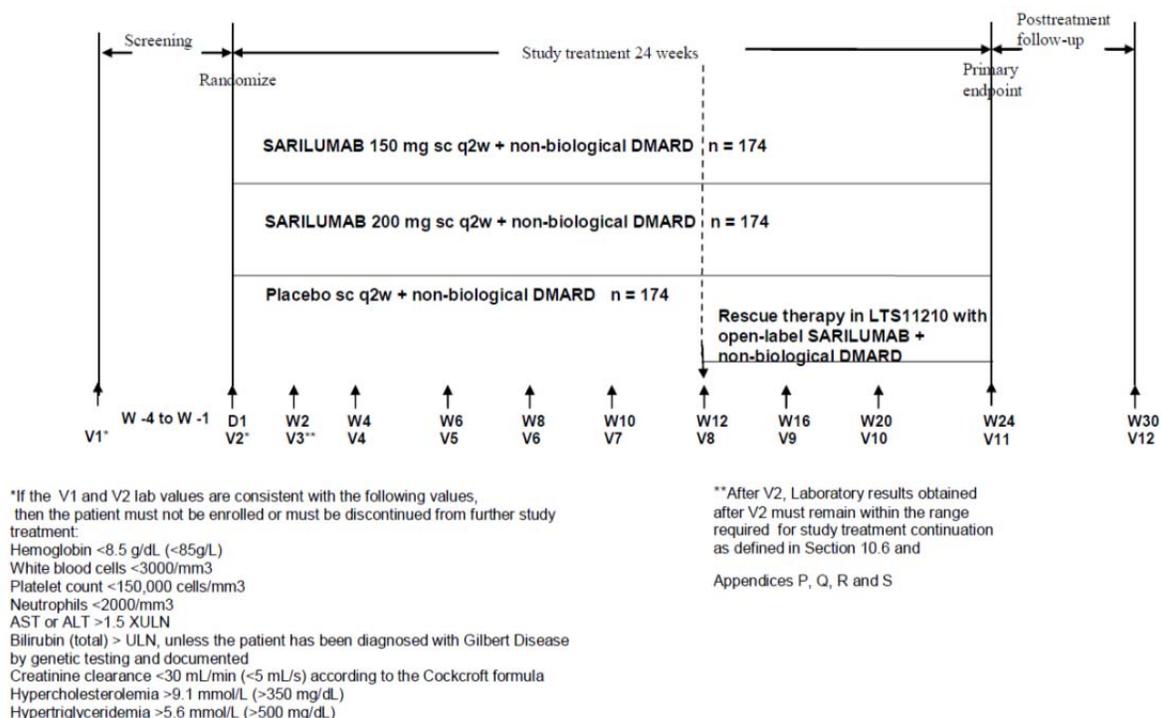
### Basic Study Design

EFC10832 was a 3-arm, multicenter, randomized, double-blind, parallel group, placebo-controlled 24-week phase 3 study. Patients and investigators were blinded to the allocation to active or placebo treatments. Patients were stratified by region at study entry and number of previous anti-TNF inhibitors (1 versus >1).

Figure 9 is the study schema of EFC10832. Patients were randomized in a 1:1:1 ratio to receive SC injections of sarilumab 150mg q2w or sarilumab 200mg q2w or placebo q2w. 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 LTS11210.

All subjects (completed or discontinued) were scheduled to complete an end of treatment (EOT) visit. Subjects who completed the treatment phase were also allowed to enter LTS11210. Subjects who declined participation in LTS11210 or who discontinued study were scheduled to have their last patient visit at the end of a 6-week safety follow-up period. The total maximum duration of participation for a patient in this study was 34 weeks (up to 4 weeks screening, 24 weeks double-blind treatment, and 6 weeks post-treatment follow-up). The schedule of assessments for EFC10832 is displayed in Table 141 in the Appendix (Section 13.3).

**Figure 9. Study Schema of EFC10832**



Source: EFC10832 Clinical Study Report, Figure 1, dated July 24, 2015, page 20.

**Choice of control group**

Sanofi notes that it has been repeatedly demonstrated that the placebo response for ACR20 in the RA population is large and variable, anywhere from 20-30%. Therefore, Sanofi noted the necessity of having a placebo arm in order to demonstrate that sarilumab had a true and clinically meaningful effect. The selection of the timing of rescue therapy and the length of time that all patients had to remain on placebo treatment was chosen based on the belief that 12 weeks would generally be the time period accepted for administration of placebo treatment in RA clinical trials.

*Reviewer Comment: Evaluation for lack of efficacy and administration of rescue therapy at Week 12 are reasonable. It does, however, complicate the analyses of data. For efficacy,*

Clinical Review  
Reviewer: Suzette Peng, MD  
NME/BLA 761037  
Sarilumab/Kevzara

*subjects who are rescued will be considered non-responders. For safety, the most informative information will likely be the time period prior to rescue.*

### **Key inclusion/exclusion criteria**

In general, the inclusion and exclusion criteria for EFC10832 were very similar to those of EFC11072. Differences in the study population are listed below.

### **Inclusion Criteria**

- ACR Class I-III functional status, based on 1991 revised criteria

*Reviewer's Comment: No definition of functional status was included in the inclusion criteria for EFC11072.*

- Anti-TNF $\alpha$  therapy failures, defined as patients with an inadequate clinical response defined by the Investigator, after being treated for at least 3 consecutive months, and/or intolerance to at least 1 anti-TNF $\alpha$  blocker(s), resulting in or requiring its discontinuation
  - TNF $\alpha$  blockers could have included (but were not limited to) etanercept, infliximab, adalimumab, golimumab, and/or certolizumab

*Reviewer's Comment: In both studies EFC11072 and EFC10832, subjects could have had previous treatment with TNF blockers, but this treatment could not be within 3 months of randomization. However, in study EFC11072, subjects could not be previous non-responders to TNF blockers. In study EFC10832, previous TNF therapy failure is one of the inclusion criteria. This could possibly lead to a study population who is more recalcitrant to therapy.*

- Moderate-to-severely active RA defined as the following:
  - At least 8 of 68 tender joints and 6 of 66 swollen joints at screening and baseline visits AND
  - hs-CRP  $\geq$  8 mg/L at screening

*Reviewer's Comment: Subjects in EFC11072 had a slightly different definition of active arthritis. Subjects needed to have the same number of swollen and tender joints. However, subjects were required to have an hsCRP > 10 mg/L. Lastly, subjects in EFC11072 Part B needed to have evidence of more aggressive disease with a known presence of a bony erosion or RF positivity or CCP-Ab positivity.*

- Continuous treatment with 1 or a combination of non-biologic DMARDs (except for simultaneous use of leflunomide and methotrexate) for at least 12 consecutive weeks prior to randomization and on a stable dose(s) for at least 6 consecutive weeks prior to screening

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

- Methotrexate (MTX): 10 – 25 mg/week PO or IM (or per local labeling requirements for the treatment of RA)
- Leflunomide (LEF): 10 – 20 mg PO daily
- Sulfasalazine (SSZ): 1000 – 3000 mg PO daily
- Hydroxychloroquine (HCQ): 200 – 400 mg PO daily

*Reviewer's Comment: In EFC11072, subjects could only be treated with concomitant MTX. No other conventional DMARDs were allowed during the study.*

### Exclusion Criteria

- Treatment with previous RA-directed biologic agents (other than TNF $\alpha$  antagonists)
  - Anakinra: within 28 days prior to randomization
  - Abatacept: within 42 days prior to randomization
  - Rituximab or other cell depleting agent: within 6 months prior to randomization or until total lymphocyte count and CD-19+ lymphocyte count are normalized, whichever is longer

*Reviewer's Comment: The exclusion criteria for EFC11072 were not quite as specific regarding previous biologic use. There was just a general statement that TNF $\alpha$  antagonists or other biologics could not have been received within 3 months prior to randomization.*

- Prior treatment with a Janus kinase inhibitor (such as tofacitinib)

*Reviewer's Comment: The protocol for EFC11072 did not specifically list tofacitinib as a prohibited medication. This may be related to timing of tofacitinib entering the US market.*

**Dose selection:** The doses used in EFC10832 were those selected to be evaluated in the phase 3 program, as described for EFC11072 Part B.

### Concomitant medications

As above, all subjects were required to be treated with a non-biologic DMARD. Unlike EFC11072, all conventional DMARDs were allowed. The other allowed and prohibited concomitant medications were similar to the other pivotal study (EFC11072 Part B) and were detailed in the Inclusion/Exclusion Criteria.

**Study treatments:** The IMPs in this study were sarilumab and placebo. These products were the same as what was described for EFC11072 Part B.

The noninvestigational products (e.g., DMARDs) were not provided by Sanofi but were dispensed according to local practice. All subjects continued to receive regular treatment with

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

1 or a combination of non-biologic DMARDs (MTX, SSZ, LEF, HCQ) which should have been started at least 12 weeks prior to baseline. Subjects should have been on a stable dose for at least 6 weeks prior to screening and during the treatment period. At any time, the DMARD dose could be reduced for safety or tolerability reasons, but the dose could not be increased during the study.

### **Assignment to treatment**

Subjects were randomized to 1 of the treatment arms via a centralized randomization system using an IVRS stratified by region and number of previous anti-TNF inhibitors (1 versus >1). A patient was considered randomized when the treatment number had been provided by IVRS. Subjects were randomized 1:1:1 to 1 of the treatment arms of sarilumab or to the placebo arm. At subsequent visits during the treatment period, the site coordinator called IVRS to obtain the next treatment kit numbers.

### **Blinding**

Investigators and subjects were blinded to the allocation of active or placebo treatment arms. Sarilumab and placebo were provided in matching glass prefilled syringes in identical kits. The list of treatment kit numbers was generated by the Sanofi Biostatistics Department. A randomization list was generated by the IVRS. Both the randomization and treatment kit lists were loaded into the IVRS. The treatment kit numbers were obtained by the Investigator at the time of patient randomization and subsequent patient scheduled visits via IVRS that was available 24 hours a day. In accordance with the double-blind design, Investigators remained blind to study treatment and did not have access to the randomization (treatment codes) except under exceptional medical circumstances.

### **Administrative structure**

Dr. Roy Fleischmann was the Principal Investigator for this study. The other aspects of the administrative structure, such as the data monitoring committee (DMC) and independent cardiovascular adjudication committee (CAC), were similar to what was described for EFC11072 Part B.

### **Treatment compliance**

Administration of the first dose of IMP was supervised by the Investigator or Sub-Investigator. Administration of doses (post-first dose) of IMP could be done by the subject at home or by a healthcare provider after documented training. Compliance was assessed by entries in the patient diary.

### **Subject completion, discontinuation, or withdrawal**

In general, Sanofi's guidance for temporary or permanent discontinuation was the same as that described for EFC11072 Part B. The following details were added to the events that could lead to permanent discontinuation.

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

- Similar to EFC11072, subjects with opportunistic infections were to be discontinued. More details were provided in this study protocol.
  - The diagnosis of TB could be made either by symptoms or by a chest radiograph suggestive of active TB. Subjects should be referred to appropriate medical specialists, and culture confirmation should be obtained.
  - Subjects who were at risk through close contact with a person with active TB but who refused to undergo TB evaluation
- For EFC11072, ALT and bilirubin abnormalities were listed as reasons for permanent discontinuation. For this study, the following detailed criterion was added.
  - Confirmed ALT >5x ULN or confirmed ALT >3x ULN and concomitant total bilirubin >2x ULN (unless the subject has documented Gilbert's Syndrome)
- Any adverse events, per Investigator's judgment, that might jeopardize the patient's safety

## Study Endpoints

### Efficacy Assessments

The co-primary endpoints in the study were ACR20 response rate at Week 24 and the change from baseline in HAQ-DI at Week 12.

*Reviewer Comment: Efficacy assessments that were previously described for study EFC11072 Parts A and B will not be described again here. Please refer to the previous protocol descriptions (Sections 6.1.1 and 6.2.1) for details.*

### Primary efficacy endpoints

- ACR20 response rate at Week 24
- Change in HAQ-DI at Week 12

*Reviewer Comment: As with EFC11072 Part B, ACR20 response rate and change in HAQ-DI are appropriate measures of improvement in signs and symptoms in rheumatoid arthritis. The timing of the assessments is reasonable to detect a clinically significant change. Sanofi notes that it has been suggested that maximal therapeutic benefit may take up to 6 months for IL-6 inhibitors in RA. As with EFC11072 Part B, it should be noted that the assessment of ACR20 occurred after the opportunity to escape based on lack of efficacy. Therefore, the analysis of the primary endpoint is complicated by the possible dose change/escape. Of note, for the primary analysis, these subjects who escape will be considered non-responders, and this is reasonable.*

### Secondary efficacy endpoints

- ACR20/50/70 at Week 12 and ACR50/70 at Week 24
- ACR-N at Weeks 12 and 24
- Change from baseline in the ACR components at Weeks 12 and 24

CDER Clinical Review Template 2015 Edition

Version date: November 5, 2015 for initial rollout (NME/original BLA reviews)

126

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

- EULAR response based on DAS28-CRP at Weeks 12 and 24
- DAS28-CRP < 2.6 (defined as “remission”) at Weeks 12 and 24
  
- ACR/EULAR remission (Boolean-based) at Weeks 12 and 24  
To fulfill the criteria for ACR/EULAR remission, a patient had to satisfy all of the following:
  - Tender joint count (68 joints)  $\leq 1$
  - Swollen joint count (66 joints)  $\leq 1$
  - C-reactive protein  $\leq 1$  mg/dL
  - Patient global assessment  $\leq 1$  cm
  
- Proportion of subjects achieving SDAI remission ( $\leq 3.3$ ) at Weeks 12 and 24
- Proportion of subjects in CDAI remission ( $\leq 2.8$ ) at Weeks 12 and 24
- Change from baseline in CDAI at Weeks 12 and 24
- Change from baseline in SDAI at Weeks 12 and 24

### Safety assessments

The timing of safety assessments is displayed in the table of schedule assessments located in the Appendix, Table 141.

Sanofi’s definition of the observation period, adverse events (including SAEs), laboratory safety parameters, chest x-ray, and vital signs were the same as the descriptions provided for study EFC11072 Part B. In addition, the same AESIs as those for EFC11072 Part B were identified for this study with the addition of infections requiring prolonged (>14 days) medication, parenteral antibiotics, or parenteral antifungal agents. Please refer to the previously described protocols for full details regarding the various safety assessments.

### Patient Reported Outcomes (PROs)

- Short-Form-36 (SF-36, Version 2.0)
  
- EuroQOL (EQ-5D-3L)  
The Eq-5D-3L is a standardized, generic measure of health outcome. EQ-5D was designed for self-completion by patients. Instructions to respondents were included in the questionnaire. The EQ-5D was specifically included to address concerns regarding the health economic impact of RA, which have been considered in cost effectiveness arguments. The EQ-5D-3L comprises 5 questions on mobility, self-care, pain, usual activities, and psychological status with 3 possible answers for each item (1=no problem, 2=moderate problems, 3=severe problems) and a vertical visual analog scale (VAS) that allows the patients to indicate their health state today that can range from 0 (worst imaginable) to 100 (best imaginable).
  
- Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue Scale

CDER Clinical Review Template 2015 Edition

Version date: November 5, 2015 for initial rollout (NME/original BLA reviews)

127

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

- **Morning stiffness Visual Analog Scale (VAS)**  
Rheumatoid arthritis is associated with stiffness of joints, especially in the morning after prolonged stationary state. The degree of stiffness can be an indicator of disease severity. The effect of sarilumab on the severity of morning stiffness was assessed on a VAS scale from 0 mm (no problem) to 100 mm (major problem).
- **The Rheumatoid Arthritis-Work Productivity Survey (WPS-RA)**  
The WPS-RA is a validated questionnaire that evaluates productivity limitations within work and within home associated with RA over the previous month. The questionnaire was interviewer-administered and is based on patient self-report. It contains 9 questions addressing employment status (1 item), productivity at work (3 items), and within and outside the home (5 items).
- **Rheumatoid Arthritis Impact of Disease (RAID)**  
The RAID score is a composite measure of the impact of RA on patients that takes into account 7 domains: pain, functional disability, fatigue, physical and emotional well-being, quality of sleep, and coping. The RAID is calculated based on 7 numerical rating scales (NRS) questions. Each NRS is assessed as a number between 0 and 10, which correspond to the domains mentioned above. The values for each of these domains were weighted by patient assessment of relative importance and combined in a single score. The instrument has been validated in a cross-sectional study of 570 patients with RA. Sanofi noted that the study found that the RAID assessment does indeed display robust reliability, is sensitive to change, and correlates highly with patient global assessments and other patient-related outcomes.

### **PK and Immunogenicity Assessments**

The PK and immunogenicity parameters were the same as those for study EFC11072 Part B. The schedule of assessments (Table 141) shows the timing of blood sample collection.

The selection of candidate genes and other biomarkers is also the same as those used in EFC11072 Part B.

### **Statistical Analysis Plan**

**Sample size:** Initially, the sample size determination was based on change from baseline in HAQ-DI at Week 24 with the following assumptions:

- Mean changes of -0.05 and -0.35 in the placebo and sarilumab groups, respectively
- A common standard deviation (SD) of 0.79
- A 2 group t-test of equal means at a 2-sided  $\alpha = 0.025$  level with 90% power

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

Based on the above assumptions, 174 patients per treatment group, resulting in a total of 522 patients were needed. The assumed mean changes and SD are based on results from the tocilizumab program. Alpha = 0.025 was used for this calculation since the Bonferroni approach was used to account for multiple testing of the 2 active dose regimens at one-half of the family-wise type I error rate of 0.05.

However, the protocol was later amended to change the timing of the HAQ primary endpoint from 24 weeks to 12 weeks. Using the sample size of 174 per group, the study power was calculated based on the data from study EFC11072 Part B (MOBILITY Part B): SD = 0.52 and treatment difference = 0.2 in the low dose group and 0.28 in the high dose group at Week 12. Using these assumptions, the power for HAQ-DI at Week 12 is 90% for the low dose group and >90% for the high dose group. For ACR20 at Week 24, the samples size provided 99% power. Computations for ACR20 were based on the following assumptions:

- Week 24 ACR20 response rates of 20% in the placebo group versus 50% in the treatment group
- A two-sided  $\chi^2$  test with an alpha of 0.025 to address the multiplicity across the 2 active dose regimens

**Analysis populations:** The definitions for the primary efficacy analysis population and PK population were similar to those in the other pivotal study EFC11072 Part B.

The safety population was defined slightly differently. The safety population consisted of all patients from the randomized population who received at least 1 dose or part of a dose of IMP. The safety analysis was performed on the safety population. Patient data were analyzed according to the treatment actually received (as treated population). Nonrandomized but treated patients were not part of the safety population; their safety data were presented separately. Randomized patients for whom it was unclear whether they took the study medication were included in the safety population. For patients receiving more than 1 study treatment during the trial, the treatment group allocation for as-treated analysis was the treatment group in which the patient was treated for the longest duration.

### Analysis of efficacy:

*Reviewer Comment: Please see the review of Dr. Yongman Kim (primary statistical reviewer) for full details of the statistical plan for the efficacy endpoints. The majority of this overview is derived from Dr. Kim's review.*

The statistical methods including analysis set, models, handling data for subjects who escaped to rescue from Week 12, and handling missing data due to dropout were the same as the methods used in Study EFC11072 Part B.

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

*Reviewer Comment: As commented with Study EFC11072 Part B, the statistical team requested additional sensitivity analyses including tipping point analyses for the primary endpoint. Sanofi submitted these analyses as a response to an IR after the filing meeting.*

In order to protect the family-wise type 1 error rate at  $\alpha=5\%$  (2-sided), the applicant proposed a similar hierarchical testing procedure with a Bonferroni correction to adjust for the multiple doses and endpoint as in the other pivotal study, EFC11072 Part B. A hierarchical testing procedure was used for the multiple endpoints at  $\alpha = 0.025$  for each dose regimen separately. The hierarchy follows the order below:

1. Incidence of ACR20 response at Week 24
2. Change from baseline HAQ-DI at Week 12
3. Change from baseline in DAS28-CRP at Week 24
4. Incidence of ACR50 response at Week 24
5. Incidence of ACR70 response at Week 24
6. Incidence of DAS28-CRP <2.6 response at Week 24
7. Change from baseline in CDAI at Week 24
8. Change from baseline in HAQ-DI at Week 24
9. Change from baseline in SF36-PCS at Week 24
10. Change from baseline in SF36-MCS at Week 24
11. Change from baseline in FACIT-Fatigue at Week 24
12. Change from baseline in Morning Stiffness VAS at Week 24
13. Change from baseline in WPS-RA at Week 24
14. Change from baseline in RAID at Week 24
15. Change from baseline in EQ-5D-3L at Week 24

**Analysis of safety:** The safety analyses were based on the reported AEs, clinical laboratory evaluations, vital signs, and 12-lead ECGs. Overall, the analyses were the same as the ones performed for EFC11072 Part B. Some differences are described below.

- Adverse events reported in this study were coded using MedDRA, version 17.1.
- The following adjudicated event summaries were generated for the safety population:
  - MACE (primary) and MACE (narrow), showing number (%) of patients with at least 1 adjudicated treatment-emergent CV AE and number of AEs per 100 patient-years
  - All adjudicated treatment-emergent CV AEs by CV event categories, showing number (%) of patients with at least 1 adjudicated treatment-emergent CV AE and number of AEs per 100 patient-years, sorted by alphabetical order
  - All AEs that underwent adjudication, all AEs adjudicated as non-CV events, and all AEs that were not evaluable, showing number (%) of patients
- In addition to the clinical laboratory evaluation already described for EFC11072 Part B, some further details were provided for this study.

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

- Time to onset of the initial LDL elevation, time to onset of the initial total cholesterol evaluation, and time to onset of the initial G3 or G4 neutropenia (ANC <1.0 Giga/L), time to onset of the initial lymphocyte count <1 Giga/L, and time to onset of the initial platelet count <100 Giga/L were analyzed using Kaplan-Meier estimates, using the midpoint of the time interval between the first assessment showing the elevation and the previous assessment, presented by treatment groups.
- Lymphopenia: The incidence of lymphopenia by maximal grade (lowest lymphocyte count reported during the TEAE period) was summarized.
  - Grade 1:  $\geq 0.8$  Giga/L-LLN
  - Grade 2:  $\geq 0.5$  Giga/L - < 0.8 Giga/L
  - Grade 3:  $\geq 0.2$  Giga/L - < 0.5 Giga/L
  - Grade 4: < 0.2 Giga/L
- Thrombocytopenia: The incidence of thrombocytopenia by the lowest platelet count reported during the TEAE period was summarized by the below categories:
  - $\geq 75$  Giga/L – LLN
  - $\geq 50$  Giga/L - < 75 Giga/L
  - $\geq 25$  Giga/L - < 50 Giga/L
  - <25 Giga/L

### **Analyses of PK and PD variables**

The PK and immunogenicity analyses were the same as previously described for study EFC11072. See the description of the protocols above.

### **Analyses of quality of life/health economics variables**

Change from baseline at Week 12 and Week 24 for the following variables were analyzed with an MMRM approach described previously for the continuous secondary efficacy variables.

- 2 summary measures of SF-36 (physical component summary score and mental component summary score) and the 8 domains
- Quantitative variables of EQ-5D-3L (VAS and single index utility)
- FACIT-Fatigue
- Morning stiffness VAS
- RAID
- 8 WPS-RA scores

The model, including treatment, region, number of previous anti-TNFs, visit, and treatment-by-visit interaction as fixed effects, and baseline as covariate, were used to test the difference of least-square means (LS means) between each active treatment group versus placebo in the change from baseline in each variable. Descriptive statistics including number of subjects, mean, standard error, and LS means were provided. In addition, difference in LS means, the corresponding 95% CI, and the p-value was provided for comparisons of each dose against placebo.

Clinical Review  
Reviewer: Suzette Peng, MD  
NME/BLA 761037  
Sarilumab/Kevzara

### **Protocol Amendments**

There were a total of 3 amendments to the protocol. They will be briefly described here.

- The first amendment (September 6, 2012) was introduced before the inclusion of any subjects and, thus, was applied to all subjects. New safety measures were implemented to prevent administration of sarilumab to subjects at risk for developing severe thrombocytopenia ( $<100,00/\text{mm}^3$ ) and grade 3/4 neutropenia. Additionally, subjects, who met criteria for lack of efficacy and could receive rescue therapy, no longer received open-label sarilumab. Instead, these subjects directly enrolled into the open-label extension study LTS11210. It was clarified that SAEs and AESIs must be reported to the monitoring team within 24 hours.
- The second amendment (April 3, 2013) was mostly updates to language and text. No major clinical changes were made.
- The third amendment modified the analyses for the co-primary endpoint related to change in physical function as measured by HAQ-DI. Instead of the “average of change from baseline in the HAQ-DI from Week 8 to Week 24,” the co-primary endpoint was changed to “the change from baseline in the HAQ-DI at Week 12.” Sanofi noted that this change was done to ensure that a robust analysis was performed at the time point where the amount of missing data was minimal but where there is still a sufficiently long period of treatment with study drug. The other changes in this amendment were related to removing certain references or replacing wording, and these will not be described in detail here.

### **Data Quality and Integrity: Sponsor's Assurance**

In order to assure data quality and integrity, Sanofi provided several assurances. Regular site monitoring ensured the quality of trial conduct. Sanofi conducted Investigator meetings and training sessions for clinical research associates as well as individual site initiation meetings to develop a common understanding of the clinical study product, case report form, and study procedures, in compliance with GCP.

Management of clinical trial data was performed according to the following rules and procedures. Data entry, verification, and validation were carried out using standard computer software (Medidata Rave 2014.1.0) where data were stored. A double-entry method was used to ensure that the PRO data (except comments) were transferred accurately from the case report forms to the database. Moreover, every modification in the database was traced using an audit trail.

#### **6.3.2. Study Results**

### **Compliance with Good Clinical Practices**

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

As with Study EFC11072, Sanofi reported compliance with Good Clinical Practices (GCP). The protocol complied with recommendations of the 18<sup>th</sup> World Health Congress (Helsinki, 1964), all applicable amendments issued by the World Medical Assemblies, and the ICH guideline for GCP. The protocol also complied with the laws, regulations, and any applicable guidelines of the countries where the study was conducted. Informed consent was obtained prior to the conduct of any study-related procedures. The patient informed consent form (ICF) was modified according to local regulations and requirements. The Investigator (according to the applicable regulatory requirements) or a person designated by the Investigator fully informed the patient of all pertinent aspects of the clinical trial including the written information giving approval/favorable opinion by the IRB/IEC. All participants were informed to the fullest extent possible about the study in language and term that they could understand. Prior to a patient's participation in the clinical trial, the written informed consent form and the optional pharmacogenetic informed consent form were signed, name filled, and personally dated by the patient and by the person who conducted the informed consent discussion.

### Financial Disclosure

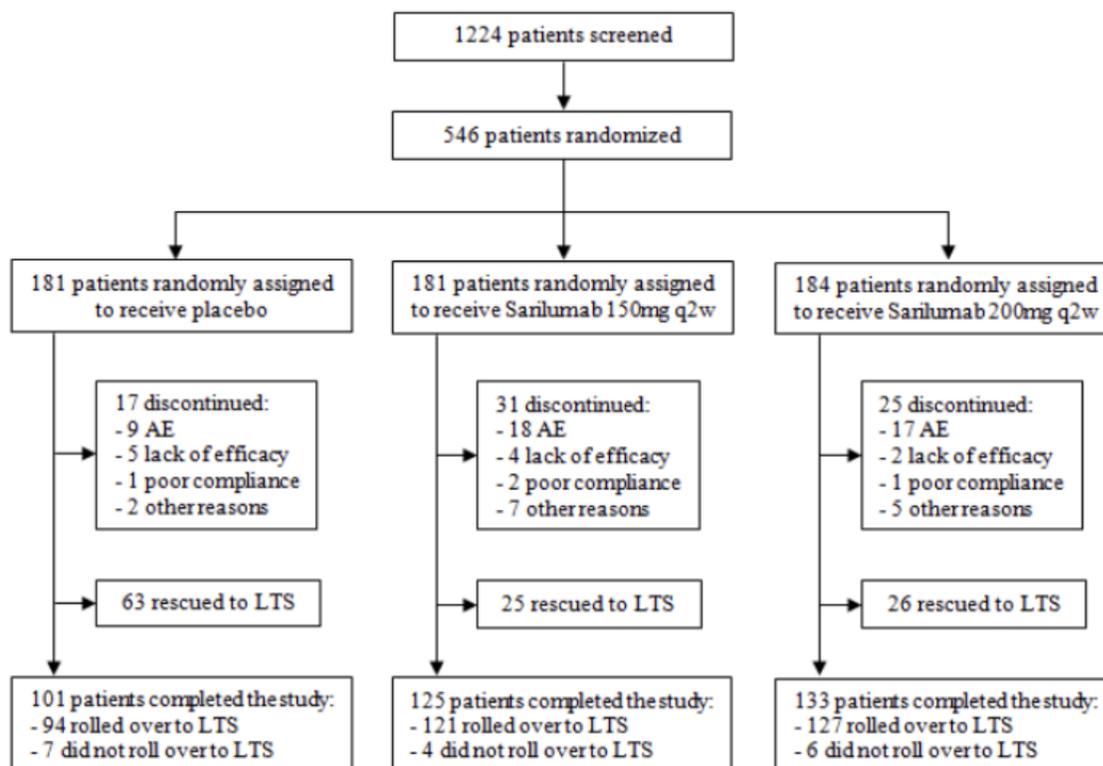
Sanofi has adequately disclosed financial interests/arrangements with clinical investigators for this study. See Table 138 in Appendix Section 13.2 for a full review of Sanofi's financial disclosure.

### Patient Disposition

Figure 10 is a diagram illustrating the disposition of subjects randomized in study EFC10832. A total of 1224 subjects were screened, but there were 678 screen failures (55.4%). Screen failures were mainly due to failure to meet certain inclusion criteria (severity of disease [53%] or not having a hs-CRP  $\geq$  8 mg/L) or ability to meet certain exclusion criterion (tuberculosis [21%]). Therefore, 546 subjects were randomized and treated. These subjects, thus, represented the ITT/efficacy population as well as the safety population.

The proportion of subjects who completed the study through Week 12 was essentially the same for all treatment arms at 91%. However, more subjects on sarilumab completed the 24-week treatment period compared to placebo. In the placebo arm, 55.8% of subjects completed the study, and 51.9% rolled over to LTS11210. In the sarilumab 150mg q2w arm, 69.1% of subjects completed the study, and 66.9% rolled over to open-label extension. Lastly, in the sarilumab 200mg q2w arm, 72.3% of subject completed the 24-week treatment period, and 69.0% rolled over to LTS11210. The most common reason for treatment discontinuation was adverse events for all arms although the proportions of subjects who discontinued due to AEs were higher in the sarilumab arms.

**Figure 10. Patient Disposition for EFC10832**



Source: EFC10832 CSR, Figure 2, dated July 24, 2015; page 64.

*Reviewer Comment: Much like EFC11072 Part B, Dr.Kim (the primary statistical reviewer) noted that more subjects were rescued due to lack of efficacy in the placebo arm compared to sarilumab. In the placebo arm, 63 of 181 subjects (34.8%) were rescued by Week 24 compared to 25 of 181 subjects (13.8%) on sarilumab 150mg q2w and 26 of 184 subjects (14.1%) on sarilumab 200mg q2w. At Week 12, Dr.Kim noted that, when looking at the number of subjects who met criteria for “lack of efficacy,” more subjects on placebo were rescued compared to subjects on sarilumab. Please see the Reviewer Comment about this issue for study EFC11072. Also, see Dr.Kim’s detailed review. Dr.Kim asked Sanofi to explain this discrepancy, and the applicant essentially argued that the differences were due to clinical judgment and better PROs and self-assessments in the sarilumab arms. Thus, fewer subjects on sarilumab were rescued.*

### Protocol Violations/Deviations

A total of 6 subjects experienced what Sanofi deemed as an “important protocol deviation” that might have a potential impact on the efficacy analyses. One subject in each treatment arm did not meet the TNF inhibitor failure inclusion criteria. Additionally, there were 3 other subjects on sarilumab who did not meet the exclusion criterion of treatment with a biologic other than TNF antagonists and the inclusion criterion of continuous treatment of a conventional DMARD

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

for at least 12 weeks prior to screening. Sanofi noted that the data from these subjects were not excluded for analyses.

*Reviewer Comment: With such few deviations, it is unclear whether these would truly have an impact on efficacy analyses. It is appropriate that Sanofi include these subjects' data in the analyses of safety and efficacy.*

Randomization and dosing irregularities were defined prior to database lock. More randomization and dosing irregularities were reported in the sarilumab groups than the placebo group. The etiology for these irregularities was essentially 2 things: kits not available and stratification error.

There were 4 subjects (1 in the placebo arm and 3 in the sarilumab 150mg q2w arm) who had "other important protocol deviations." The actual events included not permanently discontinuing a subjects with an ALT >5x ULN (placebo), presence of severe uncontrolled hypercholesterolemia or hypertriglyceridemia at baseline, and the use of other biologics during study treatment.

There were 177 major qualitative deviations. Some of these included errors in a direct –to-patient letter for recruitment purposes, incorrect programming of urine microscopy panels due to misunderstanding of the protocol which led to 1185 missing urine microscopy tests, 86 events where ANA titers equal to 1:160 were not reflexively tested for dsDNA Ab, and discrepancy between the protocol and consent form with the laboratory collection requirement for DNA sampling (12mL on consent instead of 6 mL in actuality). Corrective measures were performed for many of these events.

Lastly, in regards to breaking of the blind, there were no subjects for whom the blind was broken by the Investigator. However, there were 3 subjects (1 in each treatment arm) who experienced SAEs for which the blind was subsequently broken for regulatory purposes.

### **Table of Demographic Characteristics**

In study EFC10832, the majority of subjects were less than 65 years-old, female, and Caucasian. The mean weight ranged from 77-79kg across treatment arms. Table 14 presents the baseline characteristics of the patient population for EFC10832. Overall, the baseline patient characteristics are comparable across treatment arms.

**Table 14. Baseline Demographics and Patient Characteristics for Study EFC10832**

	Placebo + DMARD (N=181)	Sarilumab	
		150mg q2w + DMARD (N=181)	200mg q2w + DMARD (N=184)
<b>Age (years)</b>			
Number	181	181	184
Mean (SD)	51.9 (12.4)	54.0 (11.7)	52.9 (12.9)
Median	53.0	54.0	54.0
Min: Max	24: 79	23:88	19:87
<b>Age Group [n(%)]</b>			
Number	181	181	184
<65 years	152 (84.0%)	150 (82.9%)	154 (83.7%)
≥65-75 years	26 (14.4%)	24 (13.3%)	21 (11.4%)
≥ 75 years	3 (1.7%)	7 (3.9%)	9 (4.9%)
<b>Sex [n(%)]</b>			
Number	181	181	184
Male	27 (14.9%)	39 (21.5%)	33 (17.9%)
Female	154 (85.1%)	142 (78.5%)	151 (82.1%)
<b>Race [n(%)]</b>			
Number	181	181	184
Caucasian	124 (68.5%)	134 (74.0%)	130 (70.7%)
Black	7 (3.9%)	8 (4.4%)	5 (2.7%)
Asian	1 (0.6%)	3 (1.7%)	1 (0.5%)
Other	49 (27.1%)	36 (19.9%)	48 (26.1%)
<b>Ethnicity [n(%)]</b>			
Number	181	181	184
Hispanic	77 (42.5%)	77 (42.5%)	88 (47.8%)
Non-Hispanic	104 (57.5%)	104 (57.5%)	96 (52.2%)
<b>Weight (kg)</b>			
Number	181	181	184
Mean (SD)	79.41 (21.30)	78.59 (22.04)	76.68 (21.25)
<60	36 (19.9%)	29 (16.0%)	45 (24.5%)
≥60 and <100	112 (61.9%)	132 (72.9%)	109 (59.2%)
≥100	33 (18.2%)	20 (11.0%)	30 (16.3%)
<b>BMI (kg/m<sup>2</sup>)</b>			
Number	181	181	184
Mean (SD)	30.24 (7.78)	29.14 (6.92)	29.21 (6.75)
<25	46 (25.4%)	48 (26.5%)	60 (32.6%)
≥25 and <30	61 (33.7%)	71 (39.2%)	54 (29.3%)
≥30	74 (40.9%)	62 (34.3%)	70 (38.0%)
<b>Region [n(%)]</b>			
Number	181	181	184

Clinical Review  
 Reviewer: Suzette Peng, MD  
 NME/BLA 761037  
 Sarilumab/Kevzara

Region 1	77 (42.5%)	77 (42.5%)	79 (42.9%)
Region 2	74 (40.9%)	74 (40.9%)	74 (40.2%)
Region 3	30 (16.6%)	30 (16.6%)	31 (16.8%)
<b>Smoking status [n(%)]</b>			
Number	181	181	184
Never	120 (66.3%)	113 (62.4%)	130 (70.7%)
Former	36 (19.9%)	36 (19.9%)	42 (22.8%)
Current	25 (13.8%)	32 (17.7%)	12 (6.5%)
<b>Alcohol habits<sup>a</sup> [n(%)]</b>			
Number	181	181	184
Never	139 (76.8%)	131 (72.4%)	150 (81.5%)
Monthly	29 (16.0%)	28 (15.5%)	22 (12.0%)
Weekly	12 (6.6%)	18 (9.9%)	10 (5.4%)
Daily	1 (0.6%)	4 (2.2%)	2 (1.1%)

Number = number of patients assessed. Percentages are calculated using number of patients assessed as denominator.  
 Region 1 (Western Countries): Australia, Canada, Czech Republic, Germany, Greece, Hungary, Israel, Italy, New Zealand, Portugal, Spain, USA  
 Region 2 (South American): Argentina, Brazil, Chile, Colombia, Ecuador, Guatemala, Mexico, Peru  
 Region 3 (Rest of the world): South Korea, Lithuania, Poland, Russia, Taiwan, Turkey, Ukraine  
 a Alcohol habits: how often subject has a drink containing alcohol in the last 12 months  
 Source: EFC10832 CSR, Table 10, dated July 24, 2015; page 72-73.

*Reviewer Comment: The majority of subjects were younger than 65 years of age, female, and Caucasian. These characteristics are consistent with the general US RA population. Like EFC11072 Part B, there is a greater representation from the “other” race category too, which is good because RA can occur in all races. However, the “other” category does not really detail which other races are included. In study EFC10832, the majority of subjects are also from Regions 1 and 2, which represented North America, South America, Western Europe, and Australia/New Zealand. Therefore, there may be more direct representation from the US population in this study.*

### **Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)**

At baseline, the mean duration of RA in the patient population for EFC10832 was 12.1 years (range 0.6 to 54.0 years). Most subjects had Class II disease and were seropositive (RF and anti-CCP antibody positive). Per protocol, all subjects were previously treated with a biologic DMARD with most (51-54%) having been treated with 1 biologic. The mean DAS28-CRP score was 6.09-6.29, consistent with high disease activity. Overall, the baseline disease characteristics were comparable across treatment arms.

**Table 15. Baseline Disease Characteristics for Study EFC10832**

	Placebo + DMARD (N=181)	Sarilumab	
		150mg q2w + DMARD (N=181)	200mg q2w + DMARD (N=184)
<b>Duration of RA since diagnosis (Years)</b>			
Number	181	181	184
Mean (SD)	12.04 (9.99)	11.55 (8.55)	12.68 (9.63)
Median	9.53	10.20	10.34
Min: Max	0.6: 54.0	0.7: 45.6	0.6: 46.2
<b>RA functional class [n(%)]</b>			
Number	181	181	184
I	13 (7.2%)	20 (11.0%)	19 (10.3%)
II	110 (60.8%)	100 (55.2%)	105 (57.1%)
III	58 (32.0%)	61 (33.7%)	60 (32.6%)
IV	0	0	0
<b>Rheumatoid factor [n(%)]</b>			
Number	180	181	181
Positive	142 (78.9%)	135 (74.6%)	132 (72.9%)
Negative	38 (21.1%)	46 (25.4%)	49 (27.1%)
<b>Anti CCP antibody [n(%)]</b>			
Number	180	180	180
Positive	150 (83.3%)	135 (75.0%)	137 (76.1%)
Negative	30 (16.7%)	45 (25.0%)	43 (23.9%)
<b>Number of non-biological DMARDs [n(%)]</b>			
Number	181	181	184
None	0	0	0
1	98 (54.1%)	93 (51.4%)	101 (54.9%)
2	50 (27.6%)	50 (27.6%)	50 (27.2%)
≥ 3	33 (18.2%)	38 (21.0%)	33 (17.9%)
<b>Number of previous anti-TNFs [n(%)]</b>			
Number	181	180	183
1	135 (74.6%)	143 (79.4%)	140 (76.5%)
≥ 1	46 (25.4%)	37 (20.6%)	43 (23.5%)
<b>Tender joint count (0-68)</b>			
Number	181	181	184
Mean (SD)	29.42 (14.54)	27.66 (15.57)	29.55 (15.54)
Median	29.00	24.00	26.50
Min: Max	8.0: 68.0	5.0: 68.0	4.0: 68.0
<b>Swollen joint count (0-66)</b>			

Clinical Review  
 Reviewer: Suzette Peng, MD  
 NME/BLA 761037  
 Sarilumab/Kevzara

Number	181	181	184
Mean (SD)	20.21 (11.34)	19.60 (11.23)	19.97 (11.94)
Median	17.00	16.00	17.00
Min: Max	6.0: 60.0	6.0: 66.0	3.0: 62.0
<b>CRP (mg/L)</b>			
Number	181	181	184
Mean (SD)	26.02 (25.20)	23.60 (23.44)	30.77 (28.35)
Median	17.00	16.80	21.70
Min: Max	1.2: 147.0	0.2: 148.0	0.3: 142.0
<b>CRP (<math>\leq 15</math>mg/L, <math>&gt;15</math>mg/L) [n(%)]</b>			
Number	181	181	184
$\leq 15$ mg/L	82 (45.3%)	83 (45.9%)	68 (37.0%)
$> 15$ mg/L	99 (54.7%)	98 (54.1%)	116 (63.0%)
<b>HAQ-DI (0-3)</b>			
Number	181	181	184
Mean (SD)	1.80 (0.64)	1.72 (0.62)	1.82 (0.62)
Median	1.88	1.75	1.88
Min: Max	0.0: 2.9	0.0: 3.0	0.0: 3.0
<b>DAS28-CRP</b>			
Number	181	181	184
Mean (SD)	6.23 (0.86)	6.09 (0.90)	6.29 (0.98)
Median	6.14	6.13	6.27
Min: Max	4.4: 8.1	3.3: 8.0	3.9: 8.3

Number = number of patients assessed. Percentages are calculated using number of patients assessed as denominator.

DAS28-CRP $>5.1$  = high disease activity

Source: EFC10832 CSR, Table 11, dated July 24, 2015; page 74-5.

### Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment compliance was ascertained from records of medication treatment packs and/or diaries. The vast majority of subjects (98.9% to 99.4%) were compliant at  $\geq 80\%$ . Only 1 subject in the placebo arm, 1 subjects in the sarilumab 150mg q2w arm, and 2 subjects in the sarilumab 200mg q2w arm had a compliance  $<80\%$ . As with EFC11072 Part B, for most of these subjects, compliance was less because of protocol-specified temporary treatment discontinuation. One subject in the sarilumab 200mg q2w arm mistakenly received placebo on 2 occasions. Lastly, 22 subjects (4 in placebo arm, 8 in the 150mg q2w arm, and 10 in the 200mg q2w arm) received an “overdose” as defined in the protocol.

*Reviewer Comment: Overall, treatment compliance was good. It is unlikely that the data from subjects who received an incorrect dose or an overdose should affect the data analyses.*

### Efficacy Results - Primary Endpoint

Clinical Review  
Reviewer: Suzette Peng, MD  
NME/BLA 761037  
Sarilumab/Kevzara

The co-primary endpoints and major secondary endpoints will be presented from both pivotal studies (EFC11072 Part B Cohort 2 and EFC10832) in Section 7. These endpoints include the co-primary endpoints: ACR20 at Week 24 and change from baseline in HAQ-DI at Week 12. Other secondary endpoints in Section 7 include ACR20 reponse over time, major clinical response, change in baseline in DAS28-CRP, ACR50/70, DAS28-CRP <2.6, and SF-36 (physical and mental components).

The dose response, durability of response, and persistence of effect will also be reviewed in the Integrated Review of Efficacy in Section 7.

### **Data Quality and Integrity - Reviewers' Assessment**

There are no issues with data quality and integrity. No audits were performed on the case report forms or clinical source data. There were no significant OSI findings that would affect the data or require exclusion of data from any sites. As will be discussed in Section 7, the major efficacy assessments were supported by various sensitivity analyses and confirmed by the Agency's statistical team.

### **Efficacy Results - Secondary and other relevant endpoints**

The results for SDAI remission, CDAI remission, and the ACR/EULAR Boolean-based definition of remission will be presented here. As noted above in Section 6.2.2, in the "treat-to-target" strategy, remission is now the recommend goal for treatment of RA. Therefore, the proportion of subjects who achieve these accepted definitions of remission will be reviewed. As these endpoints do not appear on the hierarchy for statistical analyses for either pivotal trial, these results will not be described in the Integrated Analyses of Efficacy below. Rather, they will be presented for each respective pivotal trial in Section 6.

The definition of remission utilizing SDAI is  $SDAI \leq 3.3$ . The proportion of subjects who achieved SDAI remission was numerically higher in subjects on sarilumab at Weeks 12 and 24 compared with placebo. At Week 12, no subjects on placebo, 6.1% of subjects on sarilumab 150mg q2w (nominal p-value 0.0007), and 5.4% of subjects on sarilumab 200mg q2w (nominal p-value 0.0014) achieved SDAI remission. At Week 24, 2.4% of subjects on placebo, 9.9% of subjects on sarilumab 150mg q2w (nominal p-value 0.0044), and 8.7% of subjects on sarilumab 200mg q2w (nominal p-value 0.0146) achieved SDAI remission.

CDAI remission is defined as  $CDAI \leq 2.8$ . The proportion of subjects who achieved CDAI remission was higher in the sarilumab group at both Weeks 12 and 24. The proportions of subjects who achieved CDAI remission were 0.6% for placebo, 3.3% for sarilumab 150mg q2w (nominal p-value 0.0551), and 4.9% for sarilumab 200mg q2w (nominal p-value 0.0106) at Week 12 and 5.0% for placebo, 9.4% for sarilumab 150mg q2w (nominal p-value 0.0971), and 8.2% for sarilumab 200mg q2w (nominal p-value 0.2134) at Week 24.

CDER Clinical Review Template 2015 Edition  
*Version date: November 5, 2015 for initial rollout (NME/original BLA reviews)*

140

Clinical Review  
Reviewer: Suzette Peng, MD  
NME/BLA 761037  
Sarilumab/Kevzara

Lastly, the proportion of subjects achieving the Boolean-based ACR/EULAR definition of remission was also numerically higher for subjects on sarilumab compared to placebo. At Week 12, the proportion of subjects achieving remission was no subjects on placebo, 3.3% of subjects on sarilumab 150mg q2w (nominal p-value 0.0129), and 2.7% of subjects on sarilumab 200mg q2w (nominal p-value 0.252). At Week 24, 2.8% in the placebo arm, 5.5% in the sarilumab 150mg q2w arm (nominal p-value 0.1794), and 6.0% in the sarilumab 200mg q2w arm (nominal p-value 0.1309) achieved this definition of remission.

In summary, more subjects on sarilumab achieved these different definitions of remission compared to placebo. Overall, though, the proportions are low, and, in this study, the nominal p-values are not quite as impressive as in study EFC11072 Part B. The smaller differences may be related to the earlier timepoints of assessment (Weeks 12 and 24) in EFC10832. These results, though, are consistent with the efficacy data from the primary and major secondary endpoints and support the efficacy of sarilumab compared to placebo.

#### **Additional Analyses Conducted on the Individual Trial**

Safety analyses of the pivotal study 10832 will not be presented individually here. It will be reviewed as part of the integrated safety assessment with the other studies from the entire sarilumab clinical development program in Section 8.

### **6.4. SFY13370 (SARIL-RA-ASCERTAIN)**

#### **6.4.1. Study Design**

##### **Overview and Objective**

SFY13370 was a randomized, double-blind, double-dummy, parallel-group, 3-arm 24-week study to assess the safety and tolerability of sarilumab and tocilizumab in patients with RA who are inadequate responders to or intolerant of TNF antagonists. The study was not designed to show statistical differences between the treatments but was designed to establish additional context for safety of sarilumab and tocilizumab.

The primary objective was to assess the safety of sarilumab and tocilizumab in patients with RA in the same study. Exploratory objectives included (1) exploring the clinical effects of sarilumab and tocilizumab in patients with RA and (2) collecting DNA and other biomarkers for future use for the purpose of discovery of predictive biomarkers.

##### **Trial Design**

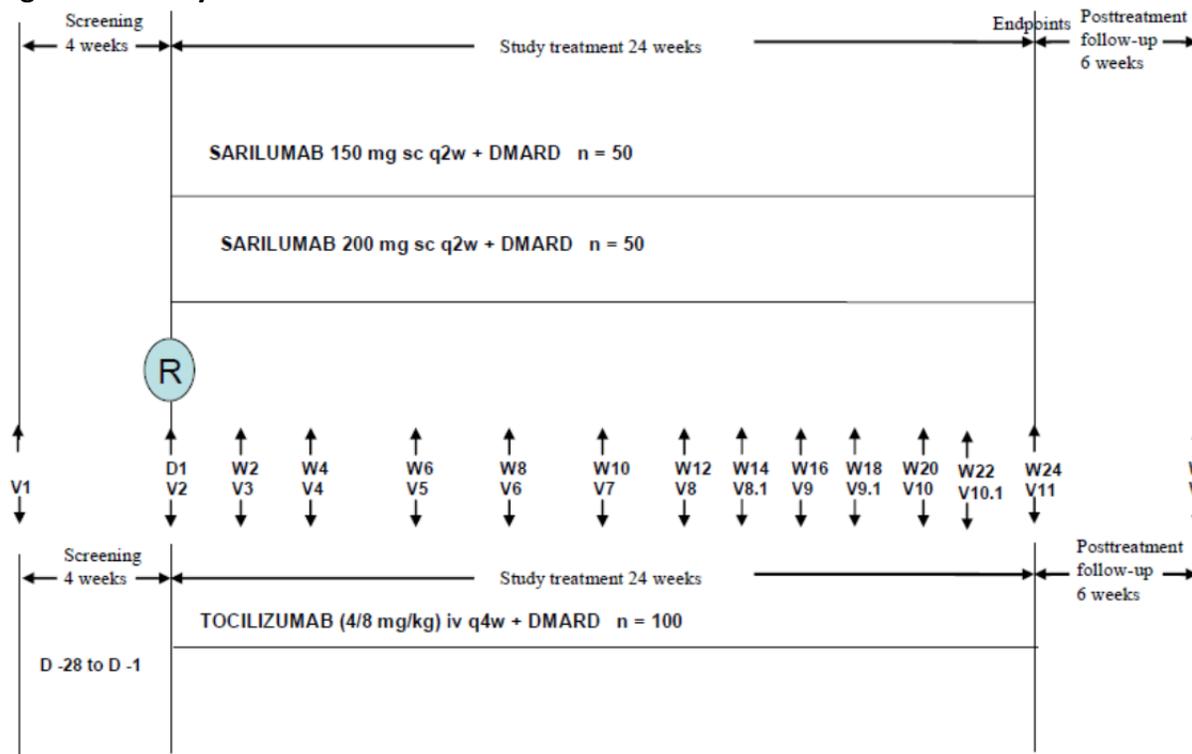
Clinical Review  
 Reviewer: Suzette Peng, MD  
 NME/BLA 761037  
 Sarilumab/Kevzara

**Basic Study Design**

SFY13370 was a 24-week, randomized, double-blind study. Patients were randomized in a 1:1:2 ratio to receive SC sarilumab 150mg q2w or 200mg q2w or IV tocilizumab. The dose of tocilizumab was the approved dose at the time (October 2012), a starting dose of IV 4 mg/kg followed by 8 mg/kg based on clinical response. Sarilumab and tocilizumab were added to non-biologic DMARD background therapy. Figure 11 illustrates the study design.

The total maximum duration of participation for a subject was 34 weeks, which comprised of 4 weeks of screening, 24 weeks of double-blind treatment, and 6 weeks of post-treatment follow-up. See the schedule of assessments in the Appendix, Table 144. Patients who completed the treatment phase could enter the long-term safety study LTS11210.

**Figure 11. Study Schema of SFY13370**



Source: SFY13370 Clinical Study Report, dated August 12, 2015, Figure 1, page 20.

*Reviewer Comment: This is an active comparator study, which is appropriate for the objective of comparing safety of sarilumab to the only approved IL-6 receptor blocking agent, tocilizumab. Tocilizumab has been on the market in the US since 2010, and, thus, there are over 5 years of experience and understanding of its benefit-risk profile. The doses selected are appropriate, as the sarilumab doses are the same as those in the pivotal trials (and are the doses that Sanofi wishes to market). Although tocilizumab is available in a subcutaneous formulation now, the CDER Clinical Review Template 2015 Edition*

*Version date: November 5, 2015 for initial rollout (NME/original BLA reviews)*

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

*dose and formulation used in this study are appropriate given what was approved at the time. Sanofi argues that the study duration (24 weeks) was long enough “to provide useful data about the safety profiles of sarilumab and tocilizumab.” Twenty-four weeks, however, may not be sufficient to compare rarer safety events that may take longer to occur, such as cardiovascular events and malignancy. In addition, the study was not designed to make any statistical comparisons. Nevertheless, this active comparator study may be quite informative in the evaluation of safety and even efficacy of sarilumab.*

### **Key inclusion/exclusion criteria**

The inclusion and exclusion criteria were essentially the same as those for the pivotal trial, EFC10832. The major difference is listed below.

- Moderately to severely active RA was defined as the following
  - At least 4 of 68 tender joints and 4 of 66 swollen joints
  - hs-CRP  $\geq$  4 mg/L at screening

*Reviewer’s Comment: The definition of “active” disease was different than both pivotal trials. EFC11072 and EFC10832 both required at least 8 tender joints and 6 swollen joints and higher hsCRP (10 mg/L in EFC11072 and 8 mg/L in EFC10832). Therefore, patients in this trial essentially had less active disease.*

### **Concomitant medications**

Similar to pivotal study EFC10832, subjects continued to receive regular treatment with one or a combination of non-biologic DMARDs such as MTX, SSZ, LEF, and HCQ. These DMARDs should have been started at least 12 consecutive weeks prior to screening and should be taking a stable dose for at least 6 consecutive weeks prior to screening. Non-biologic DMARDs could be reduced at any time for safety or tolerability.

The allowed and prohibited concomitant medications are the same as those for study EFC10832.

### **Study treatments**

Sarilumab and its matching placebo were previously discussed for studies EFC11072 Part B. The same description of study treatment applies here.

Tocilizumab and its matching placebo were dispensed in single-use vials. The tocilizumab was provided at a concentration of 20 mg/mL. An on-site, third-party, unblinded pharmacist diluted IV IMP to 100 mL in 0.9% sodium chloride for IV infusion using aseptic techniques. The IV IMP was administered q4w as a 60-minute single IV infusion. The tocilizumab starting dose was 4 mg/kg but was increased to 8mg/kg based on clinical response.

Clinical Review  
Reviewer: Suzette Peng, MD  
NME/BLA 761037  
Sarilumab/Kevzara

### **Assignment to treatment**

Subjects were randomized to one of the treatment arms via the centralized randomization system using an IVRS stratified by region and by screening value of ANC. A patient was considered randomized when the treatment number was provided by the IVRS. Subjects were randomized at a ratio of 1:1:2 (sarilumab 150mg q2w: sarilumab 200mg q2w: tocilizumab IV 4mg/kg q4w).

### **Blinding**

The investigators and patients were blinded to the allocation of sarilumab or tocilizumab treatment arms. Sarilumab/matching placebo and tocilizumab/matching placebo had different routes of administration. Consequently, double-dummy techniques were used to preserve blinding between sarilumab and tocilizumab. All patients received SC and IV IMPs to maintain the blinding between sarilumab (SC administration) and tocilizumab (IV administration). Patients randomized to sarilumab were administered active sarilumab and IV placebo. Patients randomized to placebo were administered tocilizumab and SC placebo. Sarilumab 150mg, sarilumab 200mg, and matching placebo were provided in undistinguishable matching glass prefilled syringes in identical kits. Tocilizumab and placebo, however, were provided in unmatched glass vials but in identical/matching kits. IV IMPs were prepared similarly, and, once prepared, tocilizumab and placebo infusions were undistinguishable.

To maintain the blind, tocilizumab and unmatched placebo were dispensed and prepared by an unmasked third-party pharmacist. Also, to maintain blind after infusion preparation, the unmasked third-party injector disposed of the needles in an appropriate dispenser, returned the used vials in the original box, and completed the treatment log form.

### **Administrative structure**

A total of 86 sites located in Europe (including Asia), North America, and South America participated in this study. Out of these 86 sites, 78 sites screened patients, and 68 sites enrolled patients.

The administrative structure was, otherwise, the same as the pivotal trials. See descriptions for studies EFC11072 and EFC10832.

### **Dose modifications**

Sarilumab doses were not changed throughout the study.

Tocilizumab started at a dose of 4 mg/kg and could be increased to 8 mg/kg based on clinical response. The Investigator could also decrease to 4 mg/kg based on clinical judgement.

### **Treatment compliance**

CDER Clinical Review Template 2015 Edition  
*Version date: November 5, 2015 for initial rollout (NME/original BLA reviews)*

144

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

Administration of the first dose IMPs was supervised by the Investigator or Subinvestigator. Administration of all doses of IV IMP was completed on site. Administration of doses (post-first dose) of SC IMP could be done by the patient at home or by a healthcare provider after documented training. Compliance was assessed by entries in the patient diary.

### **Subject completion, discontinuation, or withdrawal**

Subjects could withdraw from treatment with IMP if they decided to do so at any time, irrespective of reason, or if the Investigator decided. All efforts were made to document the reasons for treatment discontinuation in the e-CRF. If a temporary discontinuation of SC IMP exceeded 31 days or a temporary discontinuation of IV IMP exceeded 42 days, the discontinuation was considered permanent.

The IMP was permanently discontinued for the following reasons:

- Opportunistic infections including TB. TB could be diagnosed based on symptoms or a CXR suggestive of active TB. Whenever possible, culture confirmation of the disease had to be obtained and then recorded in the e-CRF.
- The patient was at risk through close contact with a person with active TB, and the patient refused to undergo TB evaluation.
- Culture positive for nontuberculous mycobacteria
- Symptoms of systemic hypersensitivity or anaphylactic reactions
- Severe neurologic disease such as demyelinating disease or PML
- Significant laboratory abnormalities
  - ALT >5 x ULN or ALT >3x ULN with concomitant total bilirubin >2x ULN
  - Neutrophil count < 500/mm<sup>3</sup> or neutrophil count <1000/mm<sup>3</sup> with evidence of infection
  - Platelet count <50,000/mm<sup>3</sup> or platelet count <100,000/mm<sup>3</sup> with evidence of bleeding
- Acute renal failure
- Pregnancy
- Use of any biologic DMARD other than IMP
- Any adverse events, per Investigator's judgment, that could jeopardize the patient's safety
- Any treatment unblinding by the Investigator
- Visit 2 laboratory results meeting any of the laboratory values in the exclusion criteria

All abnormal laboratory values or ECG parameters were immediately rechecked for confirmation before making a decision about permanent discontinuation.

For patients who failed to return to the site, the Investigator made the best effort to recontact the patient (e.g., contacting patient's family or physicians, etc.); attempts to contact the subject

Clinical Review  
Reviewer: Suzette Peng, MD  
NME/BLA 761037  
Sarilumab/Kevzara

were documented in the subject's records. Investigators also made the best effort to determine his/her current health status.

### **Study Endpoints**

The primary endpoint of this study was safety and tolerability. Efficacy endpoints were exploratory.

### **Safety assessments**

The observation period was divided into 4 phases: screening, treatment, followup, and post-study. The TEAE period was made up of the treatment and followup periods.

- The SCREENING phase was defined as the time from the signed informed consent date up to the time prior to the first dose of IMP.
- The TREATMENT phase was defined as the time from first dose of IMP to last dose of sarilumab +13 days for patient randomized to sarilumab OR to last dose of tocilizumab + 27 days for patients randomized to tocilizumab.
- The FOLLOWUP phase was defined as the time from the end of the TREATMENT phase to the last dose of IMP + 60 days (for both sarilumab, tocilizumab, or matching placebo)
- The POST-STUDY phase was defined as the last dose of IMP + 60 days.

Safety variables were assessed according to the timeline in the Schedule of Assessments, Table 144. Safety endpoints included those generally used in studies in RA and IL-6 antagonists, including neutropenia, increases in liver associated enzymes, and lipid elevations. The safety variables (AEs, AESIs), laboratory safety parameters, chest x-ray, vital signs, physical examination, and ECG variables were essentially the same as what was previously described in the pivotal trials.

### **Exploratory efficacy assessments**

- ACR 20/50/70 at Week 24
- DAS28 <2.6 at Week 24

### **PK assessments**

Pre-dose blood samples were collected for determination of functional sarilumab concentrations and anti-sarilumab antibody (ADA) in serum, as designated in the Schedule of Assessments. If an SAE occurred, blood samples were collected for determination of functional sarilumab concentration and ADA assessment at or near the onset of the occurrence of the event and its completion.

### **Statistical Analysis Plan**

Clinical Review  
Reviewer: Suzette Peng, MD  
NME/BLA 761037  
Sarilumab/Kevzara

**Sample size:** Determination of sample size was based on practical considerations and clinical judgment, not on formal sample size calculations.

**Analysis populations:** The different analysis populations included the randomized population, the safety population, the efficacy analysis population (modified intent-to-treat), and the PK population. The populations were defined the same as they were for the pivotal studies.

**Analyses of safety data:** TEAEs, SAEs, TEAEs leading to discontinuation, and AESIs were summarized for each treatment group based on MedDRA coding of verbatim terms reported by Investigators. For laboratory parameters, vital signs, ECG, incidences of potentially clinically significant abnormality (PCSA) values, actual values, and change from baseline were summarized by treatment group.

The method for analysis was essentially the same as that for the pivotal trials. See review of the SAP for the pivotal trials for full details.

**Analyses of efficacy data:** The study was not powered for efficacy comparisons, as the primary objective was safety. Efficacy variables were summarized descriptively by treatment group and visit (Week 4, 8, 12, and 24) using counts, proportions, and 95% CI. No inferential statistics were calculated. For the primary approach, ACR20/50/70 responder status was determined using available data, and subjects automatically became non-responders for all the time points beyond the time at which study treatment was discontinued. Change from baseline in DAS28 and ACR components were summarized by treatment group and visit (W4, 8, 12, 24) using mean, standard error, and the corresponding 95% CI.

**Analysis of PK data:** Serum concentrations of functional sarilumab were summarized using descriptive statistics by treatment group for each visit. Immunogenicity analyses were also assessed utilizing the same descriptors, ADA negative and ADA positive (treatment-emergent or treatment-boosted). Sanofi summarized ADA prevalence and titer, ADA incidence and titer, ADA and clinical safety, ADA and clinical efficacy, and ADA and PK.

No PK analysis was performed for the tocilizumab group. Additionally, there was no ADA assessment in the tocilizumab group.

### Protocol Amendments

There were 2 formal protocol amendments.

- (February 1, 2013) The first amendment changed the wording of the contraceptive guidance for female patients of childbearing potential in clinical trials in the UK to comply with Medicines and Healthcare products Regulatory Agency guidances .

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

- (September 10, 20103) The second amendment made a few additional changes including adding laboratory visits at Weeks 14, 18, and 22 for additional hematology assessments and updating the AEIS with immediate notification section. Also several inconsistencies within the protocol were corrected.

Additionally, there were a few “notes to file” regarding (1) the volume of infusion and the infusion duration and (2) timing of supine blood pressure checks (2 minutes at rest).

Lastly, there were changes in the planned analyses from the protocol to the SAT, from the SAP to the database lock, and after database lock. Most were minor changes and corrections. The most significant may be the decision to further assess safety between sarilumab and tocilizumab after database lock. Ad hoc analyses were conducted by examining 2 subsets of the tocilizumab group: (1) patients who remained on tocilizumab 4 mg/kg and (2) patients who increased dose to 8 mg/kg at Week 8 and remained on the higher dose. Ad hoc analyses were performed on some selected important safety parameters such as ANC, ALT, and lipids.

### **Data Quality and Integrity: Sponsor's Assurance**

Regular site monitoring ensured the quality of trial conduct. Sanofi conducted Investigator meetings and training sessions for clinical research associates as well as individual site initiation meetings to develop a common understanding of the clinical study protocol, case report form, and study procedures, in compliance with GCP.

The same rules and procedures as described in the other protocols were performed in order to manage the clinical trial data.

## 6.4.2. Study Results

### **Compliance with Good Clinical Practices**

The clinical trial was conducted in accordance with the principles laid down by the 18<sup>th</sup> World Medical Assembly (Helsinki, 1964) and all applicable amendments laid down by the World Medical Assemblies and the ICH guidelines for GCP. In compliance with Sanofi public disclosure commitments, the clinical trial was recorded in the public registry website [clinicaltrials.gov](http://clinicaltrials.gov) before the enrollment of the first patient.

### **Financial Disclosure**

Sanofi has adequately disclosed financial interests/arrangements with clinical investigators for this study. See Table 138 in Appendix Section 13.2 for a full review of Sanofi’s financial disclosure.

### Patient Disposition

Three hundred eight-eight patients were screened, but 187 patients were screen failure. Therefore, a total of 202 patients were randomized.

Table 16 presents the disposition of all randomized patients based on the treatment arms. What is notable is that more subjects (94.1%) in the tocilizumab arm completed the study treatment period. On the other hand, more subjects on both doses of sarilumab discontinued from the study (18.4% of subjects on sarilumab 150mg q2w and 23.5% of subjects on sarilumab 200mg q2w) with adverse events being the most common reason. Most of the sarilumab discontinuations occurred before Week 16.

**Table 16. SFY13370 Patient Disposition**

	Tocilizumab q4w + DMARD N=102	Sarilumab		
		150mg q2w + DMARD N=49	200mg q2w + DMARD N=51	All N=202
Randomized and not treated	0	0	0	0
Randomized and treated	102 (100%)	49 (100%)	51 (100%)	202 (100%)
Complete the study treatment period	96 (94.1%)	40 (81.6%)	39 (76.5%)	175 (86.6%)
Discontinued from the study	6 (5.9%)	9 (18.4%)	12 (23.5%)	27 (13.4%)
Subject's request for treatment discontinuation	3 (2.9%)	2 (4.1%)	10 (19.6%)	15 (7.4%)
Reason for treatment discontinuation				
Adverse event	4 (3.9%)	7 (14.3%)	8 (15.7%)	19 (9.4%)
Lack of efficacy	1 (1.0%)	1 (2.0%)	3 (5.9%)	5 (2.5%)
Poor compliance to protocol	0	0	0	0
Other reasons	1 (1.0%)	1 (2.0%)	1 (2.0%)	3 (1.5%)
Status at last study contact				
Alive	101 (99.0%)	49 (100%)	51 (100%)	201 (99.5%)
Dead	1 (1.0%)	0	0	1 (0.5%)
Rolled over to LTS study				
Yes	93 (91.2%)	37 (75.5%)	38 (74.5%)	168 (83.2%)
No	9 (8.8%)	12 (24.5%)	13 (25.5%)	34 (16.8%)

Source: SFY13370 Clinical Study Report, Table 4, dated August 12, 2015, page 58.

### Protocol Violations/Deviations

There were no subjects with an important protocol deviation that had a potential impact on the analyses. No patients had randomization or dosing irregularities, as defined by the protocol.

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

The protocol-defined randomization or dosing irregularities included events such as kit dispensation without IVRS transaction, erroneous kit dispensation, kit not available, stratification error, and subject switched to another site. However, there were several dosing errors that did occur that did not meet the protocol definitions. These events includes cases of 2 SC IMPs being administered on site (instead of 1 on-site and 1 at home), extra doses of SC IMP because of confusion on rules of entering LTS11210, extra doses of IV IMP (placebo), and higher doses of IV IMP (tocilizumab, not meeting definition for IV IMP overdose). In addition, there were 11 patients (5.4%) with “other important protocol deviations.” These deviations were not felt to affect efficacy analyses or randomization and drug allocation irregularities. Most of these deviations occurred in the tocilizumab arm: 8 (7.8%) subjects on tocilizumab, 1 (2.0%) subject on sarilumab 150mg q2w, 2 (3.9%) subjects on sarilumab 200mg q2w. The most common of these deviations occurred in 5 subjects on the tocilizumab arm who did not meet the inclusion criteria of an inadequate response to at least one TNF $\alpha$  after being treated for at least 3 consecutive months any time before randomization.

*Reviewer Comment: Although it is unlikely that these deviations would affect analyses of the results from these studies, the possible effect is not entirely clear. For example, TNF $\alpha$  inadequate responders tend to be more recalcitrant to therapy; therefore, the 5 subjects in the tocilizumab arm, who were not TNF $\alpha$  inadequate responders, may be more naïve to therapy and, therefore, may be more responsive to therapy.*

### **Table of Demographic Characteristics**

The baseline demographics of the randomized subjects are described in Table 17. The majority were less than 65 years-old, female, and Caucasian. Thus, these characteristics were consistent with the subjects enrolled and randomized in the other sarilumab trials. Subjects in all treatment arms had generally similar patient demographics.

**Table 17. Baseline Demographics and Patient Characteristics (Study SFY13370)**

	Tocilizumab q4w + DMARD (N=102)	Sarilumab	
		150mg q2w (N=49)	200mg q2w (N=51)
<b>Age (years)</b>			
Number	102	49	51
Mean (SD)	50.4 (13.0)	54.8 (12.1)	51.7 (13.1)
Median	51.0	53.0	53.0
Min: Max	23: 77	21: 82	24: 79
<b>Age Group [n(%)]</b>			
Number	102	49	51
<65 years	87 (85.3%)	41 (83.7%)	45 (88.2%)
≥65-75 years	12 (11.8%)	5 (10.2%)	5 (9.8%)
≥ 75 years			
<b>Sex [n(%)]</b>			
Number	102	49	51
Male	20 (19.6%)	8 (16.3%)	12 (23.5%)
Female	82 (80.4%)	41 (83.7%)	39 (76.5%)
<b>Race [n(%)]</b>			
Number	102	49	51
Caucasian	94 (92.2%)	47 (95.9%)	46 (90.2%)
Black	2 (2.0%)	0	1 (2.0%)
Asian	0	0	0
Other	6 (5.9%)	2 (4.1%)	4 (7.8%)
<b>Ethnicity [n(%)]</b>			
Number	102	49	51
Hispanic	29 (28.4%)	13 (26.5%)	13 (25.5%)
Non-Hispanic	73 (71.6%)	36 (73.5%)	38 (74.5%)
<b>Weight (kg)</b>			
Number	102	49	51
Mean (SD)	73.21 (15.39)	72.62 (17.61)	77.17 (20.61)
<60	23 (22.5%)	10 (20.4%)	10 (19.6%)
≥60 and <100	72 (70.6%)	36 (73.5%)	33 (64.7%)
≥100	7 (6.9%)	3 (6.1%)	8 (15.7%)
<b>BMI (kg/m<sup>2</sup>)</b>			
Number	102	49	51
Mean (SD)	27.27 (5.15)	27.26 (5.73)	28.13 (6.61)
<25	36 (35.3%)	20 (40.8%)	18 (35.3%)
≥25 and <30	38 (37.3%)	17 (34.7%)	14 (27.5%)
≥30	28 (27.5%)	12 (24.5%)	19 (37.3%)
<b>Region [n(%)]</b>			
Number	102	49	51
Region 1	41 (40.2%)	21 (42.9%)	20 (39.2%)

Region 2	25 (24.5%)	11 (22.4%)	13 (25.5%)
Region 3	36 (35.3%)	17 (34.7%)	18 (35.3%)
<b>Smoking status [n(%)]</b>			
Number	102	49	51
Never	55 (53.9%)	35 (71.4%)	30 (58.8%)
Former	21 (20.6%)	8 (16.3%)	13 (25.5%)
Current	26 (25.5%)	6 (12.2%)	8 (15.7%)
<b>Alcohol habits<sup>a</sup> [n(%)]</b>			
Number	102	49	51
Never	59 (57.8%)	33 (67.3%)	38 (74.5%)
Monthly	27 (26.5%)	14 (28.6%)	7 (13.7%)
Weekly	16 (15.7%)	2 (4.1%)	4 (7.8%)
Daily	0	0	2 (3.9%)
<b>ANC at screening [n(%)]</b>			
Number	102	49	51
≥5.99 x 10 <sup>9</sup> /L	64 (62.7%)	31 (63.3%)	32 (62.7%)
< 5.99 x 10 <sup>9</sup> /L	38 (37.3%)	18 (36.7%)	19 (37.3%)

Number = number of patients assessed. Percentages are calculated using number of patients assessed as denominator.

ANC = absolute neutrophil count

Region 1: Belgium, Czech Republic, Finland, Hungary, Israel, Italy, Netherlands, Norway, Spain, Sweden, UK, and USA

Region 2: Argentina, Brazil, Mexico

Region 3: Estonia, Poland, Romania, Russia

a Alcohol habits: how often subject has a drink containing alcohol in the last 12 months

Source: SFY13370 CSR, Table 9, dated August 12, 2015; page 64-65.

*Reviewer Comment: As noted in other areas of this review, the baseline patient characteristics reflect those of the general RA population in the United States. The one possible exception is that, although the majority of RA patients are Caucasian, RA does affect all races. The proportion of Caucasians is 90% or greater in each of the treatment arms, which might be a little higher than the general population. At this point, the significance of that is not completely clear. See discussions under the pivotal trials and safety section 8.2.2 for a consideration of how race may be associated with disease severity.*

### **Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)**

The subjects in all treatment arms had moderate-severe, seropositive (RF, CCP positive) RA with active disease at baseline.

Table 18 describes the baseline disease characteristics for each of the treatment arms. In general, the disease characteristics are similar across treatment arms. However, the subjects in the sarilumab 150mg q2w arm appeared to have a longer history of disease with a mean around 13.59 years, whereas subjects in the tocilizumab and sarilumab 200mg q2w arms had approximately 8-9 years of disease. With longer disease duration, the concern would be that the subjects in the sarilumab 150mg q2w had more severe disease. However, as already noted,

Clinical Review  
Reviewer: Suzette Peng, MD  
NME/BLA 761037  
Sarilumab/Kevzara

the other disease characteristics were similar for this group. Therefore, it is unclear if the longer disease duration had any effect on data analysis.

APPEARS THIS WAY ON ORIGINAL



**Table 18. Baseline Disease Characteristics (SFY13370)**

	Tocilizumab q4w + DMARD (N=102)	Sarilumab	
		150mg q2w (N=49)	200mg q2w (N=51)
<b>Duration of RA since diagnosis (Years)</b>			
Number	102	49	51
Mean (SD)	10.84 (8.91)	13.59 (8.24)	10.45 (7.57)
Median	8.83	13.00	8.15
Min: Max	0.7: 44.2	0.6: 35.8	1.7: 30.9
<b>RA functional class [n(%)]</b>			
Number	102	49	51
I	16 (15.7%)	10 (20.4%)	4 (7.8%)
II	62 (60.8%)	25 (51.0%)	33 (64.7%)
III	24 (23.5%)	14 (28.6%)	14 (27.5%)
IV	0	0	0
<b>Rheumatoid factor [n(%)]</b>			
Number	101	47	50
Positive	79 (78.2%)	39 (83.0%)	29 (58.0%)
Negative	22 (21.8%)	8 (17.0%)	21 (42.0%)
<b>Anti CCP antibody [n(%)]</b>			
Number	97	47	51
Positive	82 (84.5%)	41 (87.2%)	36 (70.6%)
Negative	15 (15.5%)	6 (12.8%)	15 (29.4%)
<b>Tender joint count (0-68)</b>			
Number	102	49	51
Mean (SD)	23.45 (12.22)	23.94 (12.99)	24.71 (12.84)
Median	23.00	20.00	23.00
Min: Max	4.0: 64.0	6.0: 59.0	5.0: 60.0
<b>Swollen joint count (0-66)</b>			
Number	102	49	51
Mean (SD)	15.18 (7.59)	15.97 (8.90)	16.02 (8.09)
Median	15.00	15.00	15.00
Min: Max	4.0: 46.0	4.1: 38.0	2.0: 37.0
<b>CRP (mg/L)</b>			
Number	102	49	51
Mean (SD)	24.86 (30.37)	23.10 (32.09)	23.75 (29.81)
Median	12.95	10.40	13.90
Min: Max	0.4: 162.0	2.2: 149.0	0.2: 129.0
<b>HAQ-DI (0-3)</b>			
Number	102	49	51
Mean (SD)	1.78 (0.63)	1.63 (0.66)	1.71 (0.60)

Clinical Review  
 Reviewer: Suzette Peng, MD  
 NME/BLA 761037  
 Sarilumab/Kevzara

Median	1.88	1.63	1.75
Min: Max	0.0: 3.0	0.4: 2.9	0.4: 2.9
<b>DAS28-CRP (&gt;5.1)</b>			
Number	102	49	51
Mean (SD)	5.91 (1.01)	5.85 (0.92)	5.88 (0.97)
Median	5.91	5.84	5.89
Min: Max	3.8: 8.4	4.2: 8.1	3.7: 8.0

Number = number of patients assessed. Percentages are calculated using number of patients assessed as denominator.  
 Source: SFY13370 CSR, Table 10, dated August 12, 2015; page 66-67.

### Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment compliance was obtained from records of medications treatment packs and/or patient diaries. The compliance was high and similar for all treatment arms. Only 1 subjects in the sarilumab 150mg q2w arm was <80% compliant. Sanofi noted that the lapse in treatment may be partly explained by temporary treatment discontinuation for one of the possible lab abnormalities (neutropenia, transaminase increase, or infection). Sanofi also commented on the number of subjects who met criteria for “overdose.” Sanofi defined overdose as (1) the administration of 2 or more sarilumab doses in less than 11 calendar days, (2) at least twice the tocilizumb dose in less than 21 calendar days, or (3) at least twice of the intended dose within the intended therapeutic interval for sarilumab or tocilizumab. Subjects in all treatments arms (1 on tocilizumab, 2 on sarilumab 200mg q2w, and 2 on sarilumab 150mg q2w) experienced an “overdose.”

Per protocol, all subjects were treated with concomitant non-biologic DMARDs. The largest proportion of subjects in all treatment arms were taking MTX at baseline, 77.5% in the tocilizumab arm, 71.4% in the sarilumab 150mg q2w arm, and 72.5% in the sarilumab 200mg q2w arm. The proportion of other non-biologic DMARDs was also similar across treatment arms, except for leflunomide which was used more frequently in the sarilumab 150mg q2w arm. All subjects in all treatment arms were also treated with biologic DMARDs within 3 months prior to inclusion in the study. The types of biologic DMARDs were also similar across treatment arms and included the TNF $\alpha$  inhibitors, rituximab, abatacept, and IL-1 blockers.

### Efficacy Results

The efficacy endpoints were exploratory. Although the study was not powered to make comparative efficacy assessments, the results are still informative to get an overview of efficacy of sarilumab alongside an approved IL-6 inhibitor (tocilizumab).

At Week 24, Sanofi assessed ACR20, ACR50, ACR70, and DAS28 < 2.6. As per the statistical analysis plan, in the primary approach, patients were considered non-responders after  
 CDER Clinical Review Template 2015 Edition  
 Version date: November 5, 2015 for initial rollout (NME/original BLA reviews)

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

treatment discontinuation. Table 19 shows these efficacy assessments utilizing the primary approach. Overall, the proportion of subjects in the sarilumab arms who achieved the various measured responses was similar across doses. However, the proportions were lower than what was observed in the tocilizumab arm. For example, 63.3% of subjects in the sarilumab 150mg q2w arm and 68.6% of subjects in the sarilumab 200mg q2w achieved and ACR20 response. In the tocilizumab arm, 75.5% of subjects achieved an ACR20 response. Sanofi attributed the difference to the higher rate of discontinuations in the sarilumab arms. Treatment discontinuation is discussed in more detail in Section 8.7 where the safety of this study is presented. In an attempt to account for the discontinuation rate, Sanofi performed a sensitivity analysis with which missing data were imputed using the last value carried forward approach. Utilizing this analysis, the efficacy assessments seemed more similar across treatment arms. Again, for ACR20, the proportion of subjects on sarilumab 150mg q2w and 200mg q2w who achieved the response was 75.5% and 74.5%, respectively. The proportion of subjects in the placebo group remained the same as the primary analysis, that is, 75.5%.

*Reviewer Comment: Although Sanofi provides reasoning for the sensitivity analysis, this is not the preferred approach. Therefore, for the purpose of this review, the primary approach will be the focus.*

**Table 19. Efficacy Assessments at Week 24 for study SFY13370**

	Tocilizumab q4w + DMARD  N=102 n (%)	Sarilumab	
		150mg q2w + DMARD N=49 n (%)	200mg q2w + DMARD N=51 n (%)
ACR20	75.5%	63.3%	68.6%
ACR50	41.2%	36.7%	41.2%
ACR70	22.5%	18.4%	13.7%
DAS28 remission	29.4%	28.6%	31.4%

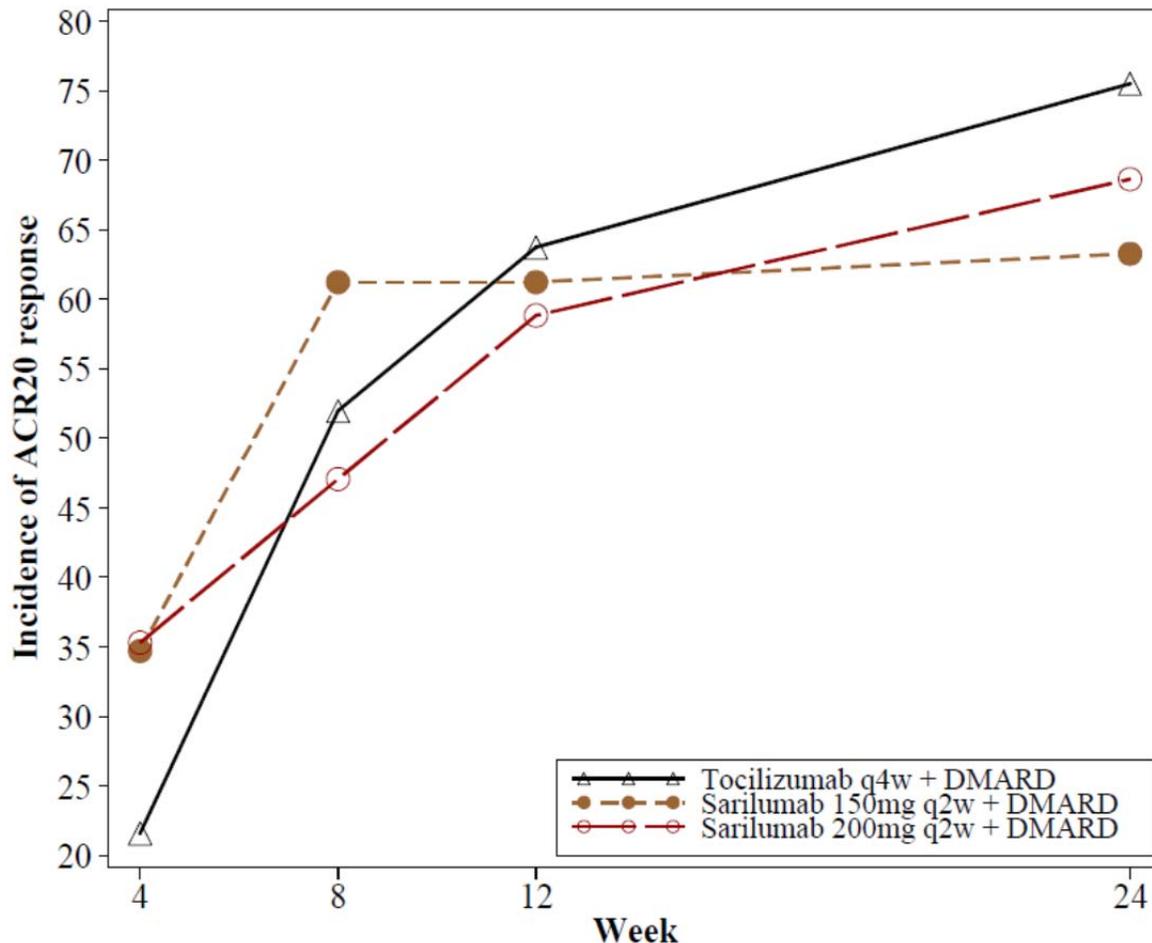
DAS28 remission = DAS28-CRP < 2.6

Percentages are calculated using the number of MITT patients in the corresponding group as the denominator

Source: SFY13370 Clinical Study Report, Table 44, dated August 12, 2015, page 131.

Figure 12 provides an alternate approach to visualizing ACR20 response over time. Tocilizumab and sarilumab 200mg q2w are generally aligned although the incidence is slightly higher for tocilizumab. The incidence of ACR20 response in the sarilumab 150mg q2w arm follows a different pattern and seems to plateau around Week 8.

**Figure 12. Incidence of ACR20 Response at Each Visit**



Source: SFY13370 Clinical Study Report, Figure 18, dated August 12, 2015, page 131.

The proportion of ACR50 was more similar across treatment arms with 41.2% in the tocilizumab arm, 36.7% in the sarilumab 150mg q2w arm, and 41.2% in the sarilumab 200mg q2w arm. The proportion of ACR70, however, was higher in the tocilizumab arm with the lowest response in the sarilumab 150mg q2w arm. Table 19 also shows DAS28-CRP < 2.6 at Week 24, which was similar across treatment (29.4% for tocilizumab, 28.6% for sarilumab 150mg q2w, and 31.4% for sarilumab 200mg q2w).

Table 20 shows the change from baseline in ACR components and DAS-28 at Week 24. In this analysis of efficacy, the change from baseline appeared similar across treatment arms.

**Table 20. Summary of ACR Components and DAS-28 at Week 24 (Study SFY13370)**

Component (mean)	Tocilizumab q4w + DMARD N=102		150mg q2w + DMARD N=49		200mg q2w + DMARD N=51	
	Baseline	Week 24 (Change <sup>a</sup> )	Baseline	Week 24 (Change <sup>a</sup> )	Baseline	Week 24 (Change <sup>a</sup> )
Tender joint count (0-68)	23.03	6.42 (-16.61)	24.03	8.00 (-16.03)	24.87	7.31 (-17.56)
Swollen joint count (0-66)	15.04	3.88 (-11.17)	15.91	3.99 (-11.92)	16.44	4.62 (-11.82)
Physician global assessment of disease activity (VAS)	63.99	18.45 (-45.54)	63.08	21.78 (-41.30)	68.46	19.67 (-48.79)
Patient global assessment of disease activity (VAS)	68.49	34.00 (-34.49)	67.15	37.80 (-29.35)	69.92	32.33 (-37.59)
Patient assessment of pain (VAS)	70.13	33.33 (-36.80)	68.85	38.05 (-30.80)	73.74	36.08 (-37.67)
HAQ-DI	1.76	1.16 (-0.60)	1.57	1.13 (-0.43)	1.77	1.21 (-0.56)
CRP (mg/dL)	2.47	0.66 (-1.81)	2.41	0.52 (-1.88)	2.39	0.21 (-2.17)
DAS28-CRP	5.88	3.17 (-2.72)	5.83	3.13 (-2.70)	5.99	3.02 (-2.97)

a Mean change from baseline at Week 24

Source: SFY13370 Clinical Study Report, Figure 18, dated August 12, 2015, page 135.

In conclusion, study SFY13370 was not designed to compare efficacy of tocilizumab (IV) and both proposed doses of sarilumab (SC), but efficacy assessments were collected at Week 24 as exploratory endpoints. The efficacy data are still informative to provide a general overview of efficacy in both IL-6 inhibitors. Some measurements of response (ACR20 and ACR70) appeared to be more robust in the tocilizumab arm. However, other measures of response (ACR50 and DAS28-CRP <2.6) seemed more similar. Dr. Yongman Kim (primary statistical reviewer) performed a comparative efficacy analysis of the 2 sarilumab doses versus tocilizumab with similar results. (See Dr. Kim's review for full details.) The small differences could be attributed to the increased treatment discontinuation in the sarilumab arms, particularly sarilumab 150mg q2w. The different formulations (IV vs. SC) may also have played a role. Lastly, as noted in the patient demographics in Table 17, subjects in the sarilumab 150mg q2w arm had a longer duration of disease and, therefore, may have been more difficult to treat. Overall, though, the efficacy of tocilizumab and sarilumab were generally similar.

#### Data Quality and Integrity - Reviewers' Assessment

Clinical Review  
Reviewer: Suzette Peng, MD  
NME/BLA 761037  
Sarilumab/Kevzara

The data quality and integrity are adequate. No audits were performed on the case report forms or clinical source data. There were no significant OSI findings that would affect the data or require exclusion of data from any sites.

### **Additional Analyses Conducted on the Individual Trial**

The objective of this study was the comparison of safety of tocilizumab and sarilumab. The presentation of the safety data is located in Section 8.7.

## **6.5. EFC13752 (SARIL-RA-ONE)**

### **6.5.1. Study Design**

#### **Overview and Objective**

Sanofi notes that biologic monotherapy has become an important consideration and is a common clinical scenario for patients with active RA. The primary objective of this study was to evaluate the immunogenicity of sarilumab

The secondary objectives included evaluation of other safety parameters of sarilumab administered as monotherapy from baseline to Week 24 and assessment of the exposure of sarilumab administered as monotherapy from baseline to Week 24. Other objectives included evaluating efficacy of sarilumab administered as monotherapy from baseline to Week 24.

#### **Trial Design**

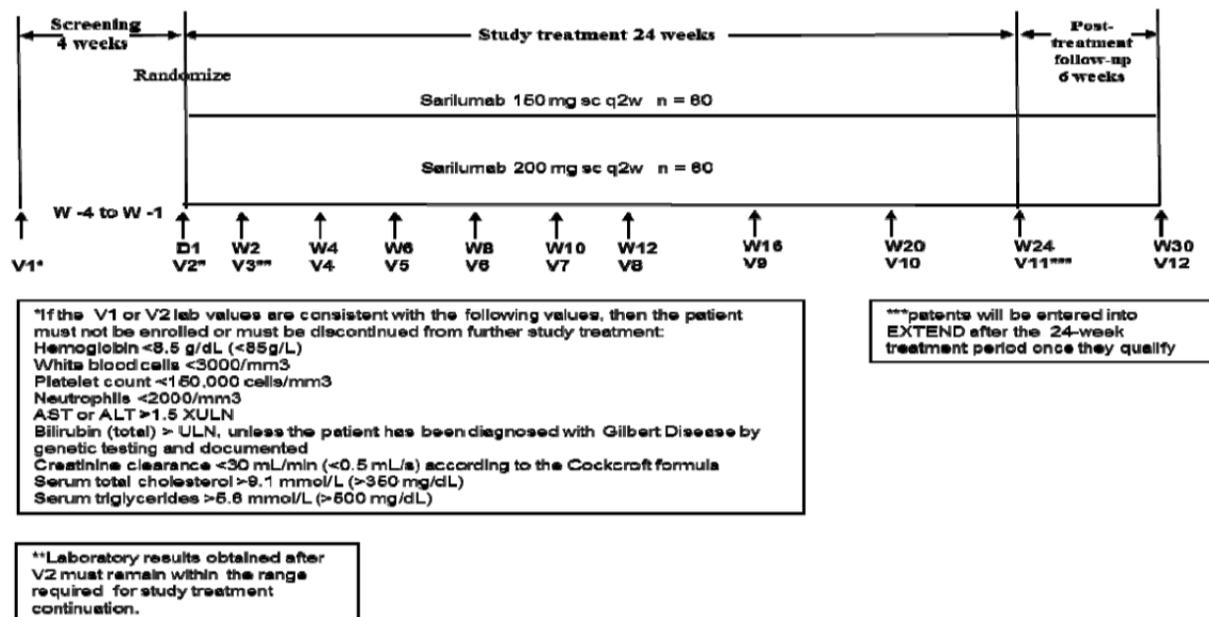
##### **Basic Study Design**

Study EFC13752 was an open-label, multicenter, randomized, parallel group study assessing the immunogenicity and safety of sarilumab administered as monotherapy for a 24-week treatment period. Figure 13 shows the study schema of this study. Patients were stratified by regions and prior biologic DMARD use and were randomized in a ratio of 1:1 to either sarilumab 150mg q2w or sarilumab 200mg q2w. The total maximum duration of participation for a patient in this study was 34 weeks, including up to 4 weeks of screening, 24 weeks of open-label treatment, and 6 weeks of post-treatment follow-up. All subjects (completed or discontinued) were scheduled to complete an End-of-Treatment (EOT) visit. Subjects with an SAE or AESI at the EOT visit were followed within the study until resolution, stabilization, or death.

The study was designed as an open-label study, as the primary assessment of the study was based on objective laboratory measurement for the development of anti-drug antibody (ADA). Consequently, blinding was felt to be unnecessary. As this was a monotherapy study and the primary endpoint was related to ADA incidence, a placebo group was not included.

The schedule of assessments for EFC13752 is displayed in Table 145 in the Appendix (Section 13.3).

**Figure 13. Study Schema of EFC13752**



Source: EFC13752 Clinical Study Report, Figure 1, dated August 18, 2015, page 17.

### Diagnostic criteria and Key inclusion/exclusion criteria

There were some differences in the inclusion/exclusion criteria in this study compared to the pivotal studies, namely in the definition of “moderately to severely active RA” and in the permitted and prohibited concomitant medications.

### Inclusion Criteria

- Moderately to severely active RA defined as the following
  - At least 4 of 66 swollen joints and 4 of 68 tender joints at screening and baseline visits
  - High sensitivity CRP  $\geq$  4mg/dL at screening

*Reviewer’s Comment: The definition of “active” disease was different than both pivotal trials. EFC11072 and EFC10832 both required at least 8 tender joints and 6 swollen joints and higher hsCRP (10 mg/L in EFC11072 and 8 mg/L in EFC10832). Therefore, patients in this trial essentially had less active disease. The definition for active RA in this trial is the same as that for study SFY13370.*

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

- Patients who were either intolerant of or incomplete responders to at least 12 weeks of an adequate dose of continuous treatment with 1 or a combination of non-biologic DMARDs including MTX, SSZ, LEF, or HCQ

*Reviewer Comment: As this is the only monotherapy study submitted with this BLA, this is the only trial that required subjects to be intolerant of non-biologic DMARDs. This is acceptable, as these would be subjects for whom monotherapy might be preferred. However, depending on the reason for "intolerance" to the non-biologic DMARDs, these subjects who were non-responders to or intolerant non-biologic DMARDs might have slightly more aggressive disease.*

### **Exclusion Criteria**

- Treatment with non-biologic DMARDs within 28 days prior to randomization (first dose of IMP administration)

*Reviewer Comment: As this is a monotherapy trial, it is reasonable that there are more exclusions regarding treatment with non-biologic DMARDs at baseline.*

### **Dose selection**

The doses of 150mg and 200mg of sarilumab q2w were those being evaluated in the phase 3 program, and, thus, it is appropriate that these were the doses studied on monotherapy.

### **Study treatments**

The formulation, presentation, routine of administration, and dose of sarilumab were the same as those of the pivotal studies.

### **Assignment to treatment**

Patients were randomized to 1 of 2 treatment arms via an IVRS. Randomization was stratified by region and prior biologic DMARD use. Both the randomization and treatment kit lists were loaded into IVRS. A patient was considered randomized as soon as IVRS provided a treatment number. The randomization ratio was 1:1 (sarilumab 150mg q2w or sarilumab 200mg q2w). At subsequent visits during the treatment period, the site coordinator called IVRS to obtain the next treatment kit numbers.

### **Administrative structure**

The primary investigator was Dr. Alvin Wells (Franklin, WI). Otherwise, the administrative structure was essentially the same as that of the phase 3 studies.

### **Concurrent medications**

In general, the permitted and prohibited concomitant medications were the same as that for the other phase 3 trials. The major difference was that treatment with all DMARDs, such as cyclosporine, cyclophosphamide, azathioprine, methotrexate, sulfasalazine, hydroxychloroquine, CDER Clinical Review Template 2015 Edition

*Version date: November 5, 2015 for initial rollout (NME/original BLA reviews)*

Clinical Review  
Reviewer: Suzette Peng, MD  
NME/BLA 761037  
Sarilumab/Kevzara

or leflunomide, was not authorized during the course of the study (i.e., from 4 weeks prior to randomization to the end-of-study).

### **Treatment compliance**

Administration of the first dose of IMPs was supervised by the Investigator or Sub-investigator. Administration of doses (post-first-dose) of SC IMP could be done by the patient at home or by a healthcare provider after documented training. Compliance was assessed by entries in the patient diary.

### **Subject completion, discontinuation, or withdrawal**

Criteria for subject withdrawal and discontinuation were the same as what was described for study SFY13370. Refer to Section 6.4.1.

### **Study Endpoints**

#### **Immunogenicity Assessments**

The primary endpoint of this study was the incidence of ADA from baseline to Week 24.

- Blood samples, including pre-dose samples, were collected for determination of ADA as designated in Table 145.
- If an SAE occurred in a patient, blood samples were collected for determination of functional sarilumab concentration and ADA assessment at or near the onset of the occurrence of the event and its completion
- The presence of ADA to sarilumab and anti-sarilumab neutralizing antibodies in serum samples were determined using validated electrochemiluminescence methods under the responsibility of Bioanalytical Operations, Regeneron Pharmaceuticals, Inc.

#### **Safety Assessments**

The observation period used for the safety population was the TEAE period. The observation period was defined as in other studies, such as SFY13370. The occurrence of AEs was collected at every visit.

The definition of adverse events, laboratory safety parameters, chest x-ray, vital signs, physical examination, and ECG variables were the same as that in other sarilumab studies. Again, see Table 145 for the timing of assessments.

#### **PK Assessments**

Immunogenicity assessments were the primary endpoint and we obtained as described above. Other PK variables included trough concentrations of functional sarilumab in the serum

#### **Efficacy Assessments**

All efficacy assessments were exploratory and included the following:

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

- ACR 20/50/70 at Week 24
- Change in DAS-28 CRP from baseline through Week 24

## Statistical Analysis Plan

**Sample size:** Based on data from EFC11072, the expected rate of ADA positivity was 15-20%. With a sample size of 100 patients (50/group), the expected width of a 90% confidence interval for ADA incidence is  $\pm 8\%$ . Therefore, this sample size was determined to be adequate to measure 50% or larger increase in ADA incidence compared to the historical rate for combination therapy. Allowance of 20% was made for dropouts, increasing the planned sample size to 120.

**Analysis populations:** The different analysis populations included the randomized population, the safety population, and the PK population. These populations were defined the same as they were for the pivotal studies. The ADA population consisted of all patients in the safety population with at least 1 pose-dose, evaluable ADA sample. Patients were analyzed according to the treatment actually received.

Analyses of **demographics and baseline characteristics** as well as **extent of IMP exposure and compliance** were the same as what was done in the previous protocols.

**Prior and concomitant medications:** The prior and concomitant medications were summarized based on the randomized population in the following 3 categories: prior medications discontinued before the first dose of IMP, prior medications that continued at the time of the first dose of IMP, and concomitant medications. As in the other protocols, the medications were summarized by treatment group according to the WHO-DD dictionary. In addition, summaries were also provided for the following treatments: vaccines; concomitant conventional synthetic DMARDs (e.g., MTX, SSZ, LEF, HCQ) along with folic acid, NSAID, and corticosteroids; prior DMARDs (synthetic and biologic) taken since diagnosis of RA and discontinued before the first dose of IMP; changes in lipid modifying agents.

**Immunogenicity analyses:** The primary endpoint was the incidence of ADA from baseline to Week 24. The definitions of a treatment-emergent positive ADA patient, treatment-boosted positive ADA patient, ADA negative patient, persistent ADA response, and transient response are provided in the safety section of this review (Section 8.3.2). The following summaries were provided separately for ADA positive patient, ADA negative patients, patients with a persistent ADA response, and patients with a transient ADA response.

- ADA prevalence and titer
- ADA incidence and titer

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

- ADA and clinical safety, focusing on hypersensitivity, anaphylaxis, injection-site reactions, and TEAEs leading to permanent treatment discontinuations
- ADA and clinical efficacy
  - The endpoints analyzed were ACR20/50 response at Week 24 as well as number (%) of patients with lack of efficacy or loss of efficacy. Both “lack of efficacy” and “loss of efficacy” are defined in the safety section, Section 8.3.2.
- ADA and PK: Descriptive summary of serum concentration of sarilumab at various timepoints were provided by ADA patient classifications (positive or negative) for each sarilumab dose regimen. Scatter plots of serum concentration versus visit were also provided by ADA sample level classifications and by treatment group for sarilumab-treated patients.

**Analyses of safety data:** The safety analyses were the same as what was performed for the pivotal trials, EFC11072 Part B and EFC10832. Please refer to Sections 6.2.1 and 6.3.1.

**Analyses of efficacy data:** This study was not powered or designed (open-label, no comparator) for efficacy comparisons, as the primary objective was the evaluation of immunogenicity. The purpose of the efficacy analyses was to determine the potential for ADA to affect efficacy.

Therefore, in summary, patients achieving ACR20/50/70 and DAS28 remission were summarized by treatment group and visit (W4, W8, W12, and W25) using counts, proportions, and 95% CI. The change from baseline in DAS28-CRP and ACR components were summarized by treatment group and visit (W4, W8, W12, and W24) using mean, standard error, and the corresponding 95% CI. The primary methods of analyses and sensitivity analyses were the same as that taken for the pivotal trials.

**Analyses of PK data:** Overall, the PK analyses were similar to what was performed for the previously described clinical trials. Please see the review of the pivotal trials above.

### Protocol Amendments

There were no protocol amendments. An earlier version of the protocol was written but not implemented. Therefore, Version 2 was used.

### Data Quality and Integrity: Sponsor's Assurance

Sanofi's process of assuring data quality for this study was the same as that for the pivotal trials.

Clinical Review  
Reviewer: Suzette Peng, MD  
NME/BLA 761037  
Sarilumab/Kevzara

## 6.5.2. Study Results

### Compliance with Good Clinical Practices

As with the other trials in the sarilumab program, this protocol complied with recommendations of the 18<sup>th</sup> World Health Congress (Helsinki, 1964), all applicable amendments issued by the World Medical Assemblies, and ICH guidelines for good clinical practice (GCP). The protocol also complied with the laws and regulations, as well as any applicable guidelines, of the countries where the study was conducted.

### Financial Disclosure

This is not one of the pivotal studies to establish efficacy, and, thus, no financial disclosure information is provided.

### Patient Disposition

Two hundred one patients were screened, and there were 69 screen failures. Therefore, a total of 132 subjects were randomized with 116 (87.9%) subjects completing the study and 111 patients (84.1%) rolling over into the open-label study LTS11210. Table 21 shows the patient disposition for all subjects in study EFC13752. As noted above, overall, 87.9% of subjects completed the study, and the proportions were similar for both doses. Slightly more subjects on sarilumab 200mg q2w (10.4%) discontinued due to adverse events compared to subjects on 150mg q2w (7.7%). Additionally, similar proportions of subjects on each dose proceeded to study LTS11210.

APPEARS THIS WAY ON ORIGINAL

**Table 21. EFC13752 Patient Disposition**

	Sarilumab		
	150mg q2w N=65	200mg q2w N=67	All N=132
Randomized and not treated	0	0	0
Randomized and treated	65 (100%)	67 (100%)	132 (100%)
Complete the study treatment period	58 (89.2%)	58 (86.6%)	116 (87.9%)
Discontinued from the study	7 (10.8%)	9 (13.4%)	16 (12.1%)
Subject's request for treatment discontinuation	5 (7.7%)	2 (3.0%)	7 (5.3%)
Reason for treatment discontinuation			
Adverse event	5 (7.7%)	7 (10.4%)	12 (9.1%)
Lack of efficacy	2 (3.1%)	0	2 (1.5%)
Poor compliance to protocol	0	0	0
Other reasons	0	2 (3.0%)	2 (1.5%)
Status at last study contact			
Alive	65 (100%)	67 (100%)	132 (100%)
Dead	0	0	0
Rolled over to LTS study			
Yes	54 (83.1%)	57 (85.1%)	111 (84.1%)
No	11 (17.0%)	10 (15.0%)	22 (16.7%)

Source: EFC13752 Clinical Study Report, Table 2, dated August 18, 2015, page 51-2.

### Protocol Violations/Deviations

Sanofi noted that no patients had an important protocol deviation that had a potential impact on the analyses. Randomization and dosing irregularities were defined before database lock. Randomization or drug allocation irregularities were reported by 3 patients in the sarilumab 150mg q2w group and 4 patients in the sarilumab 200mg q2w group. Stratification errors were reported by 3 patients in each treatment group. Erroneous kit dispensation was reported for 1 patient in the sarilumab 200mg q2w group.

Eight total patients (5 [7.7%] in sarilumab 150mg q2w and 3 [4.5%] in sarilumab 200mg q2w) were noted to have "other important protocol deviations." In the sarilumab 150mg q2w arm, there were 4 subjects who were treated with non-biologic DMARD during the course of the study, 1 subject with active/latent TB, 1 subject with a laboratory screening abnormality, and 1 subject with use of a biologic during and 6 weeks after last IMP dose. In the sarilumab 200mg q2w arm, there was 1 subjects who was treated with a non-biologic DMARD during the course of the study and 1 subjects who was treated with a non-biologic DMARD within 28 days prior to

Clinical Review  
Reviewer: Suzette Peng, MD  
NME/BLA 761037  
Sarilumab/Kevzara

randomization. Additionally, there was 1 subject whom the applicant deemed as having a condition that could potentially bias the evaluation of the endpoint.

*Reviewer Comment: Details of the “other important” protocol deviations were not provided here. Sanofi only noted that 1 subject had a deviation that could impact endpoint analyses. However, based on the brief descriptions provided, it is certainly possible that all these deviations could affect assessment of safety and efficacy. The numbers are low for both treatment arms.*

### **Table of Demographic Characteristics**

The patient characteristics at baseline for study EFC13752 was generally similar to those described in the pivotal studies. The majority of subjects were female and less than 65 years of age. The range in age was from 22 to 78 years of age. Although Caucasians made up the majority in the previously reviewed studies, the proportion was even higher in this study. In the sarilumab 150mg q2w arm, all 65 subjects (100%) were Caucasian although a small number was Hispanic (9 subjects, 13.8%). Although there were other races in the sarilumab 200mg q2w arm, the numbers were few (1 each of black, Asian, and other). The patient characteristics were generally equally represented in both sarilumab doses.

APPEARS THIS WAY ON ORIGINAL

**Table 22. Baseline Demographics and Patient Characteristics for EFC13752**

	Sarilumab	
	150mg q2w (N=65)	200mg q2w (N=67)
<b>Age (years)</b>		
Number	65	67
Mean (SD)	51.1 (12.7)	53.6 (14.1)
<65 years	54 (83.1%)	51 (76.1%)
≥65-75 years	11 (16.9%)	13 (19.4%)
≥ 75 years	0	3 (4.5%)
<b>Sex [n(%)]</b>		
Number	65	67
Male	16 (24.6%)	10 (14.9%)
Female	49 (75.4%)	57 (85.1%)
<b>Race [n(%)]</b>		
Number	65	67
Caucasian	65 (100%)	64 (95.5%)
Black	0	1 (1.5%)
Asian	0	1 (1.5%)
Other	0	1 (1.5%)
<b>Ethnicity [n(%)]</b>		
Number	65	67
Hispanic	9 (13.8%)	8 (11.9%)
Non-Hispanic	56 (86.2%)	59 (88.1%)
<b>Weight (kg)</b>		
Number	65	67
Mean (SD)	74.34 (17.17)	77.93 (19.57)
<60	13 (20.0%)	11 (16.4%)
≥60 and <100	44 (67.7%)	48 (71.6%)
≥100	8 (12.3%)	8 (11.9%)
<b>BMI (kg/m<sup>2</sup>)</b>		
Number	65	67
Mean (SD)	26.93 (5.04)	28.92 (6.96)
<25	27 (41.5%)	23 (34.4%)
≥25 and <30	21 (32.3%)	19 (28.4%)
≥30	17 (26.2%)	25 (37.3%)
<b>Region [n(%)]</b>		
Number	65	67
Region 1	34 (52.3%)	36 (53.7%)
Region 2	3 (4.6%)	5 (7.5%)
Region 3	28 (43.1%)	26 (38.8%)
<b>Smoking status [n(%)]</b>		
Number	65	67

Clinical Review  
 Reviewer: Suzette Peng, MD  
 NME/BLA 761037  
 Sarilumab/Kevzara

Never	41 (63.1%)	45 (67.2%)
Former	12 (18.5%)	9 (13.4%)
Current	12 (18.5%)	13 (19.4%)
<b>Alcohol habits<sup>a</sup> [n(%)]</b>		
Number	65	67
Never	45 (70.3%)	51 (76.1%)
Monthly	14 (21.9%)	12 (17.9%)
Weekly	4 (6.3%)	4 (6.0%)
Daily	1 (1.6%)	0
<b>ANC at screening [n(%)]</b>		
Number	65	67
≥5.99 x 10 <sup>9</sup> /L	29 (44.6%)	25 (37.3%)
< 5.99 x 10 <sup>9</sup> /L	36 (55.4%)	42 (62.7%)

Number = number of patients assessed. Percentages are calculated using number of patients assessed as denominator.

ANC = absolute neutrophil count

Region 1: Czech Republic, Hungary, and USA

Region 2: Argentina, Chile

Region 3: Estonia, Poland, Russia

a Alcohol habits: how often subject has a drink containing alcohol in the last 12 months

Source: EFC13752 CSR, Table 6, dated August 18, 2015; page 55-57.

*Reviewer Comment: As discussed with study EFC11072, the patient characteristics of the study population are similar to the general RA population in the US. However, the representation by other races is limited. Although the majority of RA patients in the US is Caucasian, RA can affect all races, and there may be some data supporting more aggressive disease in Blacks and Latinos. This study is the most limited, compared to the other sarilumab studies, in its lack of racial diversity. As this is a safety/immunogenicity study, this limitation may be reasonable but is worth monitoring. It may be important for Sanofi's other monotherapy study (which was not included as part of this application) to include a more racially diverse population.*

### **Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)**

The subjects in study EFC13752 had baseline disease features consistent with moderate to severe disease. The majority of subjects had a diagnosis of seropositive (rheumatoid factor and anti-CCP antibody positive) RA between 9-11 years with a functional class of II. Most subjects were not previously treated with a biologic DMARD, i.e., previous treatment in 30.8% of subjects on the 150mg q2w dose and 26.9% of subjects on the 200mg q2w dose. Other disease features, like swollen/tender joints, CRP, HAQ-DI, and disease activity (as measured by DAS28-CRP) were similar across treatment arms.

**Table 23. Baseline Disease Characteristics for study EFC13752**

	Sarilumab	
	150mg q2w (N=65)	200mg q2w (N=67)
<b>Duration of RA since diagnosis (Years)</b>		
Number	65	67
Mean (SD)	9.72 (8.77)	11.23 (9.18)
Median	7.43	8.36
Min: Max	0.3: 38.6	0.3: 34.8
<b>RA functional class [n(%)]</b>		
Number	65	67
I	11 (16.9%)	12 (17.9%)
II	41 (63.1%)	35 (52.2%)
III	13 (20.0%)	20 (29.9%)
IV	0	0
<b>Prior biologic DMARD use for RA [n(%)]</b>		
Number	65	67
Yes	20 (30.8%)	18 (26.9%)
No	45 (69.2%)	49 (73.1%)
<b>Rheumatoid factor [n(%)]</b>		
Number	65	66
Positive	49 (75.4%)	52 (78.8%)
Negative	16 (24.6%)	14 (21.2%)
<b>Anti CCP antibody [n(%)]</b>		
Number	63	66
Positive	49 (77.8%)	53 (80.3%)
Negative	14 (22.2%)	13 (19.7%)
<b>Tender joint count (0-68)</b>		
Number	65	67
Mean (SD)	24.78 (14.87)	25.61 (12.28)
Median	21.00	23.00
Min: Max	8.0: 68.0	7.0: 62.0
<b>Swollen joint count (0-66)</b>		
Number	65	67
Mean (SD)	17.55 (10.19)	16.48 (8.54)
Median	14.00	14.00
Min: Max	5.0: 60.0	2.0: 45.0
<b>CRP (mg/L)</b>		
Number	65	67
Mean (SD)	22.45 (21.83)	25.76 (31.48)
Median	15.90	15.50
Min: Max	0.4: 113.0	1.5: 159.0
<b>HAQ-DI (0-3)</b>		

Clinical Review  
 Reviewer: Suzette Peng, MD  
 NME/BLA 761037  
 Sarilumab/Kevzara

Number	65	67
Mean (SD)	1.43 (0.65)	1.68 (0.67)
Median	1.50	1.75
Min: Max	0.0: 2.8	0.0: 3.0
<b>DAS28-CRP (&gt;5.1)</b>		
Number	65	67
Mean (SD)	5.83 (0.97)	6.06 (0.99)
Median	5.70	6.02
Min: Max	4.0: 8.0	3.6: 8.2

Number = number of patients assessed. Percentages are calculated using number of patients assessed as denominator.  
 Source: EFC13752 CSR, Table 7, dated August 18, 2015; page 58-59.

### **Treatment Compliance, Concomitant Medications, and Rescue Medication Use**

The majority of subjects were at least 80% compliant with treatment, 92.3% in the 150mg q2w arm and 88.1% in the 200mg q2w arm. No subjects received an incorrect dose. However, 4 total subjects (1 in the 150mg q2w arm and 3 in the 200mg q2w arm) had an “overdose,” pre-defined as administration of at least twice of the intended dose in less than 11 calendar days.

In regards to prior therapy, all subjects were previously treated with a conventional DMARD which was then discontinued prior to the first dose of IMP. The vast majority of subjects were previously treated with methotraxte (96.9% in the 150mg q2w arm and 98.5% in the 200mg q2w arm). As previously noted, 30.8% of subjects in the 150mg q2w arm and 26.9% of subjects in the 200mg q2w arm had prior exposure to a biologic DMARD. The most common prior biologic DMARD was etanercept (12.3% in the sarilumab 150mg q2w arm and 11.9% in the sarilumab 200mg q2w arm).

Use of concomitant corticosteroids and NSAIDs was similar between treatment arms. Concomitant oral corticosteroid use was reported by 50% of patients in each treatment arm, and NSAIDs were reported by 75% of subjects in each arm.

### **Immunogenicity Results - Primary Endpoint**

The primary endpoint was the incidence of ADA from baseline to Week 24. Immunogenicity will not be discussed here. Rather, please refer to the safety section on immunogenicity (Section 8.4.10).

### **Data Quality and Integrity - Reviewers' Assessment**

The data quality and integrity are adequate. No audits were performed on the case report forms or clinical source data. There were no significant OSI findings that would affect the data or require exclusion of data from any sites.

### Efficacy Results - Secondary and other relevant endpoints

The efficacy endpoints were all exploratory and were assessed mainly in the context of immunogenicity. The review of ADA and efficacy will be presented below in Section 8.4.10. However, in this portion of the review, I will briefly review the efficacy endpoints that are common with the pivotal trials.

Table 24 shows the proportion of subjects who achieved ACR20, ACR50, ACR70, and DAS28 remission at Week 24. Overall, the proportions of each efficacy evaluation was similar for both doses, perhaps, numerically higher in the 150mg q2w arm for ACR20, ACR50, and DAS28 remission.

**Table 24. Overview of Efficacy Assessments at Week 24 (Study EFC13752)**

	Sarilumab	
	150mg q2w N=65	200mg q2w N=67
ACR20	73.8%	71.6%
ACR50	53.8%	50.7%
ACR70	29.2%	29.9%
DAS28 remission	43.1%	40.3%

DAS28 remission = DAS28-CRP < 2.6

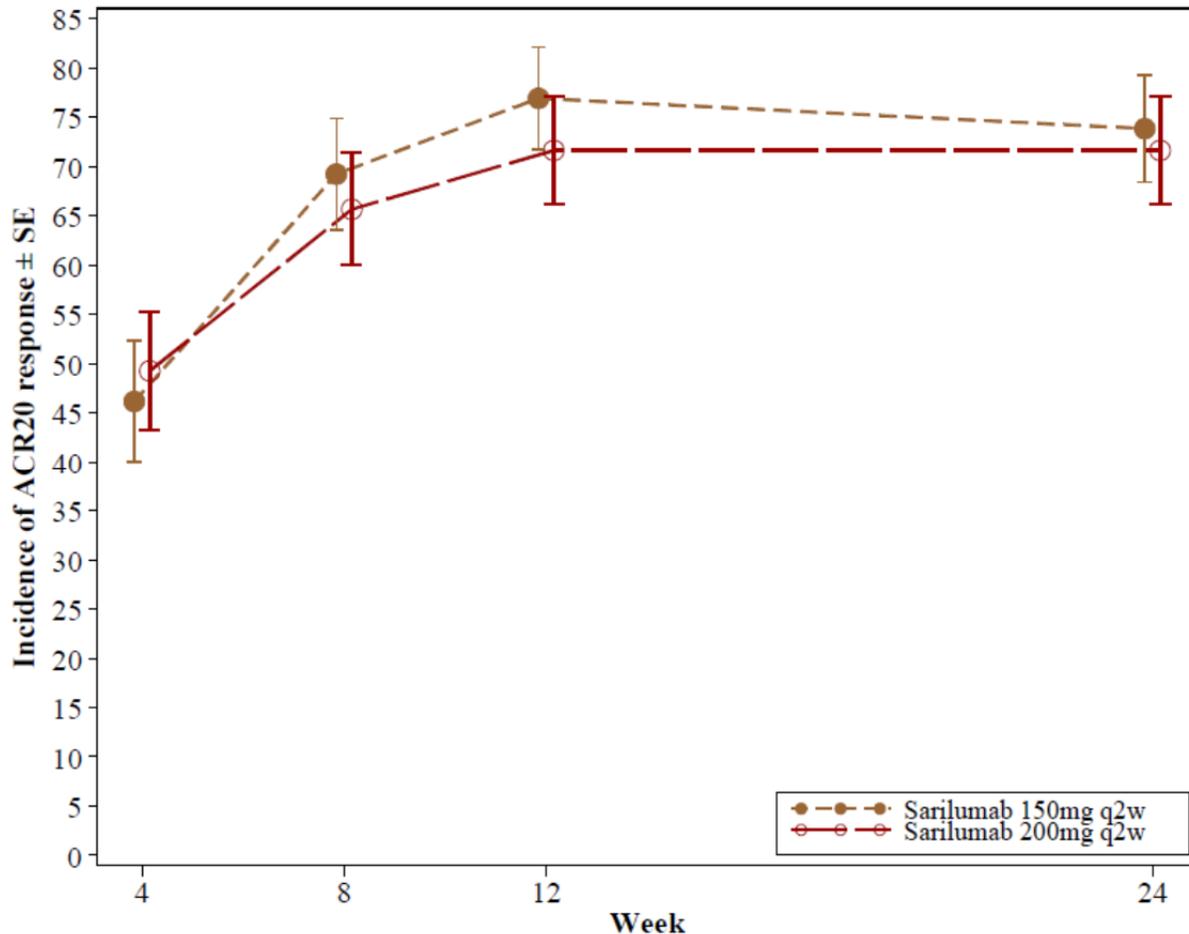
Percentages are calculated using the number of randomized patients in the corresponding group as the denominator

Source: EFC13752 Clinical Study Report, Table 30, dated August 18, 2015, page 104.

Figure 14 shows the incidence of ACR20 response over time for this study. The majority of subjects, who achieved an ACR20 response, had this response by Week 8. As noted in the previous table, this figure also seems to show a small numerically higher response in the lower dose of sarilumab.

APPEARS THIS WAY ON ORIGINAL

**Figure 14. Incidence of ACR20 Response at Each Visit for Study EFC13752**



Source: EFC13752 Clinical Study Report, Figure 11, dated August 18, 2015, page 104.

*Reviewer Comment: Interpretation of the efficacy assessments is limited, as there is no control group. Perhaps, the only conclusions that can be made are that the majority of subjects did achieve an ACR20 at Week 24, and the efficacy was generally comparable between the 2 doses. It can be noted that the proportion of subjects who achieved the various efficacy responses (ACR20/50/70) was even higher than what was seen in the pivotal studies. However, as an open-label study, it is difficult to make any true cross-study comparison.*

#### **Additional Analyses Conducted on the Individual Trial**

Multiple safety evaluations were performed. The discussion of the safety of sarilumab monotherapy will be discussed below in Section 8.7.

## 6.6. EFC11574 (SARIL-RA-COMPARE)

### 6.6.1. Study Design

#### Overview and Objective

EFC11574 was a multi-center, randomized, double-blind, double-dummy, parallel-group, 3-arm, 24-week, active comparator-controlled study with a 16-week open label adalimumab run-in phase. The primary objective of the study was to demonstrate that the combination of sarilumab and MTX is superior to the combination of etanercept and MTX for the improvement (reduction) of DAS28-CRP score at Week 24, compared to the randomization treatment phase baseline evaluation, in patients with RA and an inadequate response to 4 months of treatment adalimumab and MTX.

#### Secondary Objectives

- To demonstrate that the combination of sarilumab and MTX is superior to the combination of etanercept and MTX in patients with RA and an inadequate response to 4 months of treatment with adalimumab and MTX with respect to the following
  - Reduction of signs and symptoms of RA at Week 24
  - Improvement in quality of life, including physical function, as measured by patient reported outcomes (PROs) at Week 24
- To assess, over the course of 24 weeks, the safety and tolerability of sarilumab or etanercept in combination with MTX

#### Exploratory Objective

- To collect DNA, RNA, and other biomarkers for future use for the purpose of discovery of predictive biomarkers

#### Substudy Objective

- To assess the 12-month safety and tolerability of sarilumab in combination with MTX
- To summarize signs and symptoms of RA during 12 months of treatment with sarilumab in combination with MTX

#### Trial Design

EFC11574 was 24-week, phase 3, 3-arm, multicenter, multinational, randomized, double-blind, double-dummy, parallel-group, active-comparator controlled study of sarilumab versus etanercept in combination with MTX in patients with moderate to severe RA and an inadequate response to only 1 TNF $\alpha$  inhibitor (adalimumab 40mg q2w) in combination with MTX during a 4-month open-label adalimumab run-in phase.

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

Figure 15 is the study schema for EFC11574. There is an initial 4 month open-label run-in phase with adalimumab. After this, patients who were nonresponders were randomized in a double-blind fashion stratified by geographic region and DAS28-CRP severity score ( $>5.1$  or  $\leq 5.1$ ) to receive one of the following:

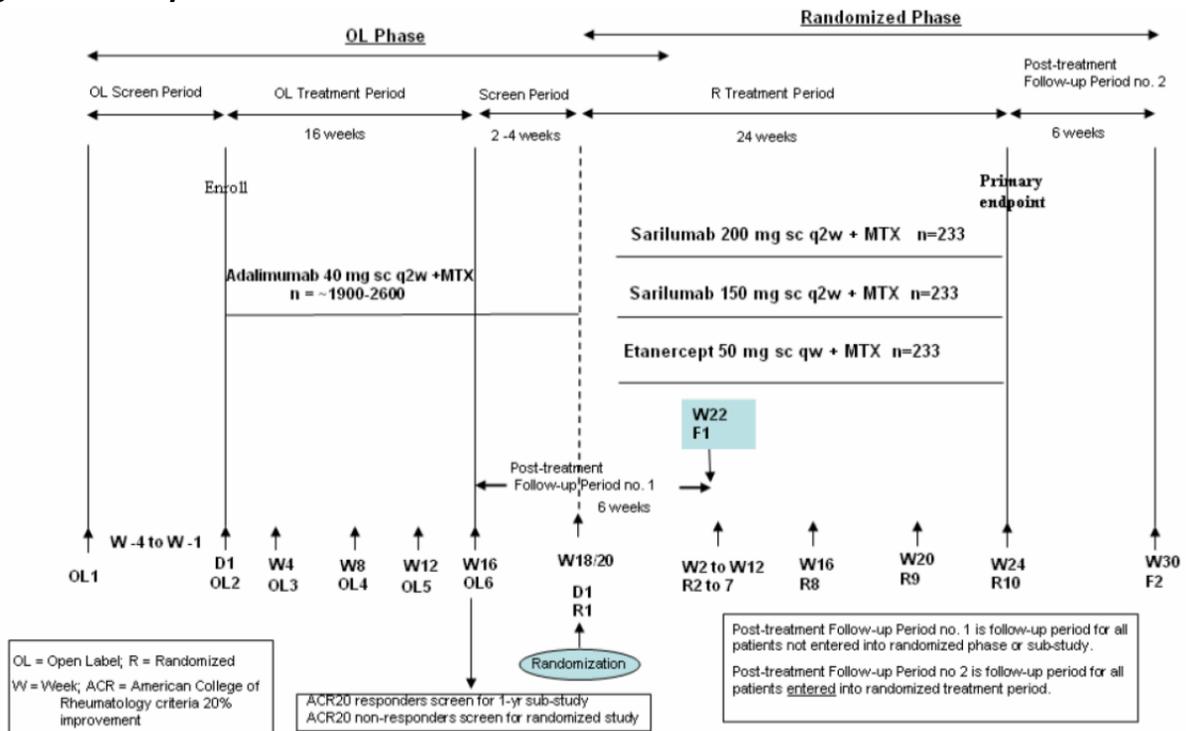
- Sarilumab 150mg or 200mg q2w or matching placebo
- Etanercept 50mg qw or matching placebo

Patients who responded to adalimumab during the run-in, i.e., achieved a  $\geq 20\%$  ACR response at any visit during the open-label adalimumab run-in phase, were offered the opportunity to enroll into the uncontrolled, open-label, 1-year substudy to assess the long-term safety and tolerability of the sarilumab 150mg q2w dose regimen. The study schema of the substudy is shown in Figure 16. Lastly, the schedule of assessments is provided in the Appendix, Table 146 (Open-label run-in phase), Table 147 (Randomized phase), and Table 148 (Substudy).

Therefore, the total maximum duration of participation for a patient who completed the open-label adalimumab run-in phase and the randomized phase was 54 weeks, including up to 4 weeks screening period, 16 weeks open-label treatment, 2-4 weeks of randomized screening, 23-24 weeks of randomized treatment, and a 6 week post-treatment follow-up. The total maximum duration of participation for a patient who participated only in the open-label adalimumab run-in phase and did not participate in the randomized phase or substudy was 26 weeks. Lastly, the total maximum duration of participation for a patient who participated in the open-label adalimumab run-in phase and was eligible for the sarilumab substudy was 82 weeks.

APPEARS THIS WAY ON ORIGINAL

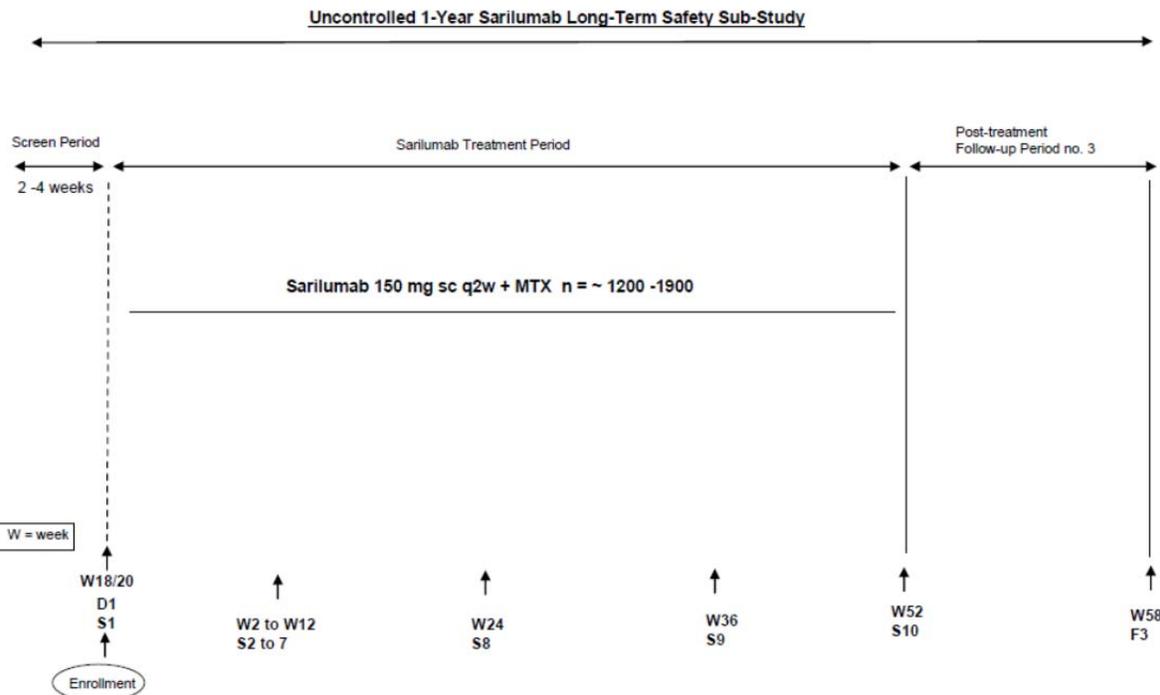
**Figure 15. Study Schema of EFC11574**



Source: EFC11574 Clinical Study Report, Figure 1, dated June 11, 2015, page 15.

APPEARS THIS WAY ON ORIGINAL

**Figure 16. Study Schema of EFC11574 Substudy**



Source: EFC11574 Clinical Study Report, Figure 2, dated June 11, 2015, page 16.

Study EFC11574 was terminated prematurely on August 7, 2014, due to the inability to provide timely results as laid out in the original study plan. Sanofi emphasizes that the decision was not related to any safety issue but was a result of study delays caused by a smaller than expected number of patients entering the randomized phase of the study. Approximately 10% of subjects who entered the adalimumab run-in qualified for the randomized study, compared with the anticipated 30-40%.

When the study was discontinued, the discontinuation procedure stipulated that patients would receive a minimum of 12 weeks of treatment in their current phase to allow the Investigator sufficient time to assess the patient response to the allocated therapy and discuss alternative therapy. When the study was terminated, 776 patients (planned 1942-2589 patients) had entered the adalimumab run-in phase, 43 patients (planned 699 patients) had entered the randomized phase, and 322 patients had entered the substudy phase. Eleven of the 43 randomized patients had completed 6 months of treatment in the randomized phase, and 2 out of the 322 patients had completed 1 year of treatment in the sarilumab substudy.

Sanofi did not analyze the efficacy endpoints, as too few patients had reached the primary efficacy time point of 6 months to draw any meaningful efficacy conclusions. Safety data from all patients who were exposed to sarilumab or etanercept during the study were reported and will be presented briefly in the synopsis below. Additionally, these subjects were included in

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

the long-term safety population (Pool 2) which is presented in the safety section of this review (Section 8). Although PK samples were collected, Sanofi did not analyze them.

<b>Coordinating Investigator:</b> Paul Emery (University of Leeds, UK)	
<b>Study Centers:</b> 228 centers in 31 countries	
<b>Study Period:</b> Subjects were first enrolled on May 9, 2013, and the last patient completed the study on January 12, 2015. This study was discontinued early. See explanation above.	
<b>Number of patients:</b> The number of subjects listed below represents those who were enrolled in the particular phase of study. All enrolled subjects were also evaluated for safety.	
Adalimumab run-in	776
Randomized (adalimumab non-responders)	43
Etanercept 50mg qw	17
Sarilumab 150mg q2w	13
Sarilumab 200mg q2w	13
Substudy (adalimumab responders)	
Sarilumab 150mg q2w	322
<b>Diagnosis and key inclusion criteria:</b> Male and female adults $\geq 18$ years of age with moderate to severe RA, according to the ACR/EULAR 2010 RA classification criteria with $\geq 3$ months disease duration.	
<b>Study treatments:</b>	
<ul style="list-style-type: none"><li>• Sarilumab 150mg q2w or 200mg q2w Formulation: single-use 1.14 mL prefilled glass syringes (131.6mg/mL for 150mg dose or 175mg/mL for 200mg dose) Administration: SC in abdomen, thigh, upper arm</li><li>• Adalimumab 40mg q2w Formulation: single-use prefilled glass syringe Administration: SC in abdomen, thigh, or per local labeling requirements</li><li>• Etanercept 50mg q2 Formulation: single-use prefilled glass syringe Administration: SC in abdomen, thigh, and upper arm</li><li>• Placebo (sarilumab PBO q2w to etanercept treatment arm; etanercept PBO qw to sarilumab arm) Formulation: single-use prefilled glass syringe Administration: SC in abdomen, thigh, and upper arm</li><li>• Noninvestigational medicinal products<ul style="list-style-type: none"><li>○ Methotrexate (doses 10-20mg/week)</li></ul></li></ul>	
<b>Statistical methods:</b>	
The planned efficacy assessments included DAS28-CRP score, ACR20/50/70 response and individual components, EULAR/ACR remission and response, DAS28-ESR, SDAI, CDAI. As noted, efficacy endpoints were not analyzed due to early study termination.	
Safety assessments included AEs, clinical laboratory values, ECGs, vital signs, and measurement of ADA. TEAEs, treatment-emergent SAEs, TEAEs leading to treatment discontinuation, and treatment-emergent AESIs were summarized for each treatment group based on MedDRA coding of verbatim terms	

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

reported by investigators. For laboratory parameters, vital signs, and ECG, indices of potentially clinically significant abnormality (PCSA) values, actual values, and change from baseline were summarized by treatment group.

### **Summary of assessments:**

**Baseline patient characteristics:** A total of 776 subjects entered the adalimumab run-in phase. Of these, 43 patients entered the randomized phase, and 322 patients entered the sarilumab substudy. Among 365 patients who entered the randomized phase or sarilumab substudy, patient age ranged from 19 to 82 years with a mean of 51.9 years. The majority of patients were female (295 [80.8%]) and Caucasian (316 [86.6%]). The mean weight for patients was 76.38kg. Subjects in the sarilumab arms had a mean disease duration of 4-8 years, whereas subjects in the etanercept arm had disease for a mean 13 years. The majority of subjects in all treatment arms were seropositive (RF/CCP positive) with a functional class of II-III.

**Safety:** The 322 subjects in the sarilumab substudy received sarilumab 150mg q2w and had a cumulative exposure of 127.3 patient-years. Exposure in the randomized sarilumab 150mg and 200mg q2w groups was 4.0 and 4.8 patient-years, respectively. Because of such low exposure to sarilumab in the randomized phase, Sanofi felt that no meaningful comparisons between treatment groups could be made. This is a reasonable conclusion, and, thus, safety from the randomized phase will not be presented.

The most frequent reported TEAEs in the sarilumab substudy were neutropenia (10.6%), upper respiratory tract infection (5.0%), and injection site erythema (4.7%). A low number of patients (3.4%) experienced an SAE. In regards to TEAEs leading to discontinuation, the most common SOC reported was the blood and lymphatic system disorders SOC (3.4%).

AESIs were assessed in the sarilumab substudy. There were cases of infections, malignancies, injection site reactions, decreased in neutrophil counts, elevation in liver enzymes, elevation in lipids, and ADA positivity. Only Infections, malignancy, neutropenia, and injection site reactions will be presented here.

- Only 2 patients in the sarilumab substudy experienced a serious infection. One subjects had severe E.Coli pyelonephritis on Day 509, and the other subject developed an acute ruptured sigmoid diverticulitis with a pericolic abscess on Day 171. There were no cases of opportunistic infections.
- Five malignancies were reported. These included squamous cell cancer (skin), metastatic cancer (unknown primary), bladder cancer, breast cancer, and cervical cancer. Thus, there were no uncommon cancers that would not be expected.
- The majority of decreased in ANC were Grade 1-2 neutropenia, i.e.,  $\geq 1.0$  Giga/L – LLN. Sanofi noted that subjects with an ANC below the LLN did not have a higher incidence of infection compared to those with normal ANC.
- Injection site reactions were reported in 6.8% of subjects. The most frequently reported injection site reactions were erythema, pruritus, and rash. No injection site reaction was severe in intensity. Injection site reaction led to treatment discontinuation for 1 patient in the sarilumab substudy.

Source: EFC11574 Study Synopsis, June 11, 2015

## 6.6.2. Study Results

As explained above, efficacy analyses were not performed for this study because of early discontinuation and the low number of subjects who completed 6 months of treatment. In regards to safety, the analyses focused on the open-label sarilumab substudy. Overall, the safety findings were consistent with what was seen in the pivotal studies and, thus, were representative of what would be anticipated of IL-6 inhibition in RA patients.

## 6.7. MSC12665 (SARIL-RA-EASY)

### 6.7.1. Study Design

#### Overview and Objective

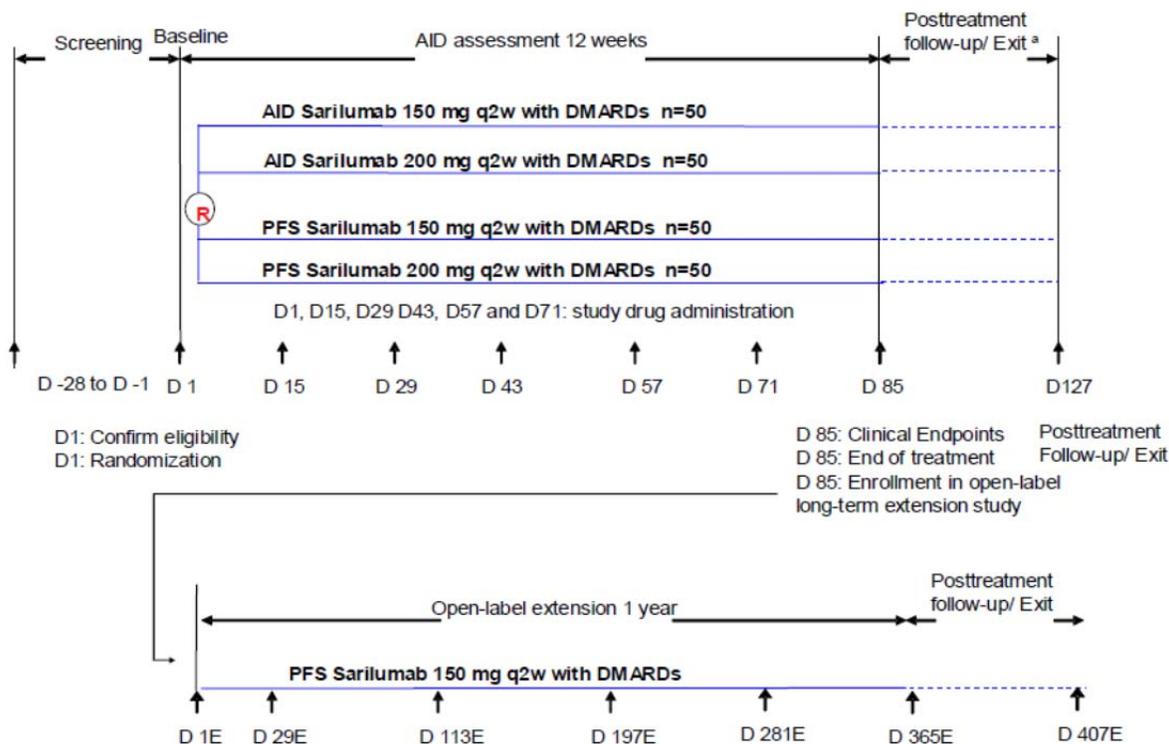
MSC12665 was a multicenter, randomized, open-label, parallel-group usability study of the sarilumab autoinjector (AI) device and the prefilled syringe (PFS) in patients with moderate to severe active RA who are candidates for anti-IL6R therapy. The primary objective was to collect 12 weeks of real-use data assessing the robustness and user interaction with the sarilumab AI when used by RA patients in unsupervised settings. The secondary study objectives included comparing sarilumab PK exposure when administered using the AI versus the PFS and assessing patient satisfaction with the sarilumab AI. Other objectives included documenting efficacy and safety of sarilumab 150mg q2w and 200mg q2w in the AI assessment phase.

#### Trial Design

MSC12665 was a phase 3, multicenter, worldwide, randomized, open-label, parallel group, 4-arm, 12-week study, followed by a 1-year open-label extension phase. Figure 17 presents the study schema for MSC12665. The 12-week study portion was also referred to as the AI assessment phase. In the AI assessment phase, patients were stratified by region and weight (<60 kg, 60-100kg, and >100kg) and were randomized in a 1:1:1:1 ratio to sarilumab 150mg q2w administered by AI or PFS or sarilumab 200mg q2w administered by AI or PFS. Each subject received concomitant background DMARD therapy. The subset of patients using the AI recorded product technical complaints (PTCs) in response to a series of questions in their home diaries. These PTCs were recorded by the Investigator, who then followed a predefined process of sending the syringe and compliance form to Sanofi to have the PTC evaluated for the presence or absence of a product technical failure (PTF). At Visit 2 (Day 1) and at the end of the 12-week AI assessment phase (Day 85), a patient satisfaction questionnaire was completed by patients using the AI. Patients who were unwilling or unable to participate in the extension phase had a follow-up/exit visit at Week 18, 6 weeks after the end-of-treatment (EOT) visit of the AI assessment phase.

The schedule of assessments for MSC12665 is displayed in Table 149 in the Appendix (Section 13.3).

**Figure 17. Study Schema of MSC12665**



Source: EFC11574 Clinical Study Report, Figure 2, dated June 11, 2015, page 16.

This study was still ongoing at the time of Sanofi’s BLA submission. For this BLA, the results of the AI assessment phase were provided, including AE data to Visit 16 (Week 12). Sanofi notes that a second clinical study report will include any events that occurred after Week 16; this second CSR will also summarize the data (safety, immunogenicity, long-term clinical response) for subjects who entered the 52-week extension phase.

*Reviewer Comment: Given that study MSC12665 is still ongoing, it will only be summarized briefly here with a focus on efficacy and safety.* (b) (4)

*Along with the brief summary of safety and efficacy here, safety data from the subjects from MSC12665 are included in Pool 2 (the long-term safety population) in this application’s safety analyses presented in Section 8.*

**Coordinating Investigator:** Joel Kremer, MD

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

<b>Study Centers:</b> 57 sites located in Europe, North America, South America, and South Africa
<b>Study period:</b> The first patient was enrolled on March 18, 2014. The last subject completed the 12-week AI assessment phase on February 19, 2015.
<b>Number of patients:</b> Planned: 50 patients per group (defined by dose and device) based upon PK requirements Randomized/Treated: 217 patients All 217 subjects were evaluated for efficacy, safety, and PK.
<b>Diagnosis and key inclusion criteria:</b> Patients ( $\geq 18$ years of age) with active, moderate to severe RA for $\geq 12$ weeks, treated with non-biologic DMARD for $\geq 12$ weeks prior to screening and with a stable dose of non-biologic DMARD for $\geq 6$ weeks prior to screening.
<b>Study treatments:</b> <ul style="list-style-type: none"><li>• Sarilumab 150mg or 200mg every other week Formulation: (1) glass prefilled syringe (PFS) with a deliverable volume of 1.14 mL of drug product at 131.6mg/mL (150mg) or 175mg/mL (200mg) (2) autoinjector (AI) containing a glass PFS with a deliverable volume of 1.14 mL Administration: subcutaneous</li><li>• Noninvestigational medicinal products: All subjects continued to receive concomitant nonbiologic DMARDs (either single or in combination).<ul style="list-style-type: none"><li>○ Methotrexate 10-25mg/week</li><li>○ Leflunomide 10-20mg daily</li><li>○ Sulfasalazine 1000-3000mg daily</li><li>○ Hydroxychloroquine 200-400mg daily</li></ul></li></ul>
<b>Duration of treatment:</b> 12 weeks <ul style="list-style-type: none"><li>• 18 weeks of observation for AI assessment phase</li></ul>
<b>Study endpoints:</b> Device-related Primary Endpoint <ul style="list-style-type: none"><li>• Number of validated AI-associated product technical failures (PTFs)</li></ul> Secondary device-related endpoints (assessed only on data from patients randomized to the AI) <ul style="list-style-type: none"><li>• Number and type of AI-associated product technical complaints (PTCs)</li><li>• Types of AI-associated PTFs</li><li>• Number and type of AI-associated failed drug deliveries (defined as patient failure to administer the full dose at a given attempt excluding PTF)</li><li>• Number and percentage of patients with an AI-associated PTF</li><li>• Number and percentage of patients with an AI-associated PTC</li><li>• Number and percentage of patients with an AI-associated failed drug delivery</li><li>• Patient satisfaction with the AI (assessed based on answers provided in the patient satisfaction questionnaire)</li></ul> Other clinical efficacy endpoints <ul style="list-style-type: none"><li>• ACR20/50/70 response at Week 12</li><li>• Change from baseline in the ACR components score at Week 12</li><li>• DAS28-CRP remission (DAS28-CRP<math>&lt;2.6</math>) at Week 12</li><li>• Change from baseline in DAS28-CRP at Week 12</li></ul> Safety <ul style="list-style-type: none"><li>• Occurrence of AEs, including SAEs and AESIs</li></ul>

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

- AEsIs include neutropenia, thrombocytopenia, elevations in hepatic enzymes, elevations in lipid panels, cardiovascular events, TB, and opportunistic infections

- Occurrence and titer of anti-sarilumab antibodies

### Pharmacokinetics (PKs)

- Full assessment of the functional sarilumab concentration-time profiles was performed after the first dose (Weeks 0-2) and after the 6<sup>th</sup> dose (Weeks 10-12) to determine the maximum plasma concentration ( $C_{max}$ ) and area under the serum concentration versus time curve calculated using the trapezoidal method duration a dose interval ( $AUC_{0-t}$ ) on Weeks 0 and 10.
- Sarilumab trough concentrations were measured at pre-dose on Week 0, Week 2, Week 4, Week 8, Week 10, and Week 12.

### Statistical methods:

Analyses of device-related endpoints: Although the primary and major secondary endpoints are the device-related endpoints, the analyses and results will not be reviewed here. (b) (4)

Analyses of clinical efficacy: For categorical variables, the number and percentage were provided from all patients who had data available at time points, and the 95% CI was calculated if appropriate. For continuous variables, descriptive statistics such as the mean, standard deviation, median, minimum, and maximum were provided, and the 95% CI of the mean was presented. There was no imputation in instances of missing values.

Analyses of PK: PK analyses were performed using the PK population, which consisted of all randomized patients who received at least 1 dose of the IMP and had at least 1 PK parameter ( $C_{max}$ ,  $AUC_{0-tr}$ , and/or  $C_{trough}$ ) calculated using non-compartmental methods following the first or sixth administration. The purpose of the PK analyses was to compare PK between the AI and PFS. Therefore, details of PK analyses and results will not be presented here. Like the device-related endpoints, the review of PK will be performed when the complete study is submitted for marketing of the AI.

Analyses of safety: Safety data were analyzed on the basis of the safety population. TEAES, treatment-emergent SAEs, TEAEs leading to discontinuation, and treatment-emergent AEsIs were summarized for each treatment group based on MedDRA, version 17.0. For laboratory parameters, vital signs, and ECG, incidences of potentially clinically significant abnormality (PCSA) values, actual values, and change from baseline were summarized by treatment group.

### Summary of assessments:

Patient disposition and baseline characteristics: Of the 217 patients randomized and treated in the study, 201 (92.6%) completed the AI assessment. Overall, 16 (7.4%) patients discontinued from the study with the majority doing so because of an AE. A total of 192 subjects (88.5%) entered the extension phase.

The mean age of patients was 53.5 years, and the subjects were mostly female (83.4%), Caucasian (88.5%), and non-Hispanic (64.5%). The mean duration of RA since diagnosis was 9.75 years. Of the 217 randomized patients, 134 (61.8%) and 47 (21.7%) had Class II and III RA, respectively; the majority of patients were seropositive (RF and anti-CCP antibody positive). Both the demographic and disease characteristics at baseline were similar across all treatment groups. Per protocol, all subjects received a

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

stable dose of 1 or a combination of conventional DMARDs (MTX, SSZ, LEF, HCQ).

During the AI assessment phase, the cumulative exposure to active treatment ranged from 11.2 to 12.7 patient-years across the treatment groups.

**Efficacy:** The proportion of patients achieving an ACR20 response at Week 12 was similar across the AI and PFS groups, ranging from 69.2% to 80.4%. The proportion of subjects achieving an ACR50 response at Week 12 was similar across the AI and PFS groups, ranging from 30.2% to 46.2%. The proportion of patients achieving an ACR70 response at Week 12 was similar across the AI and PFS groups, ranging from 15.4% to 19.6%.

The changes from baseline in DAS28-CRP at Week 12 were similar between AI and PFS groups. DAS28-CRP remission (DAS28-CRP<2.6) at Week 12 were similar across all treatment groups, ranging from 26.8% to 30.8%.

**Safety:** The primary safety assessment in the AI assessment phase was to evaluate the safety of sarilumab when administered via an AI and a PFS. Overall, the incidence of TEAEs, SAEs, TEAEs leading to discontinuation were similar in the AI and PFS groups.

The frequency of TEAEs was 75% in the AI 150mg q2w arm, 56.6% in the PFS 150mg q2w arm, 65.4% in the AI 200mg q2w arm, and 62.5% in the PFS 200mg q2w arm. Therefore, the frequency of AEs was comparable in the 200mg dose (both AI and PFS) but was slightly higher in the AI 150mg q2w arm and slightly lower in the PFS 150mg q2w arm. The SOC of Infections and infestations had the highest incidence followed by the SOCs Blood and lymphatic disorders and General site and administration disorders. Accordingly, the most common PTs reported were neutropenia, injection site erythema, and upper respiratory tract infection, in descending order.

No deaths occurred in this study. A total of 8 SAEs occurred with all but 1 occurring in the 200mg dose. The number of patients with SAEs was small and distributed across SOCs without any particular pattern. Similarly, the incidence of AEs leading to discontinuation was low with 5.4% in the AI 150mg q2w arm, 5.7% in the PFS 150mg q2w arm, 13.5% in the AI 200mg q2w arm, and 5.4% in the PFS 200mg q2w arm. The events were distributed across SOCs without any particular pattern.

AESIs were assessed in this study. Infections, leukopenia, thrombocytopenia, hepatic disorders, elevation in lipids, hypersensitivity, and injection site reactions were noted in all treatment arms. Here, I will only present briefly on serious infections and leukopenia.

- There were 3 total serious infections (1 in AI 150mg q2w group and 2 in PFS 200mg q2w group). The subject on AI 150mg q2w developed grade 3 neutropenia on Day 5 and was diagnosed with an infection olecranon bursitis (*MSSA*) on Day 8. The other 2 subjects on 200mg q2w did not have neutropenia. One had diabetes and was hospitalized for erysipelas (*Staph Aureus*) on Day 40; sarilumab was restarted on this subject. The other subject was also hospitalized for cellulitis on Day 66.
- In regards to leukopenia, subjects in all treatment arms were identified with the SMQ Hematopoietic leukopenia. The majority of subjects had Grade 1-2 neutropenia. There was a slightly higher incidence of subjects with ANC <1.0 Giga/L on the lower dose (in both

presentations) compared to the higher dose, 10.7% in the AI 150mg q2w arm, 15.1% in the PFS 150mg q2w arm, 7.7% in the AI 200mg q2w arm, and 7.2% in the PFS 200mg q2w arm.
---

Source: MSC12665 Study Synopsis, July 31, 2015.

### 6.7.2. Study Results

Study MSC12665 was still ongoing at the of BLA submission. Therefore, only a brief review of the data submitted was performed, focusing on efficacy and safety. The device-related endpoints and the PK comparability data will be reviewed once the study is complete. In general, the exposure to sarilumab in the study portion completed is low, and, thus, limited conclusions can be made. It is notable that the majority of subjects in all arms achieved ACR20 at Week 12. Additionally, the safety data were consistent with the safety from the pivotal studies and, thus, did not demonstrate any new safety signals. The adverse events described above were in line with the anticipated effect of IL-6 inhibition in the RA population. As noted above, the safety population from study MSC12665 is included in the general safety analyses for this application as part of Pool 2 (the long-term safety population). Please refer to Section 8 for the safety review of the entire application.

## 6.8. ACT11575

### 6.8.1. Study Design

#### Overview and Objective

##### Primary objective

- To demonstrate that sarilumab on top of MTX is superior in efficacy to placebo for the relief of signs and symptoms of RA in patients with active RA who have failed up to 2 TNF $\alpha$  antagonists

##### Secondary objectives

- To assess the safety of sarilumab
- To document the PK profile of sarilumab

#### Trial Design

Study ACT11575 was initiated on November 15, 2010, and then discontinued on September 15, 2011. It was a phase 2, randomized, double-blind, parallel-group, placebo- and active calibrator-controlled study assessing the clinical benefit of sarilumab (SC) on top of MTX in patients with active RA who have failed previous TNF $\alpha$  antagonists. It was discontinued early as a result of the delays incurred in the study and the impact to timeliness for completing the study. At the time of study discontinuation, 16 patients had been randomized of whom 13 completed the study as planned per protocol and 3 discontinued. No efficacy analyses were

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

performed due to insufficient data as a result of low enrollment. Safety analyses were performed.

Because this study was discontinued it will be discussed only briefly here in a table format. An overview of the safety will be summarized briefly. Subjects from ACT11575 were allowed to enter the open-label study LTS11210. Therefore, most of the safety analyses will be presented as part of the long-term safety population (Pool 2) in Section 8.

<b>Coordinating Investigator:</b> E. Fudman, MD (Austin, TX)
<b>Study Centers:</b> 10 centers in North America, South America, and Europe
<b>Basic study design:</b> This was a multicenter, multinational, randomized, double-blind, parallel-group, placebo- and active calibrator-controlled study intended to compare the efficacy and safety of sarilumab SC with placebo on top of MTX in patients with active RA who had failed previous TNF $\alpha$ antagonists. Golimumab SC (a TNF $\alpha$ mAb) was the active calibrator. Eligible patients were centrally randomized via an IVRS in a 2:1:2 ratio to one of the following 3 treatment groups: <ul style="list-style-type: none"><li>• Sarilumab 150mg/2mL qw + placebo 0.5 mL q4w</li><li>• Matching placebo 2mL qw + placebo 0.5 mL q4w</li><li>• Matching placebo 2mL qw + golimumab 50mg/0.5mL q4w</li></ul> Randomized subjects would be treated double-blind for 12 weeks. Randomization was stratified by region and by the number of prior anti-TNF $\alpha$ agents. All patients continued to receive MTX as background therapy. Patients who completed the 12-week treatment period were offered enrollment into the open-label, long-term extension study (LTS11210).
<b>Number of patients:</b> Planned: approximately 250 patients (100 in sarilumab arm, 50 in placebo arm, 100 in active calibrator arm) Actual: 16 subjects randomized and 16 treated. All subjects' data were used for safety and PK analyses.
<b>Diagnosis and key inclusion criteria:</b> Male and female patients between ages 18 and 74 years of age with moderate-severe active RA for at least 6 months. Subjects must meet ACR Class I-III functional status at screening and baseline, received continuous treatment with MTX for at least 12 weeks prior to screening and on stable doses for at least 6 weeks prior to screening, and were TNF $\alpha$ blocker nonresponders (up to 2 agents).
<b>Study treatments:</b> <ul style="list-style-type: none"><li>• Sarilumab 150mg weekly (or 150mg every other week if dose reduced) Formulation: vials (75mg/mL), 2mL Administration: SC in abdomen</li><li>• Golimumab 50mg every 4 weeks Formulation: pre-filled syringe (50mg/0.5mL) Administration: SC in abdomen</li><li>• Placebo (matched for sarilumab)</li><li>• Noninvestigational medicinal products<ul style="list-style-type: none"><li>○ Methotrexate (tablet or liquid)</li><li>○ Folic acid</li></ul></li></ul>
<b>Duration of treatment:</b> 12 weeks

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

- 22 weeks of observation (including screening, 12-week treatment period, 6-week post-treatment follow-up)

### **Statistical methods:**

Safety was assessed throughout the study by recording AEs and by clinical and laboratory examination (biochemistry, hematology, ANA/dsDNA Ab, urinalysis), vital signs, and ECG at selected visits. Blood samples for clinical laboratories were taken at Visits 1 to 7, and vital signs were collected at Visits 1 to 8. ECGs were performed at screening and at the end-of-treatment visit. Additional blood samples were taken at various specified time points to measure sarilumab concentration, anti-sarilumab antibody, CRP, IL-6, and soluble IL-6 receptor.

Safety data were analyzed descriptively by treatment group using the safety population, which included all randomized patients who received at least 1 dose of the study medication. All patients were analyzed according to the treatment which they already received. Duration of study treatment exposure was defined as last dose (injection) date – first dose (injection) date + 7 or 28 days (7 days for sarilumab and placebo patients, 28 days for golimumab patients), regardless of unplanned intermittent discontinuations. Safety analyses focused on AE data and the potentially clinically significant abnormality (PCSA) values. The same observation period was used for all safety observations. Adverse events were coded according to the MedDRA, version 14.0. Adverse events requiring prespecified monitoring (AEPs) were later referred to as AEs of special interest (AESIs) and were essentially the same as those in the other protocols: opportunistic infection (including herpes zoster), confirmed diverticulitis and GI perforation, systemic hypersensitivity reactions or anaphylaxis, autoimmune or lupus-like syndrome, drug-induced liver injury, neutropenia, thrombocytopenia, neurological disorders, pregnancy, and overdose.

### **Summary of assessments:**

Patient disposition: Forty-one subjects were screened, but 25 were screen failures. Therefore, 16 subjects were randomized and treated: 4 in placebo arm, 5 in golimumab arm, and 7 in sarilumab arm. Three subjects did not complete the study: 2 for AEs (1 in placebo and 1 in golimumab) and 1 in sarilumab for lack of efficacy. Four subjects in the sarilumab group and 3 subjects in the golimumab group rolled over into the long-term extension study.

Baseline characteristics: In general, the baseline patient characteristics were similar to that in the other sarilumab trials. The majority of subjects were female (87.5%), Caucasian (56.3%), and less than 65 years-old (75%). The mean duration of RA at baseline was 6.75 years in the placebo arm, 4.41 years in the golimumab arm, and 16.27 years in the sarilumab arm. Subjects had moderate to severe RA (43.8% Class II and 43.8% Class II), and most were seropositive (68.8% rheumatoid factor positive and 86.7% anti-CCP positive). Per protocol, all subjects received concomitant MTX.

Safety: In total, there were TEAEs reported in 3 of 4 subjects in the placebo arm, 1 of 5 subjects in the golimumab arm, and 3 of 7 subjects in the sarilumab arm. There were no SAEs during this study. There were 2 treatment discontinuations due to AEs: 1 on placebo due to urticaria and 1 on golimumab due to pre-treatment AE of grade 3 neutropenia. There were some potentially clinically significant abnormalities (PCSA) in laboratory parameters, more so in the sarilumab arm than in the tocilizumab arm. One patient in the sarilumab group had grade 2 neutropenia, but there were no cases of treatment-emergent neutropenia in the placebo or golimumab arms. Three of 7 subjects in the sarilumab arm and 1 of 5 subjects in the golimumab had PCSAs in ALT and AST; there were none in the

placebo arm. Lastly, in the sarilumab arm, 4 subjects had PCSAs in total cholesterol, and 3 had PCSAs in LDL. No subjects had PCSAs in total cholesterol or LDL in the placebo or golimumab arms.

Source: ACT11575 Study Synopsis, February 2, 2012.

## 6.8.2. Study Results

Because this study was prematurely discontinued, there was only a small number of subjects (16) treated. Therefore, no conclusions can be really made from the study results. No efficacy analyses were performed and, thus, will not be presented here. As already noted, a brief safety summary was described above, and, given the low numbers, it is difficult to make any conclusions. There were, however, no safety signals, and the laboratory abnormalities that were seen in the sarilumab group were consistent with what was expected and what was seen in the other sarilumab trials. The safety results are also rolled into the pooled safety population for any dose of sarilumab in the safety section of this review (Section 8).

## 6.9. LTS11210 (SARIL-RA-EXTEND)

### 6.9.1. Study Design

#### Overview and Objective

LTS11210 was a multi-center, uncontrolled extension study evaluating the efficacy and safety of sarilumab in patients with active RA. At that time of this application submission, this study was still ongoing. The primary objective of the study was to evaluate the long-term safety of sarilumab in patients with RA. The secondary objective of the study was to evaluate the long-term efficacy of sarilumab in patients with RA.

#### Trial Design

##### Basic Study Design

LTS11210 was an ongoing multicenter, multinational, open-label, long-term study in patients with RA. Subjects participating in this study were enrolled from the studies previously described: ACT11575, EFC11072, EFC10832, SFY13370, and EFC13752. At the time of their inclusion in the initial study, they were either inadequate responders to MTX therapy (EFC11072), inadequate responders to or intolerant of TNF $\alpha$  antagonists (EFC10832, SFY13370), inadequate responders to TNF $\alpha$  antagonists who had failed up to 2 TNF $\alpha$  antagonists (ACT11575), or inadequate responders to or intolerant of non-biologic DMARDs (EFC13752). Subjects were allowed to continue their background therapy as per the initial study. Similarly, patients, who received sarilumab monotherapy in study EFC13752, continued on sarilumab monotherapy in LTS11210.

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

Depending on from which study they initiated, subjects may have had differing exposures to sarilumab prior to LTS11210. Subjects may have been exposed to sarilumab for 12 weeks if they were initially randomized in EFC11072 Part A or ACT11575; for up to 52 weeks if initially randomized in EFC11072 Part B; for up to 24 weeks if initially randomized in EFC10832; or for 24 weeks if initially randomized in SFY13370 or EFC13752.

In this study, subjects initially received sarilumab 150mg SC once weekly, which was the highest dose studied in ACT11575, EFC11072 Part A, and EFC11072 Part B Cohort 1. A subject could reduce the dose to 150mg q2w due to neutropenia, thrombocytopenia, or an increase in liver enzymes (ALT). Once the dose regimens were selected for the Phase 3 studies (150mg q2w and 200mg q2w), newly enrolled subjects received 200mg q2w. Subjects already ongoing in this study at the highest dose were switched to the sarilumab dose of 200mg q2w as soon as permitted by administrative process. Subjects, who had previously reduced their dose to 150mg q2w due to safety reasons prior to dose selection, could remain on the same dose. After dose selection, subjects on 200mg q2w also had the option to reduce the dose to 150mg q2w for the same reasons as already described above.

Subjects from EFC11072 Part A or Part B Cohort 1 and ACT11575 entered a 1-week screening period. Subjects could also enroll directly into the treatment period; for subjects from EFC11072 Part B Cohort 2, EFC10832, SFY13370, or EFC13752, the EOT visit in the initial study corresponded to the randomization visit for this study (LTS11210). The total maximum duration of participation for a subject in the study would be 260 weeks. At the time of data extraction for this application, the longest duration of participation for a subject was 242 weeks.

The schedule of assessments for LTS11210 is displayed in Table 142 and in Table 143 in the Appendix (Section 13.3).

<b>Coordinating Investigator:</b> Gerd R. Burmester, Professor of Medicine (Berlin, Germany)
<b>Study Centers:</b> 334 sites in 40 countries
<b>Study period:</b> The first patient was enrolled on June 21, 2010. The data extraction date for this application was April 30, 2015, at which time the study was still ongoing.
<b>Number of patients:</b> Planned: approximately 2000 patients Enrolled: 1914 (sarilumab + DMARD); 90 (sarilumab monotherapy) Treated: 1910 (sarilumab + DMARD); 88 (sarilumab monotherapy)  All subjects treated were evaluated for efficacy and safety. For PK and immunogenicity, less subjects were evaluated. <ul style="list-style-type: none"><li>• PK: 1879 (sarilumab + DMARD); 54 (sarilumab monotherapy)</li><li>• Immunogenicity: 1840 (sarilumab + DMARD); 14 (sarilumab monotherapy)</li></ul>
<b>Diagnosis and key inclusion criteria:</b> Patients with RA who were randomized in a prior sarilumab clinical

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

study.

- Study EFC11072
  - Patients who completed Part A (12 weeks) or Part B (52 weeks)
  - Patients randomized in Part B to a treatment arm not retained following pivotal dose selection
- ACT11575: patients who completed the treatment period
- EFC10832
  - Patients who completed the 24-week study treatment period
  - Patients from 12 weeks onward with per-protocol defined lack of efficacy
- SFY13370: patients who completed the treatment period
- EFC13752: patients who completed the treatment period

### Study treatments:

- Sarilumab 150mg weekly (or 150mg q2w if dose reduced); after dose selection, 200mg q2w (or 150mg q2w if dose reduced)  
Formulation: (before phase 3 pivotal selection decision) vials 150mg (75mg/mL); (after phase 3 pivotal dose selection decision but prior to PFS availability) vials 150mg (75mg/mL) and 200mg (100mg/mL); (after phase 3 pivotal dose selection and after PFS availability) PFS with 150mg (131.6mg/mL) or 200mg (175mg/mL)  
Administration: SC in abdomen, thigh, or upper arm

**Concomitant medications:** For those patients who were already receiving concomitant non-biologic DMARDs in the initial study, they continued being treated with a stable dose of one or a combination of the conventional DMARDs they were receiving, except for subjects from EFC13752 (who were only receiving sarilumab monotherapy):

- EFC11072 and ACT11575
  - MTX: 10-25mg/wk (EFC11072) and 15-25mg/wk (ACT11575)
- SFY13370 and EFC10832: one or a combination of the following
  - MTX 10-25mg/wk (orally or IM)
  - LEF 10-20mg daily (orally)
  - SSZ 1000-3000mg daily (orally)
  - HCQ 200-400mg daily (orally)
- Folic acid (or folinic acid) was used according to local regulations to ameliorate side effects associated with MTX.

At any time during LTS11210, a subject could be switched to an alternate approved non-biologic DMARD for safety or tolerability reasons. If the new DMARD was initiated, the dosing as well as safety monitoring followed local labeling information. For EFC13752 patients, treatment with non-biologic DMARD(s) was not allowed at any time during the study.

**Duration of treatment:** Duration of treatment was up to 5 years (260 weeks) from first dose in the initial study to last dose in LTS11210.

The maximum duration of observation for LTS11210 was expected to be approximately 267 weeks, including up to 1 week of screening (if any), up to 260 weeks of open-label treatment phase, and 6 weeks of post-treatment follow-up.

### Study endpoints:

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

- **Safety:** The safety variables included clinical laboratory parameters, vital signs, ECG, AEs, AESIs (including leukopenia, thrombocytopenia, infections [such as opportunistic infections and TB], hepatic disorders, diverticulitis, GI perforations, GI ulcerations, elevation in lipids, anaphylaxis, hypersensitivity, lupus-like syndrome, demyelinating disorders, pregnancy, and overdose), injection site reactions, malignancy, and MACE.
- **Efficacy:** Efficacy assessments included ACR20/50/70 responses, DAS28 remission, each ACR component over time, EULAR response over time, DAS28-CRP over time, HAQ-DI results over time, Van der Heijde modified total Sharp score over time, and incidence of radiographic progression for the subset of patients who previously completed study EFC11072 Part B (Cohort 2 and Cohort 1 selected dose arms)
- **PK:** Samples for sarilumab trough analyses were collected at the timepoints described in Table 142 and Table 143. For patients who had an SAE, serum samples were collected for determination of sarilumab concentrations at or near the onset and completion of the occurrence of the event. Samples for IL-6 were also collected at specified timepoints. Serum IL-6 concentrations were determined using validated quantitative sandwich enzyme immunoassay with the lower limit of quantitation of 12.5ng/mL.
- **Immunogenicity:** Serum samples for ADA analyses were collected at specified time points as described in Table 142 and Table 143. The presence of anti-sarilumab antibody and anti-sarilumab neutralizing antibodies in serum samples were determined using validated electrochemiluminescence methods.

**Statistical methods:** Data analysis results for patients who rolled over from study EFC13752 were presented separately since sarilumab was administered as monotherapy and were continuing monotherapy in the open-label extension study. On the other hand, data from the other studies in which subjects all received sarilumab + DMARD were pooled. Patient characteristics including demographics, disease history, medical history, and subject accountability were summarized for the safety population based on data collected at baseline of the prior study. The summaries consisted of descriptive statistics, e.g., mean, standard deviation, median, minimum, and maximum for quantitative values as well as counts and percentages for qualitative variables. The primary population was the safety population. Data were presented by treatment group (sarilumab + DMARD) or sarilumab monotherapy.

**Safety:** The primary safety analyses variables were AEs. The period for reporting TEAEs was from first dose of sarilumab in study LTS11210 to 60 days post last dose. TEAE incidence was presented by SOC, HLT, HLT, and PT sorted in alphabetical order, the number (n) and percentage of patients experiencing a TEAE were presented. Multiple occurrences of the same event in the same patient were counted only once. The incidence and number of events per 100 patient-years was provided for all the TEAE summaries. In addition, the number of patients with event(s) per 100 patient-years was also provided for SAEs and for each type of AESI. Clinical laboratory changes were summarized in shift tables and plotted by treatment group. Potentially clinically significant abnormalities (PCSA) were summarized.

**Efficacy:** For efficacy endpoints, there was no statistical hypothesis and testing of efficacy variables. All analyses were done descriptively on the safety population by visit in the observed case, as appropriate. In addition to the by-visit analysis, efficacy assessments summarized on a yearly basis were provided. The baseline value for efficacy parameters was the original baseline from the initial studies. For

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

categorical variables, the number and percentage were provided from all patients who had data available at that time point, and the 95% CI was calculated if appropriate. For continuous variables, descriptive statistics such as the mean, SD, mean, minimum, and maximum were provided, and the 95% CI of the mean was presented. X-ray analyses were only performed from study EFC11072 Part B (Cohort 1 selected dose arms and Cohort 2).

PK: Serum concentrations of sarilumab were summarized up to Week 48.

PD: Serum concentrations of IL-6 were summarized up to Week 48.

Immunogenicity: ADA prevalence, incidence, and titer were summarized up to Week 216. Additional analyses of ADA and safety and ADA and efficacy were performed.

The analyses of health economics and patient-reported outcomes (PROs) were not performed.

### **Summary of assessments:**

#### Patient disposition and baseline characteristics:

See Figure 18 below for a description of the patient population in LTS11210 in regards to the number of patients from the initial studies who enrolled into LTS11210.

#### *Sarilumab + DMARD*

A total of 440 (23.0%) subject permanently discontinued the study. Of these, 274 (14.3%) discontinued due to AEs; 42 (2.2%) discontinued due to lack of efficacy; 18 (0.9%) discontinued due to poor compliance to protocol; and 106 (5.5%) of subjects discontinued due to "other reasons."

The patient age range was 19-88 years with a mean of 52.1 years. The majority of subjects were female (1552 [81.1%]) and Caucasian (1641 [85.7%]). The mean weight for subjects was 76.17 kg (range from 38.0 to 183.6 kg). The mean duration of RA baseline was 9.74 years (range 0.3 to 54.0 years). The majority of subjects had class II RA and were seropositive (RF/anti-CCP antibody positive). Given that these subjects rolled over from the other previously described studies, it would follow that these characteristics were consistent with these other studies.

At enrollment, approximately two-thirds of patients (63.8%) in the sarilumab + DMARD group were receiving sarilumab 150mg q2w (26.1%) or 200mg q2w (37.7%). The other patients were receiving sarilumab at nonselected doses (10.4% other doses), placebo (20.8%), or tocilizumab or golimumab (5.0%).

#### *Sarilumab monotherapy*

Eighty-eight (97.8%) received treatment, and 2 patients discontinued. One subject discontinued due to AE, and 1 subject died.

The ages of these subjects ranged from 23 to 78 years with a mean of 53.2 years. The majority of subjects were female (72 [80.0%]) and Caucasian (87 [96.7%]). The mean weight for these subjects was 76.70kg (range from 42.5 to 154.6 kg). The mean duration of RA at baseline was 9.45 years (range 0.3 to 38.6 years). The majority of subjects had class II RA and were seropositive (RF/anti-CCP antibody positive).

At enrollment, an almost equal number of patients were receiving sarilumab 150mg q2w (48.9%) or 200mg q2w (51.1%).

Efficacy results: The efficacy results for the sarilumab + DMARD population will be presented briefly below. Subjects in the sarilumab monotherapy group had only received sarilumab for a short period in this study (i.e., 16 subjects had reached 12 weeks); therefore, no meaningful assessments could be drawn regarding long-term treatment in this group.

Safety results: The safety results are presented as part of the overall safety evaluation for this application in Section 8 below. The sarilumab + DMARD group in study LTS11210 are included as part of the long-term safety population (Pool 2). The sarilumab monotherapy group are included as part of Pool 3. Notably, for the sarilumab monotherapy group, the small number of patients on monotherapy (i.e., 88 patients) had a mean exposure of 44.7 days; therefore, interpretation of any safety observations was limited.

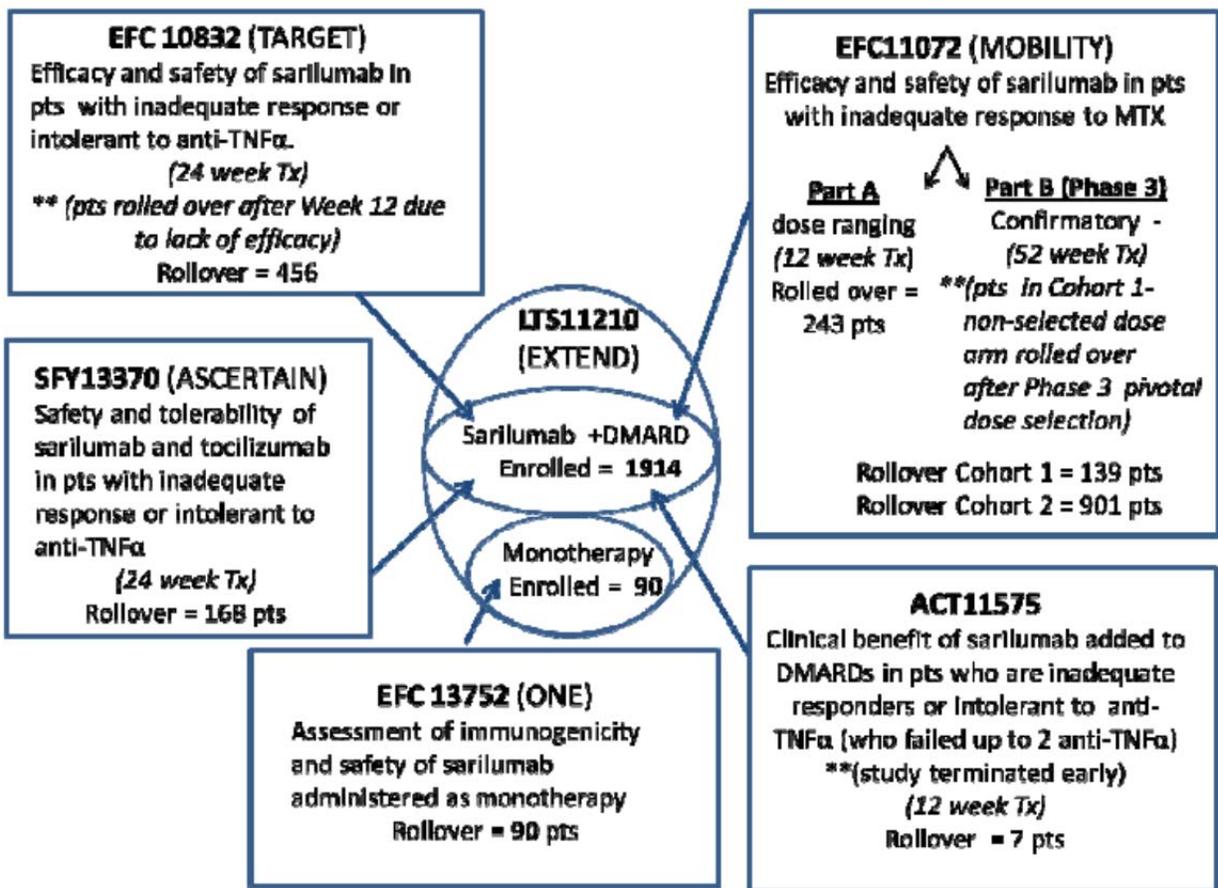
Source: LTS11210 Study Synopsis, August 24, 2015.

## 6.9.2. Study Results

### Patient Disposition

Subjects from EFC10832, EFC11072, SFY13370, and ACT1157 made up the sarilumab + DMARD arm of LTS11210. At the time of data extraction, the most recently completed studies were EFC10832 and SFY13370, so subjects from these studies have limited data available. Subjects from EFC13752 rolled over into the open-label study to make up the sarilumab monotherapy population. Figure 18 illustrates the initial studies and the number of subjects from each study that participated in LTS11210. Figure 18

Figure 18. Schematic of the Patient Population in LTS11210 Based on Initial Studies



Source: LTS11210 CSR, Figure 3, August 24, 2015; page 66.

The patient disposition for LTS11210 is summarized briefly in the synopsis table above.

### Efficacy Results

Efficacy assessments were secondary endpoints in the open-label study. At the time of data extraction, 1910 subjects were being treated, and over 57% had received at least 72 weeks of study.

Table 25 presents the proportion of subjects who achieved an ACR response (ACR20/50/70) or DAS28 remission (as defined by DAS28-CRP <2.6) through the open-label period. Overall, there appeared to be an increase in proportion of responders between Weeks 0 and 24. After Week 24, the proportion of responders appeared to remain stable. Of note, however, the number of total subjects (i.e., the denominator of these proportions) decreased gradually to less than 100 total subjects by Week 216.

**Table 25. Proportion of Subjects with ACR20/50/70 and DAS28 Remission by Every 24 Weeks (LTS11210)**

Study Week	ACR20	ACR50	ACR70	DAS28 Remission
Week 0	1318/1898 (69.4%)	824/1897 (43.4%)	435/1901 (22.9%)	569/1873 (30.4%)
Week 24	1363/1647 (82.8%)	990/1640 (60.4%)	635/1642 (38.7%)	828/1638 (50.5%)
Week 48	1114/1346 (82.8%)	844/1341 (62.9%)	541/1337 (40.5%)	735/1336 (55.0%)
Week 96	709/815 (87.0%)	549/811 (67.7%)	355/808 (43.9%)	469/807 (58.1%)
Week 144	219/255 (85.9%)	167/255 (65.5%)	112/256 (43.8%)	138/255 (54.1%)
Week 192	133/148 (89.9%)	104/148 (70.3%)	75/149 (50.3%)	91/147 (61.9%)
Week 216	58/69 (84.1%)	47/70 (67.1%)	31/69 (44.9%)	42/68 (61.8%)

DAS28 remission = DAS28-CRP < 2.6

Source: LTS11210 CSR, Table 15, August 24, 2015; page 87.

X-ray data were collected from subjects who entered from study EFC11072. A total of 860 subjects who initiated treatment in EFC11072 had x-ray data evaluated on Day 0 of study EFC11072; 856 subjects had x-ray data analyzed at Week 0 of study LTS11210. Of the 856 subjects, 848 subjects had x-ray data analyzed at baseline, Week 0, and Week 48 of study LTS11210. At Week 0 of LTS11210 (i.e., after 1 year of treatment in EFC11072), the mTSS score increased by 1.05 units relative to baseline of the initial study. At Year 2 (i.e., after 52 weeks of treatment in EFC11072 and 48 weeks of treatment in LTS11210), the score increased from baseline (of the initial study) by a mean of 1.34 units (SD 5.31) with a 95% CI of 0.98 to 1.70. Thus, the change from baseline in the mTSS score after an additional 48 weeks of treatment remained similar. Sanofi argued that this finding supported a sustained effect on prevention of structural damage.

*Reviewer Comment: As the study was still ongoing at the time of BLA submission, there were fewer total subjects at longer time points. Thus, is difficult to draw any significant conclusions from the longer duration of the extension study. Additionally and most importantly, without a placebo arm in the extension study, the interpretation of efficacy or sustained efficacy is limited.*

### **Additional Analyses Conducted on the Individual Trial**

Safety data from the open-label extension study are reviewed as part of the safety section (Section 8) below.

## **7 Integrated Review of Effectiveness**

---

### **7.1. Assessment of Efficacy Across Trials**

#### **7.1.1. Primary Endpoints**

Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

EFC11072 Part B Cohort 2 and EFC10832 are the pivotal studies from which the efficacy assessments are made. As reminder of the main inclusion and exclusion criteria from these 2 studies, Table 26 presents the inclusion/exclusion criteria, highlighting the similarities and differences in the baseline disease activity and the previous biologic therapy. Briefly, subjects in study EFC11072 Part B were MTX inadequate responders who had to have evidence of risk for progression in structural damage, whereas subjects in study EFC10832 were TNF inadequate responders. In both studies, subjects were required to take concomitant non-biologic DMARDs. However, in study EFC11072, the only permitted DMARD was MTX, and, in study EFC10832, subjects could take any conventional DMARD (MTX, LEF, SSZ, or HCQ).

APPEARS THIS WAY ON ORIGINAL

**Table 26. Main Inclusion and Exclusion Criteria of EFC11072 Part B and EFC10832**

	EFC11072 Part B	EFC10832
<b>Inclusion Criteria</b>		
<b>Diagnostic criteria</b>	1987 ACR/EULAR criteria	2010 ACR/EULAR criteria
<b>Duration of RA</b>	≥ 3 months	≥ 6 months
<b>Tender joint count</b>	≥ 8/68	≥ 8/68
<b>Swollen joint count</b>	≥ 6/66	≥ 6/66
<b>CRP (mg/L)</b>	> 6 <sup>b</sup>	≥ 8
<b>Baseline DMARD treatment</b>	MTX for ≥ 12 weeks prior to baseline and at stable dose for ≥ 6 weeks prior to baseline	MTX, LEF, SSZ, or HCQ <sup>a</sup> ≥ 12 weeks prior to baseline and at stable dose for ≥ 6 weeks prior to baseline
<b>Risk for progression of joint damage</b>	Bone erosion (radiograph documented) or RF-positive or CCP-positive	Not Applicable
<b>Prior therapy with biologics</b>	Permitted	Must have received at least 1 TNF antagonist with history of either of the following: <ul style="list-style-type: none"> <li>• Inadequate response after at least 3 months of treatment</li> <li>• Intolerance requiring discontinuation</li> </ul>
<b>Main exclusion criteria</b>		
<b>Oral DMARDs</b>	<ul style="list-style-type: none"> <li>• Any DMARD other than MTX within 4 weeks prior to screening</li> <li>• Any prior treatment with tofacitinib or other JAK inhibitor</li> </ul>	Any prior treatment with tofacitinib or other JAK inhibitor
<b>Biologic DMARDs</b>	<ul style="list-style-type: none"> <li>• Past history of non-response to TNF or other biologic</li> <li>• Any biologic DMARD for RA within 3 months</li> </ul>	<ul style="list-style-type: none"> <li>• Etanercept or anakinra within 28 days of randomization</li> <li>• Infliximab, adalimumab, golimumab, certolizumab, or abatacept within 42 days of randomization</li> <li>• Rituximab or other B-cell depleting agent within 6 months of randomization</li> <li>• Prior treatment with anti-IL-6 or anti-IL-6R</li> </ul>
<b>Corticosteroids</b>	<ul style="list-style-type: none"> <li>• Parenteral or intra-articular use within 4 weeks prior to screening</li> <li>• Systemic dose &gt;10 mg/day of prednisone or change in dose within 4 weeks prior to</li> </ul>	<ul style="list-style-type: none"> <li>• Parenteral or intra-articular use within 4 weeks prior to screening</li> <li>• Systemic dose &gt;10mg/day of prednisone or change in dose within 4 weeks prior to baseline</li> </ul>

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

	baseline	
--	----------	--

a Except for simultaneous combination use of LEF and MTX

b Study protocol was amended to reduce CRP from >8 to >6

Source: Source of Clinical Efficacy, Table 2, dated Sep 10, 2015; page 18.

In this integrated presentation of the efficacy results, the data from these 2 studies are not being pooled. Rather, the results of the primary endpoint and major secondary endpoints will be presented and reviewed alongside each other.

As described in Section 6, the protocols for both pivotal studies defined various “co-primary endpoints.” However, because of the hierarchical testing procedure, in actuality, there was one primary endpoint with several key secondary endpoints. For both studies, the primary endpoint was proportion of ACR20 responders at Week 24.

Table 27 shows the results from Sanofi’s primary analysis of ACR20 responders at Week 24. In this analysis, all dropouts prior to Week 24 were considered to be non-responders. In both studies, subjects on sarilumab had a significantly greater number of ACR20 responders compared to placebo. Additionally, the proportions of responders were numerically greater in the higher dose. These results were further supported by various sensitivity analyses performed both by the Applicant and the Agency’s statistical review team (Dr. Yongman Kim), including ACR20 response prior to rescue (Week 16 for EFC11072 Part B and Week 12 for EFC10832) and tipping point analysis. Please see Dr.Kim’s review for a detailed presentation of the results from these sensitivity analyses.

**Table 27. ACR20 Response at Week 24 for EFC11072 Part B and EFC10832**

Treatment group	n/N (%)	Comparison	Odds Ratio	95% CI	p-value
<b>EFC11072 Part B</b>					
SAR 150mg (N=400)	232/400 (58)	vs. placebo	2.8	(2.1, 3.7)	<0.0001
SAR 200mg (N=399)	265/399 (66)	vs. placebo	4.0	(3.0, 5.3)	<0.0001
Placebo (N=398)	133/398 (33)	--	--	--	--
<b>EFC10832</b>					
SAR 150mg (N=181)	101/181 (56)	vs. placebo	2.7	(1.7, 4.2)	<0.0001
SAR 200mg (N=184)	112/184 (61)	vs. placebo	3.3	(2.1, 5.1)	<0.0001
Placebo (N=181)	61/181 (34)	--	--	--	--

NRI=Nonresponder imputation; CI=confidence interval

Study EFC11072: p-value based on CMH test stratified by prior biologic use and region

Study EFC110832: CMH test stratified by number of previous anti-TNFs and region.

Source: Clinical Study Report for Study EFC11072 (page 103) and 15.2 (page 4) and Clinical Study Report for Study EFC10832 (page 81) & 15.2 (page 83), submitted 10/30/15

ACR20 response has been utilized in all clinical development programs of recently approved biologic DMARDs as a measure of improvement in signs and symptoms of RA. Thus, these results are supportive of sarilumab’s claims of improvement in signs and symptoms. Further review of the ACR components, as well as ACR50 and ACR70, are presented below.

### 7.1.2. Secondary and Other Endpoints

- *Health Assessment Questionnaire-Disability Index (HAQ-DI)*

One of the other “co-primary” endpoints that was the same in both pivotal trials was change from baseline in HAQ-DI. For both studies, this assessment of physical function was made prior to the option to escape/rescue. Table 28 presents the results for the change from baseline in HAQ-DI at Week 16 for EFC11072 Part B and at Week 12 for EFC10832. Subjects on sarilumab had a greater improvement from baseline in HAQ-DI compared to placebo. The difference from placebo was significant in both studies.

**Table 28. Change from Baseline in HAQ-DI at Week 16 (EFC11072) and Week 12 (EFC10832)**

Treatment group	n	LS Mean Change (SE)	Comparison	Mean difference	95% Confidence Interval	p-value
<b>EFC11072 Part B</b>						
SAR 150mg (N=400)	362	-0.53 (0.03)	vs. placebo	-0.24	(-0.31, -0.16)	<0.0001
SAR 200mg (N=399)	365	-0.55 (0.03)	vs. placebo	-0.26	(-0.34, -0.18)	<0.0001
Placebo (N=398)	378	-0.29 (0.03)	--	--	--	--
<b>EFC10832</b>						
SAR 150mg (N=181)	165	-0.46 (0.04)	vs. placebo	-0.20	(-0.32, -0.09)	0.0007
SAR 200mg (N=184)	171	-0.47 (0.04)	vs. placebo	-0.21	(-0.33, -0.10)	0.0004
Placebo (N=181)	170	-0.26 (0.04)	--	--	--	--

Note: All assessments are set to missing from the time a patient receives rescue medication or discontinues study medication early. No imputation is performed.

Study EFC11072: MMRM with PROC MIXED assuming an unstructured covariance structure: model = baseline, treatment, prior biological use, region, visit, and treatment-by-visit interaction.

Study EFC10832: MMRM with PROC MIXED assuming an unstructured covariance structure: model = baseline, treatment, number of previous anti-TNFs, region, visit, and treatment-by-visit interaction.

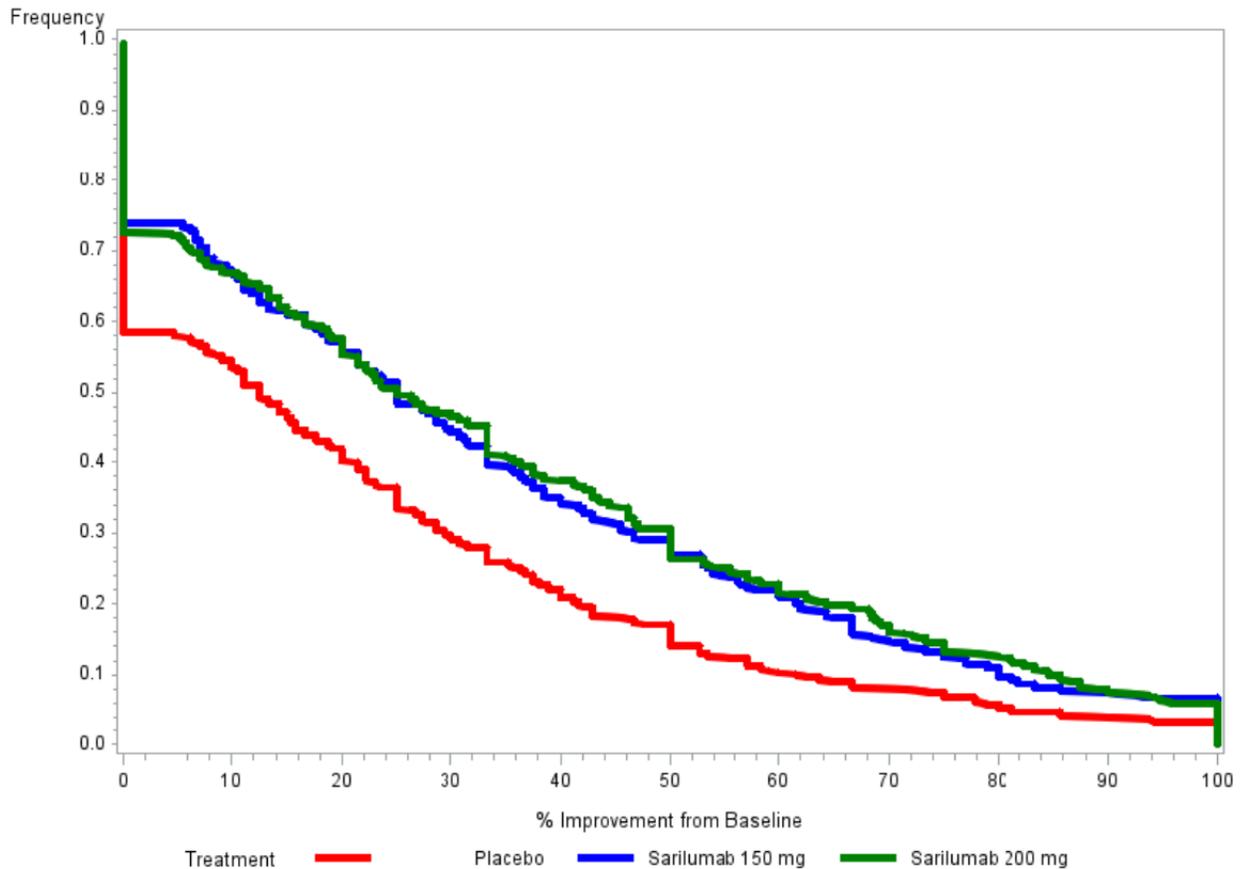
Source: Excerpted from the Clinical Study Report for Study EFC11072 (page 104) and Clinical Study Report for Study EFC10832 (page 82), submitted 10/30/15.

The Applicant’s sensitivity analysis supported the results from the primary analysis. Additionally, Dr.Yongman Kim (primary statistical reviewer) created cumulative responder curves with worst score imputation for missing data (Figure 19 and Figure 20). His cumulative

Clinical Review  
Reviewer: Suzette Peng, MD  
NME/BLA 761037  
Sarilumab/Kevzara

responder curves showed a separation of the curves between sarilumab and placebo. In study EFC10832, the separation was clearer for sarilumab 200mg than for sarilumab 150mg . Please see Dr.Kim’s review for full details.

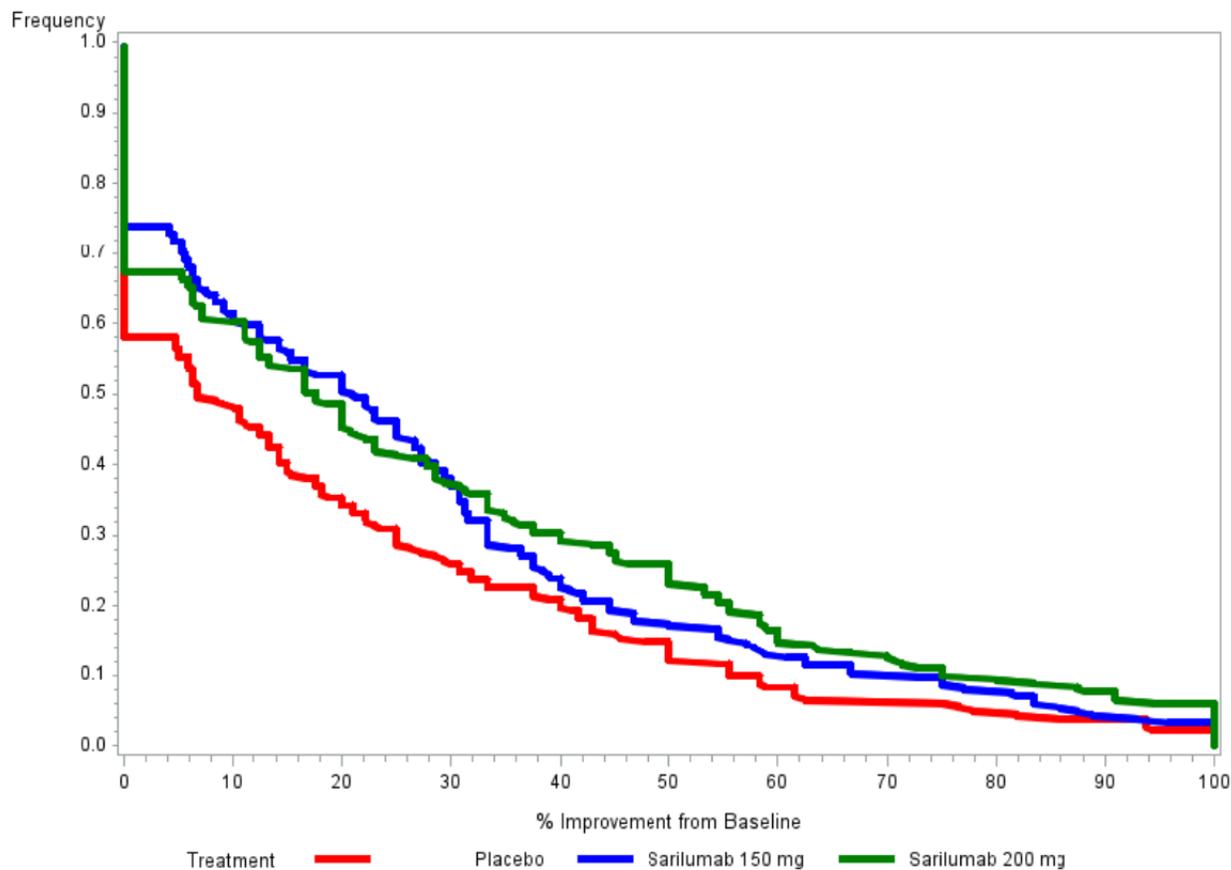
**Figure 19. Cumulative Responder Curves based on Change from HAQ-DI at Week 16 (EFC11072 Part B)**



Note: Missing data were imputed with worst score.

Source: Dr.Yongman Kim’s Primary Statistical Review, Figure 3.

**Figure 20. Cumulative Responder Curves based on Change from HAQ-DI at Week 12 (EFC10832)**



Note: Missing data were imputed with worst score.

Source: Dr. Yongman Kim's Primary Statistical Review, Figure 8.

A clinically meaningful improvement in physical function has been defined as a decrease of  $\geq 0.3$  units in HAQ-DI compared to baseline. Sanofi, therefore, evaluated the proportion of subjects with a clinically meaningful improvement in physical function at various time points for both studies (Weeks 12, 24, 52). At Week 24, in study EFC11072, the proportion of subjects with a clinically meaningful improvement in physical function ("HAQ-DI response") was noted to be 33.4% in the placebo arm, compared to 51.0% in the lower dose sarilumab arm and 51.4% in the higher dose sarilumab arm. In study EFC10832 at Week 24, the proportion of HAQ-DI responders was 31.5% in the placebo arm and 43.1% in the lower dose sarilumab arm and 47.3% in the higher dose sarilumab arm. Essentially, a larger proportion of subjects on sarilumab had an increase in HAQ-DI  $\geq 0.3$  units at all time points in both studies. The difference in proportion of responders between the sarilumab arms and placebo was statistically significant for both doses at all time points, except for the sarilumab 150mg q2w + MTX arm at Week 12 in study EFC10832.

- *Radiographic Progression*

The mean change in mTSS at Week 52 was a “co-primary” endpoint in study EFC11072. The van de Heijde mTSS is a validated and accepted radiographic measure of joint destruction in RA. The components of the score are described in Section 6.2.

Table 29 presents Sanofi’s primary analysis of change from baseline in mTSS at Week 52. In this pre-specified analysis, linear extrapolation was applied to escapers or any other missing data. As shown, the difference from baseline was robust. There also appeared to be numerically less change from baseline in the 200mg arm compared to the 150mg arm.

**Table 29. Change from Baseline in mTSS at Week 52 in EFC11072 Part B**

Treatment group	n	LS Mean Change (SE)	Comparison	Mean difference	p-value
<b>Week 52</b>					
SAR 150mg (N=400)	352	0.90 (4.66)	vs. placebo	-1.88	<0.0001
SAR 200mg (N=399)	359	0.25 (4.61)	vs. placebo	-2.53	<0.0001
Placebo (N=398)	352	2.78 (7.73)	--	--	--

Note: For Week 52 analysis, rank ANCOVA model stratified by prior biologic use and region was used with linear extrapolation for missing data due to dropout or escape to rescue.

Source: Excerpted from the Clinical Study Report for Study EFC11072 (page 105), submitted 10/30/15

Sanofi also performed a sensitivity analysis with the same model but used post-rescue data from subjects who crossed over to sarilumab after Week 16. The results are shown in Table 30. These results were consistent with the primary analysis results and showed that subjects on sarilumab had statistically significant less change in mTSS at Week 24 compared to subjects on placebo. In this analysis, there also appeared to be numerically less progression on the higher dose of sarilumab. Additionally, Dr. Kim performed an analysis of mean change in mTSS at Week 24, utilizing a similar approach as Sanofi’s sensitivity analysis at Week 52. Dr. Kim utilized the post-rescue data up to 24 weeks for subjects who crossed over to sarilumab after Week 16. There was less missing data at Week 24 compared to Week 52. These results, however, continued to support the results of the primary analysis. Although the effect sizes were smaller, subjects on sarilumab still showed significantly less change in mTSS at Week 24 compared to subjects on placebo.

**Table 30. Sensitivity Analysis of Change from baseline in mTSS at Week 52 in EFC11072 Part B**

Treatment group	n	LS Mean Change (SE)	Comparison	Mean difference	p-value
<b>Week 52</b>					
SAR 150mg (N=400)	318	0.60 (3.56)	vs. placebo	-1.44	<0.0001
SAR 200mg (N=399)	316	0.17 (2.97)	vs. placebo	-1.87	<0.0001
Placebo (N=398)	325	2.04 (4.52)	--	--	--
<b>Week 24</b>					
SAR 150mg (N=400)	340	0.43 (2.71)	vs. placebo	-0.72	0.0018
SAR 200mg (N=399)	343	0.14 (2.25)	vs. placebo	-1.01	<0.0001
Placebo (N=398)	348	1.15 (3.44)	--	--	--

Note: Rank ANCOVA model stratified by prior biologic use and region with postrescue data. The missing data due to dropout were not imputed.

For Week 24 analysis, the same model was used with postrescue data.

Source: Excerpted from the Clinical Study Report for Study EFC11072-15.2 (page 16), submitted 10/30/15; Dr.Kim's Primary Statistical Review, Table 12.

Lastly, Sanofi evaluated the proportion of subjects who had no radiographic progression defined as no change from baseline in mTSS. Table 31 presents the proportion of subjects without radiographic progression at Week 52. These results again support the results from the pre-specified analysis. A greater proportion of subjects on sarilumab showed no radiographic progression compared to subjects on placebo. The proportion was also numerically higher in the sarilumab 200mg dose.

**Table 31. Rates of No Radiographic Progression from Baseline to Week 52 in EFC11072 Part B**

Treatment group	No progression n (%)	Comparison	Odds Ratio (95% CI)	p-value
<b>Week 52</b>				
SAR 150mg (N=400)	191 (48)	vs. placebo	1.5 (1.1, 1.9)	0.0094
SAR 200mg (N=399)	222 (56)	vs. placebo	2.0 (1.5, 2.7)	<0.0001
Placebo (N=398)	154 (39)	--	--	--

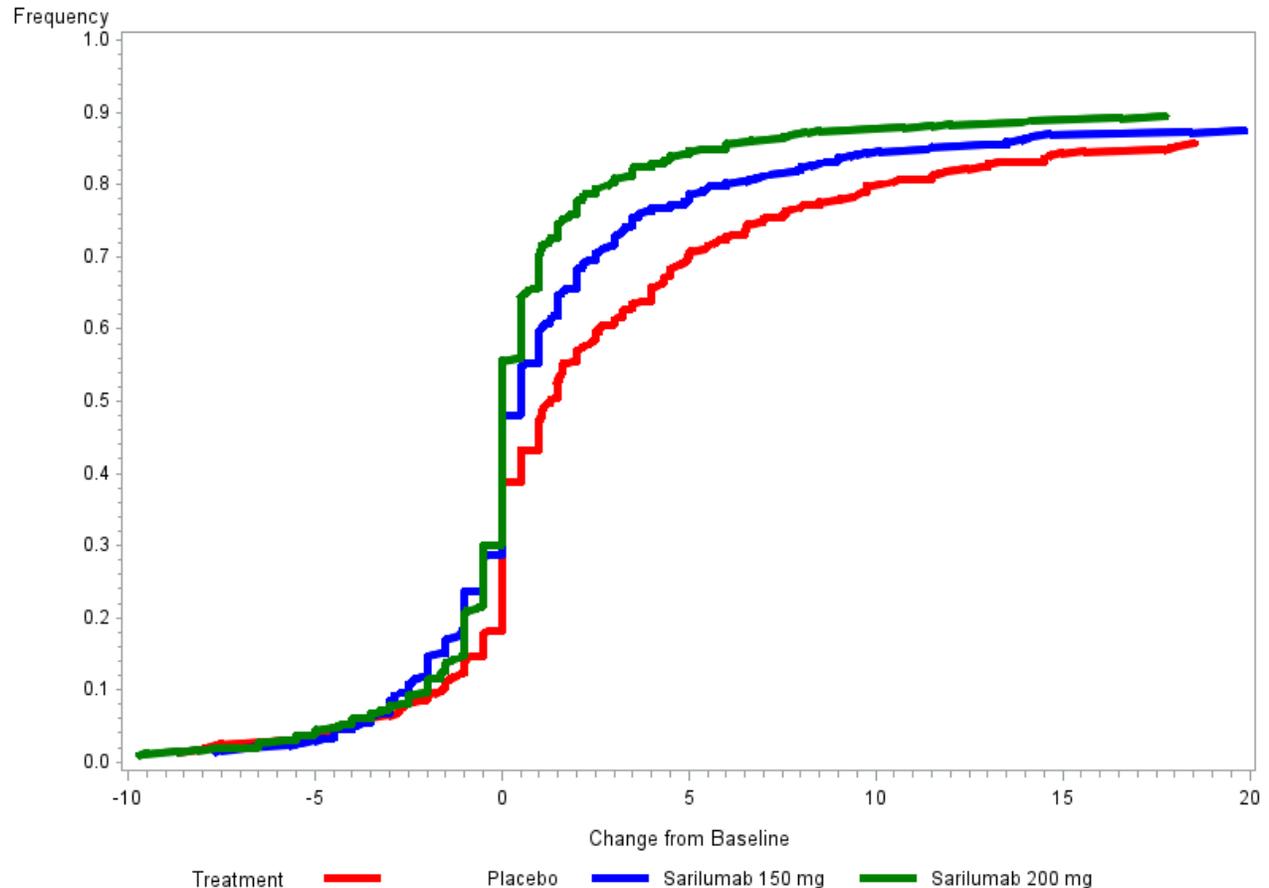
Note: Radiographic progression of the mTSS is defined as a change from baseline in the mTSS >0. The linear extrapolation method is used to impute missing or post rescue Week 52 modified total Sharp scores.

p-value based on CMH test stratified by prior biologic use and region.

Source: Excerpted from the Clinical Study Report for Study EFC11072 (page 110).

Dr.Kim also created cumulative distribution curves with worst score imputation for missing data (Figure 21). These curves showed a separation between both sarilumab doses from placebo.

**Figure 21. Cumulative Distribution of Change from Baseline in mTSS at Week 52 in EFC11072  
Part B**



Source: Figure 4 of the statistical review by Dr. Kim

Additional sensitivity analyses provided by Sanofi, such as tipping point analysis, were also performed and supported the efficacy on mTSS. Please see Dr. Kim's full statistical review for further details.

In conclusion, based on the results and various methods of analyses, subjects on sarilumab had significantly less radiographic progression compared to subjects on placebo. There also appeared to be numerically less change in mTSS in the higher dose compared to the lower dose.

- *ACR50 and ACR70 Response*

ACR50 and ACR70 were also assessed in both pivotal trials. As described in Section 6, ACR50 and ACR70 are also measures of signs and symptoms in RA but relay a greater proportion of improvement, 50% and 70%, respectively, compared to 20% with ACR20.

Table 32 presents the ACR50 and ACR70 results at Week 24 for both EFC11072 Part B and EFC10832. In both studies, a greater proportion of subjects on sarilumab had an ACR50 and ACR70 response at Week 24 compared to subjects on placebo, and the difference from placebo was statistically significant for both doses. It is also notable that the proportions were numerically for sarilumab 200mg in regards to ACR50 and ACR70 in study EFC11072. In study EFC10832, only the proportion of ACR50 responders was numerically higher for the higher dose.

**Table 32. ACR50 and ACR70 Response at Week 24 in EFC11072 Part B and EFC10832**

Treatment group	n/N (%)	Comparison	Odds Ratio	95% Confidence Interval	p-value
<b>EFC11072 Part B</b>					
<b>ACR50</b>					
SAR 150mg (N=400)	148/400 (37)	vs. placebo	3.0	(2.1, 4.1)	<0.0001
SAR 200mg (N=399)	182/399 (46)	vs. placebo	4.3	(3.1, 5.9)	<0.0001
Placebo (N=398)	66/398 (17)	--	--	--	--
<b>ACR70</b>					
SAR 150mg (N=400)	79/400 (20)	vs. placebo	3.2	(2.0, 5.0)	<0.0001
SAR 200mg (N=399)	99/399 (25)	vs. placebo	4.3	(2.7, 6.7)	<0.0001
Placebo (N=398)	29/398 (7)	--	--	--	--
<b>EFC10832</b>					
<b>ACR50</b>					
SAR 150mg (N=181)	67/181 (37)	vs. placebo	3.0	(1.8, 5.0)	<0.0001
SAR 200mg (N=184)	75/184 (41)	vs. placebo	3.4	(2.0, 5.6)	<0.0001
Placebo (N=181)	33/181 (18)	--	--	--	--
<b>ACR70</b>					
SAR 150mg (N=181)	36/181 (20)	vs. placebo	3.6	(1.8, 7.3)	<0.0001
SAR 200mg (N=184)	30/184 (16)	vs. placebo	2.7	1.3, 5.4)	<0.0001
Placebo (N=181)	13/181 (7)	--	--	--	--

Patients are considered non-responders from the time they started rescue medication or discontinued study medication  
 P-values were based on CMH test stratified by prior biologic use and region.

Source: EFC11072 Part B CSR, Tables 25 and 27, dated Aug 20, 2015; page 116 and 118.

EFC10832 CSR, 16.2.6-EN, pages 102 and 11.

Dr.Kim's review, Table 26.

Sanofi also provided the assessment of ACR50 and ACR70 at other time points (Week 12 and Week 52). In both studies, there was significantly higher proportion of responders in both

Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

sarilumab arms compared to the placebo arm at all time points. It should be noted, though, that ACR response rates at Week 12 were not part of the hierarchical order of testing in study EFC11072. Therefore, statistical significance cannot be attributed to those assessments. In summary, though, the ACR50 and ACR70 response supported the primary endpoint of ACR20 response and showed a higher proportion of responders in those subjects who were treated with sarilumab.

- *Change from Baseline in ACR Components*

The ACR response are composite scores, including measures of tender joint count (TJC), swollen joint count (SJC), pain, physician global, patient global, HAQ-DI, and CRP. See Section 6 for a more detailed description of the ACR composite scores.

Table 33 shows the change from baseline in the ACR components at Week 24 for both pivotal trials. Overall, the analyses of all components of the ACR score were statistically significant in favor of both doses of sarilumab. More importantly, no single component appeared to be driving the ACR response.

APPEARS THIS WAY ON ORIGINAL

Clinical Review  
 Reviewer: Suzette Peng, MD  
 NME/BLA 761037  
 Sarilumab/Kevzara

**Table 33. Change from Baseline in ACR Components at Week 24 for EFC11072 Part B and EFC10832**

	Treatment group	n	LS Mean Change (SE)	Comparison	LS Mean difference	95% Confidence Interval	p-value
<b>EFC11072 Part B</b>							
TJC	SAR 150mg (N=400)	312	-16.9 (0.7)	vs. placebo	-6.8	(-8.6, -4.9)	<0.0001
	SAR 200mg (N=399)	320	-17.4 (0.7)	vs. placebo	-7.3	(-9.1, -5.5)	<0.0001
	Placebo (N=398)	251	-10.1 (0.7)	--	--	--	--
SJC	SAR 150mg (N=400)	312	-10.6 (0.4)	vs. placebo	-4.0	(-5.1, -2.8)	<0.0001
	SAR 200mg (N=399)	320	-11.3 (0.4)	vs. placebo	-4.6	(-5.8, -3.5)	<0.0001
	Placebo (N=398)	251	-6.6 (0.4)	--	--	--	--
Pain VAS	SAR 150mg (N=400)	313	-28.5 (1.3)	vs. placebo	-13.1	(-16.8, -9.3)	<0.0001
	SAR 200mg (N=399)	321	-31.8 (1.3)	vs. placebo	-16.4	(-20.3, -12.7)	<0.0001
	Placebo (N=398)	253	-15.4 (1.4)	--	--	--	--
Physician global VAS	SAR 150mg (N=400)	313	-42.5 (1.1)	vs. placebo	-13.1	(-16.2, -9.9)	<0.0001
	SAR 200mg (N=399)	321	-44.3 (1.1)	vs. placebo	-14.9	(-18.0, -11.8)	<0.0001
	Placebo (N=398)	253	-29.4 (1.2)	--	--	--	--
Patient global VAS	SAR 150mg (N=400)	312	-28.4 (1.3)	vs. placebo	-12.5	(-16.1, -8.9)	<0.0001
	SAR 200mg (N=399)	319	-32.9 (1.3)	vs. placebo	-17.1	(-20.1, -13.6)	<0.0001
	Placebo (N=398)	253	-15.7 (1.4)	--	--	--	--
HAQ-DI	SAR 150mg (N=400)	313	-0.56 (0.03)	vs. placebo	-0.24	(-0.33, -0.16)	<0.0001
	SAR 200mg (N=399)	316	-0.57 (0.03)	vs. placebo	-0.25	(-0.34, -0.17)	<0.0001
	Placebo (N=398)	253	-0.32 (0.03)	--	--	--	--
CRP (mg/L)	SAR 150mg (N=400)	311	-12.6 (1.2)	vs. placebo	-12.5	(-15.9, -9.2)	<0.0001
	SAR 200mg (N=399)	317	-17.0 (1.2)	vs. placebo	-16.9	(-20.2, -13.6)	<0.0001
	Placebo	251	-0.1 (1.3)	--	--	--	--

Clinical Review  
 Reviewer: Suzette Peng, MD  
 NME/BLA 761037  
 Sarilumab/Kevzara

	(N=398)						
<b>EFC10832</b>							
TJC	SAR 150mg (N=181)	127	-14.4 (1.0)	vs. placebo	-3.9	(-6.7, -1.1)	0.0065
	SAR 200mg (N=184)	137	-17.0 (1.0)	vs. placebo	-6.4	(-9.2, -3.6)	<0.0001
	Placebo (N=181)	101	-10.6 (1.1)	--	--	--	--
SJC	SAR 150mg (N=181)	127	-11.6 (0.7)	vs. placebo	-3.4	(-5.3, -1.5)	0.0005
	SAR 200mg (N=184)	137	-11.9 (0.7)	vs. placebo	-3.8	(-5.6, -1.9)	<0.0001
	Placebo (N=181)	101	-8.2 (0.7)	--	--	--	--
Pain VAS	SAR 150mg (N=181)	127	-31.9 (2.1)	vs. placebo	-10.6	(-16.5, -4.8)	0.0004
	SAR 200mg (N=184)	135	-33.7 (2.0)	vs. placebo	-12.4	(-18.2, -6.6)	<0.0001
	Placebo (N=181)	98	-21.3 (2.3)	--	--	--	--
Physician global VAS	SAR 150mg (N=181)	127	-40.7 (1.7)	vs. placebo	-12.1	(-16.8, -7.4)	<0.0001
	SAR 200mg (N=184)	137	-43.2 (1.6)	vs. placebo	-14.7	(-19.3, -10.0)	<0.0001
	Placebo (N=181)	101	-28.6 (1.8)	--	--	--	--
Patient global VAS	SAR 150mg (N=181)	127	-29.6 (2.0)	vs. placebo	-9.8	(-15.5, -4.1)	0.0008
	SAR 200mg (N=184)	137	-31.3 (2.0)	vs. placebo	-11.5	(-17.2, -5.9)	<0.0001
	Placebo (N=181)	100	-19.8 (2.2)	--	--	--	--
HAQ-DI	SAR 150mg (N=181)	127	-0.52 (0.05)	vs. placebo	-0.18	(-0.32, -0.05)	0.0078
	SAR 200mg (N=184)	136	-0.58 (0.05)	vs. placebo	-0.24	(-0.38, -0.11)	0.0004
	Placebo (N=181)	101	-0.34 (0.05)	--	--	--	--
CRP (mg/L)	SAR 150mg (N=181)	126	-15.2 (1.5)	vs. placebo	-11.6	(-15.7, -7.6)	<0.0001
	SAR 200mg (N=184)	137	-23.3 (1.4)	vs. placebo	-19.7	(-23.6, -15.7)	<0.0001
	Placebo (N=181)	100	-3.6 (1.6)	--	--	--	--

Note: No imputation for missing data is performed. MMRM with PROC MIXED assuming an unstructured covariance structure: model = baseline, treatment, prior biologic use, region, visit, and treatment-by-visit interaction  
 Source: Dr. Kim's statistical review Tale 7; EFC11072 CSR 16.2.6 EN (pages 237, 252, 267, 297, 312, 8, 282)  
 Dr. Kim's statistical review Table 21; EFC10832 CSR 16.2.6-EN (pages 127, 138, 149, 171, 182, 46, 160)

Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

Dr.Kim noted the limitations of assessing the ACR components at Week 24 because of the numbers of subjects (particularly on placebo) who were rescued and then judged as non-responders. Therefore, Dr.Kim performed analyses of the ACR components at Week 16 for study EFC11072 Part B and at Week 12 for study EFC10832, which would precede the opportunity for rescue. Overall, these analyses supported the results at Week 24. Please see Dr.Kim's statistical review for full details.

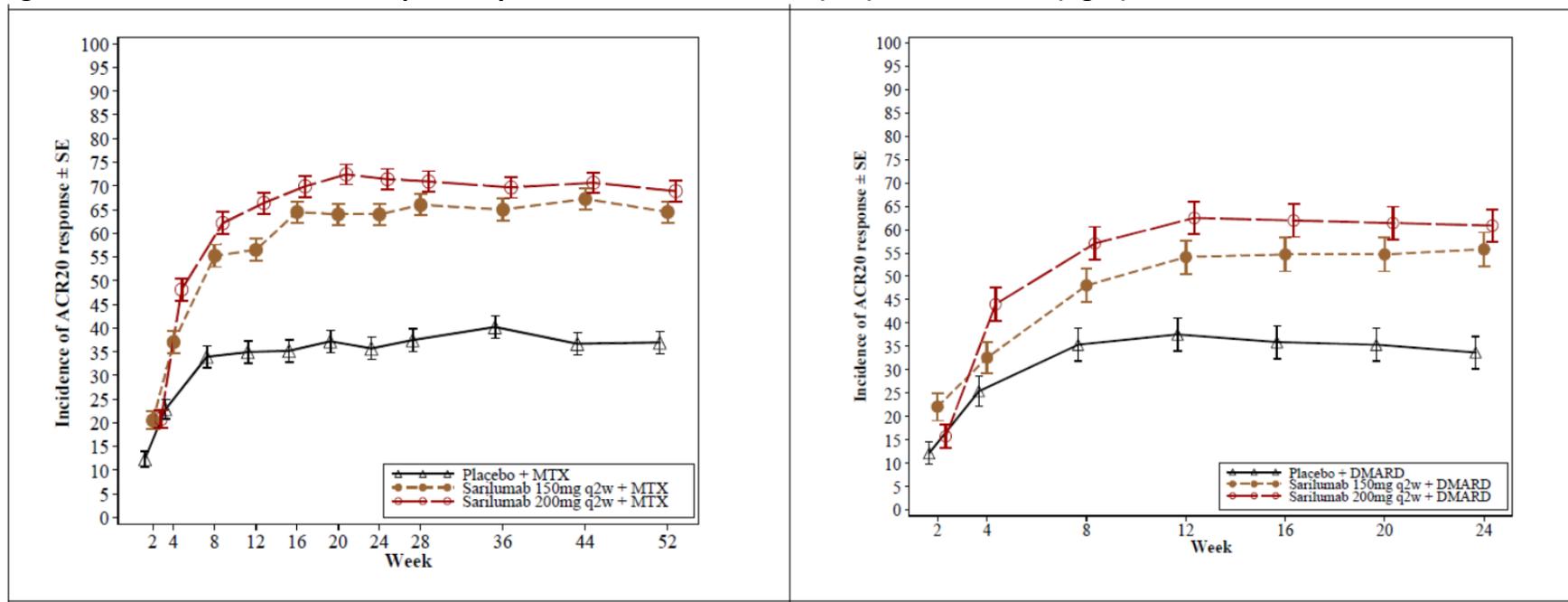
In conclusion, the individual analysis of the components of the ACR score further supported the findings from the primary endpoint and showed that no one component drove the efficacy results. Subjects on sarilumab and conventional DMARDs had a significantly greater improvement in signs and symptoms, as measured by the ACR response, compared to subjects on placebo and conventional DMARDs.

APPEARS THIS WAY ON ORIGINAL

- *ACR20 Response Over Time*

Figure 22 shows the incidence of ACR20 response over time for both pivotal trials. Both studies show a clear separation between the sarilumab arms and placebo throughout the study. The increase in proportion of ACR20 responders is most rapid between Weeks 2 and 12 and then seems to plateau. Additionally, for both studies, the incidence of responders appears to be consistently greater in the sarilumab 200mg arm compared to the placebo arm.

**Figure 22. Incidence of ACR20 Response by Visit for EFC11072 Part B (left) and EFC10832 (right)**



Source: Summary of Clinical Efficacy, Figures 1-2, dated Sep 10, 2015; page 42.

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

- *Major Clinical Response*

Sanofi defined “major clinical response” (MCR) as the event of achieving and maintaining ACR70 for at least 24 consecutive weeks during the 52-week treatment period. Therefore, it was only assessed in study EFC11072 Part B, and it was a key secondary endpoint. Table 34 shows the proportion of subjects who achieved an MCR. The number of subjects on sarilumab who achieved an MCR was higher than the number of subjects on placebo. The difference was statistically significant for both doses of sarilumab.

**Table 34. Major Clinical Response in EFC11072 Part B**

Treatment group	Response n (%)	Comparison	Odds ratio (95% CI)	p-value
<b>EFC11072 Part B</b>				
SAR 150mg (N=400)	51 (13)	vs. placebo	4.7 (2.5, 8.9)	<0.0001
SAR 200mg (N=399)	59 (15)	vs. placebo	5.6 (2.9, 10.5)	<0.0001
Placebo (N=398)	12 (3)	--	--	--

Major clinical response = Achieving ACR70 for at least 24 consecutive weeks during the 52-week period.

Patients are considered ACR70 non-responders from the time they started rescue medication or discontinued study medication.

P-value based on CMH test stratified by prior biologic use and region.

Source: Excerpted from the Clinical Study Report for Study EFC11072, page 113, submitted 10/30/15

- *Change from Baseline in DAS28-CRP*

DAS28-CRP was assessed in both pivotal trials. As described in Section 6, it is a continuous endpoint composed of clinical (SJC, TJC), laboratory (CRP), and subjective (patient global) assessments. Change from baseline in DAS28-CRP was a key secondary endpoint in EFC10832, #3 in the hierarchical testing procedure.

Table 35 shows the LS mean change in DAS28-CRP at Week 24 for both studies. There was a greater improvement in DAS28-CRP from baseline for subjects on sarilumab compared to placebo. The difference between the sarilumab arms and the placebo arm was statistically significant. The change from baseline in DAS28-CRP was numerically higher in the higher dose arm in both studies.

APPEARS THIS WAY ON ORIGINAL

**Table 35. Change in Baseline in DAS28-CRP at Week 24 in EFC11072 Part B and EFC10832**

Treatment group	n	LS Mean Change (SE)	Comparison	Mean difference	95% Confidence Interval	p-value
<b>EFC11072 Part B</b>						
SAR 150mg (N=400)	308	-2.45 (0.08)	vs. placebo	-1.29	(-1.50, -1.07)	<0.0001
SAR 200mg (N=399)	314	-2.82 (0.08)	vs. placebo	-1.65	(-1.87, -1.44)	<0.0001
Placebo (N=398)	249	-1.17 (0.08)	--	--	--	--
<b>EFC10832</b>						
SAR 150mg (N=181)	126	-2.35 (0.11)	vs. placebo	-0.97	(-1.28, -0.66)	<0.0001
SAR 200mg (N=184)	136	-2.82 (0.11)	vs. placebo	-1.44	(-1.75, -1.13)	<0.0001
Placebo (N=181)	99	-1.38 (0.12)	--	--	--	--

Note:  $DAS28-CRP = 0.56 \times \sqrt{28TJC} + 0.28 \times \sqrt{28SJC} + 0.36 \times \text{Log}(CRP+1) + 0.014 \times \text{Patient global VAS} + 0.96$ .

All assessments are set to missing from the time a patient receives rescue medication or discontinues study medication early. No imputation is performed.

EFC11072: MMRM with PROC MIXED assuming an unstructured covariance structure: model = baseline, treatment, prior biological use, region, visit, and treatment-by-visit interaction.

EFC10832: MMRM with PROC MIXED assuming an unstructured covariance structure: model = baseline, treatment, number of previous anti-TNFs, region, visit, and treatment-by-visit interaction.

Source: Excerpted from the Clinical Study Report for Study EFC11072-16.2.6-EN (page 327) and Clinical Study Report for Study EFC10832-16.2.6-EN (page 193), submitted 10/30/15

- *DAS-28 Remission*

The definition of remission utilizing the disease activity measure of DAS28-CRP is  $DAS28-CRP \leq 2.6$ . As described in Section 6, with the general treatment guidance to treat-to-target, attaining remission is the recommended goal for treatment of RA.

Table 36 displays the proportion of subjects who achieved remission as defined by  $DAS28 < 2.6$ . In both studies, more subjects on sarilumab achieved a  $DAS28 < 2.6$  during the treatment period. The difference between placebo and both doses of sarilumab was statistically significant.

APPEARS THIS WAY ON ORIGINAL

**Table 36. DAS28 < 2.6 at Week 24 in EFC110072 Part B and EFC10832**

Treatment group	n/N (%)	Comparison	Odds Ratio (95% CI)	p-value
<b>EFC11072 Part B</b>				
SAR 150mg (N=400)	111/400 (28)	vs. placebo	3.6 (2.4, 5.3)	<0.0001
SAR 200mg (N=399)	136/399 (34)	vs. placebo	4.7 (3.2, 6.9)	<0.0001
Placebo (N=398)	40/398 (10)	--	--	--
<b>EFC10832</b>				
SAR 150mg (N=181)	45/181 (25)	vs. placebo	4.6 (2.3, 9.1)	<0.0001
SAR 200mg (N=184)	43/184 (29)	vs. placebo	5.8 (2.9, 11.4)	<0.0001
Placebo (N=181)	13/181 (7)	--	--	--

Note: Subjects are not considered to be <2.6 from the time they started rescue medication or discontinued study medication  
 CMH test stratified of previous anti-TNFs and region

Source: Dr.Kim’s review Table 25 and Summary of Clinical Efficacy, Table 16, dated Sep 10, 2015; page 46.

However, it is know that this parameter for remission is not strict enough (Sheehy, et al. 269). There is evidence that, even with DAS28 scores <2.6, residual disease activity may be present and can be associated with the progression of joint damage and some functional impairment (Smolen, et al. Treating RA to target: 2014 update. 5). This is reflected in what was seen in the sarilumab trials. Nearly half of the subjects who achieved DAS28-CRP<2.6 had at least one active joint. In study EFC11072 Part B, out of the subjects who achieved a DAS28-CRP<2.6, 37.8% on sarilumab 150mg q2w and 33.1% on sarilumab 200mg q2w still had ≥3 active joints. Similarly, in study EFC10832, 31.1% of subjects who achieve DAS28 remission on sarilumab 150mg q2w and 45.3% on sarilumab 200mg q2w had ≥3 active joints.

Sanofi did evaluate other stricter measures of remission as defined by SDAI, CDAI, and the ACR/EULAR Boolean based definition. These results were reviewed in Sections 6.2.2 and 6.3.2, and they are supportive of the DAS28 remission results in that more subjects on sarilumab achieved remission compared to subjects on placebo.

- *Change from Baseline in CDAI*

CDAI is a disease activity measure scoring system used frequently in clinical practice. See Section 6 for a definition of CDAI. Change from baseline in CDAI was a secondary endpoint and was on the hierarchical testing procedure for Study EFC10832. For both studies, the change from baseline in CDAI at multiple time points (Weeks 12, 24, and 52) was greater in the sarilumab arms compared to placebo, and the difference was statistically significant for both doses of sarilumab at all time points. See Dr.Kim’s statistical review for full details of the analysis of this endpoint at Week 24, including his cumulative responder curves that also showed a separation of the curves between sarilumab dosing regimens and placebo.

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

- *Change from Baseline in SF-36 PCS and MCS*

Lastly, Sanofi also assessed sarilumab's effect on quality of life in RA patients. Various patient-reported outcomes (PROs) were assessed, but SF-36 will be presented in this review. SF-36 is defined in Section 6. Briefly, there are 8 domains that result in 2 summary scores, the Physical Component Summary (PCS) and Mental Component Summary (MCS). A higher score is reflective of better health status. In RA patients, the minimally clinically important difference (MCID) is 2.5 points for the summary scores and 5 points for the individual domain scores. In study EFC10832, the change from baseline in SF36-PCS and SF36-MCS was on the hierarchical testing procedure.

Table 37 shows the change from baseline in SF-36 PCS and MCS scores at Week 24 for both pivotal trials. In terms of PCS, the mean change from baseline was greater in the subjects on sarilumab compared to subjects on placebo. The mean difference between the sarilumab arms and placebo was greater than 2.5 and was statistically significant for both doses in both studies. In terms of MCS, the change from baseline was also numerically greater in the sarilumab treatment arms compared to the placebo arm. However, the difference between those subjects on sarilumab and those on placebo was only statistically significant in the higher dose group (200mg) in both studies.

APPEARS THIS WAY ON ORIGINAL

**Table 37. Change from Baseline in SF-36 at Week 24 in EFC11072 Part B and EFC10832**

Treatment group	n	LS Mean Change (SE)	Comparison	Mean difference	95% Confidence Interval	p-value
<b>EFC11072 Part B</b>						
<b>SF-36 PCS</b>						
SAR 150mg (N=400)	299	8.0 (0.4)	vs. placebo	2.8	(1.6, 4.1)	<0.0001
SAR 200mg (N=399)	309	8.4 (0.4)	vs. placebo	3.2	(2.0, 4.4)	<0.0001
Placebo (N=398)	246	5.2 (0.5)	--	--	--	--
<b>SF-36 MCS</b>						
SAR 150mg (N=400)	352	5.5 (0.5)	vs. placebo	1.3	(0.1, 2.7)	0.06
SAR 200mg (N=399)	345	7.5 (0.5)	vs. placebo	4.3	(2.8, 5.8)	<0.0001
Placebo (N=398)	361	4.2 (0.5)	--	--	--	--
<b>EFC10832</b>						
<b>SF-36 PCS</b>						
SAR 150mg (N=181)	123	7.7 (0.7)	vs. placebo	3.3	(1.5, 5.0)	0.0004
SAR 200mg (N=184)	134	8.5 (0.6)	vs. placebo	4.1	(2.3, 5.8)	<0.0001
Placebo (N=181)	99	4.4 (0.7)	--	--	--	--
<b>SF-36 MCS</b>						
SAR 150mg (N=181)	160	5.1 (0.8)	vs. placebo	1.6	(-0.3, 3.6)	0.1
SAR 200mg (N=184)	165	6.5 (0.7)	vs. placebo	3.0	(1, 4.9)	0.003
Placebo (N=181)	169	3.5 (0.7)	--	--	--	--

Note: All assessments are set to missing from the time a patient receives rescue medication or discontinues study medication early. No imputation is performed.

EFC11072: MMRM with PROC MIXED assuming an unstructured covariance structure: model = baseline, treatment, prior biological use, region, visit, and treatment-by-visit interaction.

EFC10832: MMRM with PROC MIXED assuming an unstructured covariance structure: model = baseline, treatment, number of previous anti-TNFs, region, visit, and treatment-by-visit interaction.

Source: Excerpted from the Clinical Study Report for Study EFC11072-16.2.6-EN (page 413) and Clinical Study Report for Study EFC10832-16.2.6-EN (page 253), submitted 10/30/15

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

Therefore, since change from baseline in SF-36 MCS was part of the hierarchical testing procedure for study EFC10832, the subsequent secondary endpoints (namely, the PROs of FACI-Fatigue, Morning stiffness VAS, WPS-RA, RAID, and EQ-5D-3L) were declared to be not statistically significant. Dr. Kim does note, though, that the nominal p-values for these PROs were smaller than 0.025. Please see details of the analysis for SF-36 and the other PROs in Dr. Kim's review.

In summary, in regards to PROs and the patients' perception of health status, there appeared to be greater improvement in subjects on sarilumab compared to subjects on placebo. However, this was only statistically significant using the measure of SF-36 PCS.

### 7.1.3. Subpopulations

Dr. Kim performed subgroup analyses on the ACR20 response at Week 24 for the pooled data from EFC11072 Part B and EFC10832. The subgroups analyzed were demographics (sex, age, race), region, and baseline disease characteristics (presence of RF and anti-CCP antibody, duration of disease). Table 38 shows the subgroup analyses for sarilumab 150mg + DMARD compared to placebo + DMARD, and Table 39 shows the analyses for sarilumab 200mg + DMARD compared to placebo + DMARD.

In general, the subgroup analyses of ACR20 responders were largely consistent with that of the overall population for both doses of sarilumab. Subjects who were seronegative (RF-negative and/or anti-CCP antibody-negative) showed smaller differences between the sarilumab arm and placebo arm. For sarilumab 200mg, these subgroups retained statistical significance, but the differences were not statistically significant for sarilumab 150mg. Based on the inclusion/exclusion criteria, particularly for study EFC11072 Part B, there were much fewer subjects who were seronegative. The smaller sample size might have contributed to the smaller effect size in this subgroup. Additionally, subjects who are seronegative tend to have less aggressive disease, and, thus, it may be more difficult to determine a difference from placebo in this subgroup.

APPEARS THIS WAY ON ORIGINAL

Clinical Review  
 Reviewer: Suzette Peng, MD  
 NME/BLA 761037  
 Sarilumab/Kevzara

**Table 38. Subgroup Analyses on ACR20 Response at Week 24 for Sarilumab 150mg vs. PBO on Pooled Data (EFC11072 Part B and EFC10832)**

	SAR 150mg		Placebo		
	N	n(%)	N	n(%)	Odds ratio (95% CI)
<b>Overall (<math>p &lt; 0.001</math>)<sup>a</sup></b>					
	581	333(57)	579	194(34)	2.8 (2.2, 3.5)
<b>Sex (<math>p = 0.72</math>)<sup>b</sup></b>					
Male	120	67(56)	104	36(35)	2.5 (1.5, 4.4)
Female	461	266(58)	475	158(33)	2.8 (2.2, 3.7)
<b>Age (<math>p = 0.68</math>)<sup>b</sup></b>					
≤50 yrs	254	149(59)	260	96(37)	2.7 (1.8, 3.8)
>50 yrs	327	184(56)	319	98(31)	2.9 (2.1, 4.0)
<b>Region (<math>p = 0.13</math>)<sup>b</sup></b>					
ROW <sup>c</sup>	200	118(59)	199	54(27)	3.9 (2.6, 6.0)
SM <sup>c</sup>	229	148(65)	229	99(43)	2.4 (1.7, 3.6)
WEST <sup>c</sup>	152	67(44)	151	41(27)	2.1 (1.3, 3.5)
<b>Race (<math>p = 0.92</math>)<sup>b</sup></b>					
White	479	274(57)	467	153(33)	2.8 (2.1, 3.6)
N-White	102	59(58)	112	41(37)	3.1 (1.7, 5.6)
<b>RF (<math>P = 0.01</math>)<sup>b</sup></b>					
Y	480	289(60)	478	153(32)	3.2 (2.5, 4.2)
N	97	42(43)	100	41(41)	1.2 (0.7, 2.2)
<b>Anti CCP (<math>P = 0.01</math>)<sup>b</sup></b>					
Y	494	297(60)	490	153(31)	3.5 (2.6, 4.5)
N	84	36(43)	88	40(45)	1.0 (0.5, 1.8)
<b>Time Since RA Diagnosis (<math>P = 0.55</math>)<sup>b</sup></b>					
≤7 yrs	264	156(59)	271	101(37)	2.6 (1.8, 3.8)
>7 yrs	317	177(56)	308	93(30)	2.9 (2.1, 4.1)

[a] Logistic regression model with same covariates as primary analysis, also adjusting for study, comparing sarilumab 200 mg to placebo.  
 [b] Logistic regression model with same terms in [a] and with interaction between treatment arm and subgroup. P-value is for the interaction.  
 [c] ROW includes South Korea, Lithuania, Poland, Russia, Taiwan, Turkey, Ukraine. SM includes Argentina, Brazil, Chile, Colombia, Ecuador, Guatemala, Mexico, Peru. WEST includes Australia, Canada, Czech Republic, Germany, Greece, Hungary, Israel, Italy, New Zealand, Portugal, Spain, USA.

Source: Dr.Yongman Kim's Primary Statistical Review, Table 34.

APPEARS THIS WAY ON ORIGINAL

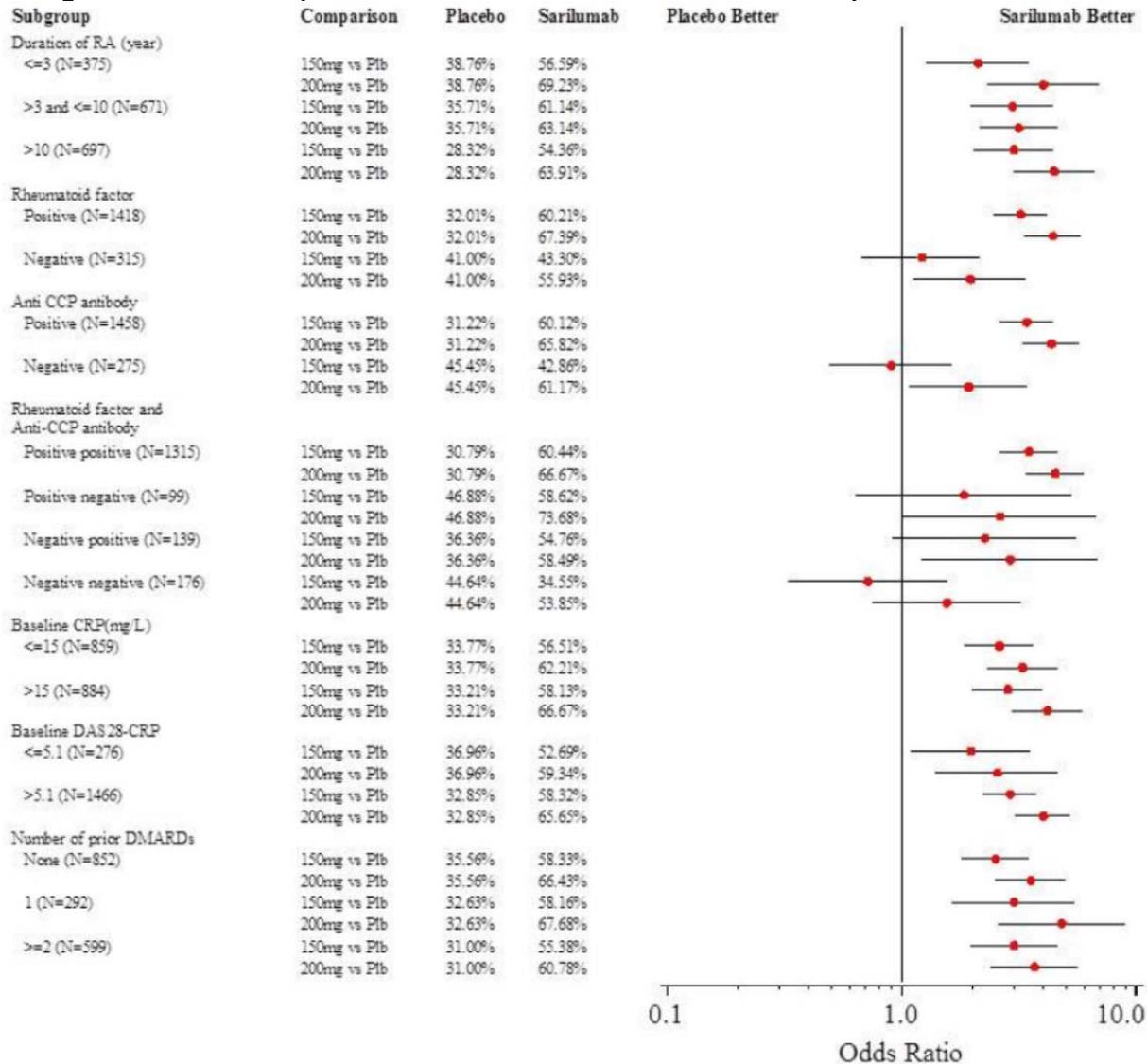
**Table 39. Subgroup Analyses of ACR20 Response at Week 24 for Sarilumab 200mg vs. PBO on Pooled Data (EFC11072 Part B and EFC10832)**

	SAR 200mg		Placebo		Odds ratio (95% CI)
	N	n(%)	N	n(%)	
<b>Overall (<math>p &lt; 0.001</math>)<sup>a</sup></b>					
	583	377(65)	579	194(34)	3.7 (2.9, 4.8)
<b>Sex (<math>p = 0.43</math>)<sup>b</sup></b>					
Male	95	57(60)	104	36(35)	3.2 (1.7, 5.8)
Female	488	320(66)	475	158(33)	4.0 (3.0, 5.2)
<b>Age (<math>p = 0.43</math>)<sup>b</sup></b>					
≤50 yrs	256	178(70)	260	96(37)	4.3 (2.9, 6.3)
>50 yrs	327	199(61)	319	98(31)	3.4 (2.5, 4.8)
<b>Region (<math>p = 0.21</math>)<sup>b</sup></b>					
ROW <sup>c</sup>	200	131(66)	199	54(27)	5.2 (3.4, 7.9)
SM <sup>c</sup>	229	162(71)	229	99(43)	3.2 (2.2, 4.7)
WEST <sup>c</sup>	154	84(55)	151	41(27)	3.3 (2.0, 5.3)
<b>Race (<math>p = 0.30</math>)<sup>b</sup></b>					
White	473	309(65)	467	153(33)	4.0 (3.0, 5.3)
N-White	110	68(62)	112	41(37)	2.9 (1.6, 5.0)
<b>RF (<math>P = 0.01</math>)<sup>b</sup></b>					
Y	460	310(67)	478	153(32)	4.5 (3.4, 6.0)
N	118	66(56)	100	41(41)	2.0 (1.2, 3.6)
<b>Anti CCP (<math>P = 0.02</math>)<sup>b</sup></b>					
Y	474	312(66)	490	153(31)	4.4 (3.4, 5.8)
N	103	63(61)	88	40(45)	2.0 (1.1, 3.5)
<b>Time Since RA Diagnosis (<math>P = 0.97</math>)<sup>b</sup></b>					
≤7 yrs	251	171(68)	271	101(37)	4.0 (2.7, 5.7)
>7 yrs	332	206(62)	308	93(30)	3.8 (2.7, 5.3)

[a] Logistic regression model with same covariates as primary analysis, also adjusting for study, comparing sarilumab 200 mg to placebo.  
 [b] Logistic regression model with same terms in [a] and with interaction between treatment arm and subgroup. P-value is for the interaction.  
 Source: Dr.Yongman Kim's Statistical Review, Table 29.

Sanofi also performed similar subgroup analyses as represented by the following Forest plots. Figure 23 is the subgroup analyses of the baseline disease characteristics and baseline treatments. Overall, the plot shows similar findings to Dr.Kim's analyses with the subgroup of seronegative (RF negative and anti-CCP antibody negative) patients having less of a response on sarilumab 150mg compared to placebo.

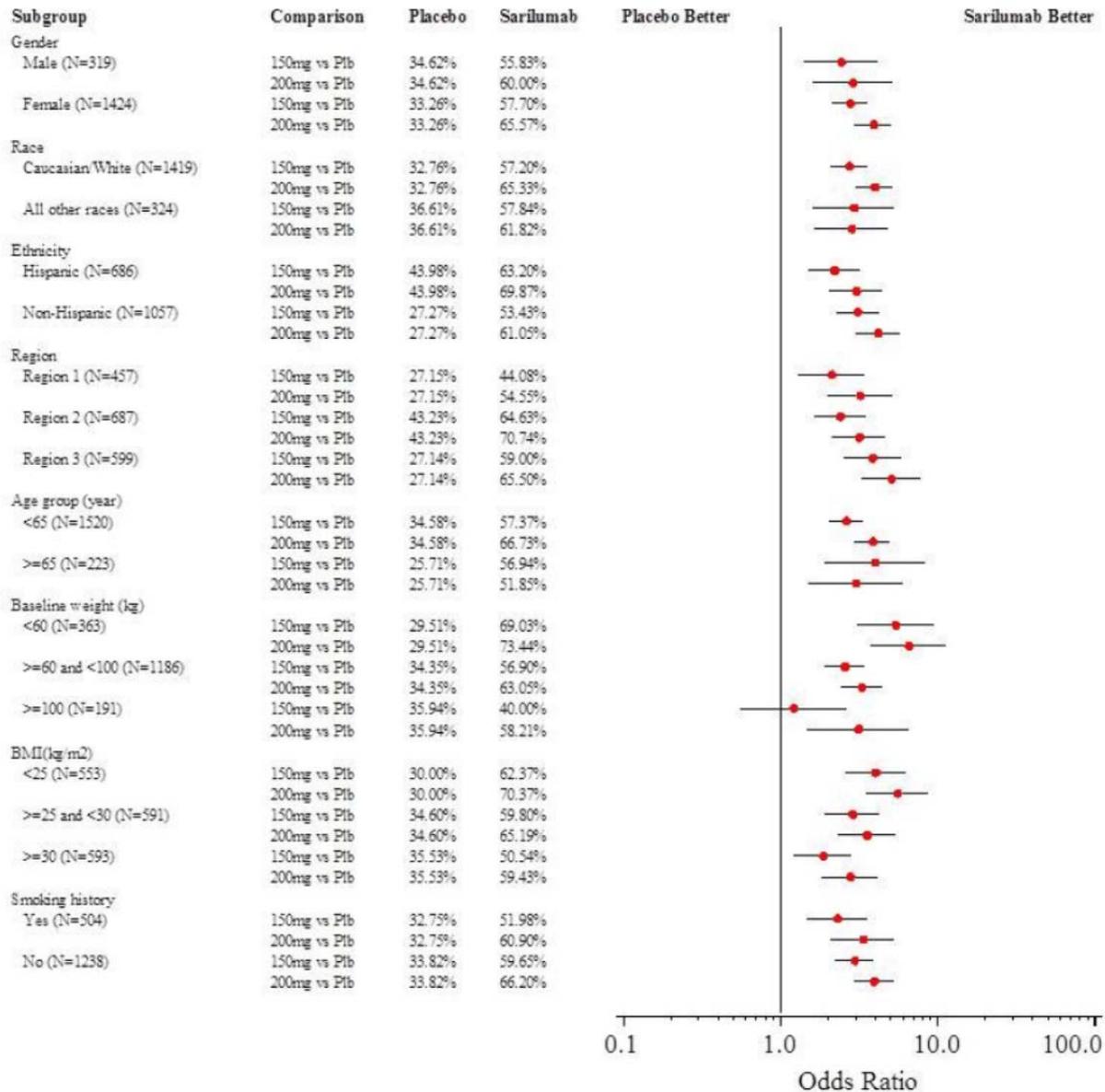
**Figure 23. Forest Plot for ACR20 Response at Week 24: Disease Characteristics and Background Treatment (Pooled Data EFC11072 Part B and EFC10832)**



Source: Summary of Clinical Efficacy, Figure 5, dated September 10, 2015; page 74.

Figure 24 is the Forest plot showing the subgroup analyses with a focus on demographic characteristics. What is notable in this plot is that the subgroup of subjects  $\geq 100$ kg on sarilumab 150mg + DMARD had lower response compared to the overall population. Similar to the seronegative group, the number of subjects  $\geq 100$ kg made up a small sample size, and, thus, it is difficult to make definitive conclusions. For the recommended dose (200 mg), efficacy was consistent in the major subgroups evaluated.

**Figure 24. Forest Plot for ACR20 Reponse at Week 24: Demographics (Pooled Data EFC11072 Part B and EFC10832)**



Source: Summary of Clinical Efficacy, Figure 4, dated September 10, 2015; page 71.

#### 7.1.4. Dose and Dose-Response

In the phase 3 clinical trials, Sanofi evaluated 2 doses of sarilumab given at the same frequency: 150mg every 2 weeks and 200mg every 2 weeks. For the primary and key secondary endpoints in both studies (ACR20 response, change from baseline in HAQ-DI, and change in mTSS), the response was numerically greater for sarilumab 200mg q2w compared to 150mg q2w. This same trend was seen for most of the secondary endpoints, including ACR50 response, major

clinical response, change in DAS28-CRP from baseline, DAS28 remission, and change from baseline in CDAI.

Furthermore, Dr.Kim compared the 2 doses for key efficacy endpoints from the placebo-controlled pre-rescue period for both studies, i.e., 16 weeks for EFC11072 Part B and 12 weeks for EFC10832. Table 40 presents the odds ratio or mean differences between the sarilumab doses with 95% confidence intervals. There was a trend toward a dose response, i.e., a greater response for sarilumab 200mg q2w than 150mg q2w, for the ACR responses, mTSS, and DAS28-CRP. Please see Dr.Kim’s review for full details.

**Table 40. Comparative Efficacy Analyses of Two Sarilumab Doses on Integrated Data (EFC11072 Part B and EFC10832)**

	Treatment Group	n/N (%) /LSMean (SE)	Comparison	Odds Ratio /LSMean Difference	95% Confidence Interval
<b>ACR20</b>	SAR 150mg (N=581)	338/581 (58)	vs. SAR 150mg	1.4	(1.1, 1.7)
	SAR 200mg (N=583)	381/583 (65)			
<b>ACR50</b>	SAR 150mg (N=581)	175/581 (30)	vs. SAR 150mg	1.5	(1.2, 1.9)
	SAR 200mg (N=583)	225/583 (39)			
<b>ACR70</b>	SAR 150mg (N=581)	89/581 (15)	vs. SAR 150mg	1.2	(0.9, 1.7)
	SAR 200mg (N=583)	106/583 (18)			
<b>HAQ-DI</b>	SAR 150mg (N=581)	-0.52 (0.03)	vs. SAR 150mg	-0.02	(-0.09, 0.06)
	SAR 200mg (N=583)	-0.54 (0.03)			
<b>DAS28-CRP</b>	SAR 150mg (N=581)	-2.17 (0.06)	vs. SAR 150mg	-0.38	(- 0.54,-0.23)
	SAR 200mg (N=583)	-2.55 (0.06)			
<b>mTSS</b>	SAR 150mg (N=400)	0.43 (2.71)	vs. SAR 150mg	-0.28	(-0.70, 0.15)
	SAR 200mg (N=399)	0.14 (2.25)			

Note: 95% confidence intervals based on logistic regression for binary endpoints and ANOVA for continuous endpoints, adjusted for prior MTX/biologic use, region and study. mTSS results come from only study 11072  
 Source: Dr.Yongman Kim’s Primary Statistical Review, Table 30.

### 7.1.5. Onset, Duration, and Durability of Efficacy Effects

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

Sanofi assessed long-term efficacy by analyzing subjects in the 2 phase 3 placebo-controlled studies (EFC11072 Part B and EFC10832) who continued into the ongoing open-label extension study (LTS11210). As a reminder, subjects in the LTS11210 study all received sarilumab 200mg q2w although they could dose reduce to 150mg q2w for laboratory abnormalities. In their analyses, the data from the 2 pivotal trials were not pooled. Overall, in regards to signs and symptoms, physical function, and prevention of radiographic progression, the data support a persistence of effect. However, the interpretation of these data is very limited given the fact that LTS11210 is an open-label, uncontrolled study. Therefore, there is no comparison to placebo, and there is potential bias toward subjects who are tolerating the drug and responding to therapy to stay in the study.

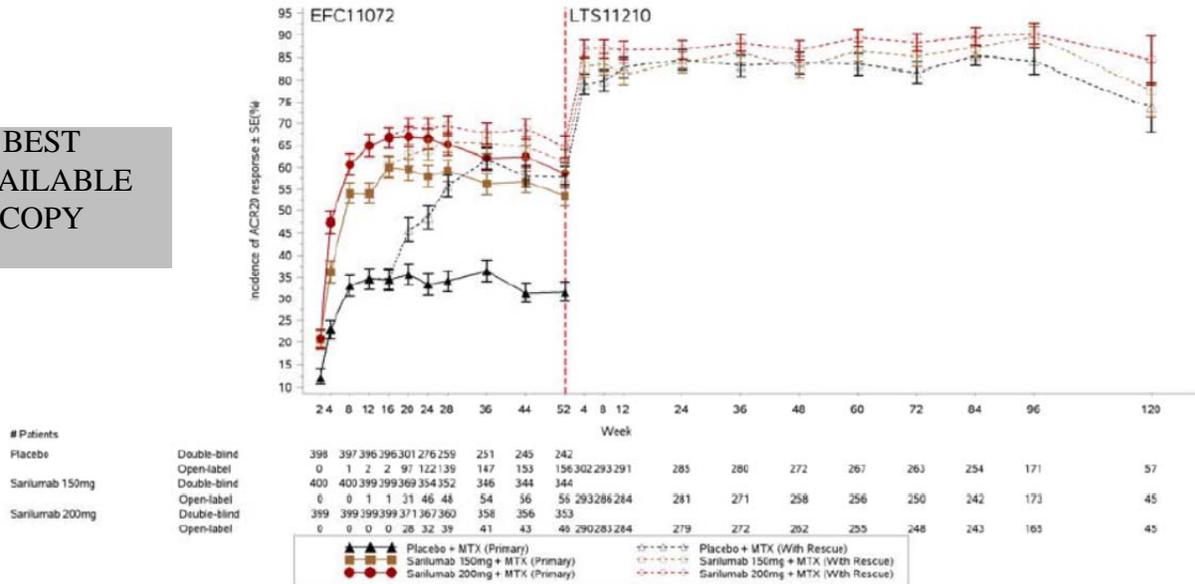
This review will only briefly present ACR20 response for subjects from both pivotal trials, as well as radiographic progression for subjects from study EFC11072 Part B. Additionally, see a brief discussion of efficacy of the long-term extension study in Section 6.9.2.

Figure 25 and Figure 26 show the incidence of ACR20 response in subjects who were initially randomized in EFC11072 Part B and EFC10832 and then continued into LTS11210, respectively. In these figures, despite all subjects receiving the same dose in LTS11210, the different colors represent the treatment groups to which the subjects were initially randomized. Also, the solid lines and filled symbols are subjects on double-blind therapy, whereas the dashed lines and open symbols are subjects on open-label therapy (rescue or LTS11210). There appears to be a persistence in ACR20 responders through 96 weeks of the open-label extension (subjects from EFC11072) and 48 weeks of open-label extension (subjects from EFC10832).

APPEARS THIS WAY ON ORIGINAL

**Figure 25. ACR20 Response Over Time for Patients Originally Randomized in EFC11072 Part B and Continued into LTS11210**

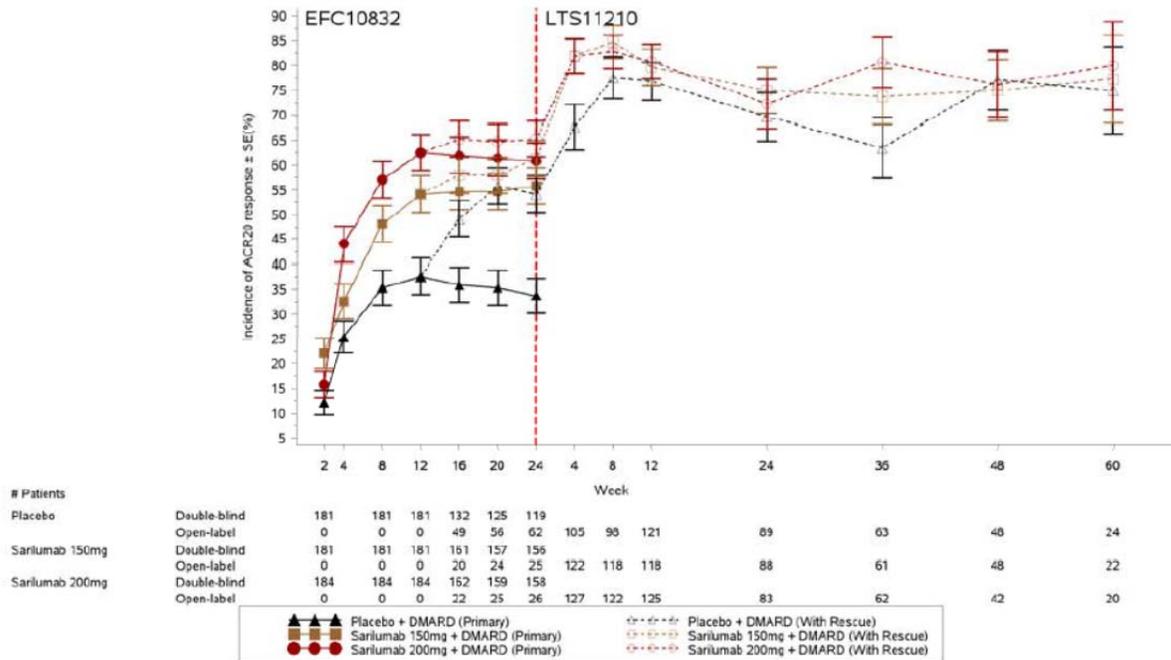
BEST  
 AVAILABLE  
 COPY



Source: Summary of Clinical Efficacy, Figure 12, dated Sep 10, 2015; page 108.

APPEARS THIS WAY ON ORIGINAL

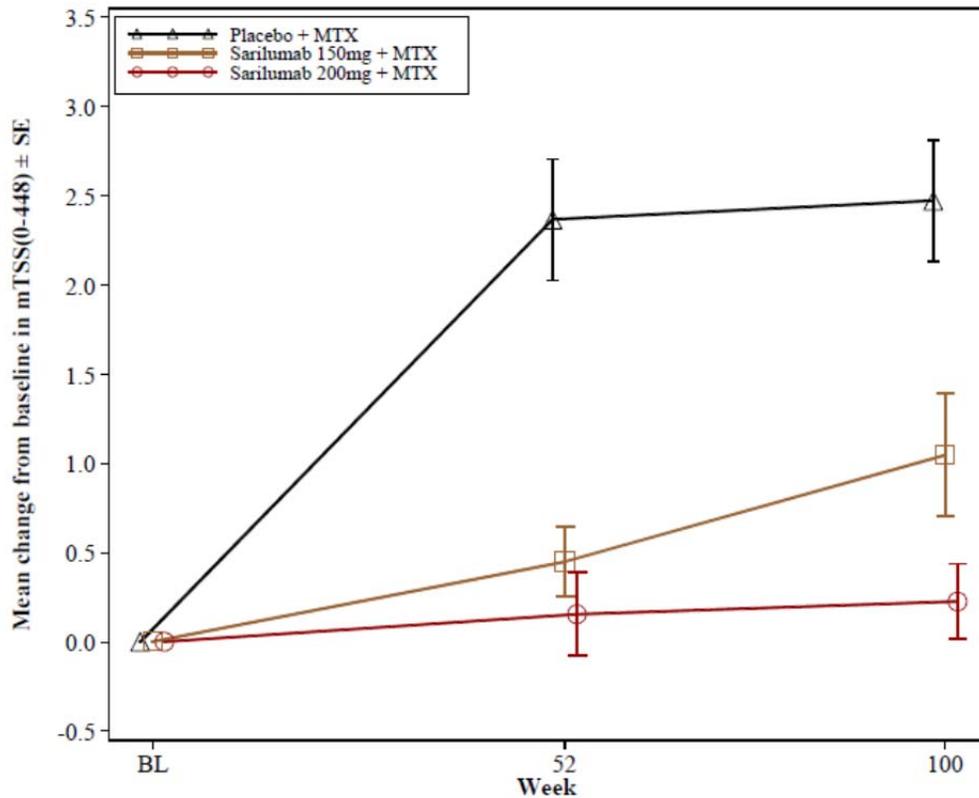
**Figure 26. ACR20 Response Over Time for Patients Originally Randomized in EFC10832 and Continued into LTS11210**



Source: Summary of Clinical Efficacy, Figure 14, dated Sep 10, 2015; page 110.

In regards to radiographic progression, Figure 27 shows change from baseline in mTSS through Week 100. It should be noted that, for this later assessment in LTS11210, radiographs from baseline, Week 52, and Week 100 were devoid of identification data and randomly read by 2 different assessors in an independent reading center. Therefore, radiographs from baseline and Week 52 were essentially re-read and could possibly have had different reading from the data analyzed during the treatment phase (reported above). In this analysis at Week 100, only subjects with radiographs at Week 100 were included. Therefore, the patient population may have differed from what was analyzed at Week 52. Lastly, all results were counted in the group to which the subjects were originally randomized. As the figure shows, there is a notable difference in radiographic progression between placebo and the sarilumab arms from baseline through Week 52. Subjects on sarilumab 200mg had the least amount of progression. After Week 52, when all subjects rolled into open-label therapy and received sarilumab 200mg q2w, there was little incremental progression in any of the treatment arms. From Week 52 to 100, patients initially randomized to 150mg q2w had less radiographic progression compared with those who had initially been randomized to placebo. At Week 100, though, there remained a difference in change in mTSS from those subjects who initially were randomized to 200mg q2w compared to those randomized to 150mg q2w and those randomized to placebo. Sanofi argues that these findings support the proposal that subjects who were initially treatment with sarilumab 200mg q2w had better radiographic outcomes.

**Figure 27. Mean Change from Baseline in mTSS at Each Visit for LTS11210**



# subjects	BL	52	100
Placebo + MTX	274	271	270
Sarilumab 150mg + MTX	262	262	259
Sarilumab 200mg + MTX	274	273	271

Source: Summary of Clinical Efficacy, Figure 20, dated Sep 10, 2015; page 118.

In summary, Sanofi evaluated persistence of efficacy through the long-term extension study. Generally, the data support the maintenance of efficacy in terms of signs and symptoms, physical function (not reviewed here), and radiographic progression. However, interpretation of open-label, uncontrolled data are very limited, and no definite conclusions can be made.

## 7.2. Additional Efficacy Considerations

### 7.2.1. Considerations on Benefit in the Postmarket Setting

The patient population in the pivotal trials, in the most part, reflected the general RA population in the US. At this point, there are no additional considerations of potential efficacy issues in the postmarket setting.

### 7.2.2. Other Relevant Benefits

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

Besides the robust efficacy, there are no additional aspects of the drug that may be considered by patients or providers to be a relevant benefit. The dosing schedule and route of administration are similar to what is currently available.

### 7.3. **Integrated Assessment of Effectiveness**

To support efficacy of sarilumab in the treatment of patients with RA, Sanofi has submitted the data from 2 phase 3 trials, EFC11072 Part B and EFC10832. EFC11072 Part B was a 52-week, randomized, double-blind, placebo-controlled trial evaluating 2 doses of sarilumab (150mg q2w and 200mg q2w) plus MTX in the treatment of moderate to severe RA. EFC10832 was a 24-week randomized, double-blind, placebo-controlled trial evaluating the same 2 doses of sarilumab plus any conventional DMARD in the treatment of RA. Both protocols are described in detail in Sections 6.2 and 6.3, respectively. In this era of drug development for rheumatoid arthritis, it is rare to have a 52-week placebo-controlled trial, so the data from study EFC11072 Part B was very informative. However, both studies had opportunities for rescue therapy with open-label sarilumab prior to assessment of the efficacy endpoints (ACR20 and mTSS). Thus, the analyses of the data are complicated. With that said, both studies definitely meet the evidentiary standard.

The primary and key secondary efficacy endpoints are accepted and validated endpoints to assess signs and symptoms (ACR response, DAS28-CRP), physical function (HAQ-DI), and radiographic progression (mTSS) in patients with rheumatoid arthritis. The results are presented in detail above in Section 7.1. For all these endpoints, sarilumab showed a statistically significant improvement compared to placebo. The primary analysis provided by Sanofi was confirmed by sensitivity analyses performed both by the Applicant and Dr. Kim (FDA statistical review team). In fact, the results for these endpoints are quite robust in favor of sarilumab. Of note, for ACR response, DAS28-CRP, and mTSS, there appeared to be a dose response with a trend toward slightly greater response on sarilumab 200mg compared to 150mg. (See Section 7.1.4.) Therefore, the data support sarilumab's efficacy in the treatment of patients with RA who are inadequate responders or intolerant of one or more DMARD. The efficacy results also appear to support the proposed initial dose of 200mg every 2 weeks.

The current 2015 ACR guidelines recommends a use of a conventional DMARD (typically, MTX) with a biologic DMARD for patients with moderate or high disease activity despite DMARD monotherapy. TNF inhibitors are frequently the first biologic DMARD used. However, between 20-30% of patients fail to respond or become intolerant to TNF inhibitors. Therefore, options for other biologic DMARDs are necessary. In study EFC11072 Part B, subjects were MTX inadequate responders, and, in study EFC10832, subjects were TNF inhibitor inadequate responders. Sarilumab would, therefore, be an option for subjects who are inadequate responders to MTX and TNF inhibitors. There is currently another IL-6 inhibitor on the market, tocilizumab. The efficacy of tocilizumab (IV) compared to sarilumab (SC) is presented in Section 6.4 (Study SFY13370) and showed comparable efficacy, perhaps numerically favoring

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

tocilizumab for ACR responses and HAQ-DI. However, study SFY13370 was not designed to compare efficacy (rather to compare safety), so the conclusions are limited. Sarilumab would essentially offer the RA population another effective IL-6 inhibitor. In clinical practice, the experience with TNF inhibitors has shown that some subjects may not have an adequate response or may be intolerant to one TNF inhibitor but then respond to another. Sarilumab would widen the options of IL-6 inhibitors to subjects who may not respond to tocilizumab.

Given the efficacy results, it is reasonable that labeling would convey that that sarilumab is effective for the treatment of adult patients with moderately to severely active RA who are inadequate responders or intolerant of one or more DMARDs. Essentially, the Agency is in agreement with labeling for benefits in signs and symptoms (ACR20 response, DAS28-CRP), physical function (HAQ-DI), radiographic response (mTSS), and general health related outcomes (SF-36). Section 10 provides full details regarding labeling recommendations. Additionally, see Section 1.3 for a discussion of the dose selection and agreement with the Applicant's proposed dose based on benefit-risk evaluation.

## 8 Review of Safety

---

### 8.1. Safety Review Approach

For the analysis of safety, the applicant utilized data obtained from the trials already described in Section 5.1 (Table of Clinical Studies), Table 41. The applicant then pooled the data from the studies in Table 5 into 3 major groups. The applicant's pooling strategy is summarized in Table 41.

APPEARS THIS WAY ON ORIGINAL

**Table 41. Summary of Safety Populations**

Pool and Population	Treatment Group (n)	Studies (Treatment Duration)
<b>Pool 1</b> Placebo-controlled population	150mg q2w + DMARD (n=660) 200mg q2w + DMARD (n=661) Placebo + DMARD (n=661)	EFC11072 Part A (12 weeks) EFC11072 Part B (52 weeks) <sup>a</sup> EFC10832 (24 weeks)
<b>Pool 1a</b> Phase 3 placebo-controlled population	150mg q2w + DMARD (n=579) 200mg q2w + DMARD (n=582) Placebo + DMARD (n=579)	EFC11072 Part B Cohort 2 (52 weeks) <sup>a</sup> EFC10832 (24 weeks)
<b>Pool 2</b> Sarilumab + DMARD long-term safety population	150mg q2w initial dose + DMARD <sup>b</sup> (n=1155) 200mg q2w initial dose + DMARD <sup>b</sup> (n=1351) Any sarilumab dose + DMARD <sup>c</sup> (n=2887)	EFC11072 Part A (12 weeks) EFC11072 Part B (52 weeks) EFC10832 (24 weeks) SFY13370 (24 weeks) EFC11574 main study <sup>d</sup> (24 weeks) EFC11574 substudy <sup>d</sup> (52 weeks) MSC12665 (52 weeks) LTS11210 <sup>e</sup> (5 years)
<b>Pool 3</b> Sarilumab monotherapy population	150mg q2w initial dose <sup>b</sup> (n=65) 200mg q2w initial dose <sup>b</sup> (n=67) Any sarilumab dose (n=132)	EFC13752 (24 weeks) LTS11210 <sup>f</sup> (5 years)

a Only data from the double-blind period are included in Pool 1 or Pool 1a.

b Only includes patients whose first sarilumab dose was either 150 or 200 mg q2w and includes data up to dose modification or discontinuation.

c Including the non-selected doses/regimens: 100 mg q2w, 100 mg qw, and 150 mg qw

d Main study: adalimumab non-responders; substudy: adalimumab responders

e Includes only patients receiving concomitant DMARDs, therefore, specifically patients from EFC11072, EFC10832, SFY13370, ACT11575

f Includes only patients receiving sarilumab as monotherapy who entered from EFC13752

Source:

Pool 1 is comprised of patients from the placebo-controlled studies, EFC11072 and EFC10832, who received sarilumab (doses of 150mg q2w or 200mg q2w) or who received placebo. This pool only includes safety data from the double-blind treatment period. Therefore, once a patient enters the rescue period and receives open-label sarilumab, the patient's data is no longer included. The duration of treatment for Pool 1 is potentially up to 52 weeks. Pool 1a is a subset of Pool 1. It only includes the patients from EFC11072 Part B Cohort 2 and EFC10832. Therefore, it is the same population used for the efficacy assessments.

Pool 2 includes all patients who received sarilumab in multiple studies that have been part of the RA clinical development, specifically, EFC11072 Parts A and B, EFC10832, SFY13370, EFC11574, MSC12665, and LTS11210. Duration of treatment for Pool 2 is up to 5 years. The applicant believes that this "long-term safety population" will allow for identification of

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

uncommon adverse events and events with longer latency periods, such as malignancy. Because of the different dosing regimens, this long-term safety population is further categorized into 3 groups.

- “Sarilumab 150mg q2w initial dose + DMARD” includes patients whose initial dose of sarilumab was 150mg q2w and only for the period that they received that dose. Therefore, no data are included after any dose medication (due to rescue or enrollment in LTS11210). After a patient was rescued or enrolled in the open-label LTS11219, all adverse events that occurred in this particular patient are also counted in the “any sarilumab dose” group.
- Similarly, “sarilumab 200mg q2w initial dose + DMARD” includes patients whose initial dose of sarilumab was 200mg q2w and only for the period that they received that dose. If a patient initiated on 200mg was enrolled in the open-label LTS11219 and continued 200mg q2w, this patient continues to be counted in this group. Additionally, if a patient, who initially received placebo, was rescued or enrolled in LTS11219, this patient is included in this group from the time point that he/she is started on 200mg q2w.
- Lastly, the group “any sarilumab dose + DMARD” includes patients on any dose of sarilumab. Therefore, this group includes subjects who received the initial dose of sarilumab 150mg or 200mg q2w, including data from both prior to and after any dose modification. Both of the previously described groups, “sarilumab 150mg q2w initial dose” and “sarilumab 200mg q2w initial dose,” are essentially subsets of this group. Additionally, this group includes subjects who received non-selected dosing regimens (e.g., 100mg q2w, 100mg qw, and 150mg qw).

Lastly, Pool 3 consists only of patients who received sarilumab as monotherapy. Thus, this includes patients from study EFC13752 and certain patients who continued monotherapy in LTS11210. Subjects in Pool 3 are grouped similarly to the subjects in the long-term safety population; that is, the subjects are grouped into 3 categories for analysis: sarilumab 150mg q2w initial dose, sarilumab 200mg q2w initial dose, and any sarilumab dose.

Another way to consider the pooling strategy is to account for the individual studies that make up each pool. The following tables display the number of patients by study contributing to Pools 1-3. What is notable from these tables is how many studies contribute to the long-term safety population (Pool 2) and, thus, includes a more diverse population who underwent differing study protocols.

Clinical Review  
 Reviewer: Suzette Peng, MD  
 NME/BLA 761037  
 Sarilumab/Kevzara

**Table 42. Number of Patients by Study Contributing to Pool 1**

	Placebo + DMARD  N=661	Sarilumab	
		150mg q2w + DMARD N=660	200mg q2w + DMARD N=661
<b>EFC11072 Part A</b>	52 (7.9%)	51 (7.7%)	51 (7.7%)
<b>EFC11072 Part B (cohort 1)</b>	30 (4.5%)	30 (4.5%)	28 (4.2%)
<b>EFC11072 Part B (cohort 2)<sup>a</sup></b>	398 (60.2%)	398 (60.3%)	398 (6.2%)
<b>EFC10832<sup>a</sup></b>	181 (27.4%)	181 (27.4%)	184 (27.8%)

% are calculated using the total number of patients in the placebo-controlled safety population as denominator

a Subjects who make up Pool 1a

Source: Integrated Summary of Safety, Table 7, dated October 6, 2015; page 44.

APPEARS THIS WAY ON ORIGINAL

**Table 43. Number of Patients by Study Contributing to Pool 2**

	Sarilumab + DMARD		
	150mg q2w Initial Dose N=1155	200mg q2w Initial Dose N=1351	Any Dose N=2887
<b>Patients who participated in the initial (base) study but were not rescued or did not participate in the LTS11210 study</b>			
EFC11072 Part A only	12 (1.0%)	12 (0.9%)	56 (1.9%)
EFC11072 Part B cohort 1 (non-selected dose) only	0	0	8 (0.3%)
EFC11072 Part B cohort 1 (selected dose) and cohort 2 only	90 (7.8%)	104 (7.1%)	194 (6.7%)
EFC10832 only	36 (3.1%)	31 (2.3%)	67 (2.3%)
SFY13370 only	12 (1.0%)	13 (1.0%)	25 (0.9%)
<b>Patient who were either rescued or participated in the LTS11210 study</b>			
EFC11072 Part A → LTS11210	39 (3.4%)	39 (2.9%)	243 (8.4%)
EFC11072 Part B cohort 1 (non-selected dose) → LTS11210	0	0	76 (2.6%)
EFC11072 Part B cohort 1 (selected dose) → LTS11210	340 (29.4%)	684 (50.6%)	1024 (35.5%)
EFC10832 → LTS11210	145 (12.6%)	309 (22.9%)	454 (15.7%)
SFY13370 → LTS11210	37 (3.2%)	38 (2.8%)	168 (5.8%)
LTS11210 study (ACT11575 patients)	0	0	7 (0.2%)
<b>Patients from EFC11574 study</b>			
EFC11574 main study	13 (1.1%)	13 (1.0%)	26 (0.9%)
EFC11574 substudy	322 (27.9%)	0	322 (11.2%)
<b>Patients from MSC12665 study</b>			
MSC12665 main study only	11 (1.0%)	14 (1.0%)	25 (0.9%)
MSC12665 → extension	98 (8.5%)	94 (7.0%)	192 (6.7%)

% are calculated using the number of patients randomized and treated (safety population) as denominator per study participation

Safety data from the non-sarilumab period (i.e., placebo or tocilizumab) in EFC11072 and SFY13370 are not included in the pooled analyses

Any dose includes exposure on all sarilumab doses, including non-selected doses: 100mg qw, 100mg q2w, 150mg qw, 150mg q2w, and 200mg q2w

a Subjects who were rescued with sarilumab therapy in the EFC11072 study are considered as if they had completed the initial study and participated in the LTS11210 study from the date of rescue

Source: Integrated Summary of Safety, Table 8, dated October 6, 2015; page 44-45.

**Table 44. Number of Patients by Study Contributing to Pool 3**

	Sarilumab + DMARD		
	150mg q2w Initial Dose N=65	200mg q2w Initial Dose N=67	Any Dose N=137
<b>EFC13752 only</b>	22 (33.8%)	22 (32.8%)	44 (33.3%)
<b>EFC13752 → LTS11210</b>	43 (66.2%)	45 (67.2%)	88 (66.7%)

% are calculated using the number of patients randomized and treated (safety population) as denominator

Any dose includes exposure on all sarilumab doses: 150mg q2w and 200mg q2w

Source: Integrated Summary of Safety, Table 9, dated October 6, 2015; page 45.

For the 3 pooled populations, the applicant provides raw incidence (number and percentage) of adverse events as well as the number of events per 100 patient-years. How the applicant calculated event rates is described in Section 8.3.2. For adverse events of special interest (AESI), cardiovascular events (MACE), AEs leading to discontinuation, and certain laboratory assessments, the applicant provides Kaplan-Meier (survival) estimates over time and plots for time to first event by treatment group. Also, for laboratory parameters, vital signs, ECGs, the applicant presents the data with descriptive statistics by visit/time and incidence of potentially clinically significant abnormalities (PCSAs).

In addition to standard analyses for each of the pooled populations, the applicant also provides a few additional analyses:

- For Pools 1 and 1a, safety analyses are provided for specific time periods (0-12 weeks, 0-24 weeks, 0-52 weeks, and pre-rescue period). Of note, the “pre-rescue period” is defined as 0-12 weeks for EFC10832 and 0-16 weeks for EFC11072 Part B. For these time periods, the applicant provided incidence and exposure-adjusted incidence rates as well as estimated incidence rate differences and 95% confidence interval for all pair-wise between-group differences.
- For Pool 1a, sensitivity analyses were performed to include events from both the placebo-controlled period as well as the rescue period. Analyses were performed for time periods of 0-12, 0-24, and 0-52 weeks.
- The applicant performed a model-based analysis on selected endpoints. The applicant proposed that this model-based analysis may help to provide additional information beyond analyses conducted on Pools 1 and 2. For this analysis, all the safety data on either placebo or sarilumab were included in order to further assess any differences between placebo and sarilumab. Therefore, this included placebo exposure from Pool 1 and sarilumab + DMARD exposure from Pool 2. A generalized estimating equation (GEE) was used for the analyses of the incidence or the number of events. Only the following endpoints were evaluated with this model-based analysis: serious infections, grade 3-4 neutropenia, ALT >3x ULN, malignancy, and MACE.

Analysis of safety is particularly complicated for sarilumab because of the design of the studies

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

included in the RA clinical development program. As already noted, there was the potential for subjects to be changed to a number of sarilumab doses for various reasons. First, lack of efficacy may have led to initiation of rescue therapy with open label sarilumab for subjects initiated on placebo or 150mg q2w. As rescue, subjects could have received 150mg qw (prior to phase 3 dose selection) or 200mg q2w (after dose selection). Another reason for a change in dose is enrollment in the long-term extension study (LTS11210) at which time the patients received the highest dose under study. Again, this dose was 150mg q2 prior to phase 3 dose selection and then 200mg q2w after phase 3 dose selection. Lastly, in the open-label extension study LTS11210, any subjects who experienced a protocol-specific laboratory abnormality would be dose reduced to 150mg q2w.

For this review, most of the safety analysis will be presented for Pool 1a with a focus on the true pre-rescue period (0-16 weeks for study EFC10832 and 0-12 weeks for study EFC11072 PartB) and, thus, represents the data least affected by the variable dosing regimens. For deaths, serious adverse events (SAEs), and certain adverse events of special interest (AESI), I will also review the additional analyses provided for the long-term safety population, any exposure-adjusted analyses, sensitivity analyses (based on exposure), and the applicant's model-based analyses. The AESIs were those that were given particular attention based on the biologic activity of IL-6, the associated effects of IL-6 inhibition, and the safety profile of other biologics used in the treatment of RA. The AESIs are presented in Section 8.5 and include infections, lipid abnormalities, cardiovascular events, malignancy, gastrointestinal perforation, hypersensitivity, lupus-like disorders, and demyelinating disorders. Cytopenias (specifically, neutropenia and thrombocytopenia) and elevated liver associated enzymes are also AESIs but are discussed in Section 8.4.6.

Two separate studies were performed to further evaluate safety under particular circumstances. As tocilizumab is an IL-6 inhibitor with the same mechanism of action as sarilumab and is already FDA-approved, study SFY13370 was conducted with the objective of assessing the safety of sarilumab and tocilizumab in patients with RA in the same study. Additionally, the safety of administering sarilumab monotherapy was evaluated in study EFC13752, specifically to establish safety and immunogenicity for sarilumab monotherapy. Alongside the results of study EFC13752, a very high level overview of Pool 3 (see description above) will be presented to ensure that the overall safety is comparable to sarilumab plus DMARD. Both the safety comparison of tocilizumab versus sarilumab and the review of sarilumab monotherapy will be presented in Section 8.7.

## 8.2. Review of the Safety Database

### 8.2.1. Overall Exposure

The size and exposure to sarilumab of the safety population are presented by the safety pools.

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

Although patient dispositions are provided under the description of each individual study in Section 6, the patient disposition for the safety pools are provided below. This information is helpful in getting a sense of the number of subjects in each pool as well as the number of subjects who discontinued treatment for a variety of reasons.

Table 45 presents the patient disposition for the placebo-controlled population (Pool 1). The number of subjects who were randomized and treated was similar across treatment arms. However, more subjects who received sarilumab completed the double-blind period as compared to placebo (54.3% in the placebo arm, 70.0% in the 150mg q2w arm, and 69.7% in the 200mg q2w arm). This difference could be attributed to more subjects in the placebo group getting rescued to open-label sarilumab. However, it should be noted that more subjects in the sarilumab arms discontinued treatment due to adverse events (4.7% in the placebo arm, 11.1% in the sarilumab 150mg q2w arm, and 12.6% in the sarilumab 200 mg q2w). A more detailed discussion of treatment discontinuation secondary to AEs will be provided below (Section 8.4.3).

**Table 45. Patient Disposition for Pool 1 (Placebo-Controlled Population)**

	Placebo + DMARD  N=661	Sarilumab	
		150mg q2w + DMARD N=660	200mg q2w + DMARD N=661
Randomized and treated	661 (100%)	660 (100%)	661 (100%)
Completed the double-blind period	359 (54.3%)	462 (70.0%)	461 (69.7%)
Rescued to sarilumab therapy	231 (34.9%)	86 (13.0%)	81 (12.3%)
Discontinued treatment during the double-blind period	71 (10.7%)	112 (17.0%)	119 (18.0%)
Reason for treatment discontinuation <sup>a</sup>			
Adverse event	31 (4.7%)	73 (11.1%)	83 (12.6%)
Lack of efficacy	13 (2.0%)	11 (1.7%)	10 (1.5%)
Poor compliance to protocol	8 (1.2%)	4 (0.6%)	6 (0.9%)
Other reasons <sup>b</sup>	19 (2.9%)	24 (3.6%)	20 (3.0%)

% are calculated using the number of patients randomized and treated (safety population) as denominator

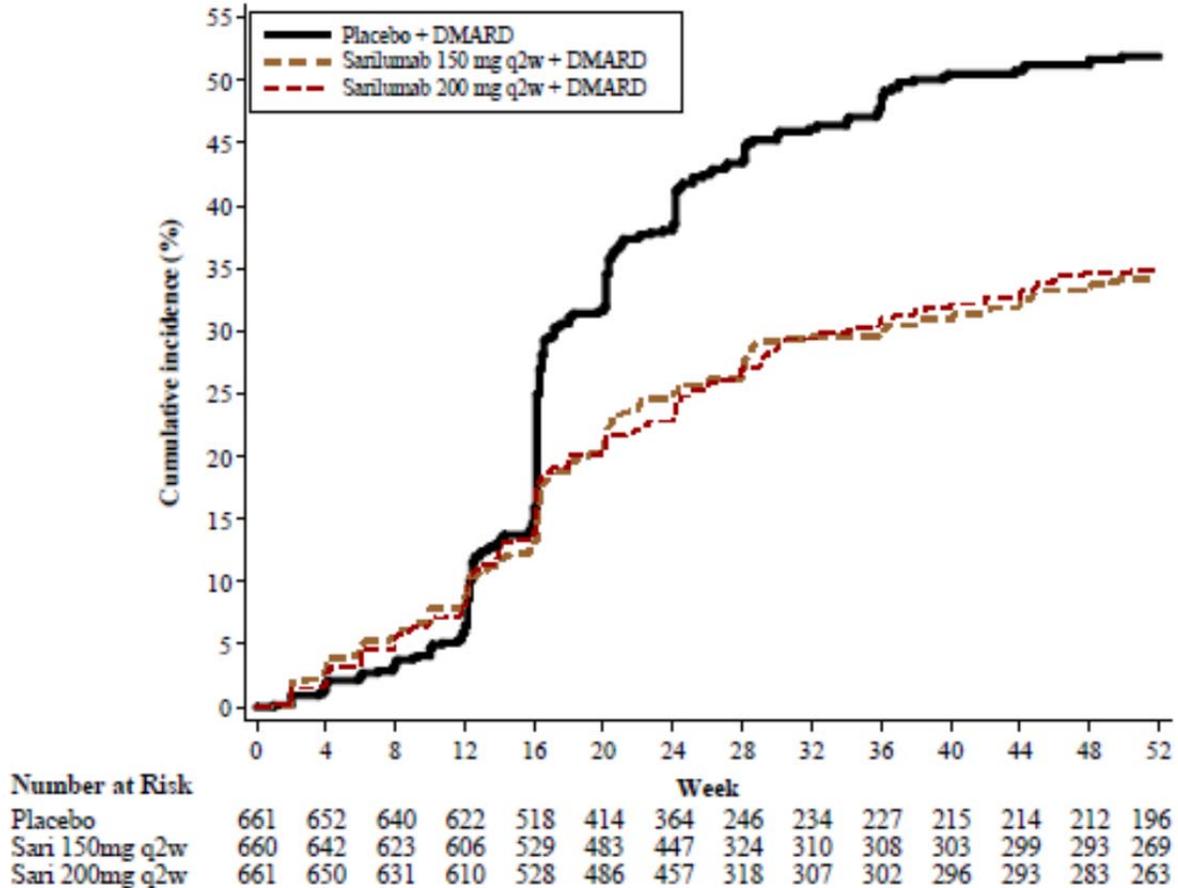
a includes only patients discontinued from the study and did not receive rescue therapy with sarilumab

b Other reasons were mainly due to personal reasons and not related to a safety issue or investigator's assessment of lack of efficacy

Source: Integrated Summary of Safety, Table 10, dated October 6, 2015; page 46.

Figure 28 is a Kaplan-Meier plot showing treatment discontinuation for Pool 1. It reiterates how more subjects in the placebo group discontinued therapy. Also, it appears that many of these discontinuations occurred around Week 12 and Week 16, which would be consistent with the timing of assessments for lack of efficacy and then rescue to open-label sarilumab for studies EFC10832 and EFC11072 Part B, respectively.

**Figure 28. Kaplan-Meier Plot for Time to Treatment Discontinuation or Rescue (Pool 1)**



Source: Integrated Summary of Safety, Figure 2, dated October 6, 2015; page 47.

As already described, Pool 1a is a subset of Pool 1. The patient disposition for Pool 1a was similar to that of Pool 1 with similar proportion of subjects in each arm who completed the double-blind period, rescued to sarilumab, and discontinued treatment during the double-blind period.

Table 46 is an overview of the patient disposition of subjects in the long-term safety population (Pool 2) with a focus on the subjects in the any sarilumab dose group. The majority of subjects in the long-term safety population were still receiving therapy at the time of the data cutoff date. Also, of note, 29.2% of subjects discontinued therapy with the majority secondary to adverse events (18.9%). These adverse events leading to discontinuation are detailed below in Section 8.4.3. Sanofi notes that, in evaluation each of the initial dose groups, there was a higher rate of discontinuation during the first 48 weeks of treatment. After 48 weeks, the rate of discontinuation seemed to stabilize around 8%.

**Table 46. Patient Disposition of Any Sarilumab Dose Group in Pool 2 (Long-Term Safety Population)**

	<b>Sarilumab + DMARD Any Dose N=2887</b>
Randomized and treated	2887 (100%)
Ongoing treatment	1638 (56.7%)
Completed treatment	405 (14.0%)
Completed the initial study <sup>a</sup> and did not participate in the LTS11210 study	84 (2.9%)
Completed the LTS11210 study	0
Completed the EFC11574 study or stopped for study closure	312 (10.8%)
Completed the MSC12665 main study and did not participate in the extension study	9 (0.3%)
Completed the MSC12665 extension study	0
Discontinued treatment	844 (29.2%)
Reason for treatment discontinuation	
Adverse event	546 (18.9%)
Lack of efficacy	86 (3.0%)
Poor compliance to protocol	30 (1.0%)
Other reasons <sup>b</sup>	182 (6.3%)

% are calculated using the number of patients randomized and treated (safety population) as denominator  
 Patients who were rescued with sarilumab therapy in the EFC11072 study are considered as if they had completed the initial study and participated in the LTS11210 study from the date of rescue  
 Any dose includes the exposure of all sarilumab doses: 100mg qw, 100mg q2w, 150mg qw, 150mg q2w, 200mg q2w  
 a includes EFC11072 (Parts A and B), EFC10832, and SFY13370  
 b Other reasons were mainly due to personal reasons and not related to a safety issue or investigator's assessment of lack of efficacy  
 Source: Integrated Summary of Safety, Table 11, dated October 6, 2015; page 48.

As Pool 3 is essentially a summary of study EFC13572 plus those who entered LTS11210, the patient disposition is not further describe here. Please refer to Section 6.5.2 for a description of the patient disposition of study EFC13752.

With the patient disposition of each safety pool in mind, one can then thoughtfully approach the extent of exposure in each safety pool. The following tables detail the exposure to sarilumab for Pools 1-3.

In Table 47, the cumulative exposure in the placebo-controlled population was higher in the sarilumab treatment arms as compared to the placebo arm (373.1 patient-years for placebo vs. 425.8 patient-years for 150mg q2w and 425.5 patient-years for 200mg q2w). The exposure in the 2 sarilumab arms is very similar. As discussed above with patient disposition, the likely reason for the decreased exposure in the placebo arm is the number of subjects who were

rescued to open-label sarilumab. This reasoning is supported by the number of patients who received treatment (by duration) are similar at >12 weeks but began to differ at >24 weeks.

**Table 47. Exposure to Sarilumab in Pool 1 (Placebo-Controlled Population)**

	Placebo + DMARD  N=661	Sarilumab	
		150mg q2w + DMARD N=660	200mg q2w + DMARD N=661
<b>Cumulative exposure to treatment (patient-years)</b>	<b>373.1</b>	<b>425.8</b>	<b>425.5</b>
<b>Duration of study treatment (days)</b>			
Number	661	660	661
Mean (SD)	206.2 (117.6)	235.6 (124.7)	235.1 (123.0)
Median	168.0	177.5	176.0
Min: Max	7: 408	14: 385	7: 408
<b>Number of patients with duration of study treatment by category [n(%)]</b>			
≥ 1 day	661 (100%)	660 (100%)	661 (100%)
> 12 weeks	600 (90.8%)	588 (89.1%)	592 (89.6%)
> 24 weeks	299 (45.2%)	377 (57.1%)	375 (56.7%)
> 36 weeks	221 (33.4%)	306 (46.4%)	300 (45.4%)
> 48 weeks	210 (31.8%)	292 (44.2%)	283 (42.8%)

Patients are counted in a treatment group based on treatment actually received  
 Source: Integrated Summary of Safety, Table 13, dated October 6, 2015; page 52.

The overall exposure for Pool 1a (only the phase 3 studies in Pool 1) is presented in Table 48. The cumulative exposure to sarilumab was slightly lower in the placebo compared to both sarilumab arms with 339.1 patient-years for placebo, 389.7 patient-years for sarilumab 150mg q2w, and 393.3 patient-years for sarilumab 200mg q2w. Overall, the trends in exposure were similar to that of Pool 1, as most of the differences in exposure started sometime between Weeks 12 and 24.

APPEARS THIS WAY ON ORIGINAL

**Table 48. Exposure to Sarilumab in Pool 1a (Phase 3 Placebo-Controlled Population)**

	Placebo + DMARD  N=579	Sarilumab	
		150mg q2w + DMARD N=579	200mg q2w + DMARD N=582
<b>Cumulative exposure to treatment (patient-years)</b>	<b>339.1</b>	<b>389.7</b>	<b>393.3</b>
<b>Duration of study treatment (days)</b>			
Number	579	579	582
Mean (SD)	213 (116.8)	245.8 (121.7)	246.8 (120.1)
Median	168.0	210.0	225.5
Min: Max	14: 408	14: 385	14:408
<b>Number of patients with duration of study treatment by category [n(%)]</b>			
≥ 1 day	579 (100%)	579 (100%)	582 (100%)
> 12 weeks	527 (91.0%)	518 (89.5%)	525 (90.2%)
> 24 weeks	279 (48.2%)	355 (61.3%)	356 (61.2%)
> 36 weeks	205 (35.4%)	285 (49.2%)	285 (49.0%)
> 48 weeks	197 (34.0%)	273 (47.2%)	270 (46.4%)

Patients are counted in a treatment group based on treatment actually received  
 Source: Integrated Summary of Safety, Table 14, dated October 6, 2015; page 53.

Table 49 summarizes the extent of sarilumab exposure in the long-term safety population (Pool 2). The total exposure to any dose of sarilumab was 4338.9 patient-years. Based on the definitions of the treatment arms 150mg q2w initial dose and 200mg q2w initial dose as well as the study design, subjects can only transition to open-label 200mg q2w (or 150mg qw prior to dose selection). Therefore, the cumulative patient exposure in the sarilumab 200mg q2w group was more than double the exposure in the 150mg q2w initial dose group, 646.0 patient-years for the 150mg q2w initial dose arm and 1712.7 patient-years for the 200mg q2w initial dose arm. It can be noted that, around treatment duration >48 weeks, the number of subjects on sarilumab 150mg q2w began to drop significantly.

APPEARS THIS WAY ON ORIGINAL

**Table 49. Exposure to Sarilumab in Pool 2 (Long-Term Safety Population)**

	Sarilumab		
	150mg q2w Initial Dose N=1155	200mg q2w Initial Dose N=1351	Any Dose N=2887
<b>Cumulative exposure to treatment (patient-years)</b>	<b>646.0</b>	<b>1712.7</b>	<b>4338.9</b>
<b>Duration of study treatment (days)</b>			
Number	1155	1351	2887
Mean (SD)	204.3 (126.2)	463.0 (374.5)	548.9 (452.3)
Median	168.0	350.0	366.0
Min: Max	14: 1204	7: 1386	7: 1786
<b>Number of patients with duration of study treatment by category [n(%)]</b>			
≥ 1 day	1155 (100%)	1351 (100%)	2887 (100%)
> 12 weeks	995 (86.1%)	1117 (82.7%)	2556 (88.5%)
> 24 weeks	560 (48.5%)	947 (70.1%)	2170 (75.2%)
> 48 weeks	296 (25.6%)	701 (51.9%)	1546 (53.6%)
> 96 weeks	6 (0.5%)	399 (29.5%)	1020 (35.3%)
> 144 weeks	1 (<0.1%)	179 (13.2%)	624 (21.6%)
> 192 weeks	0	6 (0.4%)	192 (6.7%)
> 240 weeks	0	0	22 (0.8%)

Patients are counted in a treatment group based on treatment actually received

150mg q2w initial dose or 200mg q2w initial dose is up to dose modification or end of study

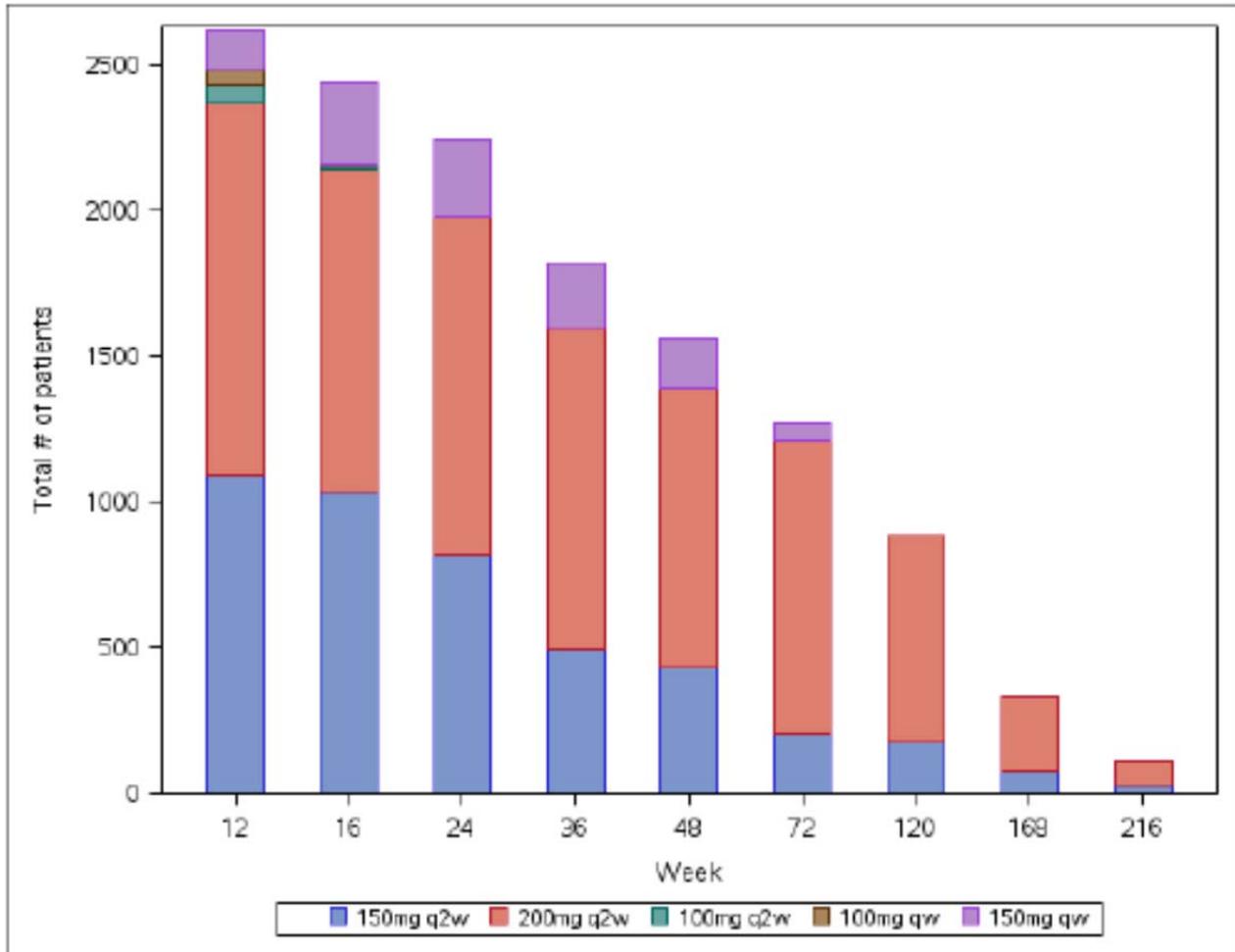
Any dose includes the exposure on all sarilumab doses, including non-selected doses: 100mg qw, 100mg q2w, 150mg qw, 150mg q2w, 200mg q2w

Source: Integrated Summary of Safety, Table 15, dated October 6, 2015; page 54-5.

The exposure in the “any dose” group better reflects all subjects who were exposed to any dose of sarilumab in Pool 2, and breaking down this group may be more reflective of all the doses received in this patient population. Figure 29 illustrates the contribution of the different doses of sarilumab to the “any dose” group in Pool 2 over time. After 72 weeks, subjects only received doses of 150mg q2w and 200mg q2w. However, throughout the treatment period included in the long-term safety population, the majority of subjects received 200mg q2w.

APPEARS THIS WAY ON ORIGINAL

**Figure 29. Contribution of Doses to Any Sarilumab Dose Arm Over Entire TEAE Period (Pool 2)**



Source: Integrated Summary of Safety, Figure 5, dated October 6, 2015; page 55.

The extent of exposure to sarilumab by all doses, as represented by Figure 29 above, was also calculated.

- 1542 subjects received 150mg q2w for a cumulative exposure of 1148.0 patient-years
- 2157 subjects received 200mg q2w for a cumulative exposure of 2912.4 patient-years
- 80 subjects received 100mg q2w for a cumulative exposure of 19.4 patient-years
- 79 subjects received 100mg qw for a cumulative exposure of 17.0 patient-years
- 328 subjects received 150mg qw for a cumulative exposure of 242.1 patient-years

Thus, in interpreting safety data from Pool 2, the differences in exposure, particularly to 200mg q2w, should always be considered.

Lastly, Pool 3 reflects subjects on sarilumab monotherapy in both study EFC13752 but also in the open-label extension. Table 50 describes the extent of exposure to sarilumab monotherapy

in Pool 3. Again, because subjects could only receive 200mg q2w during the open-label extension, the cumulative exposure was slightly higher in this treatment group. Overall, though, the exposure was quite similar in both monotherapy doses, 27.8 patient-years for 150mg q2w and 33.5 patient-years for 200mg q2w. The overall exposure to any dose of sarilumab (given as monotherapy) was 66.8 patient-years.

**Table 50. Exposure to Sarilumab in Pool 3 (Monotherapy Population)**

	Sarilumab		
	150mg q2w Initial Dose N=65	200mg q2w Initial Dose N=67	Any Dose N=132
<b>Cumulative exposure to treatment (patient-years)</b>	<b>27.8</b>	<b>33.5</b>	<b>66.8</b>
<b>Duration of study treatment (days)</b>			
Number	65	67	132
Mean (SD)	156.1 (37.8)	182.8 (58.9)	184.8 (58.1)
Median	168.0	183.0	182.0
Min: Max	29: 182	14: 256	14: 261
<b>Number of patients with duration of study treatment by category [n(%)]</b>			
≥ 1 day	65 (100%)	67 (100%)	132 (100%)
> 12 weeks	59 (90.8%)	60 (89.6%)	119 (90.2%)
> 24 weeks	18 (27.7%)	49 (73.1%)	93 (70.5%)
> 36 weeks	0	7 (10.4%)	16 (12.1%)

Patients are counted in a treatment group based on treatment actually received  
 150mg q2w initial dose or 200mg q2w initial dose is up to dose modification or end of study  
 Any dose includes the exposure on all sarilumab doses: 150mg q2w and 200mg q2w  
 Source: Integrated Summary of Safety, Table 16, dated October 6, 2015; page 56.

*Reviewer Comment: The exposure to drug in the entire development program exceeds the minimum specified in ICHE1 guidelines. Additionally, as noted in the regulatory history, the size of the safety database was discussed and generally agreed upon at the EOP2 meeting and is consistent with similar safety databases for biologic therapies for RA.*

### 8.2.2. Relevant characteristics of the safety population:

For baseline patient characteristics and disease characteristics, this review will focus on Pool 1, the placebo-controlled population. As noted, most of the safety analyses, however, will be performed on Pool 1a. Any notable differences between Pool 1 and Pool 1a will be highlighted. Overall, though, the different pools (Pool 1, Pool 1a, Pool 2, and Pool 3) displayed similar baseline characteristics. Pool 3 will not be discussed here, as the patient characteristics for EFC13752 already described in Section 6.5.2 are reflective of that of Pool 3.

Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

The majority of subjects were <65 years of age, female, and Caucasian, as described in Table 51. These patient characteristics were similar across treatment arms in the placebo-controlled population. These features represent the general patient epidemiologic characteristics of RA, except perhaps the races. In Pool 1, approximately 80% of subjects were Caucasian (non-Latino) with much smaller representation from other races. In the general RA population, all races can be affected; although the majority is Caucasian, the incidence/prevalence may be lower than what was enrolled in this study. An ACR abstract from 2012 presented the prevalence of RA in a large-multi-ethnic US managed care population, and the prevalence of Caucasian patients was 64.2% (Kawatkar et al. 2514). The significance of this is not completely clear. There are some studies that suggest that African-American and Hispanic patients may have higher disease activity (Greenberg et al. 7). Enrolled subjects were enrolled from all over the world with an overall even distribution, slightly lower in the Western countries. However, the proportions were similar across treatment arms. The baseline demographics and patient characteristics were consistent for Pool 1a as well as for Pool 2 (long-term safety population).

APPEARS THIS WAY ON ORIGINAL

**Table 51. Demographics and Patient Characteristics at Baseline (Pool 1)**

	Placebo + DMARD  N=661	Sarilumab	
		150mg q2w + DMARD N=660	200mg q2w + DMARD N=661
Age (years)			
Number	661	660	661
Mean (SD)	51.6 (11.7)	51.4 (12.0)	51.2 (12.3)
Median	52.0	53.0	52.0
Min: Max	19: 79	18: 88	19: 87
Age group [n(%)]			
Number	661	660	661
< 65 years	573 (86.7%)	574 (87.0%)	569 (86.1%)
≥ 65 and < 75 years	84 (12.7%)	79 (12.0%)	82 (12.4%)
≥ 75 years	4 (0.6%)	7 (1.1%)	10 (1.5%)
Sex [n(%)]			
Number	661	660	661
Male	123 (18.6%)	133 (20.2%)	110 (16.6%)
Female	538 (81.4%)	527 (79.8%)	551 (83.4%)
Race			
Number	661	660	661
Caucasian	543 (82.1%)	553 (83.8%)	545 (82.5%)
Black	17 (2.6%)	21 (3.2%)	18 (2.7%)
Asian	38 (5.7%)	37 (5.6%)	36 (5.4%)
Other	63 (9.5%)	49 (7.4%)	62 (9.4%)
Ethnicity [n(%)]			
Number	661	660	661
Hispanic	238 (36.0%)	254 (38.5%)	264 (39.9%)
Not Hispanic	423 (64.0%)	406 (61.5%)	397 (60.1%)
Weight (kg)			
Number	661	660	661
Mean (SD)	75.59 (18.43)	75.19 (19.26)	75.54 (19.24)
Median	73.20	72.05	73.00
Min: Max	42.0: 164.8	31.5: 183.2	36.7: 173.1
Body mass index (BMI) (kg/m <sup>2</sup> )			
Number	661	658	660
Mean (SD)	28.76 (6.52)	28.29 (6.56)	28.82 (6.62)
Median	27.39	27.34	28.14
Min: Max	16.4: 58.3	15.0: 65.2	16.4: 55.2
Region [n(%)]			
Number	661	660	661
Region 1	176 (26.6%)	177 (26.8%)	178 (26.9%)
Region 2	249 (37.7%)	249 (37.7%)	249 (37.7%)

Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

Region 3	236 (35.7%)	234 (35.5%)	235 (35.4%)
Smoking status [n(%)]			
Number	661	660	660
Never	466 (70.5%)	458 (69.4%)	480 (72.7%)
Former	109 (16.5%)	101 (15.3%)	101 (15.3%)
Current	86 (13.0%)	101 (15.3%)	79 (12.0%)
Alcohol habits [n(%)]			
Number	661	660	660
Never	512 (77.5%)	496 (75.2%)	533 (80.8%)
Monthly	94 (14.2%)	95 (14.4%)	91 (13.8%)
Weekly	45 (6.8%)	61 (9.2%)	31 (4.7%)
Daily	10 (1.5%)	8(1.2%)	5 (0.8%)

Number = number of patients assessed. % are calculated using number of patients assessed as denominator.

Region 1 (Western countries) = Austria, Belgium, Canada, Czech Republic, Estonia, Finland, Germany, Greece, Hungary, Italy, Lithuania, Norway, Portugal, Romania, Slovakia, Spain, Switzerland, Netherlands, Sweden, United Kingdom, USA

Region 2 (South America): Argentina, Brazil, Chile, Colombia, Ecuador, Guatemala, Mexico, Peru

Region 3 (Rest of the world): Australia, Belarus, Hong Kong, India, Israel, Malaysia, New Zealand, Philippines, Russia, South Africa, South Korea, Taiwan, Thailand, Ukraine, Poland

a Alcohol habits: how often patient had a drink containing alcohol in the last 12 months

Source: Integrated Summary of Safety, Table 17, dated October 6, 2015; page 57-8.

Table 52 presents the baseline disease characteristics. Most subjects had approximately 9-10 years of disease with a functional class II. The number of subjects with a history of prior biologic DMARD use was about even with slightly more subjects who had never been exposed to a biologic. Like the other baseline patient characteristics, the disease characteristics were similar in proportion in Pool 1a. Pool 2 subjects also had similar disease characteristics, except minimally numerically lower proportions of prior biologic use.

APPEARS THIS WAY ON ORIGINAL

**Table 52. Disease Characteristics at Baseline (Pool 1)**

	Placebo + DMARD  N=661	Sarilumab	
		150mg q2w + DMARD N=660	200mg q2w + DMARD N=661
Duration of RA since diagnosis (Years)			
Number	661	660	661
Mean (SD)	9.77 (8.80)	9.87 (8.42)	9.58 (8.02)
Median	7.23	7.66	7.78
Min: Max	0.3: 54.0	0.3: 45.6	0.3: 46.2
RA functional class [n(%)]			
Number	661	660	661
I	68 (10.3%)	77 (11.7%)	72 (10.9%)
II	440 (66.6%)	409 (62.0%)	432 (65.4%)
III	153 (23.1%)	174 (26.4%)	157 (23.8%)
IV	0	0	0
Prior biologic DMARD use [n(%)]			
Number	661	660	661
Yes	283 (42.7%)	283 (42.9%)	284 (43.0%)
No	379 (57.3%)	377 (57.1%)	377 (57.0%)

Source: Integrated Summary of Safety, Table 20, dated October 6, 2015; page 63.

As the pivotal studies required prior as well as concomitant DMARD use, all subjects were on a conventional DMARD at baseline in Pool 1. Table 53 breaks down the different regimens that were used by subjects in the placebo-controlled population. The majority of subjects took concomitant MTX. This may reflect the requirements of study EFC11072. The average dose of MTX was 15mg weekly across all treatment arms. The next most common conventional DMARD was leflunomide. A few subjects required more than 1 DMARD. Approximately 60% of subjects were taking baseline corticosteroids, and approximately 70% of subjects received baseline NSAIDs. Overall, the baseline medications for RA were similar for placebo and for the 2 doses of sarilumab. The baseline medications for RA in Pool 1 were consistent with the baseline medications in Pool 1a and Pool 2.

APPEARS THIS WAY ON ORIGINAL

**Table 53. Baseline Medications for RA in Pool 1**

	Placebo + DMARD  N=661	Sarilumab	
		150mg q2w + DMARD N=660	200mg q2w + DMARD N=661
<b>Any baseline non-biologic DMARD use</b>	<b>660 (99.8%)</b>	<b>659 (99.8%)</b>	<b>661 (100%)</b>
Baseline use of 1 non-biologic DMARD	652 (98.6%)	645 (97.7%)	644 (97.4%)
Methotrexate	630 (95.3%)	618 (93.6%)	617 (93.3%)
Leflunomide	15 (2.3%)	17 (2.6%)	17 (2.6%)
Hydroxychloroquine	4 (0.6%)	6 (0.9%)	6 (0.9%)
Sulfasalazine	3 (0.5%)	4 (0.6%)	4 (0.6%)
Baseline use of 2 non-biologic DMARDs	7 (1.1%)	12 (1.8%)	16 (2.4%)
Methotrexate and sulfasalazine	2 (0.3%)	6 (0.9%)	9 (1.4%)
Methotrexate and hydroxychloroquine	4 (0.6%)	6 (0.9%)	6 (0.9%)
Leflunomide and hydroxychloroquine	1 (0.2%)	0	0
Leflunomide and sulfasalazine	0	0	1 (0.2%)
Baseline use of 3 non-biologic DMARDs	1 (0.2%)	2 (0.3%)	1 (0.2%)
Methotrexate, hydroxychloroquine, and sulfasalazine	0	2 (0.3%)	1 (0.2%)
Methotrexate, leflunomide, and hydroxychloroquine	1 (0.2%)	0	0
<b>Summary of the use of non-biologic DMARDs at baseline</b>			
<b>Methotrexate</b>			
Weekly dose at baseline (mg)			
Number	637	632	633
Mean (SD)	15.77 (4.27)	15.92 (5.85)	15.63 (4.17)
Median	15.00	15.00	15.00
<b>Leflunomide</b>			
Daily dose at baseline (mg)			
Number	17	17	18
Mean (SD)	20.00 (0.00)	20.00 (0.00)	18.33 (3.83)
Median	20.00	20.00	20.00
<b>Sulfasalazine</b>			
Daily dose at baseline (mg)			
Number	5	12	15
Mean (SD)	2100.00 (547.72)	1291.67 (582.25)	1766.67 (776.13)
Median	2000	1000	2000
<b>Hydroxychloroquine</b>			
Daily dose at baseline (mg)			
Number	10	14	13
Mean (SD)	300.00 (105.41)	328.57 (99.45)	330.77 (94.73)
Median	300.00	400.00	400.00
<b>Folic acid</b>	639 (96.7%)	628 (95.2%)	634 (95.9%)

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

<b>Any baseline corticosteroids</b>	392 (59.3%)	428 (64.8%)	411 (62.2%)
<b>Any baseline NSAID use</b>	467 (70.7%)	450 (68.2%)	443 (67.0%)

Baseline medications are those that the patients were taking at the time of the first dose of IMP.

Medications are sorted by decreasing frequency in all patients.

Source: Integrated Summary of Safety, Table 26, dated October 6, 2015; page 70-71.

### 8.2.3. Adequacy of the safety database:

In conclusion, the safety database is adequate in regards to size and exposure. In general, in the placebo-controlled population, sarilumab exposure, duration of treatment, patient demographics, and disease characteristics are similar for both doses that are being investigated. The patients were recruited from all over the world with a slightly lower proportion from Western countries. The patient characteristics and disease at baseline are similar to the general US population with RA. The only notable exception is that the vast majority of subjects are Caucasian. As discussed above, the majority of the general population with RA is also Caucasian, but there are perhaps greater proportions of other races. Despite this discrepancy, in general, the population enrolled and randomized is reflective of the US population with moderate to severe RA

## 8.3. Adequacy of Applicant's Clinical Safety Assessments

### 8.3.1. Issues Regarding Data Integrity and Submission Quality

The sarilumab BLA did not have any issues regarding data integrity and submission quality. All data submitted could be used and interpreted as part of the analysis for safety.

When utilizing the site selection tool, there were no signals at any particular sites, countries, or regions that were concerning for any possible data integrity issues.

In January 2016, JumpStart service was requested from the Office of Computational Science (OCS). This service included Data Fitness and Exploratory Safety Analysis services. The JumpStart team assessed the pivotal studies EFC11072 Part B and EFC10832. Additionally, the team analyzed 2 other key studies in the clinical development program: SFY13370 (sarilumab vs. tocilizumab) and EFC13752 (sarilumab monotherapy). The team determined whether the data can be loaded into analytic tools and whether certain common analyses can be performed. Additionally, the JumpStart team assessed other data quality metrics, including availability of appropriate variables, variables populated by expected data points, appropriate use of standard terminology, and data well-described by metadata. The conclusion was essentially that the data were adequate to proceed with further analyses. However, these were the JumpStart team's specific conclusions:

- The Study Data Reviewer's Guide (SDRG) and Define.xml file were provided for each study. These items are helpful to orient the reviewer to the data and to provide useful

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

information about its format. The applicant, however, used an outdated version of the data validator which could possibly show false positives and miss newer FDA business rules.

- Sanofi provided a Supplemental Contents Report for each of the studies analyzed by the JumpStart team. The supplemental datasets are intended to capture variables that do not fit within the standard domains. As an example, the Supplemental Contents Report for study EFC110732 Part B accounted for 144 additional variables. These supplemental datasets are useful information to speed up the reviewer's analyses.
- The applicant's terminology adequately mapped to controlled terminology.
- The JumpStart team noted that there were 7 deaths in study EFC11072 Part B, 1 death in study EFC10832, and 1 death in SFY13370. Additionally, the team noted in which Study Data Tabulation Model (SDTM) domain these deaths were located. Additionally, the team noted that the applicant provided a Death Reconciliation Report for the above studies, and this report will help the reviewer compare death information across SDTM domains.
- In regards to missing data, the JumpStart team noted the following:
  - In study EFC10832, 9 adverse event records met serious criteria but were not flagged as serious events ("Y" for AESER). Because of this, these events will not be included in an analysis of serious adverse events created by filtering on the serious flag (AESER).
  - In all studies, 17-21% of adverse events were missing end time point information. The team noted that most of the recorded had a documented outcome, "not recovered/resolved" or "recovering/resolving." However, 4 records in EFC11072 Part B were noted to be "recovered/resolved," so it is unclear what actually happened with these 4 events.
  - In all studies, a small percentage (roughly 1%) of exposure records was missing key information such as "Name of Actual Treatment" or Start/End Dates. The JumpStart team noted, though, that Sanofi added the variable "Not Taken or Administered" (EXOCCUR) to denote whether an exposure record actually occurred. Therefore, the team recommended filtering the records where EXOCCUR=Y to avoid those records where exposure did not actually occur.
  - In studies EFC11072 Part B and SFY13370, the Exposure Start Date (EXSDTC) was after Date of Last Study Treatment (DM.RFXENDTC) for 13% and 3% of exposure records, respectively. This inconsistency may reflect escape to rescue. Given this finding, the JumpStart team recommended that the DM.RFXENDTC should not be utilized for analysis for these 2 studies, such as determining treatment emergent adverse events, unless it is desired to only analyze scheduled treatments.
  - In Study 13370, 52% of subjects were missing baseline test results in the PK Concentrations (PC) domain. Many of these subjects were missing PK data all together.

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

- The JumpStart team further evaluated some common issues noted in production applications to CDER. These issues include, but are not limited to, whether the applicant included key variables in the supplemental domains, whether the DS (disposition) domain contain the EPOCH variable, and whether the AE (adverse events) domain include a treatment emergent flag. The team noted that study EFC11072 Part B was missing treatment emergent information 5 records. The team noted that this may end up being an issue when comparing methodology if there was a mismatch in results.
- The JumpStart team also noted some potential duplicate results in studies EFC11072 Part B, EFC10832, and SFY13370. Some of the duplicated domains include Laboratory Results (LB), Medical History (MH), and Questionnaire. The team suggested that some of these “duplicates” may actually represent re-test. In other instances, though, if there were extra copies of certain records, this could affect analyses where records/events (instead of subjects) were counted.
- The JumpStart team provided an Adverse Event Coding Report to assist with examining MedDRA coding quality.
- In regards to term finding, the team also noted that some disposition records in studies EFC11072 Part B and EFC10832 were coded to “Other Reasons” rather than a more appropriate/specific dictionary term. This could affect the analysis of the disposition domain, and additional information in the Reported Term for the Disposition Event (DSTERM) may be needed for analysis instead.
- Sanofi utilized standard units. Less than 0.1% of tests had inconsistent standard units (all from unscheduled visits). These results might need to be standardized in order to be appropriately summarized.
- In regards to the safety population, the JumpStart team noted few inconsistencies between SDTM data and the study report. Some subjects received a different treatment from their planned arm in studies EFC11072 Part B (8 subjects) and EFC10832 (1 subject).
- In reviewing race and ethnicity, the JumpStart team noted that there were subjects in all the analyzed studies who had their race coded as “other.” This included 102 subjects in EFC11072 Part B and 251 subjects in EFC10832. The term “other” does not provide information for proper analysis. However, in SUPPDM for Races, Sanofi did provide additional information for Race values of “other.”

In conclusion, the OCS JumpStart service provided a thorough review of data fitness, and overall there are no major issues. The issues above are minor and should not affect the analysis and review of safety data.

*Reviewer Comment: Overall, Sanofi provided an abundance of safety data that was well-organized. Sanofi's ISS Appendix was particularly helpful, as it included many extra analyses performed by Sanofi, some requested by the Agency. Much of the ISS Appendix (pre-rescue period, sensitivity analysis, model-based analysis) form a large part of this review. Sanofi's*

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

*submission was generally complete for my review. A few information requests (IRs) were sent to Sanofi to clarify the location of certain patient narratives or to get further detail on some Sanofi's presentation of data, and the applicant was able to respond to all of these IRs with only a few corrections to the originally submitted data.*

### 8.3.2. Categorization of Adverse Events

The safety populations for the pooled safety analyses included all randomized subjects who received at least 1 dose (or even a partial dose) of study treatment and were analyzed according to the treatment actually received. For patients who may have inadvertently received incorrect treatment during the study, the actual treatment was defined as the one which the patient received for the longest duration. The exposure for each treatment was defined as the last dose date minus the first dose date plus 14 days for q2w regimens and plus 7 days for qw regimens, regardless of temporary dosing interruptions and/or dosing variations.

Adverse events were coded and classified according to the primary System Organ Class (SOC), High Level Grouped Term (HLGT), High Level Term (HLT), and Preferred Term (PT). Adverse events in the integrated safety database were coded using the Medical Dictionary for Regulatory Activities (MedDRA Version 17.1).

*Reviewer Comment: The applicant's coding of adverse events into MedDRA preferred terms seems reasonable and appropriate. Data from multiple studies are pooled but appear to all use the same version of MedDRA (version 17.1).*

Treatment-emergent adverse events (TEAEs) were defined as adverse events that developed or worsened during the TEAE period. For patients who completed or were permanently discontinued from a study, the post-treatment period was defined as any time after the TEAE period. Table 54 defines the TEAE period for the 3 safety populations. In general, the applicant defined the TEAE period as the time from the first dose to the last dose of double-blind IMP + 60 days. The applicant utilized 60 days in order to capture events observed within approximately 5 half-lives of sarilumab; the protocol-specified follow-up period in all studies was  $56 \pm 3$  days. It should be noted, however, that this definition was used in the ISS and all individual studies except for EFC11072 Part B. In EFC11072 Part B, the TEAE period included all events that occurred after the first dose of IMP, even if the events were reported several months after the end of study treatment. Therefore, in some analyses in the ISS, the number of TEAEs may differ from what was presented in the CSR for EFC11072 Part B.

**Table 54. Definition of TEAE Period for Each Safety Population**

Population	Treatment Groups	Definition of the TEAE Period
<b>Pool 1</b> (Placebo-controlled Population)	<b>150mg q2w + DMARD</b>  <b>200mg q2w + DMARD</b>	Patients who completed the study and did not enroll into LTS11210 or who discontinued <ul style="list-style-type: none"> <li>Time from the first dose of double-blind IMP to the last dose of double-blind IMP + 60 days, last contact date<sup>c</sup>, or the date of death, whichever came first</li> </ul>
	<b>Placebo + DMARD</b>	Patients who were rescued or enrolled into LTS11210 <ul style="list-style-type: none"> <li>Time from the first dose double-blind IMP to the date of first dose of open-label IMP</li> </ul>
<b>Pool 2</b> (Long-term Safety Population)	<b>150mg q2w initial dose + DMARD</b> (up until discontinuation or dose modification) <sup>a</sup>	Patients who discontinued or completed the study without dose modification <ul style="list-style-type: none"> <li>Time from first dose of 150 (or 200)mg q2w to the last dose of 150 (or 200)mg q2w + 60 days, last contact date<sup>c</sup>, the date of death, or the cut-off date, whichever came first</li> </ul>
	<b>200mg q2w initial dose + DMARD</b> (up until discontinuation or dose modification) <sup>a</sup>	Patient with dose modification <ul style="list-style-type: none"> <li>Time from first dose of 150 (or 200) mg q2w to the date of dose modification</li> </ul>
	<b>Any sarilumab dose + DMARD<sup>b</sup></b>	Time from first dose of sarilumab to the last dose of sarilumab + 60 days, last contact date, the date of death, or the cut-off date, whichever came first
<b>Pool 3</b> (Sarilumab monotherapy)	<b>150mg q2w initial dose</b> (up until discontinuation or dose modification)	Patients who discontinued or completed the study without dose modification <ul style="list-style-type: none"> <li>Time from the first dose of 150 (or 200) mg q2w to the last dose of 150 (or 200) mg q2w + 60 days or last contact date<sup>c</sup> or the death date or the cut-off date, whichever came first</li> </ul>
	<b>200mg q2w initial dose</b> (up until discontinuation or dose modification)	Patients with dose modification <ul style="list-style-type: none"> <li>Time from the first dose of 150 (or 200) mg q2w to the date of dose modification</li> </ul>
	<b>Any sarilumab dose</b>	Time from first dose of sarilumab to the last dose of sarilumab + 60 days or last contact date <sup>c</sup> or the death date or the cut-off date, whichever came first

a Only includes patients whose first sarilumab dose is either 150 or 200mg q2w

b Including 150mg q2w, 200mg q2w, and the non-selected dose regimens: 100mg q2w, 100mg q2, and 150mg qw

c Last contact date = maximum {last AE onset date, last visit date, last date on which subject vital status was obtained}

Source: Integrated Summary of Safety, Table 4, dated October 6, 2015; page 37.

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

*Reviewer Comment: Sanofi's definition of the TEAE period is acceptable and reasonable, as it is based on the half-life of sarilumab. The definition of TEAE period in study EFC11072 Part B is acknowledged. However, given that EFC11072 Part B is the outlier, I will utilize the definition that is use in most of the clinical development program, as well as the ISS.*

To account for potentially differential exposure time between treatment groups, 2 types of exposure-adjusted rates were provided for selected safety parameters, namely, number of treatment-emergent events per 100 patient-years and number of patients with at least one treatment-emergent event per 100 patient-years.

- The number of treatment-emergent events per 100 patient-years (i.e., the exposure-adjusted event rate) is calculated as the number of these events occurring in the population divided by the sum of the exposure over all patients (i.e., total exposure) in the TEAE period
- The number of patients with at least one treatment-emergent event per 100 patient-years (i.e., the exposure-adjusted incidence rate) is calculated as the number of patients having a specific event in question divided by the total person-years among patients at risk of an initial occurrence of the event in question. For each of the events of interest, the exposure time for patients who have experienced the specific adverse experience is defined as the time to first adverse experience in question, whereas the exposure time for those who have not had this adverse experience is the total duration of exposure in the TEAE period.

Definitions of AEs and SAEs are provided in Section 6 under the individual protocols. Sanofi utilized standardized definitions and, thus, are appropriate.

### **Adverse Events of Special Interest (AESIs)**

As already described, the AESIs were selected based on the biologic activity of IL-6 and the associated effects of IL-6 inhibition, as well as the safety profile of other biologics used in the treatment of RA. AESIs were identified using specific search criteria (e.g., Standardized MedRA Query [SMQ], SOC) that are based on a group of MedDRA PTs. Sanofi believed that this would allow for a more comprehensive assessment. However, Sanofi also recognized that the selected search criteria may include MedDRA PTs that are not truly reflective of the clinical event of interest. For example, the SMQ GI perforation also includes events of fistula and rectal abscess. Therefore, for some AESIs (e.g., GI perforation and demyelinating disorders), the unblinded cases were reviewed by Sanofi who, using clinical judgment, determined the true incidence of a clinically relevant event. Table 55 shows the MedDRA search criteria used to define the AESIs.

**Table 55. AESIs and MedDRA Search Criteria for Adverse Events**

AESI Flag	Search <sup>a</sup> Criteria
Leukopenia	SMQ: Haematopoietic leukopenia
Thrombocytopenia	SMQ: Haematopoietic thrombocytopenia
Infections (Common, Serious, Opportunistic infections, Tuberculosis)	Primary SOC: Infections and infestations Opportunistic infection: as defined in protocols Tuberculosis: HLT Tuberculosis infections
Hepatic disorders	SMQ: Drug-related hepatic disorders – comprehensive search
Diverticulitis/potential GI perforations	SMQ: Gastrointestinal perforation and HLT: Diverticulum inflammations <sup>b</sup>
GI ulcerations	SMQ: Gastrointestinal ulceration
Elevation in lipids	SMQ: Dyslipidemias
Anaphylaxis	SMQ: Anaphylactic reaction
Hypersensitivity	SMQ: Hypersensitivity
Injection site reactions	HLT: Injection site reactions
Malignancy	SMQ: Malignant or unspecified tumours Excluding non-melanoma skin cancers: SMQ Malignant or unspecified tumours excluding HLT of Skin neoplasms malignant and unspecified (excl melanoma)
Lupus-like syndrome	SMQ: Systemic lupus erythematosus
Demyelinating disorders	SMQ: Demyelination <sup>b</sup>

a All SMQs are narrow search

b Cases were medically reviewed to identify cases of GI perforation and demyelinating disorder

Source: Integrated Summary of Safety, Table 5, dated October 6, 2015; page 39.

Sanofi highlights a few things from Table 55. First, some of the AESIs and associated search criteria were broader than the associated effects of IL-6 inhibition. For example, to ensure that all possible events of neutropenia have been identified and reviewed, Sanofi utilized the broader term of “leukopenia” (which includes neutropenia) rather than just “neutropenia.” Additionally, while elevations of transaminases are the concern with IL-6 inhibitors, the clinical concern is the potential for clinically significant hepatic events. Sanofi defined the AESI as hepatic disorders and not elevation in transaminases.

Table 55 also does not include 2 AESIs, Major Adverse Cardiovascular Events (MACE) and immunogenicity, which were instead defined as the following:

- A Cardiovascular Adjudication Committee (CAC) defined MACE by adjudicating all deaths and potential cardiovascular (CV) events in a blinded manner. These events were either identified by the investigator or identified by pre-specified criteria described in the CAC charter. There were 2 composite MACE endpoints
  - MACE (primary): CV death, myocardial infarction (MI), stroke, hospitalization for unstable angina (UA), or hospitalization for transient ischemic attack (TIA)
  - MACE (narrow): CV death, MI, or stroke
- Immunogenicity was assessed using assays to detect the presence of antidrug

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

antibodies (ADA). The determination of the cut-off for the ADA assay in study EFC11072 Part A was different from what was used in the Phase 3 studies; therefore, the ADA results from EFC11072 Part A are not included in the integrated analysis of immunogenicity. Definitions of ADA positivity are defined here but will also be reviewed in Section 8.4.10 which presents the immunogenicity data.

- An ADA positive patient was defined as a patient with at least 1 “treatment-emergent” or “treatment-boosted” ADA positive sample during the TEAE period.
  - A treatment-emergent ADA positive patient was defined as a patient with non-positive assay (meaning negative or missing) response at baseline but with a positive assay response during the TEAE period. A treatment-emergent response could be further classified as persistent or transient.
    - Persistent ADA response was one that was detected at 2 or more consecutive sampling time points during the TEAE period where the first and last ADA positive samples are separated by a period of at least 16 weeks or if the last measured sample is positive.
    - Transient ADA response was a response that is not considered to be persistent.
  - A treatment-boosted ADA positive patient was defined as a patient with a positive ADA assay response at baseline and with at least a 4-fold increase in titer during the TEAE period.
- The ADA positive patient was considered to be positive for neutralizing antibodies (NAb) if the patient had at least 1 sample that was both positive in the ADA assay as defined above and also positive in the neutralizing antibody assay during the TEAE period.
- An ADA negative patient was defined as a patient without a treatment-emergent or treatment-boosted ADA positive sample during the TEAE period.

In the discussion for immunogenicity, there was a focus on the effect of ADA on safety and efficacy.

- The assessment on ADA and safety focused on the following events:
  - Hypersensitivity (MedDRA SMQ: Hypersensitivity [Narrow])
  - Anaphylaxis (MedDRA SMQ: Anaphylaxis [Narrow])
- The assessment on ADA and efficacy was evaluated with the following:
  - Lack of efficacy was defined as treatment discontinuation due to lack of efficacy. In these analyses, rescue to sarilumab therapy was not to be considered treatment discontinuation (as it was in the protocol for trial EFC10832).
  - Loss of efficacy was defined as treatment discontinuation due to lack of efficacy after achieving ACR50 or EULAR Good Response.

*Reviewer Comment: Sanofi's definitions and assessments of the AEs are appropriate.*

### Additional Analyses

In Section 8.1, a brief presentation of the additional analyses (e.g., sensitivity analyses and model-based analyses) is introduced. As many of these analyses will be reviewed as part of the safety assessment of sarilumab, the method of these analyses will be discussed in more detail here.

Table 56 presents the different safety analyses that were performed in addition to the main analyses described above. For each time period and study/pool, the following rates are calculated.

- Incidence and exposure-adjusted incidence rates (i.e., number of patients with at least 1 event per 100 patient-years)
- Estimated incidence rate differences and 95% confidence intervals (CIs) for all pair-wise between-group differences. The estimated differences and 95% CIs of the differences were derived using Miettinen & Nurminen method stratified by the study, using Cochran-Mantel-Haenszel weight. The rate difference was calculated for each dose of sarilumab compared to placebo as well as the difference between the 2 doses of sarilumab.

**Table 56. Additional Safety Analyses of Placebo-Controlled Studies**

Endpoints	EFC11072 (Part B, Cohort 2)	EFC10832	Pool 1 and 1a
<b>Common AEs (≥ 2% in at least 1 treatment group)</b>	<ul style="list-style-type: none"> <li>• 0-12 weeks</li> <li>• 0-16 weeks</li> </ul>	<ul style="list-style-type: none"> <li>• 0-12 weeks</li> </ul>	<ul style="list-style-type: none"> <li>• 0-12 weeks</li> <li>• 0-24 weeks</li> <li>• 0-52 weeks (entire TEAE period)</li> <li>• Pre-rescue period</li> </ul>
<b>Targeted Events (SAEs, AEsIs, discontinuations due to AEs, and deaths)</b>	<ul style="list-style-type: none"> <li>• 0-12 weeks</li> <li>• 0-16 weeks</li> <li>• 0-24 weeks</li> <li>• 0-52 weeks (entire TEAE period)</li> </ul>	<ul style="list-style-type: none"> <li>• 0-12 weeks</li> <li>• 0-24 weeks (entire TEAE period)</li> </ul>	<ul style="list-style-type: none"> <li>• 0-12 weeks</li> <li>• 0-24 weeks</li> <li>• 0-52 weeks (entire TEAE period)</li> <li>• Pre-rescue period</li> </ul>

Pool 1 = EFC11072 Part A (selected doses), Part B Cohort 1 (selected doses), Part B Cohort 2 and EFC10832

Pool 1a = EFC11072 Part B Cohort 2 and EFC10832

Pre-rescue period for Pool 1 = 0-12 weeks from EFC10832 and EFC11072 Part A and 0-16 weeks from EFC11072 Part B

Pre-rescue period for Pool 1a = 0-12 weeks from EFC10832 and 0-16 weeks from EFC11072 Part B

Source: Integrated Summary of Safety, Table 6, dated October 6, 2015; page 42.

### Sensitivity Analysis

For Pool 1a, a sensitivity analyses was also performed. In addition to events which occurred during the placebo-controlled period, the sensitivity analyses also accounted for the events that occurred during the sarilumab 200mg q2w rescue period. The sensitivity analyses were

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

performed for the following time periods: 0-12 weeks, 0-24 weeks, and 0-52 weeks.

### Model-Based Analysis

Model-based analyses were performed on selected endpoints. All of the safety data on either placebo or sarilumab from the integrated studies were included in the model (i.e., placebo exposure from Pool 1 and sarilumab + DMARD exposure from Pool 2). A generalized estimating equation (GEE) model was used for the analyses of the incidence or the number of events. Given the non-randomized nature of comparisons based on such analyses, the treatment exposure (i.e., time to first event), within subject correlation, differences between studies, and important baseline factors were adjusted in the GEE model. The following baseline factors were considered, and a forward selection procedure was used to decide which baseline factors were included in the final model (using criterion of p-value <0.1).

- Baseline factors (for all events)
  - Age (<65 vs. ≥65), gender (male vs. female), weight (<60 kg, 60-100 kg, ≥100 kg), RA – duration of disease, RA – functional class, geographic region, MTX vs. non-MTX DMARD, no baseline steroids vs. baseline steroids, and prior biologic use vs. no prior biologic use
- Additional baseline factors based on event
  - Serious infections: medical history of diabetes
  - Grade 3-4 neutropenia: baseline ANC
  - ALT >3x ULN: Baseline ALT
  - MACE (primary) and MACE (narrow): CV history

*Reviewer Comment: As noted in Section 8.1, this review will focus on TEAEs for Pool 1a in the pre-rescue period. This pool represents the one least affected by the various dosing changes in the pivotal studies. I will review the consistency of the data in this population with that of Pool 1 for the entire TEAE period (0-52 weeks). Frequently, in this review the entire TEAE period is referred to as the entire “double-blind period.” In the Pool 2 analyses (long-term safety data), the “entire TEAE period” is used. For some AESIs, I will present the sensitivity analysis performed on Pool 1a, focusing on 0-52 weeks, as well as the model-based analyses.*

*Additionally, given the complexity of the study design which led to dosing changes, we asked for a more granular analysis of the long-term safety population for a few AESIs, namely, MACE, serious infections, and malignancy. Specifically, we asked Sanofi to re-categorize subjects from the phase 3 clinical trials and the open-label extension into the treatment the subjects were actually receiving at the time of the event. Therefore, the treatment options for the long-term safety population were broken down into the following:*

- *(during the double-blind period) PBO, sarilumab 150mg q2w, sarilumab 200mg q2w*

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

- *(rescue or open-label extension) PBO → sarilumab 200mg q2w, sarilumab 150mg q2w → sarilumab 200mg q2w, sarilumab 200mg q2w → sarilumab 200mg q2w*
- *(dose modification after rescue or open-label extension) PBO → sarilumab 200mg q2w → sarilumab 150mg q2w; sarilumab 150mg q2w → sarilumab 200mg q2w → sarilumab 150mg q2w; sarilumab 200mg q2w → sarilumab 200mg q2w → sarilumab 150mg q2w*

In summary, Sanofi's approach to safety analyses is reasonable and appropriate. Given the adequate data integrity and quality and my agreement with Sanofi's approach to safety analyses, much of this review will utilize the safety data directly provided by Sanofi.

### 8.3.3. Routine Clinical Tests

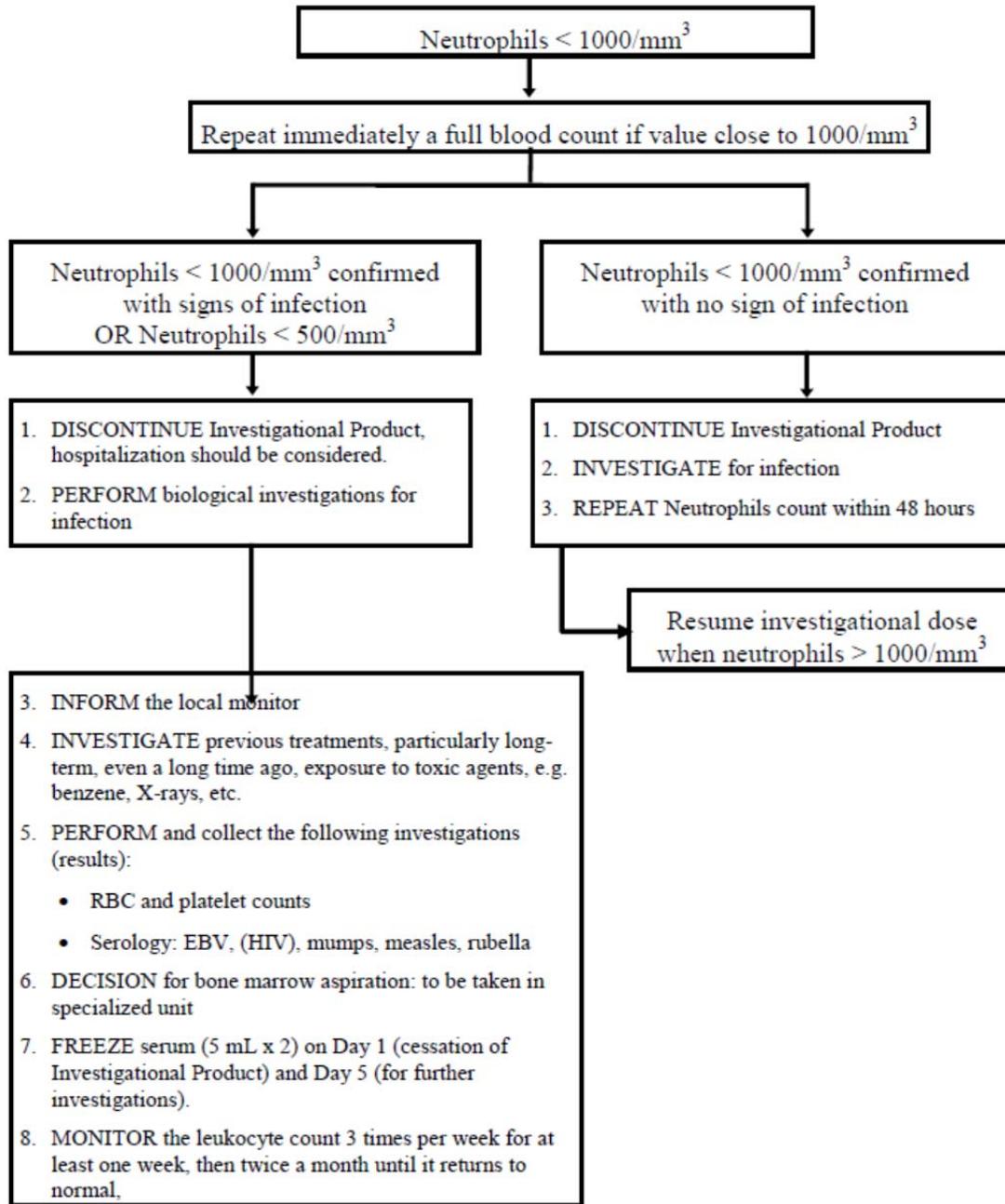
Appendix Section 13.3 displays the Schedule of Assessments for all pivotal trials (EFC11072 Part B and EFC10832), as well as the other major trials that make up the RA clinical development program. These tables specify which laboratory tests and study procedures were performed, as well as the timing of these tests. Further descriptions of various laboratory assessments can be found in Section 6. Under each trial of the clinical development program, routine laboratory testing is part of the safety assessment and encompass some of the reasons for which subjects were discontinued from the study.

The number of patients with at least one potentially clinically significant abnormality (PCSA) at any time during the overall TEAE period is summarized by biological function (hematology and differential, blood chemistry, and liver function) and treatment group. Data are summarized for all patients regardless of the baseline values and by categories according to the baseline status: normal/missing or abnormal. In addition, descriptive statistics over time are provided for the clinical laboratory parameters.

The following figures 16-18 represent how Sanofi handled the specific lab abnormalities of neutropenia, elevated ALT, and acute kidney injury.

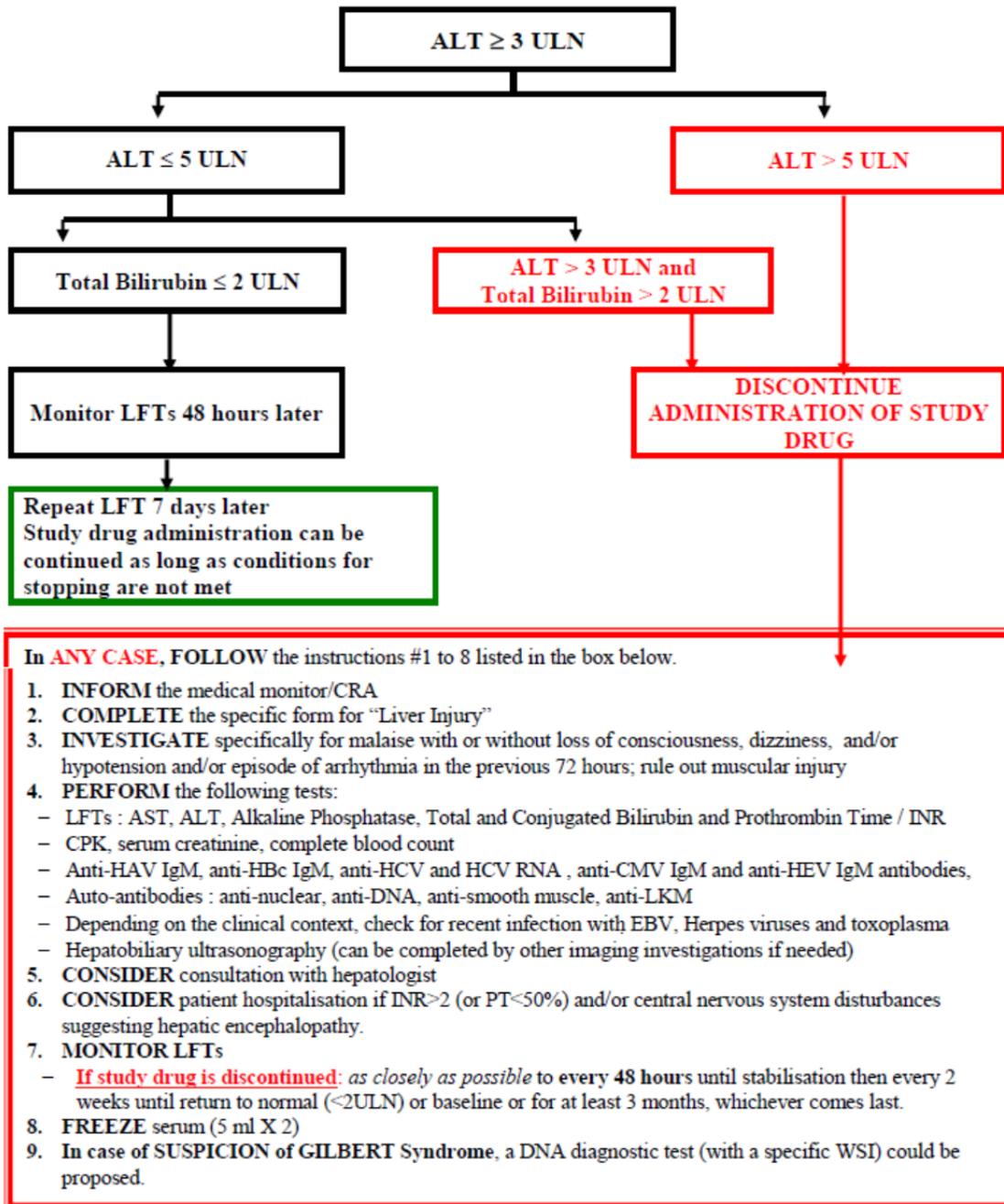
APPEARS THIS WAY ON ORIGINAL

**Figure 30. Sanofi-Aventis General Guidance for Follow-up of Neutropenia**  
**NEUTROPENIA**



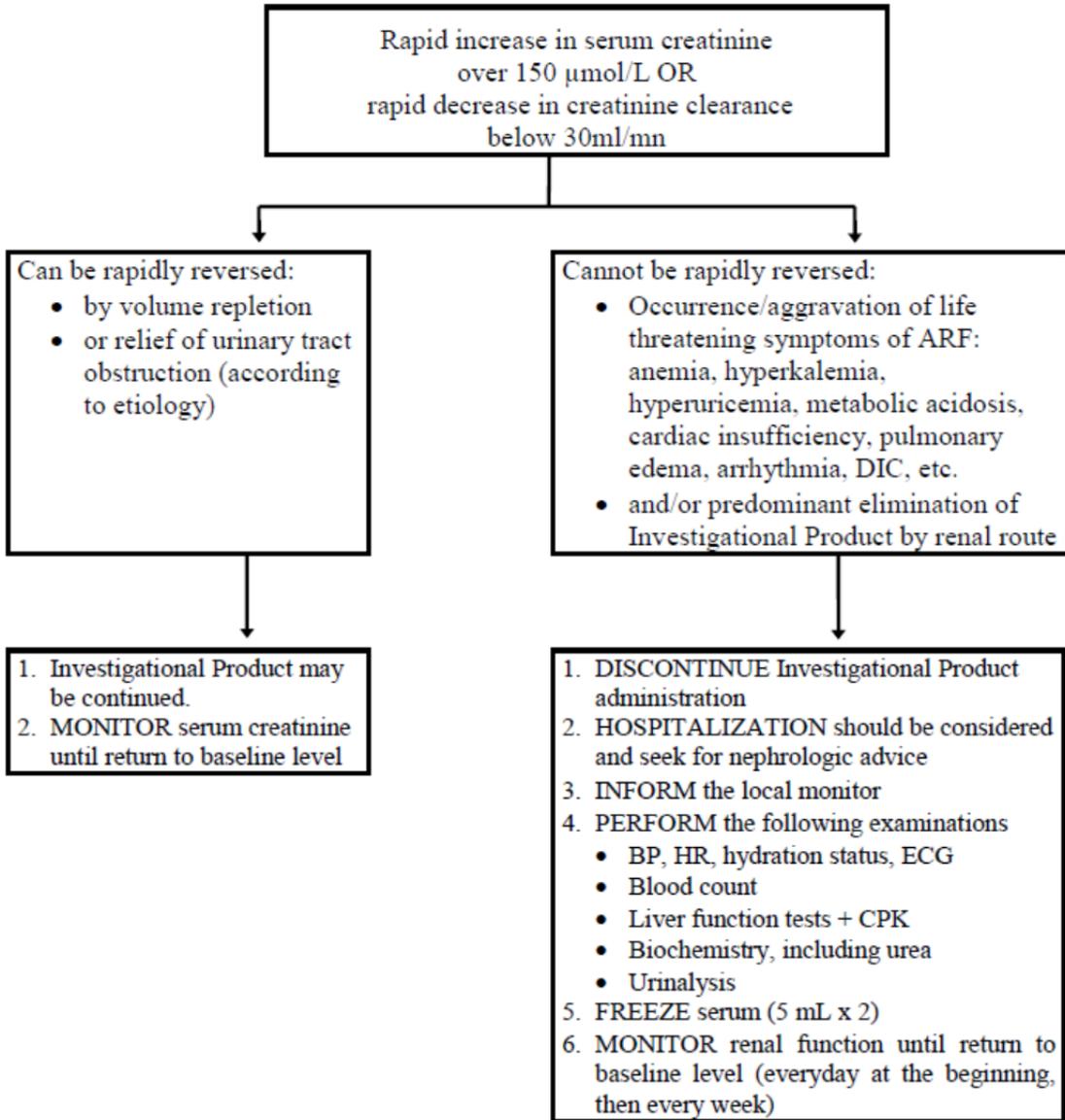
Source: EFC11072 Protocol, Appendix L, dated October 19, 2009; page 145.

Figure 31. Sanofi-Aventis General Guidance for Follow-up of an Increase in ALT



Source: EFC11072 Protocol, Appendix L, dated October 19, 2009; page 146.

**Figure 32. Sanofi-Aventis General Guidance for Follow-up on Acute Renal Failure (ARF)**



Source: EFC11072 Protocol, Appendix L, dated October 19, 2009; page 147.

*Reviewer Comment: The safety assessment methods and time points that were described in the protocol are reasonable and adequate for the RA patient population. These assessments were based on what is known about IL-6 inhibitors as well as the PK of sarilumab itself.*

## 8.4. Safety Results

### 8.4.1. Deaths

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

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. 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. Sanofi notes that the mortality rate in patients with rheumatoid arthritis is 2.7 deaths per 100 patient-years. In general, the standardized mortality ration is 2:1 to 2.5:1 compared with people of the same sex and age without RA (West and O'Dell 116). 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). Therefore, 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) (West and O'Dell 116-7). 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. There were not any unusual infections or malignancies leading to death. There were 3 subjects with ILD (2 on sarilumab 200mg q2w and 1 on sarilumab 100mg qw). 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.

APPEARS THIS WAY ON ORIGINAL

**Table 57. Summary of All Deaths**

	Deaths (Total)	Reasons for Death
<b>Placebo</b>	3	<ul style="list-style-type: none"> <li>• 1 infection (appendicitis)</li> <li>• 2 others (MVA, suicide)</li> </ul>
<b>Tocilizumab</b>	1	<ul style="list-style-type: none"> <li>• 1 infection (infectious gastroenterocolitis)</li> </ul>
<b>Sarilumab</b>		
Sarilumab 150mg q2w	4	<ul style="list-style-type: none"> <li>• 3 infections               <ul style="list-style-type: none"> <li>○ 1 HAP after cholelithiasis s/p ERCP (c/b post-ERCP pancreatitis)</li> <li>○ 1 HAP after large bleeding ulcer s/p surgery</li> <li>○ 1 pneumonia/<i>C.Diff</i> with heart failure</li> </ul> </li> <li>• 1 CV event (sudden death in the setting of neutropenia/thrombocytopenia)</li> </ul>
Sarilumab 200mg q2w	17	<ul style="list-style-type: none"> <li>• 5 infections               <ul style="list-style-type: none"> <li>○ 1 pneumonia</li> <li>○ 1 DIC/sepsis after cellulitis → compartment syndrome requiring fasciotomy</li> <li>○ 1 pneumonia (possible DAH)</li> <li>○ 1 septic arthritis, pneumonia</li> <li>○ 1 psoas abscess</li> </ul> </li> <li>• 4 CV events               <ul style="list-style-type: none"> <li>○ 1 CVA/cardiac arrest</li> <li>○ 1 sudden death after chole</li> <li>○ <b>2 CV event in setting of infection</b> <ul style="list-style-type: none"> <li>▪ 1 heart failure in setting of right axillary abscess</li> <li>▪ 1 cardiac arrest in setting of pneumonia, neutropenia, <i>C.Diff</i> with recent acute MI and CVA</li> </ul> </li> </ul> </li> <li>• 5 malignancy               <ul style="list-style-type: none"> <li>○ 1 metastatic lung CA (death Nov 2013) in setting of necrotizing fasciitis (Feb 2013) and post-op (ORIF for hip fx) wound infection (Aug 2013)</li> <li>○ 1 lung CA</li> <li>○ 1 ductal adenoCA of pancreas</li> <li>○ 1 squamous cell skin CA and bronchogenic CA</li> <li>○ 1 metastatic cervical CA</li> </ul> </li> <li>• 3 others               <ul style="list-style-type: none"> <li>○ 1 acute decompensation in setting of acute pneumonitis/ILD</li> <li>○ 1 cardiopulmonary failure in setting of acute pneumonitis/ILD</li> <li>○ 1 alcohol/amitriptyline toxicity</li> </ul> </li> </ul>
Sarilumab 150mg qw	2	<ul style="list-style-type: none"> <li>• 1 infection (RLE erysipelas → sepsis)</li> </ul>

Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

		<ul style="list-style-type: none"> <li>1 CV event (sudden death after severe back pain – possible aortic dissection)</li> </ul>
Sarilumab 100mg q2w	1	<ul style="list-style-type: none"> <li>1 ARDS, CVA in the setting of ILD</li> </ul>

MVA = motor vehicle accident; HAP = hospital acquired pneumonia; ERCP = endoscopic retrograde cholangiopancreatography; c/b = complicated by; s/p = status post; DIC = disseminated intravascular coagulation; DAH = diffuse alveolar hemorrhage; CVA = cerebrovascular accident; CA = cancer; adenoCA = adenocarcinoma; ORIF = open reduction internal fixation; ILD = interstitial lung disease; ARDS = acute respiratory distress syndrome; RLE = right lower extremity  
 Source: ISS, Tables 38-39 and Linked Narratives, dated October 6, 2016; pages 94-96.  
 LTS11210 Narratives for FDA Response (March 21, 2016)

Notably, of the 24 deaths that occurred on sarilumab, the vast majority occurred in subjects on sarilumab 200mg (17 of the 24 deaths, 70.8%). This discrepancy is better elucidated by examining Table 58, which presents the deaths by the study in which the subject was enrolled at the time of death. Thirteen of the 17 subjects who died while taking sarilumab 200mg q2w were in the open-label extension trial, during which only the highest dose of sarilumab was offered. Therefore, the increase in deaths on sarilumab 200mg q2w more likely reflects the increased exposure in this treatment arm. It does not seem that the number of deaths is related to the higher dose. During the double-blind studies (EFC11072 Part B and EFC10832), the number of deaths were actually quite even across all treatment arms (placebo, 150mg q2w, and 200mg q2w).

**Table 58. Summary of Deaths by Study and Treatment at time of Death**

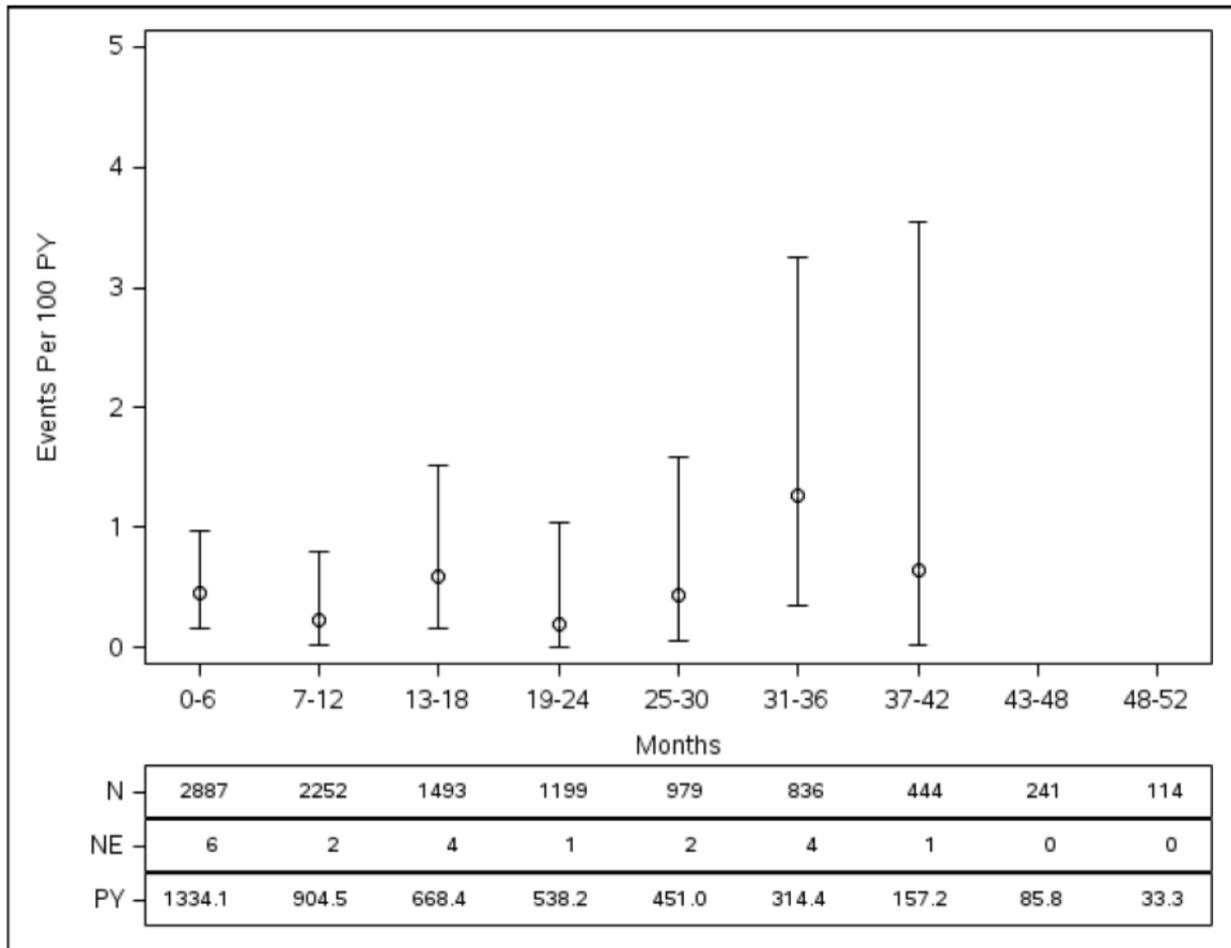
Study	Treatment	Deaths
EFC11072A	Sarilumab 100mg q2w	1
EFC11072B	Placebo	2
	Sarilumab 150mg q2w	2
	Sarilumab 200mg q2w	3
EFC10832	Placebo	1
SFY13370	Tocilizumab	1
	Sarilumab 200mg q2w	1
LTS11210	Sarilumab 150mg qw	2
	Sarilumab 150mg q2w	1
	Sarilumab 200mg q2w	13 1 (1 dose in OL study, 150mg q2w during study EFC13752, sarilumab monotherapy)

Source: ISS, Tables 38-39 and Linked Narratives, dated October 6, 2016; pages 94-96.  
 LTS11210 Narratives for FDA Response (March 21, 2016)

Furthermore, Figure 33 shows the exposure-adjusted rate of death by 6-month intervals for the

entire long-term safety population. The exposure-adjusted rate of death did not increase over time. It should be noted that, with time, though, the confidence interval also increases likely because of the decreasing number of subjects.

**Figure 33. Exposure-adjusted Rate of Death by 6-month Intervals during the Entire TEAE and Post-Study Periods (Pool 2)**



N = sample size; NE = number of events in a 6-month period; PY = patient-years  
 95% confidence interval was calculated using the exact method  
 Source: ISS, Figure 6, dated October 6, 2015; page 97.

In conclusion, the rate and causes of deaths in the sarilumab RA program are consistent with those of the general RA population. There does not appear to be an increased risk of death in the higher dose of sarilumab or with longer duration of therapy.

#### 8.4.2. Serious Adverse Events

Table 59 lists the SAEs during the pre-rescue period for Pool 1a by raw incidence rate and

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

exposure adjusted incidence rate. A rate difference is also calculated between placebo and between doses. Overall, there were more SAEs in the sarilumab treatment arms compared to placebo (2.1% in placebo vs. 3.3% in sarilumab 150mg q2w and 5.8% in sarilumab 200mg q2w). Additionally, there were more event at the higher dose of sarilumab compared to the lower dose with a rate difference of 2.7% (95% CI: 0.2, 5.1).

The most common SAE (by SOC) for all treatment arms was Infections and infestations. In this SOC, both sarilumab treatment arms were numerically higher than that of placebo (0.7% in placebo, 1.0% in sarilumab 150mg q2w, 1.0% in sarilumab 200mg q2w). There was not a difference, however, between doses. Within Infections and infestations, the most common PTs noted in the sarilumab arms were erysipelas and pneumonia.

In the sarilumab treatment arms, the other most common SAEs (by SOC) were Blood and lymphatic system disorders and Respiratory, thoracic, and mediastinal disorders. It is the Blood and lymphatic system disorders that is the major reason for the difference in SAEs between the 150mg and 200mg treatment arms. Specifically, the difference can be attributed to the PT neutropenia although there were also more events of iron deficiency anemia and leukopenia in the 200mg arm. In the pre-rescue period, no placebo patients had an SAE within this SOC. However, there were 0.2% subjects in the sarilumab 150mg q2w arm with an SAE in this SOC and 1.2% in the sarilumab 200mg q2w arm. The rate difference between the doses was 1.0% (95% CI: 0.1, 2.0). Under Respiratory, thoracic, and mediastinal disorders, there were again no patients with events in the placebo arm during the pre-rescue period, but there were 3 patients each in the sarilumab arms (0.5%). The most common PT in this SOC was chronic obstructive pulmonary disease (COPD), and the other PTs were comprised of single events. Therefore, it is difficult to make a conclusion regarding this SOC.

APPEARS THIS WAY ON ORIGINAL

**Table 59. Number (%) of Patients with SAEs during the Pre-Rescue Period (Pool 1a)**

	Placebo + DMARD	Sarilumab 150mg q2w + DMARD	Sarilumab 200mg q2w + DMARD
<b>Any SAEs</b>			
Raw incidence rate n/N (%)	12/579 (2.1%)	19/579 (3.3%)	34/582 (5.8%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	12/155.6 (7.7)	19/151.4 (12.5)	34/151.0 (22.5)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		1.3% (-0.6, 3.2)	3.9% (1.6, 6.3)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			2.7% (0.2, 5.1)
<b>Infections and infestations - SOC</b>			
Raw incidence rate n/N (%)	4/579 (0.7%)	6/579 (1.0%)	6/582 (1.0%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	4/158.8 (2.5)	6/157.5 (3.8)	6/156.9 (3.8)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		0.3% (-0.7, 1.4)	0.4% (-0.7, 1.4)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			0.0% (-1.2, 1.2)
<b>Erysipelas</b>			
Raw incidence rate n/N (%)	0/579	0/579	2/582 (0.3%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	0/161.6 (0)	0/160.0 (0)	2/160.7 (1.2)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		0.0% (-0.0, 0.0)	0.3% (-0.1, 0.8)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			0.3% (-0.1, 0.8)
<b>Bronchitis</b>			
Raw incidence rate n/N (%)	1/579 (0.2%)	0/579	1/582 (0.2%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	1/160.9 (0.6)	0/160.0 (0)	1/160.8 (0.6)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		-0.2% (-0.5, 0.2)	0.0% (-0.5, 0.5)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			0.2% (-0.2, 0.5)
<b>Conjunctivitis</b>			
Raw incidence rate n/N (%)	0/579	0/579	1/582 (0.2%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	0/161.6 (0)	0/160.0 (0)	1/161.0 (0.6)
Rate difference		0.0% (-0.0, 0.0)	0.2% (-0.2, 0.5)

vs. PBO + DMARD (95% CI) <sup>b</sup>			
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			0.2% (-0.2, 0.5)
<b>Pneumonia</b>			
Raw incidence rate n/N (%)	0/579	1/579 (0.2%)	1/582 (0.2%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	0/161.3 (0)	1/160.0 (0.6)	1/160.8 (0.6)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		0.2% (-0.2, 0.5)	0.2% (-0.2, 0.5)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			0.0% (-0.5, 0.5)
<b>Sinusitis</b>			
Raw incidence rate n/N (%)	0/579	0/579	1/582 (0.2%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	0/161.6 (0)	0/159.7 (0)	1/160.9 (0.6)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		0.0% (-0.0, 0.0)	0.2% (-0.2, 0.5)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			0.2% (-0.2, 0.5)
<b>Cellulitis</b>			
Raw incidence rate n/N (%)	1/579 (0.2%)	1/579 (0.2%)	0/582
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	1/160.5 (0.6)	1/159.9 (0.6)	0/160.7 (0)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		0.0% (-0.5, 0.5)	-0.2% (-0.5, 0.2)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			-0.2% (-0.5, 0.2)
<b>Gastroenteritis</b>			
Raw incidence rate n/N (%)	0/579	1/579 (0.2%)	0/582
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	0/161.6 (0)	1/159.9 (0.6)	0/161.2 (0)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		0.2% (-0.2, 0.5)	0.0% (-0.0, 0.0)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			-0.2% (-0.5, 0.2)
<b>Localised infection</b>			
Raw incidence rate n/N (%)	0/579	1/579 (0.2%)	0/582
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	0/161.6 (0)	1/159.8 (0.6)	0/161.2 (0)

Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		0.2% (-0.2, 0.5)	0.0% (-0.0, 0.0)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			-0.2% (-0.5, 0.2)
<b>Osteomyelitis</b>			
Raw incidence rate n/N (%)	0/579	1/579 (0.2%)	0/582
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	0/161.6 (0)	1/159.9 (0.6)	0/160.9 (0)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		0.2% (-0.2, 0.5)	0.0% (-0.0, 0.0)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			-0.2 (-0.5, 0.2)
<b>Otitis media chronic</b>			
Raw incidence rate n/N (%)	1/579 (0.2%)	0/579	0/582
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	1/161.5 (0.6)	0/160.0 (0)	0/161.2 (0)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		-0.2% (-0.5, 0.2)	-0.2% (-0.5, 0.2)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			0.0% (-0.0, 0.0)
<b>Pyelonephritis</b>			
Raw incidence rate n/N (%)	0/579	1/579 (0.2%)	0/582
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	0/161.6 (0)	1/160.0 (0.6)	0/161.2 (0)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		0.2% (-0.2, 0.5)	0.0% (-0.0, 0.0)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			-0.2% (-0.5, 0.2)
<b>Subacute endocarditis</b>			
Raw incidence rate n/N (%)	1/579 (0.2%)	0/579	0/582
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	1/161.5 (0.6)	0/160.0 (0)	0/161.2 (0)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		-0.2% (-0.5, 0.2)	-0.2% (-0.5, 0.2)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			0.0% (-0.0, 0.0)
<b>Upper respiratory tract infection</b>			
Raw incidence rate n/N (%)	0/579	1/579 (0.2%)	0/582
Exposure adjusted incidence rate	0/161.6 (0)	1/159.9 (0.6)	0/161.2 (0)

n/PY (rate per 100 PYs) <sup>a</sup>			
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		0.2% (-0.2, 0.5)	0.0% (-0.0, 0.0)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			-0.2% (-0.5, 0.2)
<b>Neoplasms benign, malignant, and unspecified (incl cysts and polyps) - SOC</b>			
Raw incidence rate n/N (%)	2/579 (0.3%)	1/579 (0.2%)	0/582
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	2/160.7 (1.2)	1/159.1 (0.6)	0/160.6 (0)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		-0.2% (-0.8, 0.4)	-0.3% (-0.8, 0.1)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			-0.2% (-0.5, 0.2)
<b>Breast cancer metastatic</b>			
Raw incidence rate n/N (%)	0/579	1/579 (0.2%)	0/582
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	0/161.6 (0)	1/160.0 (0.6)	0/161.2 (0)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		0.2% (-0.2, 0.5)	0.0% (-0.0, 0.0)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			-0.2% (-0.5, 0.2)
<b>Meningioma</b>			
Raw incidence rate n/N (%)	1/579 (0.2%)	0/579	0/582
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	1/161.1 (0.6)	0/160.0 (0)	0/161.2 (0)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		-0.2% (-0.5, 0.2)	-0.2% (-0.5, 0.2)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			0.0% (-0.0, 0.0)
<b>Squamous cell carcinoma of skin</b>			
Raw incidence rate n/N (%)	1/579 (0.2%)	0/579	0/582
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	1/161.4 (0.6)	0/160.0 (0)	0/161.2 (0)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		-0.2% (-0.5, 0.2)	-0.2% (-0.5, 0.2)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			0.0% (-0.0, 0.0)
<b>Blood and lymphatic systemic disorders - SOC</b>			
Raw incidence rate n/N (%)	0/579	1/579 (0.2%)	7/582 (1.2%)

Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	0/161.4 (0.0)	1/158.9 (0.6)	7/160.3 (4.4)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		0.2% (-0.2, 0.5)	1.2% (0.3, 2.1)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			1.0% (0.2, 2.0)
<b>Neutropenia</b>			
Raw incidence rate n/N (%)	0/579	1/579 (0.2%)	4/582 (0.7%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	0/161.6 (0)	1/159.2 (0.6)	4/160.7 (2.5)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		0.2% (-0.2, 0.5)	0.7% (0.0, 1.4)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			0.5% (-0.2, 1.3)
<b>Iron deficiency anemia</b>			
Raw incidence rate n/N (%)	0/579	0/579	1/582 (0.2%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	0/161.6 (0)	0/160.0 (0)	1/161.1 (0.6)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		0.0% (-0.0, 0.0)	0.2% (-0.2, 0.5)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			0.2% (-0.2, 0.5)
<b>Leukopenia</b>			
Raw incidence rate n/N (%)	0/579	0/579	1/582 (0.2%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	0/161.6 (0)	0/160.0 (0)	1/161.0 (0.6)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		0.0% (-0.0, 0.0)	0.2% (-0.2, 0.5)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			0.2% (-0.2, 0.5)
<b>Thrombocytopenia</b>			
Raw incidence rate n/N (%)	0/579	1/579 (0.2%)	1/582 (0.2%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	0/161.6 (0)	1/160.0 (0.6)	1/161.1 (0.6)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		0.2% (-0.2, 0.5)	0.2% (-0.2, 0.5)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			0.0% (-0.5, 0.5)
<b>Psychiatric disorders - SOC</b>			

Raw incidence rate n/N (%)	0/579	1/579 (0.2%)	1/582 (0.2%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	0/161.3 (0)	1/160.0 (0.6)	1/160.9 (0.6)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		0.2% (-0.2, 0.5)	0.2% (-0.2, 0.5)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			0.0% (-0.5, 0.5)
<b>Depression</b>			
Raw incidence rate n/N (%)	0/579	1/579 (0.2%)	1/582 (0.2%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	0/161.6 (0)	1/160.0 (0.6)	1/160.9 (0.6)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		0.2% (-0.2, 0.5)	0.2% (-0.2, 0.5)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			0.0% (-0.5, 0.5)
<b>Psychotic disorder</b>			
Raw incidence rate n/N (%)	0/579	1/579 (0.2%)	0/582
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	0/161.6 (0)	1/160.0 (0.6)	0/161.2 (0)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		0.2% (-0.2, 0.5)	0.0% (-0.0, 0.0)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			-0.2% (-0.5, 0.2)
<b>Suicide attempt</b>			
Raw incidence rate n/N (%)	0/579	1/579 (0.2%)	0/582
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	0/161.6 (0)	1/160.0 (0.6)	0/160.9 (0)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		0.2% (-0.2, 0.5)	0.0% (-0.0, 0.0)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			-0.2% (-0.5, 0.2)
<b>Nervous system disorders - SOC</b>			
Raw incidence rate n/N (%)	2/579 (0.3%)	1/579 (0.2%)	1/582 (0.2%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	2/160.9 (1.2)	1/159.6 (0.6)	1/161.0 (0.6)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		-0.2% (-0.8, 0.4)	-0.2% (-0.8, 0.4)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			-0.0% (-0.5, 0.5)

<b>Cerebrovascular accident</b>			
Raw incidence rate n/N (%)	0/579	0/579	1/582 (0.2%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	0/161.6 (0)	0/160.0 (0)	1/161.2 (0.6)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		0.0% (-0.0, 0.0)	0.2% (-0.2, 0.5)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			0.2% (-0.2, 0.5)
<b>Syncope</b>			
Raw incidence rate n/N (%)	1/579 (0.2%)	1/579 (0.2%)	0/582
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	1/161.4 (0.6)	1/159.9 (0.6)	0/161.2 (0)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		0.0% (-0.5, 0.5)	-0.2% (-0.5, 0.2)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			-0.2% (-0.5, 0.2)
<b>Transient ischaemic attack</b>			
Raw incidence rate n/N (%)	1/579 (0.2%)	0/579	0/582
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	1/161.4 (0.6)	0/160.0 (0)	0/161.2 (0)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		-0.2% (-0.5, 0.2)	-0.2% (-0.5, 0.2)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			0.0% (-0.0, 0.0)
<b>Cardiac disorders - SOC</b>			
Raw incidence rate n/N (%)	1/579 (0.2%)	2/579 (0.3%)	2/582 (0.3%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	1/160.6 (0.6)	2/159.8 (1.3)	2/160.6 (1.2)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		0.2% (-0.4, 0.8)	0.2% (-0.4, 0.8)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			0.0% (-0.7, 0.7)
<b>Angina unstable</b>			
Raw incidence rate n/N (%)	0/579	0/579	1/582 (0.2%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	0/161.6 (0)	0/160.0 (0)	1/161.1 (0.6)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		0.0% (-0.0, 0.0)	0.2% (-0.2, 0.5)
Rate difference vs. sarilumab 150mg + DMARD			0.2% (-0.2, 0.5)

(95% CI) <sup>b</sup>			
<b>Cardiac failure</b>			
Raw incidence rate n/N (%)	0/579	0/579	1/582 (0.2%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	0/161.6 (0)	0/160.0 (0)	1/161.2 (0.6)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		0.0% (-0.0, 0.0)	0.2% (-0.2, 0.5)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			0.2% (-0.2, 0.5)
<b>Myocardial ischaemia</b>			
Raw incidence rate n/N (%)	1/579 (0.2%)	0/579	0/582
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	1/161.6 (0.6)	0/160.0 (0)	0/161.2 (0)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		-0.2% (-0.5, 0.2)	-0.2% (-0.5, 0.2)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			0.0% (-0.0, 0.0)
<b>Pericarditis</b>			
Raw incidence rate n/N (%)	0/579	1/579 (0.2%)	0/582
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	0/161.6 (0)	1/159.9 (0.6)	0/161.2 (0)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		0.2% (-0.2, 0.5)	0.0% (-0.0, 0.0)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			-0.2% (-0.5, 0.2)
<b>Right ventricular failure</b>			
Raw incidence rate n/N (%)	0/579	1/579 (0.2%)	0/582
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	0/161.6 (0)	1/159.9 (0.6)	0/161.2 (0)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		0.2% (-0.2, 0.5)	0.0% (-0.0, 0.0)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			-0.2% (-0.5, 0.2)
<b>Vascular disorders - SOC</b>			
Raw incidence rate n/N (%)	0/579	0/579	2/582 (0.3%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	0/161.3 (0)	0/159.1 (0)	2/160.8 (1.2)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		0.0% (-0.0, 0.0)	0.3% (-0.1, 0.8)
Rate difference			0.3% (-0.1, 0.8)

vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			
<b>Hypertensive crisis</b>			
Raw incidence rate n/N (%)	0/579	0/579	1/582 (0.2%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	0/161.6 (0)	0/160.0 (0)	1/161.0 (0.6)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		0.0% (-0.0, 0.0)	0.2% (-0.2, 0.5)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			0.2% (-0.2, 0.5)
<b>Venous thrombosis limb</b>			
Raw incidence rate n/N (%)	0/579	0/579	1/582 (0.2%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	0/161.6 (0)	0/160.0 (0)	1/161.0 (0.6)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		0.0% (-0.0, 0.0)	0.2% (-0.2, 0.5)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			0.2% (-0.2, 0.5)
<b>Respiratory, thoracic, and mediastinal disorders - SOC</b>			
Raw incidence rate n/N (%)	0/579	3/579 (0.5%)	3/582 (0.5%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	0/161.3 (0)	3/158.9 (1.9)	3/161.0 (1.9)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		0.5% (-0.1, 1.1)	0.5% (-0.1, 1.1)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			-0.0% (-0.8, 0.8)
<b>Chronic obstructive pulmonary disease</b>			
Raw incidence rate n/N (%)	0/579	1/579 (0.2%)	1/579 (0.2%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	0/161.6 (0)	1/159.6 (0.6)	1/161.1 (0.6)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		0.2% (-0.2, 0.5)	0.2% (-0.2, 0.5)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			-0.0% (-0.5, 0.5)
<b>Dyspnoea</b>			
Raw incidence rate n/N (%)	0/579	0/579	1/582 (0.2%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	0/161.6 (0)	0/160.0 (0)	1/161.2 (0.6)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		0.0% (-0.0, 0.0)	0.2% (-0.2, 0.5)

Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			0.2% (-0.2, 0.5)
<b>Pneumonitis</b>			
Raw incidence rate n/N (%)	0/579	0/579	1/582 (0.2%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	0/161.6 (0)	0/160.0 (0)	1/161.1 (0.6)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		0.0% (-0.0, 0.0)	0.2% (-0.2, 0.5)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			0.2% (-0.2, 0.5)
<b>Pulmonary embolism</b>			
Raw incidence rate n/N (%)	0/579	1/579 (0.2%)	0/582
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	0/161.6 (0)	1/159.9 (0.6)	0/161.2 (0)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		0.2% (-0.2, 0.5)	0.0% (-0.0, 0.0)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			-0.2% (-0.5, 0.2)
<b>Pulmonary oedema</b>			
Raw incidence rate n/N (%)	0/579	1/579 (0.2%)	0/582
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	0/161.6 (0)	1/160.0 (0.6)	0/161.2 (0)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		0.2% (-0.2, 0.5)	0.0% (-0.0, 0.0)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			-0.2% (-0.5, 0.2)
<b>Gastrointestinal disorders - SOC</b>			
Raw incidence rate n/N (%)	2/579 (0.3%)	0/579	2/582 (0.3%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	2/161.5 (1.2)	0/158.9	2/160.8 (1.2)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		-0.3% (-0.8, 0.1)	0.0% (-0.7, 0.7)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			0.3% (-0.1, 0.8)
<b>Abdominal discomfort</b>			
Raw incidence rate n/N (%)	0/579	0/579	1/582 (0.2%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	0/161.6 (0)	0/160.0 (0)	1/161.1 (0.6)
Rate difference		0.0% (-0.0, 0.0)	0.2% (-0.2, 0.5)

Clinical Review  
 Reviewer: Suzette Peng, MD  
 NME/BLA 761037  
 Sarilumab/Kevzara

vs. PBO + DMARD (95% CI) <sup>b</sup>			
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			0.2% (-0.2, 0.5)
<b>Abdominal wall haematoma</b>			
Raw incidence rate n/N (%)	0/579	0/579	1/582 (0.2%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	0/161.6 (0)	0/160.0 (0)	1/161.1 (0.6)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		0.0% (-0.0, 0.0)	0.2% (-0.2, 0.5)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			0.2% (-0.2, 0.5)
<b>Constipation</b>			
Raw incidence rate n/N (%)	1/579 (0.2%)	0/579	0/582
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	1/161.5 (0.6)	0/160.0 (0)	0/161.2 (0)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		-0.2% (-0.5, 0.2)	-0.2% (-0.5, 0.2)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			0.0% (-0.0, 0.0)
<b>Duodenal ulcer</b>			
Raw incidence rate n/N (%)	1/579 (0.2%)	0/579	0/582
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	1/161.5 (0.6)	0/160.0 (0)	0/161.2 (0)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		-0.2% (-0.5, 0.2)	-0.2% (-0.5, 0.2)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			0.0% (-0.0, 0.0)
<b>Hepatobiliary disorders - SOC</b>			
Raw incidence rate n/N (%)	1/579 (0.2%)	2/579 (0.3%)	1/582 (0.2%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	1/161.2 (0.6)	2/159.5 (1.3)	1/160.9 (0.6)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		0.2% (-0.4, 0.8)	-0.0% (-0.5, 0.5)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			-0.2% (-0.8, 0.4)
<b>Cholecystitis chronic</b>			
Raw incidence rate n/N (%)	0/579	0/579	1/582 (0.2%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	0/161.6 (0)	0/160.0 (0)	1/161.2 (0.6)

Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		0.0% (-0.0, 0.0)	0.2% (-0.2, 0.5)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			0.2% (-0.2, 0.5)
<b>Cholelithiasis</b>			
Raw incidence rate n/N (%)	0/579	1/579 (0.2%)	0/582
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	0/161.6 (0)	1/159.9 (0.6)	0/161.2 (0)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		0.2% (-0.2, 0.5)	0.0% (-0.0, 0.0)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			-0.2% (-0.5, 0.2)
<b>Drug-induced liver injury</b>			
Raw incidence rate n/N (%)	0/579	1/579 (0.2%)	0/582
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	0/161.6 (0)	1/159.9 (0.6)	0/161.2 (0)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		0.2% (-0.2, 0.5)	0.0% (-0.0, 0.0)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			-0.2% (-0.5, 0.2)
<b>Mixed liver injury</b>			
Raw incidence rate n/N (%)	1/579 (0.2%)	0/579	0/582
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	1/161.5 (0.6)	0/160.0 (0)	0/161.2 (0)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		-0.2% (-0.5, 0.2)	-0.2% (-0.5, 0.2)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			0.0% (-0.0, 0.0)
<b>Musculoskeletal and connective tissue disorders - SOC</b>			
Raw incidence rate n/N (%)	1/579 (0.2%)	1/579 (0.2%)	4/582 (0.7%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	1/160.1 (0.6)	1/159.3 (0.6)	4/160.5 (2.5)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		-0.0% (-0.5, 0.5)	0.5% (-0.2, 1.3)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			0.5% (-0.2, 1.3)
<b>Intervertebral disc disorder</b>			
Raw incidence rate n/N (%)	0/579	0/579	1/582 (0.2%)
Exposure adjusted incidence rate	0/161.6 (0)	0/160.0 (0)	1/161.2 (0.6)

Clinical Review  
 Reviewer: Suzette Peng, MD  
 NME/BLA 761037  
 Sarilumab/Kevzara

n/PY (rate per 100 PYs) <sup>a</sup>			
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		0.0% (-0.0, 0.0)	0.2% (-0.2, 0.5)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			0.2% (-0.2, 0.5)
<b>Lumbar spinal stenosis</b>			
Raw incidence rate n/N (%)	0/579	0/579	1/582 (0.2%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	0/161.6 (0)	0/160.0 (0)	1/161.2 (0.6)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		0.0% (-0.0, 0.0)	0.2% (-0.2, 0.5)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			0.2% (-0.2, 0.5)
<b>Osteoarthritis</b>			
Raw incidence rate n/N (%)	0/579	0/579	1/582 (0.2%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	0/161.0 (0)	0/159.7 (0)	1/160.9 (0.6)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		0.0% (-0.0, 0.0)	0.2% (-0.2, 0.5)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			0.2% (-0.2, 0.5)
<b>Rheumatoid arthritis</b>			
Raw incidence rate n/N (%)	1/579 (0.2%)	0/579	1/582 (0.2%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	1/160.7 (0.6)	0/160.0 (0)	1/160.9 (0.6)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		-0.2% (-0.5, 0.2)	0.0% (-0.5, 0.5)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			0.2% (-0.2, 0.5)
<b>Intervertebral disc protrusion</b>			
Raw incidence rate n/N (%)	0/579	1/579 (0.2%)	0/582
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	0/161.6 (0)	1/159.9 (0.6)	0/161.2 (0)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		0.2% (-0.2, 0.5)	0.0% (-0.0, 0.0)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			-0.2% (-0.5, 0.2)
<b>Renal and urinary disorders - SOC</b>			
Raw incidence rate n/N (%)	0/579	0/579	1/582 (0.2%)

Clinical Review  
 Reviewer: Suzette Peng, MD  
 NME/BLA 761037  
 Sarilumab/Kevzara

Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	0/161.3	0/159.7	1/582 (0.2%)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		0.0% (-0.0, 0.0)	0.2% (-0.2, 0.5)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			0.2% (-0.2, 0.5)
<b>Renal failure</b>			
Raw incidence rate n/N (%)	0/579	0/579	1/582 (0.2%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	0/161.6 (0)	0/160.0 (0)	1/161.1 (0.6)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		0.0% (-0.0, 0.0)	0.2% (-0.2, 0.5)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			0.2% (-0.2, 0.5)
<b>General disorders and administration site conditions - SOC</b>			
Raw incidence rate n/N (%)	1/579 (0.2%)	0/579	0/582
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	1/161.5 (0.6)	0/160.0 (0)	0/160.3 (0)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		-0.2% (-0.5, 0.2)	-0.2% (-0.5, 0.2)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			0.0% (-0.0, 0.0)
<b>Pyrexia</b>			
Raw incidence rate n/N (%)	1/579 (0.2%)	0/579	0/582
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	1/161.5 (0.6)	0/160.0 (0)	0/161.2 (0)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		-0.2% (-0.5, 0.2)	-0.2% (-0.5, 0.2)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			0.0% (-0.0, 0.0)
<b>Investigations - SOC</b>			
Raw incidence rate n/N (%)	0/579	2/579 (0.3%)	3/582 (0.5%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	0/161.6 (0)	2/159.5 (1.3)	3/160.7 (1.9)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		0.3% (-0.1, 0.8)	0.5% (-0.1, 0.1)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			0.2% (-0.6, 0.9)
<b>Alanine aminotransferase increased</b>			

Raw incidence rate n/N (%)	0/579	1/579 (0.2%)	1/582 (0.2%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	0/161.6 (0.0)	1/159.9 (0.6)	1/161.1 (0.6)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		0.2% (-0.2, 0.5)	0.2% (-0.2, 0.5)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			0.0% (-0.5, 0.5)
<b>Blood alkaline phosphatase increased</b>			
Raw incidence rate n/N (%)	0/579	0/579	1/582 (0.2%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	0/161.6 (0)	0/160.0 (0)	1/161.1 (0.6)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		0.0% (-0.0, 0.0)	0.2% (-0.2, 0.5)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			0.2% (-0.2, 0.5)
<b>Neutrophil count decreased</b>			
Raw incidence rate n/N (%)	0/579	0/579	1/582 (0.2%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	0/161.6 (0)	0/160.0 (0)	1/161.1 (0.6)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		0.0% (-0.0, 0.0)	0.2% (-0.2, 0.5)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			0.2% (-0.2, 0.5)
<b>Transaminases increased</b>			
Raw incidence rate n/N (%)	0/579	1/579 (0.2%)	0/582
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	0/161.6 (0)	1/160.0 (0.6)	0/161.0 (0)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		0.2% (-0.2, 0.5)	0.0% (-0.0, 0.0)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			-0.2% (-0.5, 0.2)
<b>Injury, poisoning, and procedural complications - SOC</b>			
Raw incidence rate n/N (%)	2/579 (0.2%)	2/579 (0.3%)	3/582 (0.5%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	2/161.5 (1.2)	2/159.6 (1.3)	3/160.3 (1.9)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		0.0% (-0.7, 0.7)	0.2% (-0.6, 0.9)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			0.2% (-0.6, 0.9)

<b>Ligament rupture</b>			
Raw incidence rate n/N (%)	0/579	0/579	1/582 (0.2%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	0/161.6 (0)	0/160.0 (0)	1/161.2 (0.6)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		0.0% (-0.0, 0.0)	0.2% (-0.2, 0.5)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			0.5% (-0.2, 0.5)
<b>Procedural pain</b>			
Raw incidence rate n/N (%)	0/579	0/579	1/582 (0.2%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	0/161.6 (0)	0/160.0 (0)	1/161.2 (0.6)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		0.0% (-0.0, 0.0)	0.2% (-0.2, 0.5)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			0.2% (-0.2, 0.5)
<b>Tendon rupture</b>			
Raw incidence rate n/N (%)	0/579	0/579	1/582 (0.2%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	0/161.6 (0)	0/160.0 (0)	1/161.0 (0.6)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		0.0% (-0.0, 0.0)	0.2% (-0.2, 0.5)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			0.2% (-0.2, 0.5)
<b>Ankle fracture</b>			
Raw incidence rate n/N (%)	1/579 (0.2%)	0/579	0/582
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	1/161.5 (0.6)	0/160.0 (0)	0/161.2 (0)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		-0.2% (-0.5, 0.2)	-0.2% (-0.5, 0.2)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			0.2% (-0.0, 0.0)
<b>Hip fracture</b>			
Raw incidence rate n/N (%)	0/579	1/579 (0.2%)	0/582
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	0/161.6 (0)	1/159.9 (0.6)	0/161.2 (0)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		0.2% (-0.2, 0.5)	0.0% (-0.0, 0.0)
Rate difference vs. sarilumab 150mg + DMARD			-0.2% (-0.5, 0.2)

(95% CI) <sup>b</sup>			
<b>Road traffic accident</b>			
Raw incidence rate n/N (%)	1/579 (0.2%)	1/579 (0.2%)	0/582
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	1/161.6 (0.6)	1/160.0 (0.6)	0/161.2 (0)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		0.0% (-0.5, 0.5)	-0.2% (-0.5, 0.2)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			-0.2% (-0.5, 0.2)

Note: SOCs shaded in orange; PTs shaded in blue. Table sorted by SOC internationally agreed order and decreasing frequency of PT in the sarilumab 200mg q2w treatment group.

n (%) = number and percentage of patients with at least one TEAE

a Number of patients with at least 1 event per 100 patient-years, where the exposure time for patients who have experienced the specific adverse event experience was defined as the time to first adverse experience of interest whereas the exposure time for those who have not had this adverse experience was total TEAE period duration

b The rate difference and its 95% confidence interval were estimated using the M&N method stratified by the study, using the CMH weight

Source: Sanofi Response to MCC Agency Request (April 19, 2016), Appendix Table 5, dated May 2, 2016; page 13-28.

As already noted, Pool 1a is a subset of Pool 1. In general, for SAEs, the overall incidence of SAEs was similar between Pool 1a and Pool 1. The incidence rates were higher than what was seen in Pool 1a in the pre-rescue period, but the general trends remained. There were more events in the sarilumab doses as compared to placebo, and there were more event in sarilumab 200mg q2w treatment arm compared to the sarilumab 150mg q2w arm. The raw incidence rate of SAEs of any class was 4.7% for placebo, 6.4% for sarilumab 150mg q2w, and 8.9% for sarilumab 200mg q2w. Similar to the pre-rescue period, the most common SAEs were in the following SOCs: Infections and infestations, Blood and lymphatic system disorders, and Respiratory, thoracic, and mediastinal disorders. Table 60 presents the SAEs for the entire double-blind treatment period (52 weeks) for the placebo-controlled population (Pool 1). Only SOCs are listed in this table.

APPEARS THIS WAY ON ORIGINAL

**Table 60. Overview of SAEs in the Double-Blind Treatment Period (Pool 1)**

Primary SOC	PBO + DMARD		Sarilumab 150mg q2w + DMARD		Sarilumab 200mg q2w + DMARD	
	Raw incidence rate (N=661) n (%)	Exposure adjusted event rate (PY= 382.3) n <sub>E</sub> (n <sub>E</sub> /100 PYs)	Raw incidence rate (N=660) n (%)	Exposure adjusted event rate (PY=440.7) n <sub>E</sub> (n <sub>E</sub> /100 PYs)	Raw incidence rate (N=661) n (%)	Exposure adjusted event rate (PY=441.4) n <sub>E</sub> (n <sub>E</sub> /100 PYs)
<b>Any class</b>	31 (4.7%)	49 (12.8)	42 (6.4%)	67 (15.2)	59 (8.9%)	81 (18.4)
Infections and Infestations	12 (1.8%)	15 (3.9)	12 (1.8%)	16 (3.6)	19 (2.9%)	23 (5.2)
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	5 (0.8%)	6 (1.6)	4 (0.6%)	4 (0.9)	2 (0.3%)	2 (0.5)
Blood and lymphatic system disorders	1 (0.2%)	1 (0.3)	5 (0.8%)	6 (1.4)	8 (1.2%)	8 (1.8)
Metabolism and nutrition disorders	2 (0.3%)	2 (0.5)	1 (0.2%)	2 (0.5)	1 (0.2%)	1 (0.2)
Psychiatric disorders	1 (0.2%)	1 (0.3)	1 (0.2%)	3 (0.7)	2 (0.3%)	3 (0.7)
Nervous system disorders	3 (0.5%)	3 (0.8)	2 (0.3%)	2 (0.5)	2 (0.3%)	2 (0.5)
Cardiac disorders	4 (0.6%)	4 (1.0)	2 (0.3%)	2 (0.5)	5 (0.8%)	6 (1.4)
Vascular disorders	1 (0.2%)	1 (0.3)	4 (0.6%)	5 (1.1)	3 (0.5%)	4 (0.9)
Respiratory, thoracic, and mediastinal disorders	1 (0.2%)	1 (0.3)	6 (0.9%)	7 (1.6)	3 (0.5%)	3 (0.7)
Gastrointestinal disorders	2 (0.3%)	2 (0.5)	4 (0.6%)	6 (1.4)	4 (0.6%)	4 (0.9)
Hepatobiliary disorders	2 (0.3%)	2 (0.5)	3 (0.5%)	3 (0.7)	2 (0.3%)	2 (0.5)
Musculoskeletal and connective tissue disorders	7 (1.1%)	7 (1.8)	3 (0.5%)	3 (0.7)	6 (0.9%)	6 (1.4)
Renal and urinary disorders	1 (0.2%)	1 (0.3)	1 (0.2%)	1 (0.2)	3 (0.5%)	3 (0.7)
Pregnancy, puerperium, and perinatal conditions	0	0	0	0	1 (0.2%)	1 (0.2)
Reproductive system and breast disorders	0	0	1 (0.2%)	1 (0.2)	0	0
General disorders and administration site conditions	1 (0.2%)	1 (0.3)	0	0	3 (0.5%)	3 (0.7)
Investigations	0	0	3 (0.5%)	3 (0.7)	4 (0.6%)	4 (0.9)
Injury, poisoning, and procedural complications	2 (0.3%)	2 (0.5)	3 (0.5%)	3 (0.7)	6 (0.9%)	6 (1.4)

n(%) = number and % of patients with at least 1 TEAE

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

nE (nE/100 PY) = number of events and number of events per 100 patient-years

Source: ISS, Table 41, dated October 6, 2015; page 102-8.

In the long-term safety population, the exposure-adjusted event rate was very similar for all treatment groups (13.7 events per 100 patient-years for 150mg q2w initial dose, 15.6 events per 100 patient-years for 200mg q2w initial dose, and 15.2 events per 100 patient-years for any sarilumab dose). The event rate was similar to that in Pool 1 for 150mg and was actually lower for 200mg. It can be noted that the incidence rate of SAEs in the 200mg q2w initial dose group (13.8%) was numerically higher than that in the 150mg q2w initial dose group (5.4%), but the exposure-adjusted event rates were more similar, as it took into account the different exposures and follow-up times in each arm. In the long-term safety population, the exposure adjusted event rate was more similar in the 200mg q2w arm and the 150mg q2w arm for the Infections and Infestations SOC and was actually lower in the 200mg q2w arm compared to 150mg q2w arm for the Blood and lymphatic system disorders SOC. Numerically (as noted by incidence rates and actual events), there still were more events in the 200mg q2w group for both of these SOCs. The lower event rates in the 200mg q2w reflect the increased exposure.

Table 61 displays the common SAEs (by SOC) for the long-term safety population. The most common SAEs (by SOC) remained Infections and Infestations. Some other SOCs, however, became the next most common: Musculoskeletal and connective tissue disorders (represented by the PTs RA, OA, and foot deformity) and Injury, poisoning, and procedural complications (represented by the PTs Tendon rupture, Femur fracture, Femoral neck fracture, Hip fracture, Humerus fracture, and Joint dislocation). Thus, these were mostly serious musculoskeletal events.

APPEARS THIS WAY ON ORIGINAL

**Table 61. Overview of SAEs in ≥ 3 patients in the Entire TEAE Period (Pool 2)**

Primary SOC	Sarilumab + DMARD					
	150mg q2w Initial Dose		200mg q2w Initial Dose		Any Dose	
	Raw incidence rate (N=1155)  n (%)	Exposure adjusted event rate (PY= 701.9)  n <sub>E</sub> (n <sub>E</sub> /100 PYs)	Raw incidence rate (N=1351)  n (%)	Exposure adjusted event rate (PY=1758.6)  n <sub>E</sub> (n <sub>E</sub> /100 PYs)	Raw incidence rate (N=2887)  n (%)	Exposure adjusted event rate (PY=4481.8)  n <sub>E</sub> (n <sub>E</sub> /100 PYs)
<b>Any class</b>	62 (5.4%)	96 (13.7)	187 (13.8%)	275 (15.6)	439 (15.2%)	681 (15.2)
Infections and Infestations	17 (1.5%)	22 (3.1)	64 (4.7%)	75 (4.3)	158 (5.5%)	190 (4.2)
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	8 (0.7%)	8 (1.1)	11 (0.8%)	12 (0.7)	34 (1.2%)	35 (0.8)
Blood and lymphatic system disorders	7 (0.6%)	8 (1.1)	12 (0.9%)	12 (0.7)	29 (1.0%)	31 (0.7)
Immune system disorders	0	0	0	0	1 (<0.1%)	1 (0.0)
Metabolism and nutrition disorders	1 (<0.1%)	2 (0.3)	1 (<0.1%)	1 (0.1)	9 (0.3%)	10 (0.2)
Psychiatric disorders	1 (<0.1%)	3 (0.4)	4 (0.3%)	5 (0.3)	8 (0.3%)	13 (0.3)
Nervous system disorders	2 (0.2%)	2 (0.2)	13 (1.0%)	14 (0.8)	34 (1.2%)	38 (0.8)
Eye disorders	1 (<0.1%)	1 (0.1)	2 (0.1%)	3 (0.2)	4 (0.1%)	5 (0.1)
Cardiac disorders	4 (0.3%)	4 (0.6)	13 (1.0%)	16 (0.9)	31 (1.1%)	36 (0.8)
Vascular disorders	6 (0.5%)	7 (1.0)	8 (0.6%)	9 (0.5)	22 (0.8%)	24 (0.5)
Respiratory, thoracic, and mediastinal disorders	9 (0.8%)	11 (1.6)	10 (0.7%)	11 (0.6)	27 (0.9%)	32 (0.7)
Gastrointestinal disorders	4 (0.3%)	6 (0.9)	14 (1.0%)	16 (0.9)	31 (1.1%)	37 (0.8)
Hepatobiliary disorders	3 (0.3%)	3 (0.4)	15 (1.1%)	16 (0.9)	24 (0.8%)	25 (0.6)
Skin and subcutaneous tissue disorders	1 (<0.1%)	1 (0.1)	1 (<0.1%)	1 (0.1)	4 (0.1%)	4 (0.1)
Musculoskeletal and connective tissue disorders	3 (0.3%)	3 (0.4)	22 (1.6%)	28 (1.6)	61 (2.1%)	77 (1.7)
Renal and urinary disorders	1 (<0.1%)	1 (0.1)	6 (0.4%)	6 (0.3)	10 (0.3%)	10 (0.2)
Pregnancy, puerperium, and perinatal conditions	0	0	2 (0.1%)	2 (0.1)	3 (0.1%)	3 (0.1)
Reproductive system and breast disorders	2 (0.2%)	2 (0.3)	6 (0.4%)	6 (0.3)	13 (0.5%)	13 (0.3)
General disorders and administration site conditions	0	0	7 (0.5%)	7 (0.4)	14 (0.5%)	14 (0.3)

Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

Investigations	3 (0.3%)	3 (0.4)	10 (0.7%)	11 (0.6)	15 (0.5%)	16 (0.4)
Injury, poisoning, and procedural complications	8 (0.7%)	9 (1.3)	20 (1.5%)	23 (1.3)	55 (1.9%)	65 (1.5)
Surgical and medical procedures	0	0	1 (<0.1%)	1 (0.1)	2 (<0.1%)	2 (0.0)

n(%) = number and % of patients with at least 1 TEAE

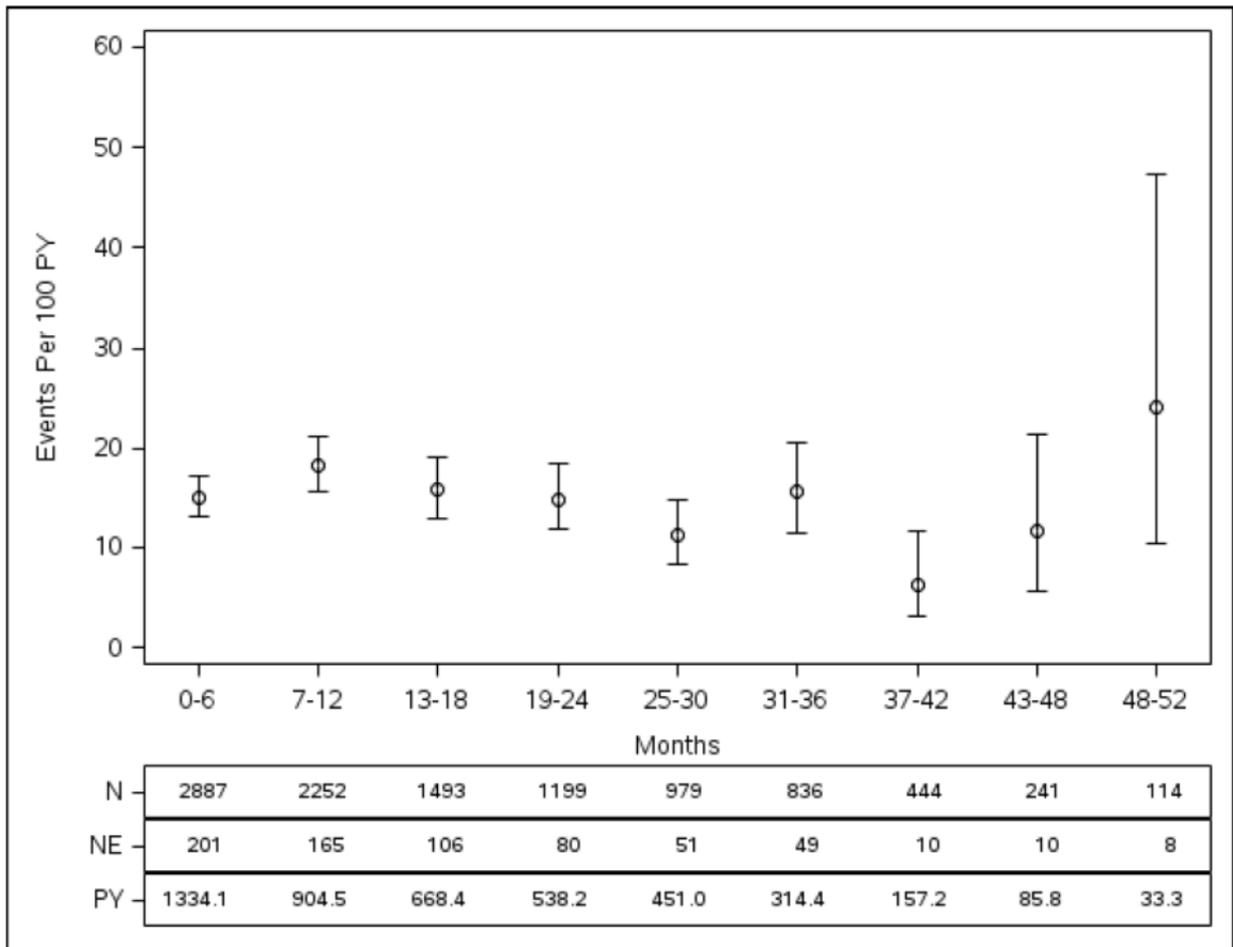
nE (nE/100 PY) = number of events and number of events per 100 patient-years

Source: ISS, Table 42, dated October 6, 2015; page 112-5.

APPEARS THIS WAY ON ORIGINAL

In general, over time, the event rate of SAEs is stable. Figure 34 illustrates the exposure-adjusted rate of SAE by 6-month intervals for the long-term safety population. The exposure-adjusted event rates are similar, but the confidence interval widens with time as well.

**Figure 34. Exposure-Adjusted Rate of SAEs by 6-month Interval during the Entire TEAE Period (Pool 2)**



N = sample size; NE = number of events in a 6-month period; PY = patient-years  
 95% confidence interval was calculated using the exact method  
 Source: ISS, Figure 7, dated October 6, 2015; page 116.

In conclusion, more serious adverse events occurred in patients being treatment with sarilumab as compared to those treated with placebo. Numerically, there were more events in the higher dose arm (200mg q2w). These differences are readily illustrated by the raw and exposure-adjusted incidence rates in the double-blind, placebo-controlled, pre-rescue period: 2.1% and 7.7 subjects per 100 patient-years in the placebo arm vs. 3.3% and 12.5 subjects per 100 patient-years in the sarilumab 150mg q2w arm vs. 5.8% and 22.5 subjects per 100 patient-years

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

in the sarilumab 200mg q2w arm. The most common SAEs in the placebo-controlled period were events that occurred in the Infections SOC and Blood and lymphatic disorders SOC. The greatest difference between doses was seen in the Blood and lymphatic disorders SOC (specifically, neutropenia). These SOCs do represent events that were generally expected with IL-6 inhibition in the RA population.

### 8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

In Section 8.2.1, the patient disposition of each safety population is presented. More subjects on sarilumab discontinued the IMP secondary sarilumab as compared to placebo (11.1% in sarilumab 150mg q2w arm vs. 12.6% in sarilumab 200mg q2w arm vs. 4.7% in placebo). However, more subjects in the placebo were rescued to open-label sarilumab.

As a reminder, the study protocol required permanent discontinuation of the IMP for patients who met following specified laboratory criteria:

- 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)
- Opportunistic infections, as defined by the protocol

Figure 35 is a summary of adverse events that led to permanent discontinuation during the pre-rescue period for the phase 3 placebo-controlled population (Pool 1a). More subjects on sarilumab suffered adverse events that led to IMP discontinuation than subjects on placebo (6.4% in the sarilumab 150mg q2w arm, 7.6% in the sarilumab 200mg q2w arm, 3.1% in the placebo arm). There was a notable rate difference in each of the sarilumab arms compared to placebo. However, there were also more subjects with events leading to discontinuation in the sarilumab 200mg q2w arm compared to the 150mg q2w arm with a rate difference of 1.2% (95% CI: -1.8, 4.3).

### Figure 35. Summary of Adverse Events Leading to Discontinuation in the Pre-Rescue Period (Pool 1a)

APPEARS THIS WAY ON ORIGINAL

	Placebo + DMARD	Sarilumab 150mg q2w + DMARD	Sarilumab 200mg q2w + DMARD
<b>AEs leading to permanent treatment discontinuation</b>			
Raw incidence rate n/N (%)	18/579 (3.1%)	37/579 (6.4%)	44/582 (7.6%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	18/156.3 (11.5)	37/147.0 (25.2)	44/146.8 (30.0)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		3.6% (1.0, 6.1)	4.8% (2.1, 7.5)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			1.2% (-1.8, 4.3)

n (%) = number and percentage of patients with at least one TEAE

a Number of patients with at least 1 event per 100 patient-years, where the exposure time for patients who have experienced the specific adverse event experience was defined as the time to first adverse experience of interest whereas the exposure time for those who have not had this adverse experience was total TEAE period duration

b The rate difference and its 95% confidence interval were estimated using the M&N method stratified by the study, using the CMH weight

Source: ISS Appendix 1.12.1.50, dated September 29, 2015; page 8279.

To get a better idea of which adverse events led to discontinuation in each treatment arm, Sanofi provided data as presented in Table 62 on Pool 1 for the entire double-blind period. In general, the data on this population are similar to that in Pool 1a for the pre-rescue period. More subjects on sarilumab experienced AEs leading to discontinuation than subjects on placebo, and numerically more subjects on the higher dose of sarilumab had AEs leading to discontinuation. The raw incidence rate of subjects with AEs leading to permanent discontinuation was 4.7% in the placebo arm, 10.9% in the sarilumab 150mg q2w arm, and 12.6% in the sarilumab 200mg q2w arm. The most common AEs (by PT) in the sarilumab arms leading to discontinuation were neutropenia, increased ALT, and herpes zoster, in descending order. The protocol defined herpes zoster as an opportunistic infection. The most common AE (by PT) leading to discontinuation in the placebo arm was rheumatoid arthritis.

APPEARS THIS WAY ON ORIGINAL

**Table 62. Overview of Adverse Events Leading to Discontinuation in the Double-Blind Period (SOCs and PTs reported in ≥ 2 patients, Pool 1)**

Primary SOC Preferred Term	PBO + DMARD		Sarilumab 150mg q2w + DMARD		Sarilumab 200mg q2w + DMARD	
	Raw incidence rate (N=661)  n (%)	Exposure adjusted event rate (PY= 382.3)  n <sub>E</sub> (n <sub>E</sub> /100 PYs)	Raw incidence rate (N=660)  n (%)	Exposure adjusted event rate (PY=440.7)  n <sub>E</sub> (n <sub>E</sub> /100 PYs)	Raw incidence rate (N=661)  n (%)	Exposure adjusted event rate (PY=441.4)  n <sub>E</sub> (n <sub>E</sub> /100 PYs)
<b>Any class</b>	<b>31 (4.7%)</b>	<b>33 (8.6)</b>	<b>72 (10.9%)</b>	<b>90 (20.4)</b>	<b>83 (12.6%)</b>	<b>91 (20.6)</b>
Infections and Infestations	7 (1.1%)	7 (1.8)	20 (3.0%)	24 (5.4)	20 (3.0%)	21 (4.8)
Herpes zoster	3 (0.5%)	3 (0.8)	3 (0.5%)	3 (0.7)	5 (0.8%)	5 (1.1)
Cellulitis	0	0	2 (0.3%)	3 (0.7)	2 (0.3%)	2 (0.5)
Pneumonia	0	0	2 (0.3%)	2 (0.5)	2 (0.3%)	2 (0.5)
Oral herpes	0	0	2 (0.3%)	2 (0.5)	1 (0.2%)	1 (0.2)
Urinary tract infection	1 (0.2%)	1 (0.3)	2 (0.3%)	2 (0.5)	0	0
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	2 (0.3%)	2 (0.5)	3 (0.5%)	3 (0.7)	1 (0.2%)	1 (0.2)
Meningioma	2 (0.3%)	2 (0.5)	0	0	0	0
Blood and lymphatic system disorders	3 (0.5%)	3 (0.8)	17 (2.6%)	18 (4.1)	19 (2.9%)	19 (4.3)
Neutropenia	2 (0.3%)	2 (0.5)	15 (2.3%)	15 (3.4)	13 (2.0%)	13 (2.9)
Thrombocytopenia	0	0	1 (0.2%)	1 (0.2)	3 (0.5%)	3 (0.7)
Leukopenia	0	0	0	0	2 (0.3%)	2 (0.5)
Metabolism and nutrition disorders	0	0	1 (0.2%)	2 (0.5)	0	0
Psychiatric disorders	1 (0.2%)	1 (0.3)	1 (0.2%)	1 (0.2)	2 (0.3%)	3 (0.7)
Depression	0	0	0	0	2 (0.3%)	2 (0.5)
Nervous system disorders	2 (0.3%)	2 (0.5)	2 (0.3%)	2 (0.5)	3 (0.5%)	3 (0.7)
Eye disorders	0	0	0	0	1 (0.2%)	1 (0.2)
Cardiac disorders	1 (0.2%)	1 (0.3)	1 (0.2%)	1 (0.2)	3 (0.5%)	4 (0.9)

Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

Vascular disorders	0	0	3 (0.5%)	4 (0.9)	0	0
Respiratory, thoracic, and mediastinal disorders	2 (0.3%)	2 (0.5)	3 (0.5%)	4 (0.9)	2 (0.3%)	2 (0.5)
Gastrointestinal disorders	3 (0.5%)	3 (0.8)	3 (0.5%)	6 (1.4)	2 (0.3%)	2 (0.5)
Hepatobiliary disorders	1 (0.2%)	1 (0.3)	3 (0.5%)	3 (0.7)	1 (0.2%)	1 (0.2)
Skin and subcutaneous disorders	1 (0.2%)	1 (0.3)	5 (0.8%)	5 (1.1)	6 (0.9%)	7 (1.6)
Musculoskeletal and connective tissue disorders	6 (0.9%)	6 (1.6)	1 (0.2%)	1 (0.2)	3 (0.5%)	3 (0.7)
Rheumatoid arthritis	5 (0.8%)	5 (1.3)	0	0	2 (0.3%)	2 (0.5)
Renal and urinary disorders	0	0	0	0	1 (0.2%)	1 (0.2)
Pregnancy, puerperium, and perinatal conditions	0	0	0	0	1 (0.2%)	1 (0.2)
General disorders and administration site conditions	0	0	1 (0.2%)	2 (0.5)	4 (0.6%)	4 (0.9)
Investigations	3 (0.5%)	3 (0.8)	13 (2.0%)	13 (2.9)	15 (2.3%)	16 (3.6)
Alanine aminotransferase increased	0	0	11 (1.7%)	11 (2.5)	9 (1.4%)	9 (2.0)
Transaminases increased	1 (0.2%)	1 (0.3)	2 (0.3%)	2 (0.5)	4 (0.6%)	4 (0.9)
Injury, poisoning, and procedural complications	1 (0.2%)	1 (0.3)	1 (0.2%)	1 (0.2)	2 (0.3%)	2 (0.5)

n(%) = number and % of patients with at least 1 TEAE

nE (nE/100 PY) = number of events and number of events per 100 patient-years

Table sorted by SOC internationally agreed order and decreasing frequency of PT in sarilumab 200mg group

Source: ISS, Table 47, dated October 6, 2015; page 127-128.

The exposure-adjusted rate of AEs leading to discontinuation was the same in the long-term safety population for the sarilumab 150mg q2w arm. However, the exposure-adjusted rate for the sarilumab 200mg q2w arm was lower. The lower exposure-adjusted rate again reflects the longer exposure on sarilumab 200mg q2w. The raw incidence rates are higher in the sarilumab 200mg q2w arm. Table 63 presents these overall rates of adverse events leading to permanent discontinuation in the long-term safety population. The exposure-adjusted rates of AEs were 20.5 events per 100 patient-years in the sarilumab 150mg q2w arm and 13.6 events per 100 patient-years in the 200mg q2w initial dose arm. The three most common PTs leading to discontinuation were the same as the ones from the double-blind period, that is, neutropenia, alanine aminotransferase increased, and herpes zoster.

Clinical Review  
 Reviewer: Suzette Peng, MD  
 NME/BLA 761037  
 Sarilumab/Kevzara

**Table 63. Overview of Adverse Events Leading to Discontinuation in the Entire TEAE Period (SOCs and PTs in ≥ 3 patients, Pool 2)**

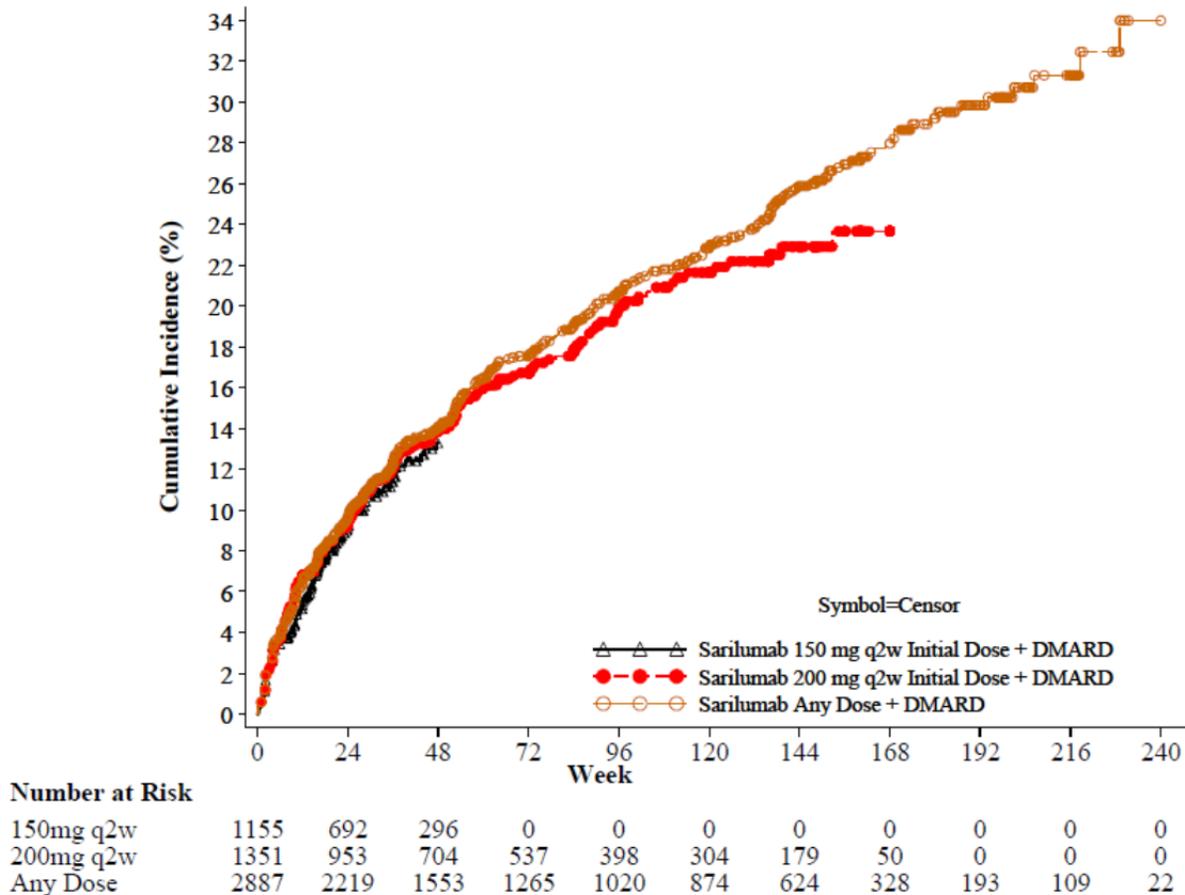
Primary SOC Preferred Term	Sarilumab + DMARD					
	150mg q2w Initial Dose		200mg q2w Initial Dose		Any Dose	
	Raw incidence rate (N=1155)	Exposure adjusted event rate (PY= 701.9)	Raw incidence rate (N=1351)	Exposure adjusted event rate (PY=1758.6)	Raw incidence rate (N=2887)	Exposure adjusted event rate (PY=4481.8)
n (%)	n <sub>E</sub> (n <sub>E</sub> /100 PYs)	n (%)	n <sub>E</sub> (n <sub>E</sub> /100 PYs)	n (%)	n <sub>E</sub> (n <sub>E</sub> /100 PYs)	
<b>Any class</b>	<b>116 (10.0%)</b>	<b>144 (20.5)</b>	<b>211 (15.6%)</b>	<b>240 (13.6)</b>	<b>538 (18.6%)</b>	<b>617 (13.8)</b>

n(%) = number and % of patients with at least 1 TEAE  
 nE (nE/100 PY) = number of events and number of events per 100 patient-years  
 Source: ISS, Table 48, dated October 6, 2015; page 130-132.

APPEARS THIS WAY ON ORIGINAL

In looking at the long-term safety population, Figure 36 shows the incidence over time. The incidence of discontinuation due to AEs is higher earlier in the study, specifically, the first 48 weeks. After 48 weeks, it is estimated that the rate of treatment discontinuation was approximately 5%.

**Figure 36. Kaplan-Meier Plot for Time to Discontinuation due to Adverse Events (Pool 2)**



Source: ISS, Figure 8, dated October 6, 2015; page 133.

In conclusion, for adverse events leading to discontinuation, there were more subjects and more events in the sarilumab treatment arms compared to placebo. Additionally, during the double-blind period, more subjects on sarilumab 200mg q2w developed AEs leading to discontinuation than subjects on 150mg q2w, but the rate difference was small with the 95% confidence interval including zero. It should be noted, though, that the most common AEs leading to discontinuation were those defined in the protocol; these events were neutropenia, increased ALT, and herpes zoster. Thus, the AEs leading to discontinuation in the sarilumab arms were consistent with what was expected.

#### 8.4.4. Significant Adverse Events

The severity of adverse of events was not a major aspect of the safety assessment for sarilumab. Rather, for each AE and, particularly, for AESIs, severity was assessed and described based on the event being analyzed. Therefore, as part of this review, the grading of adverse events will not be described separately. See the individual AEs of special interest.

#### 8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

More subjects in the sarilumab arms experienced any TEAE as compared to subjects in the placebo arm. In the pre-rescue period, the phase 3 placebo-controlled population experienced the following incidence rates of total number of TEAEs: 44.6% in the placebo arm, 54.2% in the sarilumab 150mg q2w arm, and 57.2% in the sarilumab 200mg q2w arm. The rate difference between sarilumab doses was quite small at 3.6% (95% CI: -2.3, 9.5). For the entire placebo-controlled population (Pool 1, up to 52 weeks), the incidence rates are higher but show a similar pattern to the pre-rescue period. More subjects on sarilumab experienced TEAEs overall, but the rates are similar between doses. The incidence rates for all TEAEs were 57.2% in the placebo arm, 70.5% in the sarilumab 150mg q2w arm, and 73.8% in the sarilumab 200mg q2w arm. The rate difference between doses was 3.4% (95% CI: -1.4, 8.2). The exposure-adjusted incidence rate of subjects with TEAEs in this same population was 173.3 per 100 patient-years for placebo, 215.7 per 100 patient-years for sarilumab 150mg q2w, and 252.0 per 100 patient-years for sarilumab 200mg q2w. The exposure-adjusted rates stayed generally consistent in the long-term safety population with 218.7 subjects with TEAEs per 100 patient-years for sarilumab 150mg q2w and 188.3 subjects with TEAEs per 100 patient-years for sarilumab 200mg q2w. For any dose of sarilumab, the raw incidence rate was 80.2% with an exposure-adjusted incidence of 172.7 per 100 patient-years.

Common TEAEs were any event that occurred in  $\geq 2\%$  of subjects in any 1 treatment arm. In the pre-rescue period, the most common TEAEs (by PT) were neutropenia, increased ALT, and injection site erythema. All of these TEAEs occurred more frequently in subjects on sarilumab. Table 64 presents the common TEAEs for the pre-rescue period (Pool 1a). For neutropenia and increased ALT, the incidence of subjects with these AEs occurred more frequently in the higher dose group. Both of the AEs will be discussed in greater detail in Section 8.4.6 and 8.5, as these were both AESIs and were expected events. In fact, most of the common TEAEs were anticipated as possible AEs with IL-6 inhibition in the RA population.

**Table 64. Summary of Common TEAEs (incidence  $>2\%$  subjects in one of the treatment groups) by PT during the Pre-Rescue Period (Pool 1a)**

Clinical Review  
 Reviewer: Suzette Peng, MD  
 NME/BLA 761037  
 Sarilumab/Kevzara

	Placebo + DMARD	Sarilumab 150mg q2w + DMARD	Sarilumab 200mg q2w + DMARD
<b>Neutropenia</b>			
Raw incidence rate n/N (%)	1/579 (0.2%)	40/579 (6.9%)	59/582 (10.1%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	1/160.9 (0.6)	40/148.2 (27.0)	59/146.2 (40.4)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		7.0% (4.8, 9.2)	10.3% (7.8, 12.9)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			3.3% (-0.0, 6.6)
<b>Alanine aminotransferase increased</b>			
Raw incidence rate n/N (%)	10/579 (1.7%)	27/579 (4.7%)	28/582 (4.8%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	10/157.8 (6.3)	27/152.5 (17.7)	28/152.1 (18.4)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		3.0% (1.0, 5.1)	3.2% (1.1, 5.3)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			0.2% (-2.3, 2.7)
<b>Injection site erythema</b>			
Raw incidence rate n/N (%)	5/579 (0.9%)	26/579 (4.5%)	23/582 (4.0%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	5/160.0 (3.1)	26/153.8 (16.9)	23/154.7 (14.9)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		3.7% (1.8, 5.5)	3.2% (1.4, 4.9)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			-0.5% (-2.9, 1.8)
<b>Upper respiratory tract infection</b>			
Raw incidence rate n/N (%)	14/579 (2.4%)	21/579 (3.6%)	20/582 (3.4%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	14/155.4 (9.0)	21/151.8 (13.8)	20/151.7 (13.2)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		1.3% (-0.8, 3.3)	1.1% (-0.9, 3.1)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			-0.2% (-2.4, 2.0)
<b>Accidental overdose</b>			
Raw incidence rate n/N (%)	18/579 (3.1%)	17/579 (2.9%)	19/582 (3.3%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	18/156.1 (11.5)	17/154.0 (11.0)	19/153.1 (12.4)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		-0.2% (-2.2, 1.8)	0.2% (-1.9, 2.3)

Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			0.4% (-1.7, 2.4)
<b>Urinary tract infection</b>			
Raw incidence rate n/N (%)	11/579 (1.9%)	18/579 (3.1%)	17/582 (2.9%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	11/155.8 (7.1)	18/154.2 (11.7)	17/153.7 (11.1)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		1.2% (-0.6, 3.1)	1.1% (-0.8, 2.9)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			-0.2% (-2.2, 1.9)
<b>Diarrhoea</b>			
Raw incidence rate n/N (%)	14/579 (2.4%)	7/579 (1.2%)	15/582 (2.6%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	14/158.5 (8.8)	7/156.8 (4.5)	15/156.7 (9.6)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		-1.2% (-2.8, 0.3)	0.2% (-1.6, 2.0)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			1.4% (-0.2, 3.0)
<b>Nasopharyngitis</b>			
Raw incidence rate n/N (%)	14/579 (2.4%)	18/579 (3.1%)	14/582 (2.4%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	14/155.8 (9.0)	18/152.7 (11.8)	14/155.8 (9.0)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		0.7% (-1.2, 2.7)	-0.0% (-1.8, 1.8)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			-0.8% (-2.7, 1.2)
<b>Hypertension</b>			
Raw incidence rate n/N (%)	8/579 (1.4%)	7/579 (1.2%)	13/582 (2.2%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	8/157.5 (5.1)	7/156.6 (4.5)	13/157.3 (8.3)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		-0.2% (-1.5, 1.1)	0.9% (-0.7, 2.4)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			1.0% (-0.5, 2.5)
<b>Leukopenia</b>			
Raw incidence rate n/N (%)	0/579	5/579 (0.9%)	13/582 (2.2%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	0/161.6	5/157.9 (3.2)	13/157.1 (8.3)
Rate difference		0.9% (0.1, 1.6)	2.3% (1.0, 3.5)

vs. PBO + DMARD (95% CI) <sup>b</sup>			
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			1.4% (-0.0, 2.8)
<b>Bronchitis</b>			
Raw incidence rate n/N (%)	9/579 (1.6%)	5/579 (0.9%)	12/582 (2.1%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	9/157.7 (5.7)	5/156.2 (3.2)	12/155.9 (7.7)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		-0.7% (-2.0, 0.6)	0.5% (-1.0, 2.1)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			1.2% (-0.2, 2.6)
<b>Sinusitis</b>			
Raw incidence rate n/N (%)	5/579 (0.9%)	6/579 (1.0%)	12/582 (2.1%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	5/159.2 (3.1)	6/156.8 (3.8)	12/158.6 (7.6)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		0.2% (-1.0, 1.3)	1.2% (-0.2, 2.6)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			1.0% (-0.4, 2.5)
<b>Injection site pruritus</b>			
Raw incidence rate n/N (%)	1/579 (0.2%)	13/579 (2.2%)	11/582 (1.9%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	1/161.3 (0.6)	13/157.0 (8.3)	11/158.3 (6.9)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		2.1% (0.8, 3.3)	1.7% (0.6, 2.9)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			-0.4% (-2.0, 1.3)
<b>Headache</b>			
Raw incidence rate n/N (%)	15/579 (2.6%)	14/579 (2.4%)	10/582 (1.7%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	15/157.5 (9.5)	14/156.7 (8.9)	10/156.9 (6.4)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		-0.2% (-2.0, 1.6)	-0.9% (-2.6, 0.8)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			-0.7% (-2.3, 1.0)
<b>Rheumatoid arthritis</b>			
Raw incidence rate n/N (%)	15/579 (2.6%)	3/579 (0.5%)	9/582 (1.5%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	15/155.5 (9.6)	3/158.9 (1.9)	9/156.9 (5.7)

Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		-2.1% (-3.6, -0.7)	-1.1% (-2.8, 0.6)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			1.0% (-0.1, 2.2)
<b>Hypertriglyceridemia</b>			
Raw incidence rate n/N (%)	3/579 (0.5%)	16/579 (2.8%)	8/582 (1.4%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	3/160.7 (1.9)	16/157.4 (10.2)	8/159.1 (5.0)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		2.3% (0.8, 3.7)	0.9% (-0.3, 2.0)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			-1.4% (-3.0, 0.2)

Note: Preferred Terms (PTs) shaded in blue

n (%) = number and percentage of patients with at least one TEAE

a Number of patients with at least 1 event per 100 patient-years, where the exposure time for patients who have experienced the specific adverse event experience was defined as the time to first adverse experience of interest whereas the exposure time for those who have not had this adverse experience was total TEAE period duration

b The rate difference and its 95% confidence interval were estimated using the M&N method stratified by the study, using the CMH weight

Source: ISS Appendix 1.12.1.51, dated September 29, 2015; page 8280-86.

In the entire double-blind period (Pool 1), the common TEAEs are similar. The most common SOC for all 3 treatment arms was Infections and infestations (28.6% in placebo, 34.2% in sarilumab 150mg q2w, and 35.2% in sarilumab 200mg q2w). The top three most common PTs were neutropenia with raw incidence rate of 0.5% in placebo, 9.8% in 150mg q2w group, and 14.2% in the 200mg q2w group. The next most common PTs were an upper respiratory infection (URI) (4.8% in placebo, 6.4% in 150mg q2w group, 7.1% in 200mg q2w group) and alanine aminotransferase increased (2.6% in placebo, 6.7% in 150mg q2w, 6.8% in 200mg q2w). As discussed below (Section 8.4.6), neutropenia appears to be markedly related to sarilumab use and is dose-dependent. There appears to be less of a relationship to dose with URI and increased ALT.

As has been noted with most of the AEs, analysis of the long-term safety population reveals more events, likely related to the increased exposure. The overall number of subjects with adverse events with a PT ≥ 2% was 764/1155 (66.1%) in the sarilumab 150mg initial dose group and 1101/1351 (81.5%) in the sarilumab 200mg initial dose group. For any dose of sarilumab, the raw incidence rate was 2314/2887 (80.2%). The exposure adjusted event rate for both dosing regimens were 339.9 per 100 patient-years for sarilumab 150mg and 289.5 events per 100 patient-years for sarilumab 200mg. Overall, the common adverse events are similar to that of the double-blind period with just more PTs under the Infections and Infestations SOC included. In fact, the three most common adverse events (PTs) in the long-term safety population are the same as that for the double blind period.

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

- Neutropenia:
  - sarilumab 150mg initial dose (incidence rate 11.3%, event rate 28.6 per 100 patient-years)
  - sarilumab 200mg initial dose (incidence rate 16.9%, event rate 20.1 per 100 patient-years)
  - any sarilumab dose (incidence rate 16.8%, event rate 20.0 per 100 patient-years)
- Upper respiratory tract infection
  - sarilumab 150mg initial dose (incidence rate 6.2%, event rate 12.5 per 100 patient-years)
  - sarilumab 200mg initial dose (incidence rate 9.0%, event rate 9.3 per 100 patient-years)
  - any sarilumab dose (incidence rate 10.3%, event rate 9.5 per 100 patient-years)
- Alanine aminotransferase increased
  - sarilumab 150mg initial dose (incidence rate 5.3%, event rate 10.0 per 100 patient-years)
  - sarilumab 200mg initial dose (incidence rate 9.5%, event rate 8.6 per 100 patient-years)
  - any sarilumab dose (incidence rate 9.3%, event rate 7.6 per 100 patient-years)

In summary, the most common TEAEs in the sarilumab clinical development program were neutropenia and increased ALT. These remained generally consistent through all safety populations and treatment periods. Other common TEAEs included injection site erythema and upper respiratory tract infection with slightly different rankings in frequency with the different safety population. However, for the purpose of analyses and labeling, the most common TEAEs in the placebo-controlled populations (Pools 1 and 1a) are most relevant, specifically, Pool 1a in the pre-rescue period. The most common TEAEs occurred more frequently in the sarilumab arms as compared to the placebo arm; thus, these TEAEs can be attributed to study drug. Additionally, neutropenia appeared to be dose-dependent. The common TEAEs were consistent with the expected effects of IL-6 inhibition on the RA population.

### 8.4.6. Laboratory Findings

#### **Elevated Liver Associated Enzymes**

Elevation in liver associated enzymes was an anticipated adverse event with IL-6 inhibition. Specifically, Sanofi notes that elevations in transaminases without apparent associated clinical hepatotoxicity have been observed with tocilizumab, and these elevations were reversible with modification or discontinuation of tocilizumab. Therefore, elevation in liver enzymes was an AESI. Although it was an AESI, it will be discussed here.

Because of the anticipated effect on liver enzymes, patients with ALT or AST >1.5 x ULN,

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

elevated total bilirubin, history of hepatitis B (or at risk of hepatitis B reactivation based on serology), or history of hepatitis C were excluded from sarilumab clinical trials. These exclusion criteria are described in detail in Section 6. The protocols also provided instruction on management of liver enzyme elevations, including criteria for discontinuation of drug or decreasing the dose (in study LTS11210. Investigators, based on clinical judgment, could also reduce the dose of MTX or other non-investigational medicinal products that could contribute to hepatotoxicity. The protocol defined that the occurrence of ALT >3x ULNT was to be reported as an AE.

To assess potential hepatotoxicity, Sanofi assessed the following:

- Mean changes in liver function parameters
- Incidence of ALT elevation by maximum severity
- Report of AEs related to hepatic disorders
- MedDRA SMQ drug-hepatic disorder adverse events – comprehensive search
- Association of increased transaminases with clinical events

This review will focus on liver enzyme elevations for the different safety populations: pre-rescue period (Pool 1a), double-blind treatment period (Pool 1), and long-term safety population (Pool 2). Then, an analysis of the SMQ “hepatic disorders” will also be presented.

Table 65 presents subjects with potentially clinically significant abnormalities (PCSA) in ALT, and Table 66 presents subjects specifically with ALT >3x ULN, both in the pre-rescue period (Pool 1a). More subjects on sarilumab experienced an elevation in ALT than subjects on placebo. The majority of subjects who had an elevation in ALT experienced the elevation at a lower level, between 1-1.5x ULN, in all treatment arms. Six subjects (1.0%) on placebo experienced an elevated ALT >3x ULN, compared to 29 subjects (5.0%) on sarilumab 150mg q2w and 22 subjects (3.8%) on sarilumab 200mg q2w. The rate difference between doses was minimal, 1.2% (95% CI: -3.6, 1.2), thus, including 0. No subjects on placebo had an ALT measured >5x ULN, whereas subjects on sarilumab had elevations of ALT up to 10-20x ULN.

APPEARS THIS WAY ON ORIGINAL

**Table 65. Number (%) of Patients with Elevated ALT by Maximum Grade during the Pre-Rescue Period (Pool 1a)**

	Placebo + DMARD	Sarilumab 150mg q2w + DMARD	Sarilumab 200mg q2w + DMARD
<b>ALT</b>			
> 1-1.5 x ULN	97/579 (16.8%)	130/578 (22.5%)	142/579 (24.5%)
> 1.5-3 x ULN	46/579 (7.9%)	92/578 (15.9%)	109/579 (18.8%)
> 3-5 x ULN	6/579 (1.0%)	22/578 (3.8%)	18/579 (3.1%)
> 5-10 x ULN	0/579	4/578 (0.7%)	4/579 (0.7%)
> 10-20 x ULN	0/579	3/578 (0.5%)	0/579
> 20 x ULN	0/579	0/578	0/579

ALT = alanine aminotransferase

n = subset of total number of pts who met the criterion at least once during treatment

N (denominator) = number of patients for the treatment group who had that parameter assessed post-baseline

Source: ISS Appendix 1.12.1.56, dated September 29, 2015, page 8297.

**Table 66. Number (%) of Patients with ALT >3x ULN during the Pre-Rescue Period (Pool 1a)**

	Placebo + DMARD	Sarilumab 150mg q2w + DMARD	Sarilumab 200mg q2w + DMARD
<b>ALT &gt;3x ULN</b>			
Raw incidence rate n/N (%)	6/579 (1.0%)	29/578 (5.0%)	22/579 (3.8%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	6/159.6 (3.8)	29/151.8 (19.1)	22/151.6 (14.5)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		4.1% (2.1, 6.1)	2.9% (1.1, 4.7)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			-1.2% (-3.6, 1.2)

ALT = alanine aminotransferase

n = subset of total number of pts who met the criterion at least once during treatment

N (denominator) = number of patients for the treatment group who had that parameter assessed post-baseline

a Number of patients with at least 1 event per 100 patient-years, where the exposure time for patients who have experienced the specific adverse event experience was defined as the time to first adverse experience of interest whereas the exposure time for those who have not had this adverse experience was total TEAE period duration

b The rate difference and its 95% confidence interval were estimated using the M&N method stratified by the study, using the CMH weight

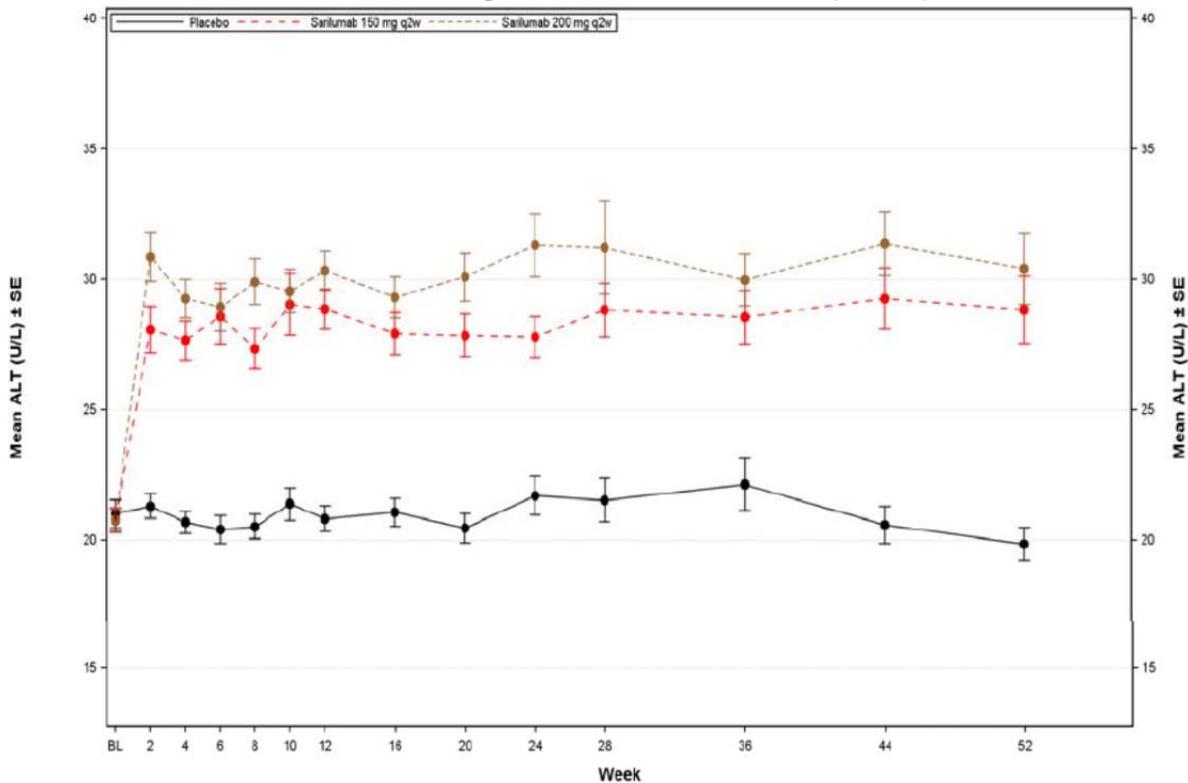
Source: ISS Appendix 1.12.1.57, dated September 29, 2015, page 8298.

Sanofi provided the trend in all the liver associated enzymes (ALT, AST, alkaline phosphatase [ALP], total bilirubin [T Bili]) over the entire double-blind period (Figures 23-26). In general, these liver enzymes remained relatively stable for the placebo group through the double-blind treatment period. The elevation in ALT and AST occurred within the first 2 weeks of therapy after which the levels seemed to plateau. For ALT, the sarilumab 200mg q2w dose appeared to have a slightly higher elevation, but there was a greater overlap between doses for AST.

Clinical Review  
 Reviewer: Suzette Peng, MD  
 NME/BLA 761037  
 Sarilumab/Kevzara

The elevation in total bilirubin was also most notable in the first 2 weeks, but there appeared to be a more gradual increase to about Week 16-20. The elevation in T Bili in the sarilumab 200mg q2w dose was slightly higher than that for the sarilumab 150mg q2w dose. Sanofi noted that the T Bili elevation was mostly due to unconjugated bilirubin. ALP decreased in the sarilumab doses compared to placebo. The decrease was greatest between Weeks 0-6 with a more gradual decrease between Weeks 6-28. The reason for the decrease in ALP was unclear, and Sanofi noted that the ALP was not fractionated to further elucidate.

**Figure 37. Mean ALT across Visits during the Double-Blind Period (Pool 1)**



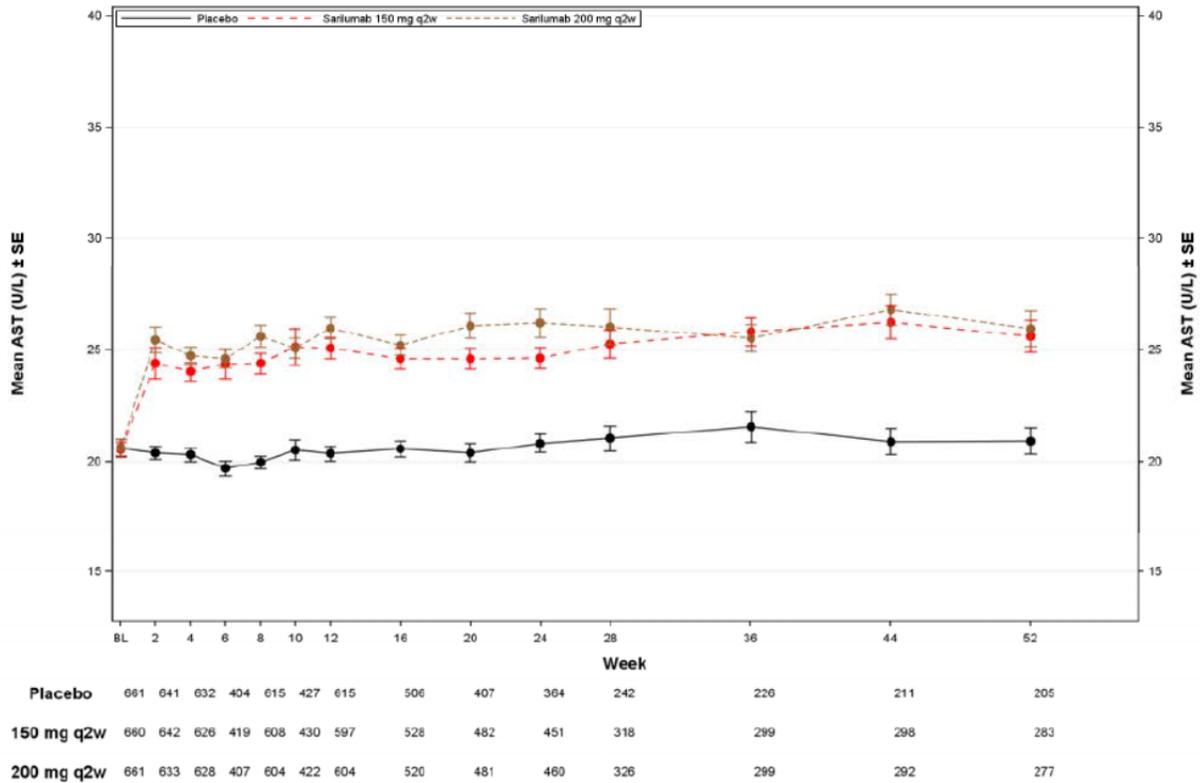
<b>Placebo</b>	651	646	633	407	618	431	617	510	409	368	246	229	212	206
<b>150 mg q2w</b>	660	644	629	421	609	435	598	531	483	455	321	302	302	283
<b>200 mg q2w</b>	661	636	630	468	611	425	605	521	466	465	327	300	296	277

ALT = alanine aminotransferase

Normal range: 6-34 IU/L (U/L)

Source: Integrated Summary of Safety, Figure 17, dated October 6, 2015; page 184.

**Figure 38. Mean AST across Visits during the Double-Blind Period (Pool 1)**

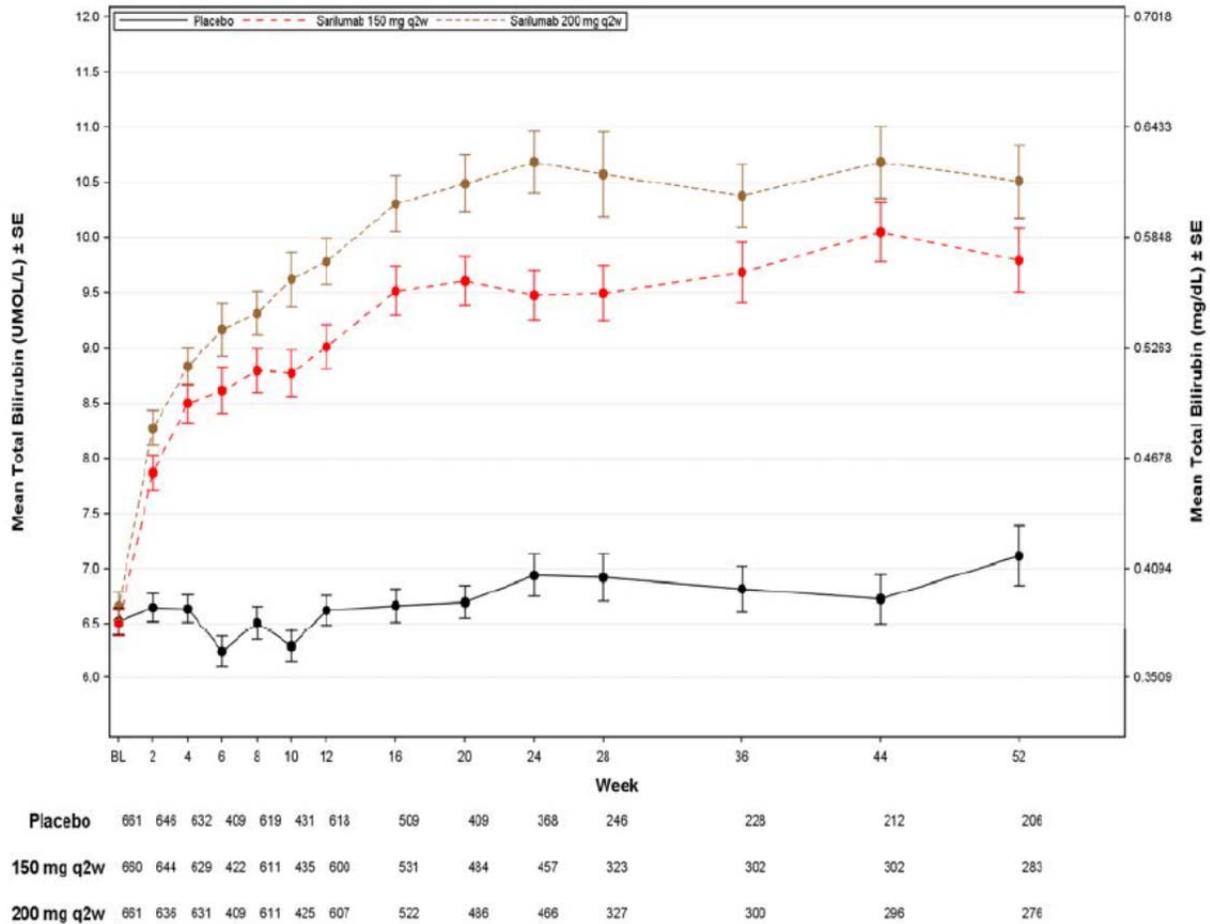


AST = aspartate aminotransferase  
 Normal range: 9-34 IU/L (U/L)

Source: Integrated Summary of Safety, Figure 18, dated October 6, 2015; page 185.

APPEARS THIS WAY ON ORIGINAL

**Figure 39. Mean T Bili across Visits during the Double-Blind Period (Pool 1)**



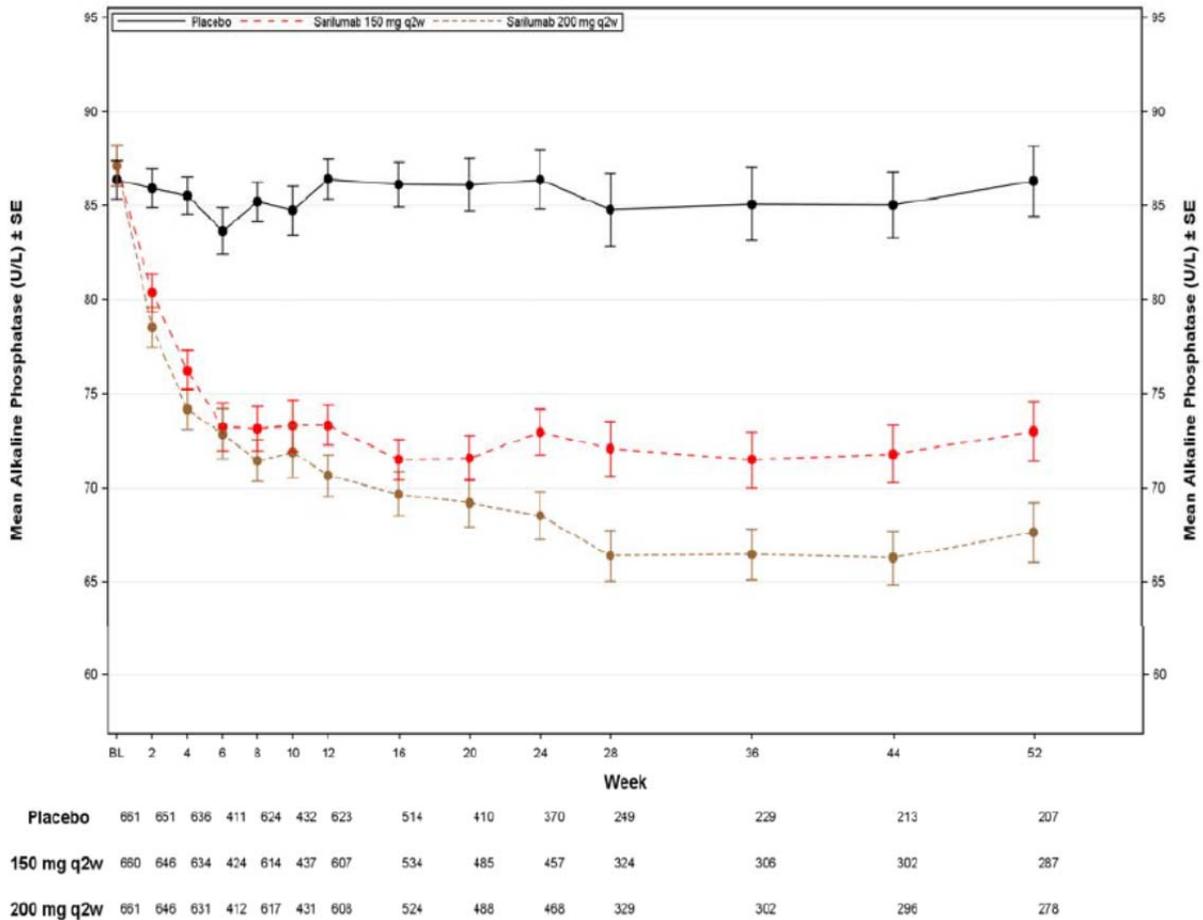
T Bili = total bilirubin

Normal range: 3-21 µmol/L (0.176-1.23 mg/dL)

Source: Integrated Summary of Safety, Figure 20, dated October 6, 2015; page 187.

APPEARS THIS WAY ON ORIGINAL

**Figure 40. Mean ALP across Visits during the Entire Double-Blind Period (Pool 1)**



ALP = alkaline phosphatase

Normal range: 35-123 IU/L (U/L)

Source: Integrated Summary of Safety, Figure 19, dated October 6, 2015; page 186.

To better analyze the elevations in the liver associated enzymes, Sanofi provided the potentially clinically significant abnormalities of ALT alongside the other liver enzymes for the entire double-blind treatment period. In general, the proportions of subjects with elevations in ALT were similar to those in the pre-rescue period. Proportions of AST elevations were similar to those of ALT elevations. Most of the elevations in total bilirubin in the sarilumab arms could be attributed to unconjugated bilirubin. In the double-blind period, 4 subjects did have ALT >3x ULN and TB >2x ULN, but all of these subjects had other possible reasons for these liver enzyme elevations. Therefore, they did not fulfill criteria for Hy's law.

**Table 67. Number of Patients with PCSA in Liver Enzymes during the Double-Blind Period (Pool 1)**

	Placebo + DMARD	Sarilumab 150mg q2w + DMARD	Sarilumab 200mg q2w + DMARD
<b>ALT</b>			
> 1-1.5 x ULN	127/661 (19.2%)	163/659 (24.7%)	178/657 (27.1%)
> 1.5-3 x ULN	70/661 (10.6%)	124/659 (18.8%)	162/657 (24.7%)
> 3-5 x ULN	10/661 (1.5%)	36/659 (5.5%)	31/657 (4.7%)
> 5-10 x ULN	1/661 (0.2%)	9/659 (1.4%)	10/657 (1.5%)
> 10-20 x ULN	0/661	4/659 (0.6%)	1/657 (0.2%)
> 20 x ULN	0/661	0/659	1/657 (0.2%)
<b>ALT</b>			
> 1-1.5 x ULN	86/661 (13.0%)	153/659 (23.2%)	149/657 (22.7%)
> 1.5-3 x ULN	37/661 (5.6%)	82/659 (12.4%)	92/657 (14.0%)
> 3-5 x ULN	3/661 (0.5%)	12/659 (12.4%)	15/657 (14.0%)
> 5-10 x ULN	0/661	4/659 (1.8%)	3/657 (0.5%)
> 10-20 x ULN	0/661	3/659 (0.5%)	0/657
> 20 x ULN	0/661	0/659	1/657 (0.2%)
<b>Total bilirubin</b>			
> 1.5 x ULN	1/661 (0.2%)	17/659 (2.6%)	18/657 (2.7%)
> 2 x ULN	1/661 (0.2%)	5/659 (0.8%)	5/657 (0.8%)
<b>Conjugated bilirubin</b>			
> 1.5 x ULN	1/661 (0.2%)	1/659 (0.2%)	2/657 (0.3%)
> 2 x ULN	1/661 (0.2%)	0/659	2/657 (0.3%)
<b>ALT and total bilirubin</b>			
ALT >3x ULN and T Bili >2x ULN	1/661 (0.2%)	2/659 (0.3%)	1/657 (0.2%)

PCSA = potentially clinically significant abnormalities

ALT = alanine aminotransferase; T Bili = total bilirubin

n = subset of total number of pts who met the criterion at least once during treatment

N (denominator) = number of patients for the treatment group who had that parameter assessed post-baseline

Source: Integrated Summary of Safety, Table 73, dated October 6, 2015; page 188-9.

In the long-term safety population, the trend in liver enzyme elevation was consistent with what was seen in the placebo-controlled population. In fact, the incidence rate of subjects who experienced an ALT 1-1.5x ULN was nearly the same as that in the double-blind population, 23.4% in subjects on sarilumab 150mg q2w and 27.7% in subjects on sarilumab 200mg q2w. The vast majority of elevations occurred in the range of ALT 1-3x ULN. Numerically, more subjects on sarilumab 200mg q2w had an elevation in ALT compared to subjects on 150mg q2w. The rate of ALT elevation (>3x ULN) was greatest between Weeks 0-24 and then seemed to plateau after Week 72.

Figure 41 shows a scatter plot of peak values of ALT and peak values of total bilirubin for individual subjects in the long-term safety population. Six patients had ALT >3x ULN and total

Clinical Review

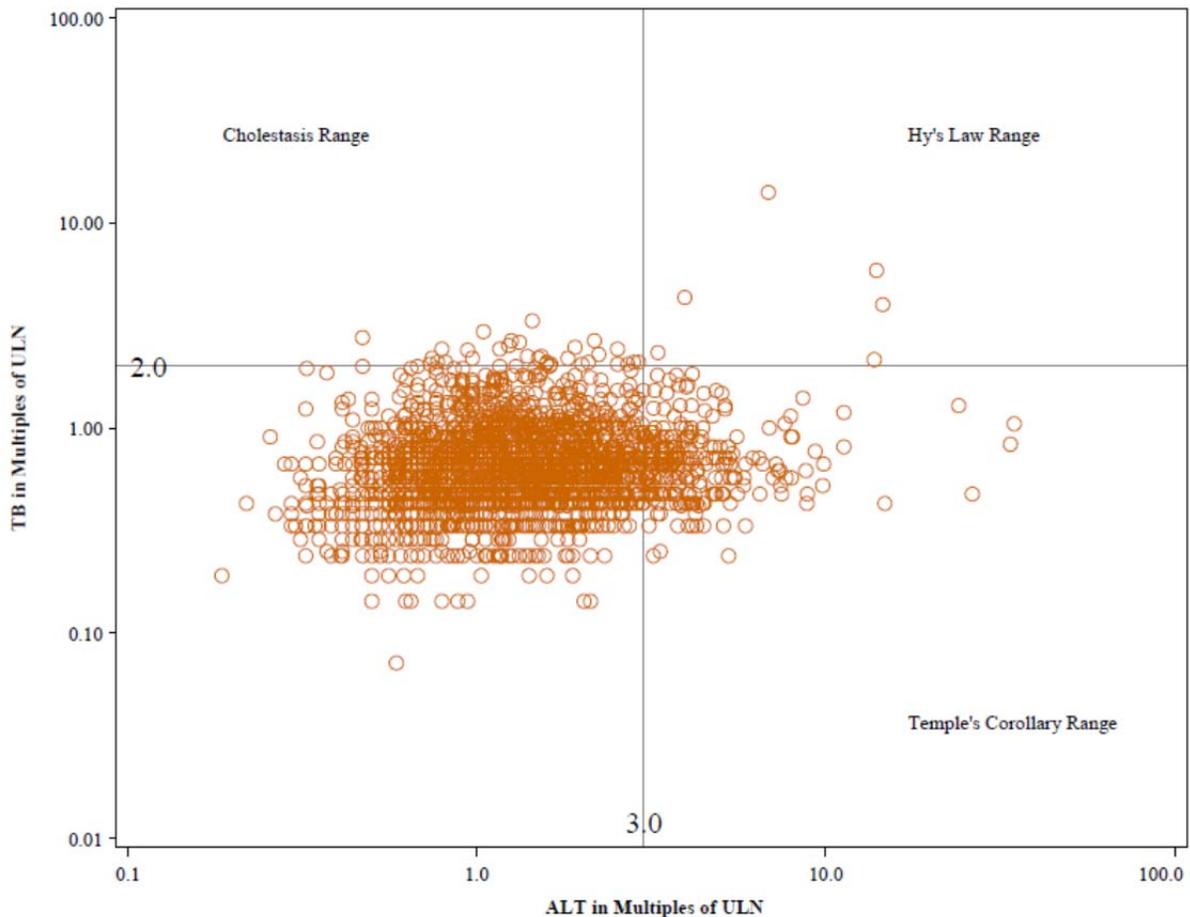
Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

bilirubin >2x ULN. Sanofi concluded that these subjects did not meet criteria for Hy's law. For some of these subjects, the elevation in ALT and total bilirubin did not occur at the same. Additionally, many had alternative possible explanations for the elevated enzymes, including biliary pancreatitis, suspected bile duct stone, recent chemical exposure (sulfuric and hydrochloric acid vapors)/hepatic abscess, and cholelithiasis.

**Figure 41. Scatter Plot of Peak Values of ALT vs. Peak Value of T Bili during the Entire TEAE Period (Pool 2)**



ALT = alanine transferase

T Bili = total bilirubin

Source: Integrated Summary of Safety, Figure 21, dated October 6, 2015; page 195.

The model-based analysis, where data from Pool 1 and Pool 2 were analyzed together, again showed an increased raw and exposure-adjusted incidence rate of ALT elevation in the sarilumab arms compared to placebo. The exposure-adjusted incidence rate was 2.9 per 100 patient-years in the placebo arm versus 9.3 per 100 patient-years in sarilumab 150mg q2w arm and 6.9 per 100 patient-years in sarilumab 200mg q2w arm. The rate ratio between the 2 doses of sarilumab was 0.69 (95% CI: 0.51, 0.95).

**Table 68. Model-based Analyses on Patients with at least one ALT >3x ULN during the TEAE period**

	Placebo + DMARD	Sarilumab 150mg q2w + DMARD	Sarilumab 200mg q2w + DMARD	Any Sarilumab + DMARD
<b>Elevated ALT</b>				
Raw incidence rate n/N (%)	11/661 (1.7)	63/1155 (5.5)	117/1351 (8.7)	254/2887 (8.8)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	11/379.1 (2.9)	63/678.1 (9.3)	11/1701.3 (6.9)	254/4240.1 (6.0)
Rate ratio vs. PBO + DMARD (95% CI)		4.29 (1.99, 9.24) <sup>b</sup>	2.98 (1.39, 6.38) <sup>b</sup>	2.79 (1.29, 6.06) <sup>c</sup>
Rate ratio vs. sarilumab 150mg + DMARD (95% CI)			0.69 (0.51, 0.95) <sup>b</sup>	

a Number of patients with at least one event per 100 patient-years (PYs), where the exposure time for patients who have experienced the specific adverse experience was defined as the time to first adverse experience of interest whereas the exposure time for those who have not had this adverse experience was total TEAE period duration

b The rate ratio and its 95% confidence interval (CI) were estimated using the GEE (Poisson distribution with exposure calculated based on the time to first event as an offset), adjusted for treatment and the important baseline factors (gender, RA duration of disease, geographic region, baseline ALT), assuming an exchangeable covariance structure for the within-subject correlations

c The rate ratio and its 95% confidence interval (CI) were estimated using the GEE (Poisson distribution with exposure calculated based on the time to first event as an offset), adjusted for treatment and the important baseline factors (gender, RA duration of disease, geographic region, baseline ALT), assuming an exchangeable covariance structure for the within-subject correlations

Source: Sanofi response to IR (June 10 and 13, 2016), Appendix B 1.12.3.4, dated June 15, 2016, page 11.

Sanofi provided follow-up on the subjects (from the long-term safety population) who had an elevation in liver enzymes. Two hundred fifty-four subjects (8.7%) on any sarilumab dose had an elevation in ALT >3x ULN. Of these subjects, 132 subjects (52%) normalized on-treatment (i.e., at least 1 ALT value was normal within ≤ 17 days after last dose of sarilumab); 57 subjects (22%) normalized after discontinuation of sarilumab; and 65 subjects (26%) did not normalize at the time of last available assessment. Interestingly, 23 of the 65 subjects (42%), who continued to have elevated ALT, were still receiving sarilumab as part of the trial. Sanofi also noted that the majority of subjects, who discontinued sarilumab but normalization was not documented, had values of ALT <3x ULN, perhaps consistent with a slower normalization of values. Of the 254 subjects on any dose of sarilumab with an ALT >3x ULN, 182 subjects (72%) were able to re-initiate sarilumab. The majority of the 182 subjects (128 or 70%) did not experience another occurrence of an elevation in ALT >3x ULN, whereas 28 subjects (15%) had 1 recurrence and 26 subjects (14%) had 2 or more recurrences. Therefore, from the follow-up information provided, it seemed reasonable to conclude the elevation in liver enzymes was reversible or transient for more, and many of these subjects were able to re-initiate therapy.

Another way that Sanofi evaluated hepatotoxicity was to use the search criteria SMQ drug-

Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

related hepatic disorders. The preferred terms in this search criteria included “alanine aminotransferase increased,” “transaminases increased,” “aspartate aminotransferase increased,” “hepatic enzyme increased,” “drug-induced liver injury,” “hepatitis toxic,” and “mixed liver injury.” Utilizing this search criterion, there were also more hepatic disorders in the sarilumab arms compared to placebo during the pre-rescue period, but the rates between doses had little difference. For placebo, there were 16 subjects with “hepatic disorder” (2.8%, 16/579). For sarilumab, the raw incidence rate was 6.7% (39/579) for sarilumab 150mg treatment arm and 6.4% (37/582) for sarilumab 200mg treatment arm. The exposure adjusted incidence rate was 10.2 per 100 patient-years for placebo, 26.2 per 100 patient-years for sarilumab 150mg, and 25.5 per 100 patient-years for sarilumab 200mg. Table 69 shows the raw incidence rates and exposure-adjusted incidence rates of hepatic disorders in the pre-rescue period.

**Table 69. Number (%) of Patients with Hepatic Disorders during the Pre-Rescue Period (Pool 1a)**

	Placebo + DMARD	Sarilumab 150mg q2w + DMARD	Sarilumab 200mg q2w + DMARD
<b>Hepatic disorders</b>			
Raw incidence rate n/N (%)	16/579 (2.8%)	39/579 (6.7%)	37/582 (6.4%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	16/156.3 (10.2)	39/148.6 (26.2)	37/145.3 (25.5)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		4.2% (1.7, 6.7)	3.9% (1.4, 6.4)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			-0.2% (-3.2, 2.7)

Search criteria: SMQ Drug-related hepatic disorders – comprehensive search

n = subset of total number of pts who met the criterion at least once during treatment

N (denominator) = number of patients for the treatment group who had that parameter assessed post-baseline

a Number of patients with at least 1 event per 100 patient-years, where the exposure time for patients who have experienced the specific adverse event experience was defined as the time to first adverse experience of interest whereas the exposure time for those who have not had this adverse experience was total TEAE period duration

b The rate difference and its 95% confidence interval were estimated using the M&N method stratified by the study, using the CMH weight

Source: ISS Appendix 1.12.1.52, dated September 29, 2015, page 8288-9.

For the entire double-blind period, the rates of hepatic disorders were higher but showed a similar pattern, that is, higher in sarilumab compared to placebo but similar between doses. Twenty-five subjects (3.8%) on placebo experienced a hepatic disorder. Subjects on sarilumab experienced more with 63 subjects (9.5%) on sarilumab 150mg q2w and 72 subjects (10.9%) on sarilumab 200mg q2w. The exposure-adjusted incidence rates were lower than that calculated for the pre-rescue period: 6.7 per 100 patient-years in placebo arm, 15.3 per 100 patient-years in sarilumab 150mg q2w arm, and 17.5 per 100 patient-years in sarilumab 200mg q2w arm. There were a few “hepatic disorders” that were considered serious in the double-blind period in all treatment arms (1 subjects [0.3%] in the placebo arm, 5 subjects [1.1%] in the 150mg q2w arm,

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

and 2 subjects [0.5%] in the 200mg q2w arm). More subjects on sarilumab discontinued the IMP because of a hepatic disorder, 2.3% of subjects on sarilumab 150mg q2w, 2.1% of subjects on sarilumab 200mg q2w, and 0.5% of subjects on placebo.

Over time, in the long-term safety population, the exposure-adjusted incidence of subjects with hepatic disorders was slightly lower than during the double-blind period. The exposure-adjusted incidence was 13.1 per 100 patient-years for the sarilumab 150mg q2w arm and 11.0 per 100 patient-years for the 200mg q2w arm. The rates of serious hepatic disorders and hepatic disorders leading to discontinuation were similar to what was seen in the double-blind period.

Lastly, Sanofi also presented to support that dose reduction seemed to correlate with an improvement in liver enzyme elevations. As noted in the protocol for the open-label extension study LTS11210, investigators could reduce sarilumab dose to 150mg q2w for an ALT  $\geq 3-5 \times$  ULN. Dose reduction from 200mg q2w was reported in 15.2% of patients. Neutropenia was the most common reason for dose reduction, but an elevation in ALT was the second most common cause. Table 70 shows the number of subjects who had a dose reduction secondary to ALT increase, and Table 71 shows the general improvement in elevations in ALT after dose reduction.

APPEARS THIS WAY ON ORIGINAL

**Table 70. Dose Reduction for Elevated ALT in Study LTS11210**

	Treatment prior to dose reduction to 150mg q2w				Total (N=1998) n(%)
	150mg qw (N=87) n(%)	150mg qw → 200mg qw (N=213) n(%)	200mg q2w (N=1630) n(%)	150mg q2w <sup>b</sup> (N=68) n(%)	
Number of patients with dose reduction not due to error <sup>a</sup>	43 (49.4%)	28 (13.1%)	248 (15.2%)	35 (51.5%)	354 (17.7%)
<b>ALT increase</b>	9 (10.3%)	10 (4.7%)	51 (3.1%)	8 (11.8%)	78 (3.9%)
ALT increase >3x ULN and ≤5x ULN	8 (9.2%)	10 (4.7%)	44 (2.7%)	1 (1.5%)	63 (3.2%)
Precautionary measure to avoid ALT increase >3x ULN	1 (1.1%)	0	7 (0.4%)	7 (10.3%)	15 (0.8%)

a Dose reduction due to reason 8 on CRF (by mistake and continued reduced dose regimen and did not go back to top dose) or reason 9 on CRF (by mistake and injected at least 1 reduced dose and went back to top dose) is excluded

b Per protocol, initial dose in LTS11210 was to be 150mg q2w or 200mg q2w. However, at the investigator’s discretion, some patient’s initial dose in LTS11210 was 150mg q2w. No further dose reduction.

Source: Integrated Summary of Safety, Table 142, dated October 6, 2015; page 327.

APPEARS THIS WAY ON ORIGINAL

**Table 71. Summary of ALT for Patients on 200mg q2w who Dose Reduced due to ALT Increase in Study LTS11210**

ALT <sup>a</sup>	Prior to dose reduction <sup>b</sup> (N=61)	1 month after dose reduction <sup>c</sup> (N=34)	3 month after dose reduction <sup>d</sup> (N=46)	6 months after dose reduction <sup>e</sup> (N=46)
≤ ULN	1 (1.6%)	6 (17.6%)	13 (28.3%)	16 (34.8%)
> 1 and ≤ 1.5 x ULN	1 (1.6%)	8 (23.5%)	12 (26.1%)	11 (23.9%)
>1.5 and ≤ 3 x ULN	7 (11.5%)	12 (35.3%)	20 (43.5%)	17 (37.0%)
>3 and ≤ 5 x ULN	50 (82.0%)	7 (20.6%)	1 (2.2%)	2 (4.3%)
>5 and ≤ 10 x ULN	2 (3.3%)	1 (2.9%)	0	0
>10 and ≤ 20 x ULN	0	0	0	0
>20 x ULN	0	0	0	0

Patient's dosing regimen in LTS11210 was either 200mg q2w or 150mg qw→200mg q2w prior to dose reduction.

The denominator (/N) is the number of patients who dose reduced due to ALT increase and had ALT measured during that period.

a Reason for 1<sup>st</sup> dose reduction was due to either ALT increase >3x ULN and ≤5x ULN or precautionary measure to avoid ALT increase >3x ULN

b Maximum value prior to dose reduction was summarized

c Maximum value from day after dose reduction to 1 month (days from dose reduction ≤30) was summarized

d Maximum value between Month 1 and 3 (days from dose reduction >30 and ≤90) was summarized

e Maximum value between Month 3 and 6 (days from dose reduction >90 and ≤180) was summarized

Source: Integrated Summary of Safety, Table 145, dated October 6, 2015; page 331.

APPEARS THIS WAY ON ORIGINAL

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

Sarilumab monotherapy would interestingly take away any contribution of concomitant DMARDs that can be hepatotoxic, such as methotrexate or leflunomide. A discussion of liver associated enzymes with sarilumab monotherapy is provided below in Section 8.7.

In conclusion, sarilumab appears to be associated with an elevation in liver enzymes, based on trends in the enzymes over the study period and the proportion of subjects with hepatic disorders. In the pre-rescue period, there was little to no difference between doses in regards to elevation in ALT or proportion of subjects with hepatic disorders. However, in the entire double-blind period, more subjects developed elevated liver enzymes on the higher dose of sarilumab, but the difference was small. The overall trends were consistent across safety populations. There were no cases of Hy's law. Follow-up safety data showed that the majority of the liver enzyme elevation was reversible. Additionally, in the open-label extension study, it was noted that decreasing the dose from 200mg q2w → 150mg q2w did improve the overall number of subjects with elevations in liver enzymes. These findings are consistent with what was expected, as an elevation in liver enzymes was an anticipated effect of IL-6 inhibition in the RA population based on the known experience with tocilizumab.

### **Neutropenia/Leukopenia**

Like the adverse event of elevation in liver associated enzymes, it was anticipated that subjects on sarilumab might develop neutropenia because of previous experience with IL-6 inhibition in RA patients. Namely, neutropenia was observed with tocilizumab and in pre-clinical trials with sarilumab.

Given this anticipated risk, as described in Section 6, patients with a white blood cell (WBC) count < 3.0 Giga/L or neutrophil count < 2.0 Giga/L were excluded from the sarilumab clinical development program. Section 6 and 8.3.3 also describe the criteria in the protocols for discontinuing the drug based on the neutrophil count and presence of infection. Also, as with the liver enzymes, the dose of sarilumab could be reduced in study LTS11210 based on specific ANC grade. The ANC <1.0 Giga/L was required to be reported as an adverse event.

To analyze neutropenia, Sanofi approached the safety data by analyzing the following:

- Mean change in ANC over the course of the study
- Incidence of ANC decrease by maximum severity
- Reports of adverse events: PT "leukopenia," SMQ "leukopenia," PT "neutropenia"
- Association of decrease in ANC with infections

In this review, the trend in ANC will first be presented for the safety populations (pre-rescue period, double-blind period, long-term safety population). A brief discussion of the correlation between the decline in ANC and infection will also be reviewed. Lastly, the adverse events related to leukopenia and neutropenia will be discussed.

Table 72 presents the number of subjects with a decrease in neutrophils (by grade) in the pre-rescue period (Pool 1a). The number of subjects on sarilumab with a decrease in neutrophils far outnumbered the number of subjects on placebo, and there appeared to be a dose-response. In total, 19 subjects (3.3%) on placebo had a lab measuring a decrease in neutrophils in the pre-rescue period, whereas 146 subjects (25.2%) on sarilumab 150mg q2w and 191 subjects (32.9%) on sarilumab 200mg q2w had a decrease in neutrophils. Grade 1 neutropenia is defined as an ANC  $\geq$  1.5 Giga/L to the lower limit of normal; grade 2 neutropenia is defined as an ANC between 1 to 1.5 Giga/L; grade 3 neutropenia is defined as an ANC between 0.5 to 1 Giga/L; lastly, grade 4 neutropenia is defined as an ANC less than 0.5 Giga/L. The majority of all subjects in all treatment arms had Grade 1-2 neutropenia. No subjects on placebo had Grade 3-4 neutropenia, but subjects on both doses of sarilumab had Grade 3-4 neutropenia.

**Table 72. Number (%) of Patients with Decreased ANC by Maximum Grade during the Pre-Rescue Period (Pool 1a)**

	Placebo + DMARD	Sarilumab 150mg q2w + DMARD	Sarilumab 200mg q2w + DMARD
<b>ANC</b>			
Grade 1: $\geq$ 1.5 Giga/L-LLN	14/579 (2.4%)	68/579 (11.7%)	81/580 (14.0%)
Grade 2: $\geq$ 1-1.5 Giga/L	5/579 (0.9%)	53/579 (9.2%)	75/580 (12.9%)
Grade 3: $\geq$ 0.5 – 1 Giga/L	0/579	21/579 (3.6%)	31/580 (5.3%)
Grade 4: < 0.5 Giga/L	0/579	4/579 (0.7%)	4/580 (0.7%)

n = subset of total number of pts who met the criterion at least once during treatment

N (denominator) = number of patients for the treatment group who had that parameter assessed post-baseline

ANC = absolute neutrophil count

Source: ISS Appendix 1.12.1.54, dated September 29, 2015, page 8295.

Clinically, “neutropenia” becomes concerning at an ANC < 0.5 Giga/L or < 1 Giga/L and trending down. Therefore, Sanofi did specifically evaluate subjects with ANC < 1 Giga/L, as in Table 73. In the pre-rescue period, more subjects on sarilumab developed an ANC < 1 Giga/L, as no subjects on placebo had an ANC < 1 Giga/L. In the pre-rescue period, the rate difference between doses was small, 1.8% (95% CI: -0.8, 4.4).

APPEARS THIS WAY ON ORIGINAL

**Table 73. Summary of ANC < 1.0 Giga/L in the Pre-Rescue Period (Pool 1a)**

	Placebo + DMARD	Sarilumab 150mg q2w + DMARD	Sarilumab 200mg q2w + DMARD
<b>ANC &lt; 1.0 Giga/L</b>			
Raw incidence rate n/N (%)	0/579	25/579 (4.3%)	35/580 (6.0%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	0/161.4 (0.0)	25/153.1 (16.3)	35/152.0 (23.0)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		4.4% (2.7, 6.1)	6.2% (4.2, 8.1)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			1.8% (-0.8, 4.4)

n (%) = number and percentage of patients with at least one TEAE

ANC = absolute neutrophil count

a Number of patients with at least 1 event per 100 patient-years, where the exposure time for patients who have experienced the specific adverse event experience was defined as the time to first adverse experience of interest whereas the exposure time for those who have not had this adverse experience was total TEAE period duration

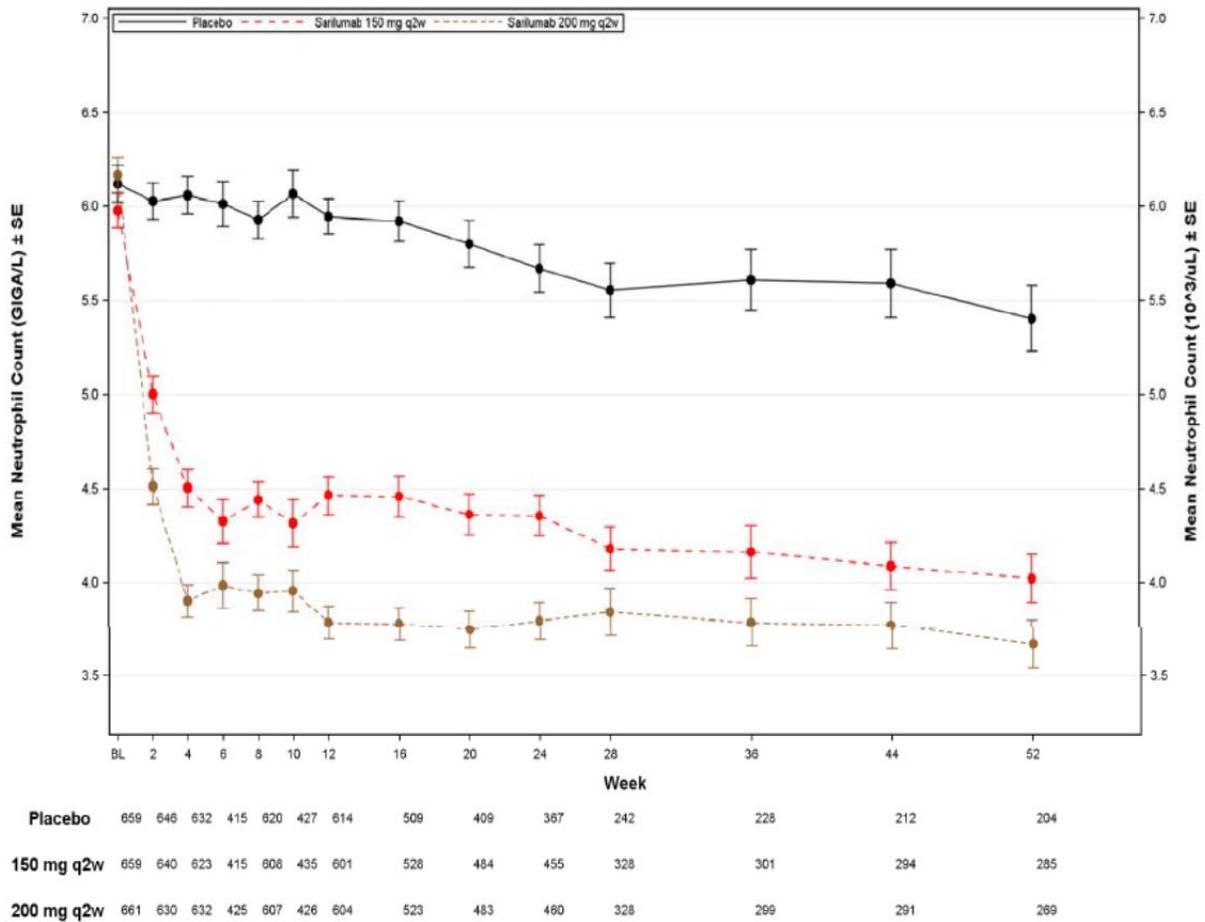
b The rate difference and its 95% confidence interval were estimated using the M&N method stratified by the study, using the CMH weight

Source: ISS Appendix 1.12.1.55, dated September 29, 2015, page 8296.

Over the entire double-blind treatment period (Pool 1), 40.6% of subjects on sarilumab 200mg q2w and 31.9% of subjects receiving sarilumab 150mg q2w had a drop in neutrophil count. Only 4.9% of subjects on placebo had a decline in neutrophils. The subjects on placebo had very gradual decline in the ANC, whereas subjects on sarilumab showed a sharp decline between Weeks 0-4. Figure 42 trends the mean ANC for all treatment arms through the entire double-blind period for the placebo-controlled population (Pool 1). After Week 4, the ANC of subjects on sarilumab began to plateau. Throughout the double-blind period, the ANC of subjects on sarilumab 200mg q2w decreased to a lower level than subjects on sarilumab 150mg q2w. Thus, the dose-response seemed more evident in the entire double-blind period. This held true for subjects with ANC <1 Giga/L. The incidence of ANC <1.0 Giga/L was 9.2% in sarilumab 200mg q2w group, 6.1% in the sarilumab 150mg q2w group, and 0.2% in the placebo group. The rate difference between the sarilumab doses was 3.2% (95% CI: 0.3, 6.0).

APPEARS THIS WAY ON ORIGINAL

**Figure 42. Mean ANC across Visits during the Double-Blind Treatment Period (Pool 1)**



Normal range: 1.96 – 7.23 Giga/L

Source: Integrated Summary of Safety, Figure 11, dated October 6, 2015; page 157.

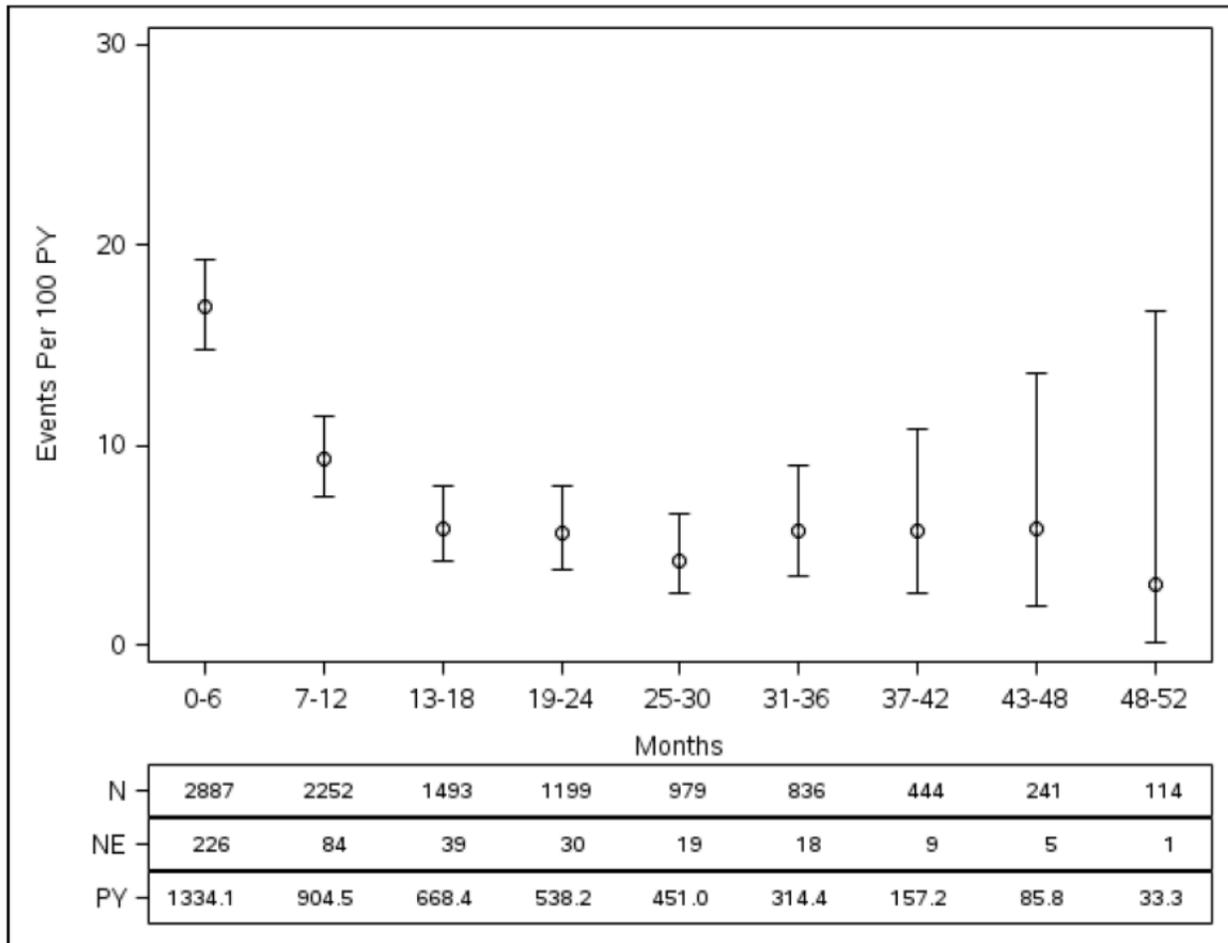
It should be noted that that other types of WBCs (lymphocytes, monocytes, eosinophils, and basophils) did not have meaningful changes during the double-blind treatment period.

With longer exposure, the incidence of ANC <1.0 Giga/L was numerically higher in the long-term safety population and also higher in the sarilumab 200mg treatment arm as compared to the sarilumab 150mg arm. The incidence of ANC <1.0 Giga/L in the long-term safety population (Pool 2) was 6.9% in the 150mg q2w initial dose arm and 10.8% in the 200mg q2w initial dose arm. The difference between treatment arms might be related to the fact that subjects were all transitioned to 200mg in the open-label study. However, for neutropenia, there was a more consistent dose-response for all the safety populations.

Figure 43 shows the exposure-adjusted rate of patients with ANC <1.0 Giga/L by 6-month intervals for the entire TEAE period for the long-term safety population. As it has already been

noted, the incidence rate of neutropenia was greatest initially. However, after the first 6 months, the exposure-adjusted rate was lower and stable.

**Figure 43. Exposure-adjusted Rate of Patients with at least 1 ANC <1.0 Giga/L by 6 month Interval during the Entire TEAE Period (Pool 2)**



N = sample size; NE = number of events in a 6-month period; PY = patient-years  
 95% confidence interval was calculated using the exact method  
 ANC = absolute neutrophil count  
 Source: ISS, Figure 13, dated October 6, 2015; page 162.

Sanofi provided model-based analyses of subjects with ANC <1.0 Giga/L in order to combine the safety data for Pools 1 and 2. This analysis showed a raw incidence rate of 0.2% in the placebo arm, 6.8% in the sarilumab 150mg q2w arm, 10.8% in the sarilumab 200mg q2w arm, and 11.2% in the any dose sarilumab arm. For any dose of sarilumab, the rate ratio against placebo was 28.92 (95% CI: 4.74, 176.45). The rate ratio between doses was much smaller at 0.91 (95% CI: 0.68, 1.22). Thus, this model-based analysis seems to support the association of sarilumab use with a decline in neutrophils and a dose-response.

**Table 74. Model-based Analyses on Patients with at least one Absolute Neutrophil Count <1.0 Giga/L during the TEAE period**

	Placebo + DMARD	Sarilumab 150mg q2w + DMARD	Sarilumab 200mg q2w + DMARD	Any Sarilumab + DMARD
<b>Neutropenia</b>				
Raw incidence rate n/N (%)	1/661 (0.2)	79/1155 (6.8)	146/1351 (10.8)	322/2887 (11.2)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	1/382.3 (0.3)	79/674.4 (11.7)	146/1713.0 (8.5)	322/4176.7 (7.7)
Rate ratio vs. PBO + DMARD (95% CI)		36.38 (6.18, 214.22) <sup>b</sup>	33.05 (5.60, 194.88) <sup>b</sup>	28.92 (4.74, 176.45) <sup>c</sup>
Rate ratio vs. sarilumab 150mg + DMARD (95% CI)			0.91 (0.68, 1.22) <sup>b</sup>	

a Number of patients with at least one event per 100 patient-years (PYs), where the exposure time for patients who have experienced the specific adverse experience was defined as the time to first adverse experience of interest whereas the exposure time for those who have not had this adverse experience was total TEAE period duration

b The rate ratio and its 95% confidence interval (CI) were estimated using the GEE (Poisson distribution with exposure calculated based on the time to first event as an offset), adjusted for treatment and the important baseline factors (weight, geographic region, and baseline ANC), assuming an exchangeable covariance structure for the within-subject correlations

c The rate ratio and its 95% confidence interval (CI) were estimated using the GEE (Poisson distribution with exposure calculated based on the time to first event as an offset), adjusted for treatment and the important baseline factors (weight, RA duration of disease, geographic region, and baseline ANC), assuming an exchangeable covariance structure for the within-subject correlations

Source: Sanofi response to IR (June 10 and 13, 2016), Appendix B 1.12.3.3, dated June 15, 2016, page 10.

Sanofi provided follow-up on subjects with an ANC <1.0 Giga/L in the long-term safety population. As a reminder of what was presented in Section 6, there were criteria in the protocol based on ANC for discontinuing study drug. These included the following:

- Permanently discontinue if ANC < 0.5 Giga/L (Grade 4 neutropenia)
- Permanently discontinue if ANC > 0.5 Giga/L and < 1.0 Giga/L (Grade 3 neutropenia) associated with infection
- Temporarily discontinue if Grade 3 neutropenia without associated infection. IMP could be re-administered if neutrophil count recovered to ≥ 1.0 Giga/L

Three hundred twenty-two subjects on any dose of sarilumab had an ANC <1.0 Giga/L. Of these subjects, 215 patients (67%) normalized on-treatment (i.e., at least 1 ANC value was normal within ≤ 17 days after last dose of sarilumab), 75 patients (23%) normalized after discontinuation of sarilumab, and 32 patients (10%) had not normalized as of the last available assessment. Sanofi concluded that, for many of the subjects who had not normalized, there was inadequate follow-up time to assess for normalization. Of the same 322 subjects who had an ANC <1.0 Giga/L on any dose of sarilumab, 270 (84%) re-initiated sarilumab. The majority of the subjects who were able to re-initiate therapy had no or a single recurrence of ANC <1.0

Giga/L. Therefore, it appears that the decline in neutrophils is reversible.

For Pool 2, Sanofi also analyzed whether there was an association between neutropenia and actual infection. Table 75 presents the incidence of infection in subjects based on whether they had an ANC measured lower than the lower limit of normal. Overall, it appears that the number of overall infection and serious infections were generally the same whether subjects had measured neutropenia. The proportion of subjects with a decline in neutrophils who developed an infection remained stable around 48-49% or lower, even for the higher grades of neutropenia (i.e., Grades 3-4, <1.0 Giga/L). From this analysis, one could potentially question the clinical meaningfulness of the decline in neutrophils.

**Table 75. Incidence of Infection in Subjects with and without ANC < LLN in the Long-Term Safety Population (Pool 2)**

Criteria, n(%)	Sarilumab + DMARD		
	150 mg q2w Initial Dose (PY=701.9)	200 mg q2w Initial Dose (PY=1758.6)	Any Dose (PY=4481.8)
Patients with infection and ANC ≥ LLN	240/743 (32.3%)	295/687 (42.9%)	642/1487 (43.2%)
Patients with infection and ANC < LLN	125/410 (30.5%)	277/659 (42.0%)	671/1392 (48.2%)
Patients with serious infection and ANC ≥LLN	11/743 (1.5%)	29/687 (4.2%)	76/1487 (5.1%)
Patients with serious infection and ANC <LLN	6/410 (1.5%)	35/659 (5.3%)	82/1392 (5.9%)

ANC = absolute neutrophil count; LLN = lower limit of normal

Maximum grade of neutropenia defined based on the lowest ANC during the entire TEAE period was selected for each patient

Infection may have occurred before or after the laboratory assessment

Source: ISS, Table 64, dated October 6, 2015; page 165.

Alongside trending the actual neutrophil counts, Sanofi also evaluated leukopenia and neutropenia as a reported adverse event. Leukopenia and neutropenia were analyzed as PTs. Additionally, Sanofi utilized the SMQ Haematopoietic leukopenia, which included (but was not limited to) the following PTs: neutropenia, leukopenia, lymphopenia, neutrophil count decreased, white blood cell count decreased, and lymphocyte count decreased. Table 76 presents the number of subjects who experienced leukopenia and neutropenia (based on preferred terms) in the pre-rescue period (Pool 1a), as well as the proportion of subjects who met the criteria for the SMQ Haematopoietic leukopenia in the same safety population. Overall, the AEs of leukopenia and neutropenia showed a similar pattern as the general trends in neutrophils. More subjects on sarilumab experienced one of these AEs compared to placebo, and numerically more subjects on the higher dose were noted to have these events than subjects on the lower dose. For the SMQ leukopenia, 0.5% of subjects on placebo compared to 7.6% of subjects on sarilumab 150mg q2w and 11.0% of subjects on sarilumab 200mg q2w met this search criterion. Both sarilumab doses had a higher proportion compared to placebo, and the rate difference between doses was 3.5% (95% CI: 0.0, 6.9). As already discussed in Section

8.4.5, neutropenia was the most common PT in the sarilumab arms for all safety populations.

**Table 76. Summary of Adverse Events in Leukopenia and Neutropenia in the Pre-Rescue Period (Pool 1a)**

	Placebo + DMARD	Sarilumab 150mg q2w + DMARD	Sarilumab 200mg q2w + DMARD
<b>Leukopenia†</b>			
Raw incidence rate n/N (%)	8/579 (1.4%)	7/579 (1.2%)	13/582 (2.2%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	8/157.5 (5.1)	7/156.6 (4.5)	13/157.3 (8.3)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		-0.2% (-1.5, 1.1)	0.9% (-0.7, 2.4)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			1.0% (-0.5, 2.5)
<b>Neutropenia</b>			
Raw incidence rate n/N (%)	1/579 (0.2%)	40/579 (6.9%)	59/582 (10.1%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	1/160.9 (0.6)	40/148.2 (27.0)	59/146.2 (40.4)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		7.0% (4.8, 9.2)	10.3% (7.8, 12.9)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			3.3% (-0.0, 6.6)
<b>Leukopenia‡</b>			
Raw incidence rate n/N (%)	3/579 (0.5%)	44/579 (7.6%)	64/582 (11.0%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	3/160.6 (1.9)	44/146.2 (30.1)	64/144.0 (44.4)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		7.4% (5.2, 9.8)	10.9% (8.2, 13.6)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			3.5% (-0.0, 6.9)

n (%) = number and percentage of patients with at least one TEAE

† Based on PT "leukopenia"

‡ Based on SMQ "leukopenia"

a Number of patients with at least 1 event per 100 patient-years, where the exposure time for patients who have experienced the specific adverse event experience was defined as the time to first adverse experience of interest whereas the exposure time for those who have not had this adverse experience was total TEAE period duration

b The rate difference and its 95% confidence interval were estimated using the M&N method stratified by the study, using the CMH weight

Source: ISS Appendix 1.12.1.51 and 1.12.1.52, dated September 29, 2015, page 8283, 8288.

The proportion of subjects meeting the SMQ leukopenia was consistent in the double-blind population (Pool 1) and the long-term safety population (Pool 2). The exposure-adjusted incidence of subjects with leukopenia was generally lower with longer exposure, 22.5 subjects with leukopenia per 100 patient-years on sarilumab 150mg q2w initial dose, 16.3 per 100 patient-years on sarilumab 200mg q2w initial dose, and 14.4 per 100 patient-years on any dose

Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

of sarilumab.

Lastly, just as with elevated liver enzymes, in the open-label study (LTS11210), investigator could reduce the dose of sarilumab 150mg q2w based on neutrophil counts, specifically ANC  $\geq$  0.5 to 1.0 Giga/L without concomitant infection. Sanofi reported that 15.2% of subjects required dose reduction from 200mg q2w, and neutropenia was the most common cause at 10% of subjects on sarilumb 200mg q2w. Table 77 displays the number of subjects who required dose reduction secondary to a decrease in neutrophil count, and Table 78 shows the general trend in ANC after dose reduction. It appears that there was an improvement in neutrophil count after dose reduction, and, in fact, the neutrophil count in a large proportion of subjects (34.7-48.1%) corrected to the normal range.

APPEARS THIS WAY ON ORIGINAL

**Table 77. Dose Reduction in Study LTS11210 Secondary to Neutrophil Count Decrease**

	Treatment prior to dose reduction to 150mg q2w				Total (N=1998) n(%)
	150mg qw (N=87) n(%)	150mg qw → 200mg qw (N=213) n(%)	200mg q2w (N=1630) n(%)	150mg q2w <sup>b</sup> (N=68) n(%)	
Number of patients with dose reduction not due to error <sup>a</sup>	43 (49.4%)	28 (13.1%)	248 (15.2%)	35 (51.5%)	354 (17.7%)
<b>Neutrophil count decrease</b>	24 (27.6%)	12 (5.6%)	163 (10.0%)	23 (33.8%)	222 (11.1%)
Neutrophil count <1.0 Giga/L and ≥0.5 Giga/L	20 (23.0%)	5 (2.3%)	87 (5.3%)	4 (5.9%)	116 (5.8%)
Precautionary measure to avoid ANC <1.0 Giga/L	4 (4.6%)	7 (3.3%)	76 (4.7%)	19 (27.9%)	106 (5.3%)

a Dose reduction due to reason 8 on CRF (by mistake and continued reduced dose regimen and did not go back to top dose) or reason 9 on CRF (by mistake and injected at least 1 reduced dose and went back to top dose) is excluded

b Per protocol, initial dose in LTS11210 was to be 150mg q2w or 200mg q2w. However, at the investigator’s discretion, some patient’s initial dose in LTS11210 was 150mg q2w. No further dose reduction.

Source: Integrated Summary of Safety, Table 142, dated October 6, 2015; page 327.

APPEARS THIS WAY ON ORIGINAL

**Table 78. Summary of ANC for Patients on 200mg q2w who Required Dose Reduction in Study LTS11210**

ANC <sup>a</sup>	Prior to dose reduction <sup>b</sup> (N=175)	1 month after dose reduction <sup>c</sup> (N=121)	3 month after dose reduction <sup>d</sup> (N=146)	6 months after dose reduction <sup>e</sup> (N=131)
> LLN	6 (3.4%)	42 (34.7%)	68 (46.6%)	63 (48.1%)
Grade 1: ≥ 1.5 Giga/L to LLN	23 (13.1%)	26 (21.5%)	21 (14.4%)	21 (16.0%)
Grade 2: ≥ 1.0 - 1.5 Giga/L	51 (29.1%)	33 (27.3%)	39 (26.7%)	39 (29.8%)
Grade 3: ≥ 0.5 - 1.0 Giga/L	95 (54.3%)	17 (14.0%)	15 (11.6%)	8 (6.1%)
Grade 4: < 0.5 Giga/L	0	3 (2.5%)	1 (0.7%)	0

ANC = absolute neutrophil count

Patient’s dosing regimen in LTS11210 was either 200mg q2w or 150mg qw→200mg q2w prior to dose reduction.

The denominator (/N) is the number of patients who dose reduced due to ALT increase and had ALT measured during that period.

a Reason for 1<sup>st</sup> dose reduction was due to neutrophil count <1.0 Giga/L and ≥0.5 Giga/L or precautionary measure to avoid neutrophil count <1.0 Giga/L

b Lowest value prior to dose reduction was summarized

c Lowest value from day after dose reduction to 1 month (days from dose reduction ≤30) was summarized

d Lowest value between Month 1 and 3 (days from dose reduction >30 and ≤90) was summarized

e Lowest value between Month 3 and 6 (days from dose reduction >90 and ≤180) was summarized

Source: Integrated Summary of Safety, Table 144, dated October 6, 2015; page 331.

APPEARS THIS WAY ON ORIGINAL

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

In conclusion, based on the safety data, there does appear to be an association between sarilumab and a decline in neutrophil counts. The proportion of subjects with ANC <1.0 Giga/L was low in the pre-rescue period, but there was a clear association with sarilumab with no events in the placebo arm. In the pre-rescue and double-blind period, there also appeared to be a dose-response with more subjects on sarilumab 200mg q2w with low neutrophil counts compared to those on sarilumab 150mg q2w. From the follow-up data provided, it appears that the neutropenia is reversible. Also, in the open-label study, dose reduction is associated with an improvement in neutrophil counts. Interestingly, it is unclear whether the drop in neutrophil counts was clinically significant, as there does not seem to be an association between infections and neutropenia, even ANC <1.0 Giga/L. A decrease in neutrophil counts was an expected adverse event with IL-6 inhibition, and the data support this association with sarilumab as well.

### **Thrombocytopenia**

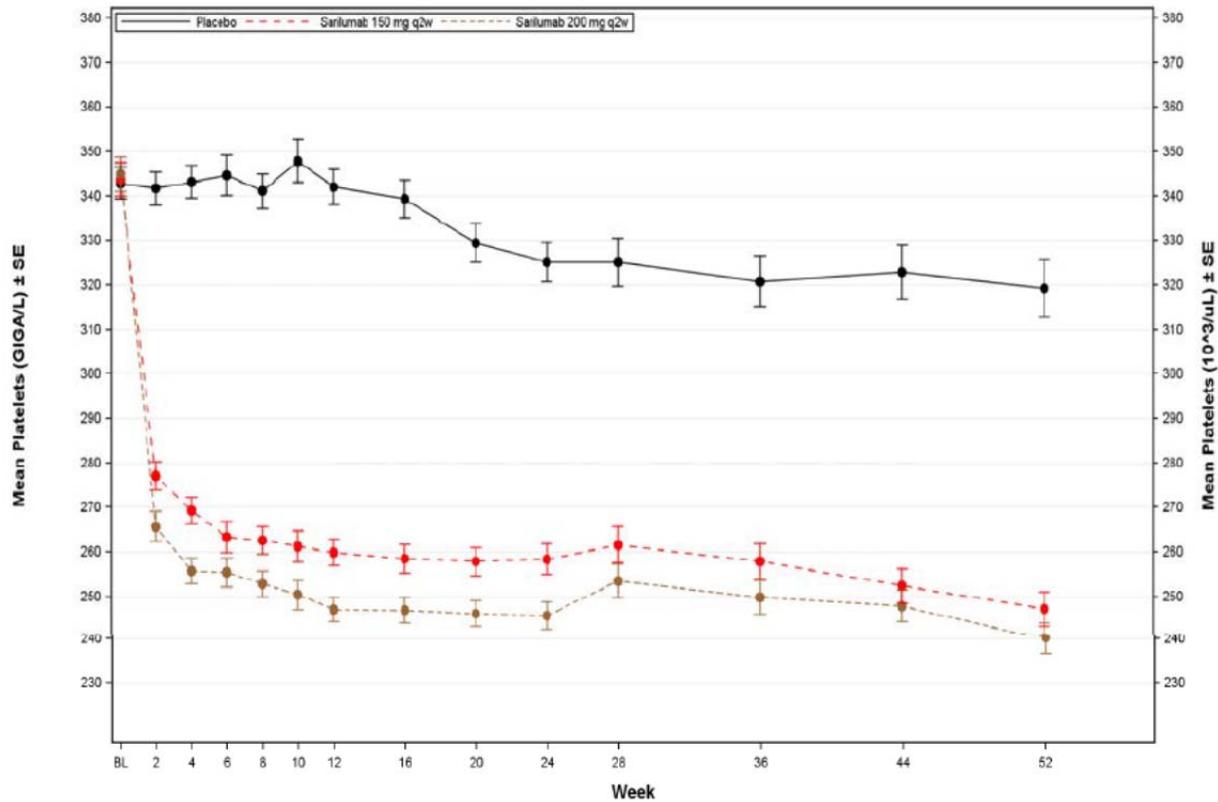
Much like elevated liver enzymes and neutropenia, a transient decrease in platelets has been associated with IL-6 inhibition; that is, it was noted with tocilizumab. Therefore, the sarilumab trials were designed to exclude subjects with platelet counts <150 Giga/L. Much like the last 2 laboratory findings, there were criteria in the protocol for IMP discontinuation based on platelet count and bleeding. In study LTS 11210, sarilumab dose could be reduced based on platelet count. Additionally, investigators were required to report a platelet count <100 Giga/L as an adverse event.

Sanofi evaluated thrombocytopenia by assessing for mean changes in platelet count, frequency of platelet count by maximum severity, the reporting of adverse events of based on the SMQ “thrombocytopenia,” and whether decreases in platelet counts were associated with bleeding.

In this review, the trend in platelet counts over the different safety populations will be presented. Additionally, Sanofi’s follow-up analysis of subjects with thrombocytopenia and association of thrombocytopenia and bleeding are discussed. Lastly, the review presents the proportion of subjects who fulfilled the SMQ “hematopoietic thrombocytopenia” in the different safety populations.

Over the double-blind treatment period (Pool 1), there was a clear trend toward a decline in platelets in subjects on sarilumab. Figure 44 displays the mean platelet counts over time through the end of the double-blind period. In general, there was very little change in the placebo arm, but both sarilumab arms had a decline in platelets. As with the liver enzymes and white blood cell counts, most of the decline occurred within the first 4 weeks of the study. There appears to be a small difference between doses with the higher dose having a slightly greater decline in platelets.

**Figure 44. Mean Platelets Across Visits during the Double-Blind Period (Pool 1)**



	BL	2	4	6	8	10	12	16	20	24	28	36	44	52
<b>Placebo</b>	659	641	627	414	613	425	607	505	404	365	241	226	212	202
<b>150 mg q2w</b>	659	634	617	413	802	429	596	525	480	453	325	298	291	282
<b>200 mg q2w</b>	660	624	627	423	805	421	603	522	479	460	327	299	291	268

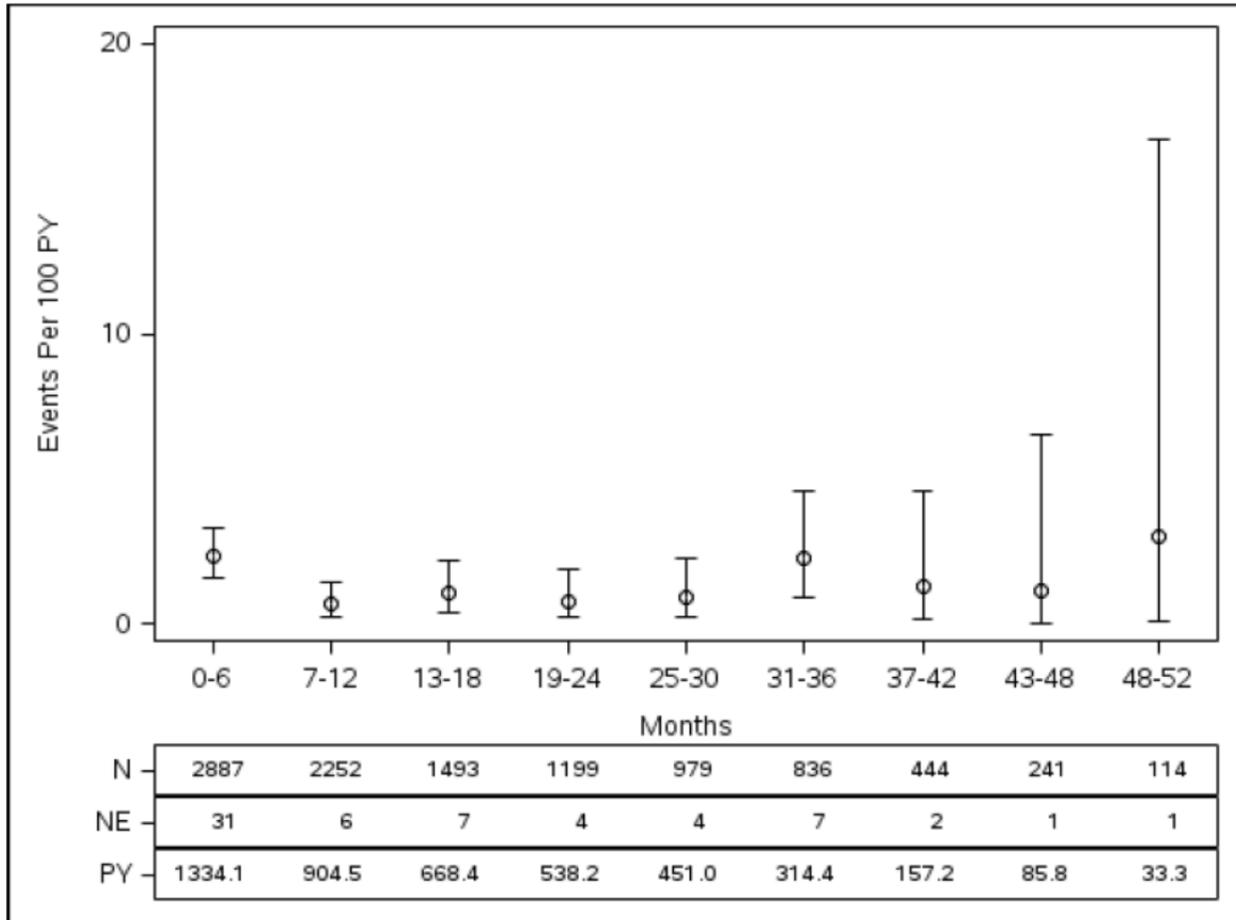
Normal range: 140-400 Giga/L

Source: Integrated Summary of Safety, Figure 14, dated October 6, 2015; page 173.

Clinically, any platelet count <150,000 is considered to be significant and worth further investigation. However, from a clinical trial perspective, Grade 1 thrombocytopenia is defined as a platelet count <75 Giga/L; Grade 3 thrombocytopenia is defined as a platelet count <50 Giga/L with bleeding; Grade 4 thrombocytopenia is a platelet count <25 Giga/L. Sanofi provided descriptive statistics for the proportion of subjects with a platelet count <100 Giga/L. In the double-blind period, 11 subjects (1.7%) in the sarilumab 200mg q2w arm and 4 subjects (0.6%) in the sarilumab 150mg q2w arm had a drop in platelets <100 Giga/L. No subjects in the placebo arm developed this level of thrombocytopenia. Generally, the proportion of subjects with this level of thrombocytopenia remained consistent in the long-term safety population (Pool 2). A total of 8 subjects (0.7%) in the sarilumab 150mg q2w initial dose arm, 30 subjects (2.2%) in the sarilumab 200mg q2w initial dose arm, and 57 subjects (2.0%) in the any dose arm had a platelet count <100 Giga/L. In the long-term safety population, only 5 subjects on any dose of sarilumab had a platelet count <50 Giga/L.

Figure 45 shows the exposure-adjusted rate of subjects with platelet counts < 100 Giga/L in the long-term safety population. The incidence rate was highest early in the study (0-6 months), and the incidence rate did not change through the rest of the long-term safety period.

**Figure 45. Exposure-adjusted Rate of Patients with at least 1 Platelet Count < 100 Giga/L by 6-month Intervals during the Entire TEAE Period (Pool 2)**



N = sample size; NE = number of events in a 6-month period; PY = patient-years  
 95% confidence interval was calculated using the exact method  
 Source: ISS, Figure 16, dated October 6, 2015; page 179.

Sanofi further assessed whether there was cases of concomitant thrombocytopenia and bleeding. Sanofi found that there were 5 subjects who met the criteria of a platelet count <100 Giga/L and any TEAE captured by the SMQ “Haemorrhages.” For 4 of the subjects, these did not occur concurrently; therefore, the bleeding event was not likely related to the thrombocytopenia. The fifth subject had a platelet count between 58-91 Giga/L and experienced “injection site ecchymosis.” Thus, in the safety data, the correlation between platelets and bleeding events was low.

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

As with elevated liver enzymes and neutropenia, Sanofi also provided follow-up on subjects from the long-term safety population with platelets <100 Giga/L. The discontinuation criteria for thrombocytopenia in the sarilumab trials were a platelet count <50 Giga/L or <100 Giga/L with bleeding. If platelet count was 50-100 Giga/L with no evidence of bleeding, investigators should temporarily discontinue the IMP. As noted, fifty-seven subjects on any dose of sarilumab had a platelet count <100 Giga/L. Of these, 33 subjects (58%) normalized on treatment (i.e., at least 1 platelet count was normal within  $\leq 17$  days after last dose of sarilumab); 12 subjects (21%) normalized after discontinuation of sarilumab; 12 subjects (21%) also did not normalize platelet counts at the last available assessment. Therefore, in summary, the platelet counts did reverse in the majority of subjects.

Alongside trending actual platelet counts, Sanofi evaluated the number of subjects who developed adverse events of thrombocytopenia. Sanofi utilized the search criteria SMQ "Haematopoietic thrombocytopenia," which included PTs such as thrombocytopenia and platelet count decreased. In the pre-rescue period, there were low number of events of "thrombocytopenia" overall. There were no events in the sarilumab arm. Five subjects (0.9%) on sarilumab 150mg q2w and 9 subjects (1.5%) on sarilumab 200mg q2w had thrombocytopenia. The rate difference between doses was 0.7% (95% CI: -0.6, 1.9), thus, including 0. For the entire double-blind period, no subjects on placebo had an AE consistent with thrombocytopenia, and the proportions in the sarilumab arms were consistent with the pre-rescue period. The general proportions of subjects with thrombocytopenia were similar in the sarilumab arms in the long-term safety population. For subjects on any dose of sarilumab, 2.4% of subjects experienced  $\geq 1$  event of thrombocytopenia for an exposure-adjusted incident rate of 1.6 per 100 patient-years.

APPEARS THIS WAY ON ORIGINAL

**Table 79. Summary of Thrombocytopenia during the Pre-Rescue Period (Pool 1a)**

	Placebo + DMARD	Sarilumab 150mg q2w + DMARD	Sarilumab 200mg q2w + DMARD
<b>Thrombocytopenia</b>			
Raw incidence rate n/N (%)	0/579	5/579 (0.9%)	9/582 (1.5%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	0/161.6 (0.0)	5/159.2 (3.1)	9/159.8 (5.6)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		0.9% (0.1, 1.6)	1.6% (0.5, 2.6)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			0.7% (-0.6, 1.9)

n (%) = number and percentage of patients with at least one TEAE

a Number of patients with at least 1 event per 100 patient-years, where the exposure time for patients who have experienced the specific adverse event experience was defined as the time to first adverse experience of interest whereas the exposure time for those who have not had this adverse experience was total TEAE period duration

b The rate difference and its 95% confidence interval were estimated using the M&N method stratified by the study, using the CMH weight

Source: ISS Appendix 1.12.1.52, dated September 29, 2015, page 8288.

Lastly, in the long-term safety study (LTS11210), one of the 3 reasons for sarilumab dose reduction was a platelet count  $\geq 50$  to 100 Giga/L in the absence of bleeding. From the subjects on 200mg q2w who required dose reduction, a total of 19 subjects reduced their sarilumab dose because of platelet counts. Sanofi did not provide what happened to the platelet levels after dose reduction. However, since the majority of these subjects (89.5%) were able to remain on sarilumab after dose reduction, it seems to imply, at the very least, that the platelet levels did not further decrease.

In conclusion, the overall number of subjects with low platelets was low in the sarilumab clinical trials. There was a trend toward lower mean platelet levels for subjects on sarilumab during the double-blind period. With such low numbers, it is difficult to determine if there is a true dose-response. For most subjects, the reduction in platelets was reversible. In the open-label study, subjects who developed thrombocytopenia were able to reduce the dose and stay on therapy. As transient thrombocytopenia was seen with tocilizumab, these findings in sarilumab were expected.

### Lipid Abnormalities

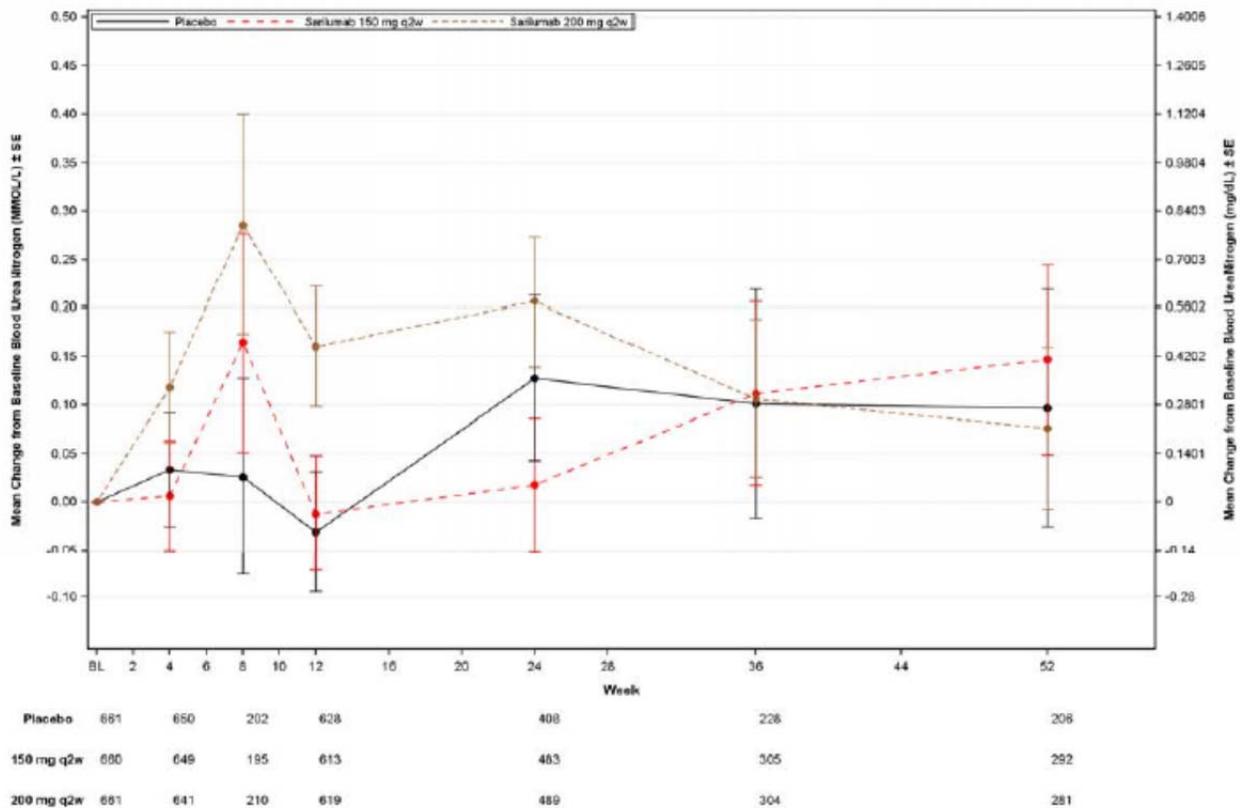
The review of lipid elevations is discussed as an Adverse Event of Special Interest in Section 8.5.2.

### Renal function

Unlike the previously discussed laboratory abnormalities, a change in renal function was not

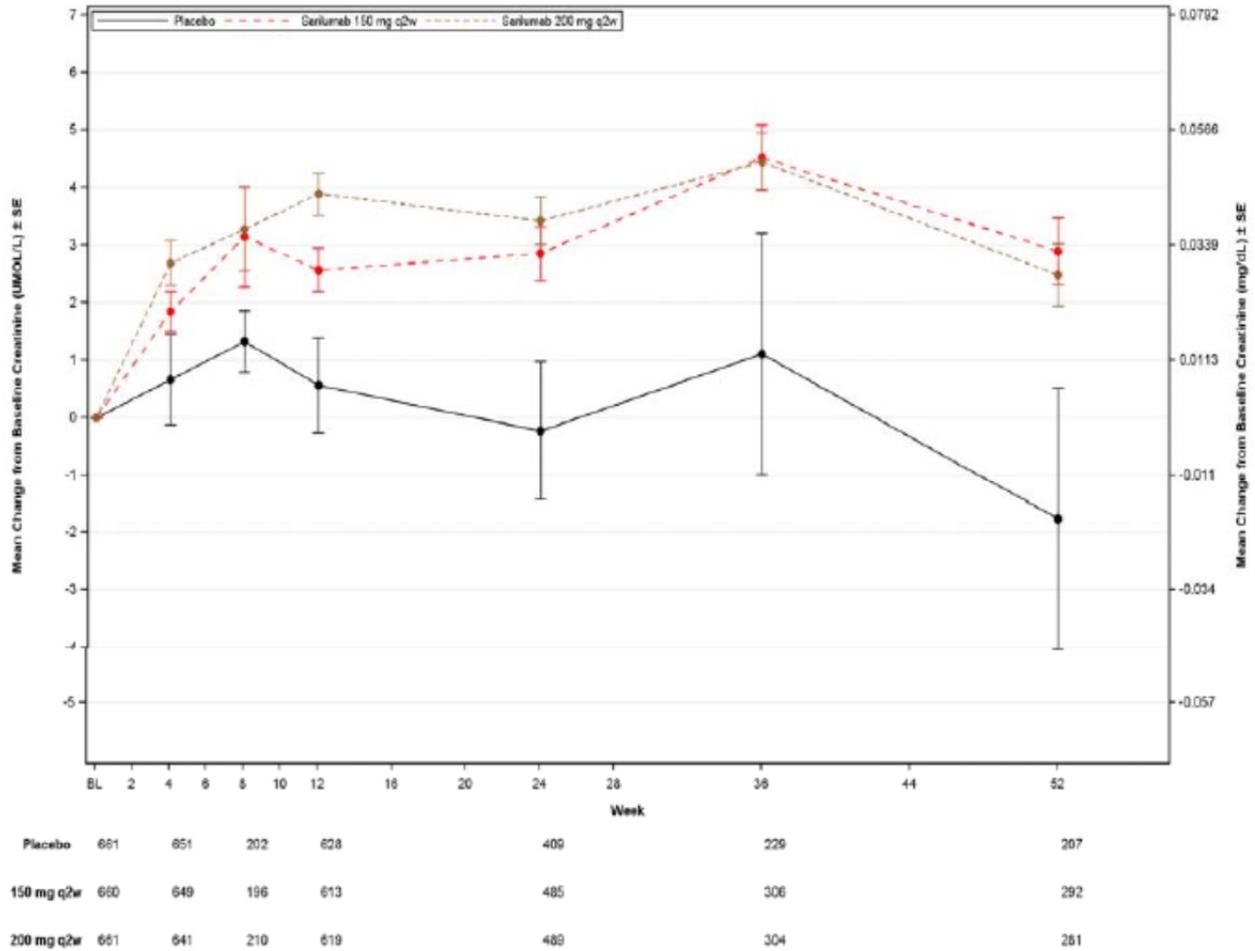
one of the anticipated effects of IL-6 inhibition in the RA population. Figure 46 and Figure 47 show the mean change in serum blood urea nitrogen (BUN) and mean change in serum creatinine (SCr) for the entire double-blind population (Pool 1). There does not appear to be a trend in BUN with variability noted in all treatment arms and with each arm exhibiting similar measurements. However, the change in SCr does seem to higher in the sarilumab arms compared to the placebo arm, but there is not a major difference between doses. Analysis of both the double-blind and long-term safety population showed that the initial increase in SCr seemed to plateau after Week 24.

**Figure 46. Mean Change from Baseline in BUN across Visits during the Double-Blind Period (Pool 1)**



BUN = blood urea nitrogen  
 Normal range: 1.428-8.57 mmol/L (4.00-24.00 mg/dL)  
 Source: Integrated Summary of Safety, Figure 33, dated October 6, 2015; page 299.

**Figure 47. Mean Change from Baseline in SCr Across Visits during the Entire Double-Blind Period (Pool 1)**



SCr = serum creatinine  
 Normal range: 35.36-97.24 µmol/L (0.40-1.10 mg/dL)  
 Source: Integrated Summary of Safety, Figure 34, dated October 6, 2015; page 300.

In the double-blind period, the incidence of an increase of  $\geq 30\%$  in SCr was numerically higher in the sarilumab groups compared to placebo: 9.4% in placebo vs. 13.7% in 150mg q2w and 14.5% in 200mg q2w. In the long-term safety population, the overall incidence of an increase of  $\geq 30\%$  in SCr in the any dose group was similar to that of the double-blind population, that is, 566 patients (19.8%).

Overall, in the long-term safety population, a total of 10 patients reported an adverse event in the HLT Renal failure and impairment with the following PTs: acute renal failure (4 patients), renal failure (2 patients), chronic renal failure (2 patients), pre-renal failure (1 patient), and renal impairment (1 patient). Sanofi noted that the 7 patients with the PTs of acute renal failure, pre-renal failure, and renal failure had concurrent illnesses that could have been the

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

etiologies of the renal failure; these illnesses included infection and dehydration due to hyperglycemia. In the 2 patients with chronic renal failure, the events were attributed to nephrolithiasis and CKD stage 3 due to age, hypertension, and chronic NSAID and MTX use.

In conclusion, there does appear to be a change in SCr in subjects on sarilumab. However, the difference from placebo is small, and there does not appear to be a dose-response. There is also not a clear mechanistic rationale for an elevation in creatinine with a monoclonal antibody, such as sarilumab, and the very small change is unlikely to have clinical consequences. In the clinical trials, there was not clear clinical association with the elevation in SCr, as there were very few events of renal failure, none of which could be attributed to sarilumab.

### **Electrolytes and Glucose**

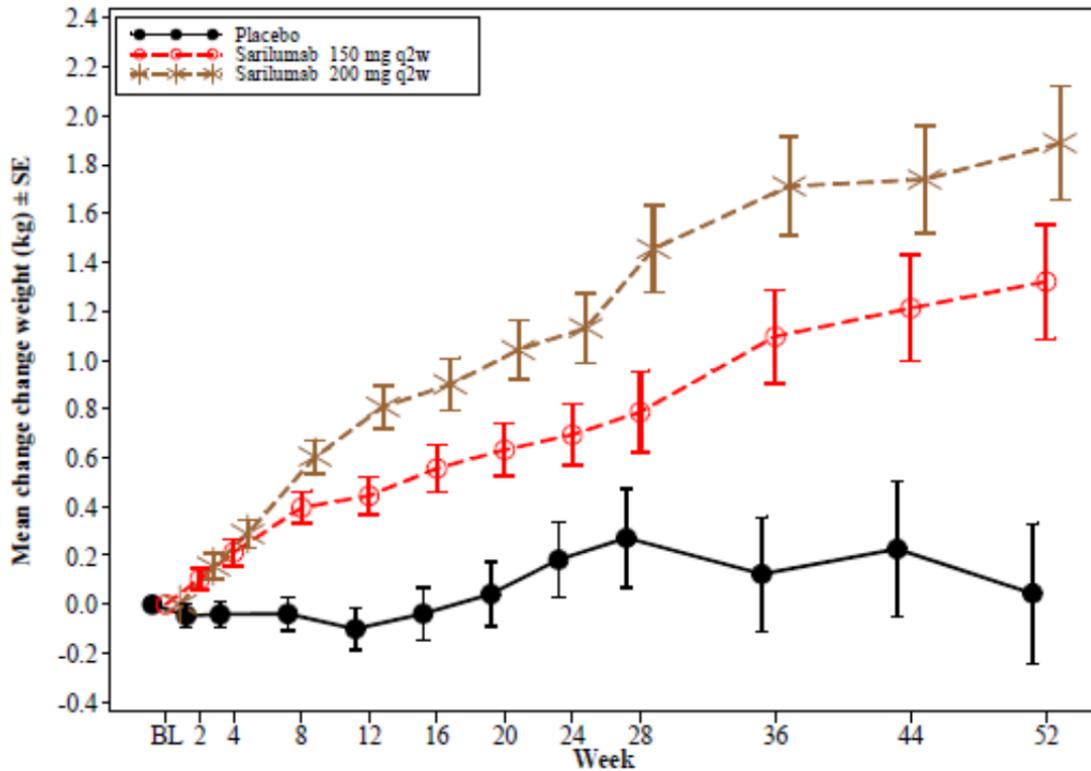
No major findings were noted with the other laboratory evaluations when compared to baseline at Weeks 24 and 52. A mean decrease in sodium and potassium was observed in all treatment arms. A mean increase in chloride was observed in the sarilumab groups, whereas a mean decrease was observed in the placebo group. There were no trends noted with the other electrolytes (bicarbonate, calcium, phosphate, mean glucose, or HbA1C).

#### **8.4.7. Vital Signs**

Vital signs were assessed throughout the entire study period, as described in the Schedule of Assessments for each protocol in Section 13.3. The trends for weight, blood pressure, and heart rate will be reviewed here.

Sanofi tracked weight change from baseline through the study, as shown in Figure 48. Both sarilumab arms (greater in the 200mg q2w arm) experienced an increase in weight, whereas there was generally no change in weight in the placebo arm. The etiology for this weight gain in the sarilumab arms is unclear. Sanofi suggested that RA patients with systemic symptoms associated with active inflammation tend to lose weight; therefore, the placebo arm may have had more active disease and, thus, no change in weight or even weight loss. However, so many variables can contribute to body weight that it is difficult to attribute the weight gain solely to differences in systemic inflammation. Other possible contributors would be concomitant therapy, as more subjects in the sarilumab arm were taking corticosteroids at baseline. Chronic corticosteroid use is an established cause of weight gain. Reassuringly, the greatest change in weight remained low, not exceeding a weight gain of 2 kg. Of note, the increase in body weight persisted in the long-term safety population but appeared to plateau after 48 weeks of initiation of therapy.

**Figure 48. Mean Weight Change from Baseline Across Visits during the Double-Blind Period (Pool 1)**

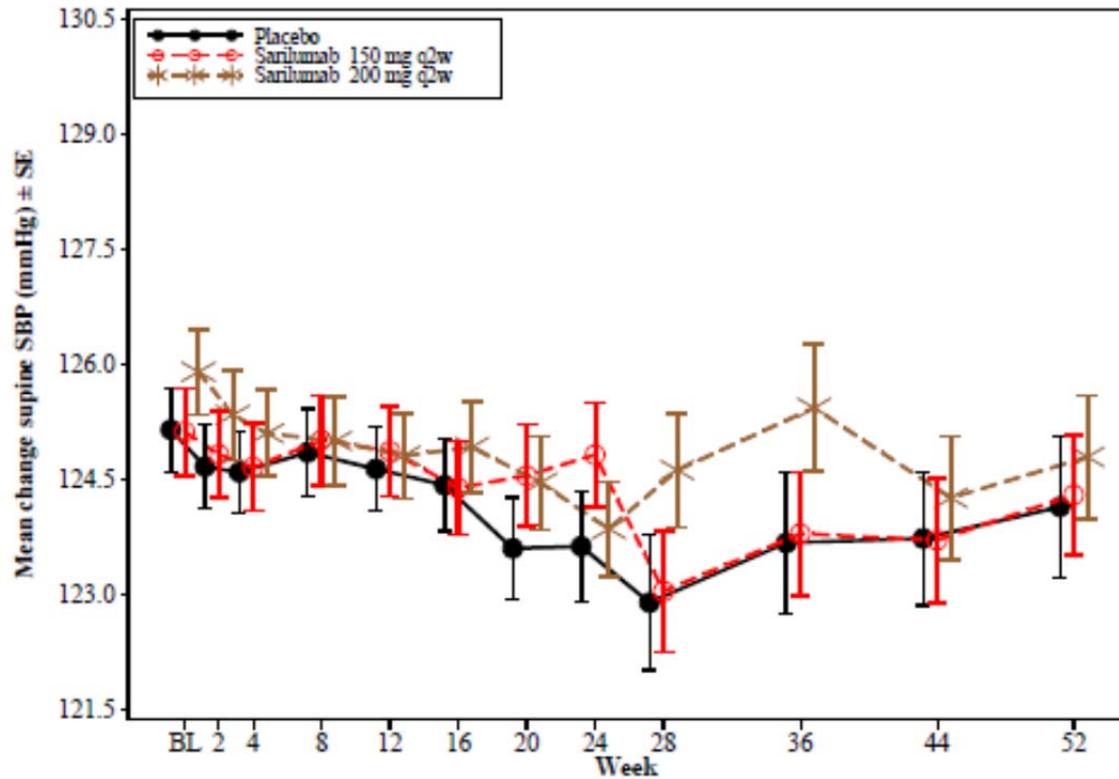


# subjects	BL	2	4	8	12	16	20	24	28	36	44	52
Placebo	661	476	646	638	631	523	413	377	250	231	213	209
Sarilumab 150 mg q2w	660	476	643	631	608	534	489	461	329	309	300	290
Sarilumab 200 mg q2w	661	474	645	639	619	532	490	470	327	304	297	283

Source: Integrated Summary of Safety, Figure 37, dated October 6, 2015; page 306.

Blood pressure (both systolic and diastolic) trended pretty similarly across all treatment arms. Figure 49 and Figure 50 show the systolic and diastolic blood pressures, respectively, over time. There was some variability in all treatment arms, but there does not appear to be a consistent change in any arm. Sanofi does note that there was a higher incidence of subjects on sarilumab with a supine systolic blood pressure  $\geq 160$  mmHg and increase from baseline  $\geq 20$  mmHg: 4.7% in 200mg q2w, 5.2% in 150mg q2w, and 3.8% in placebo. However, the overall incidence was low, and the differences were small.

**Figure 49. Mean Supine SBP Across Visits during the Double-Blind Period (Pool 1)**



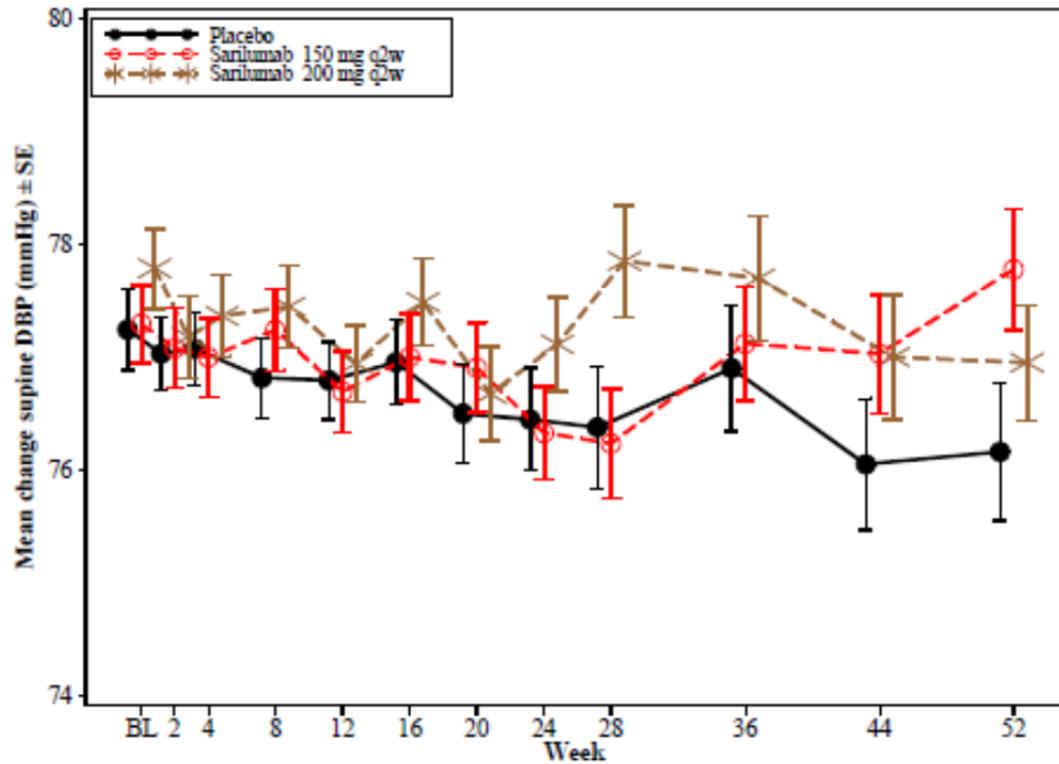
# subjects	BL	2	4	8	12	16	20	24	28	36	44	52
Placebo	654	652	645	637	631	523	415	378	251	232	214	210
Sarilumab 150 mg q2w	653	645	640	631	607	535	491	461	330	312	302	291
Sarilumab 200 mg q2w	657	649	644	639	619	531	490	472	328	304	297	282

SBP = systolic blood pressure

Source: Integrated Summary of Safety, Figure 39, dated October 6, 2015; page 309.

APPEARS THIS WAY ON ORIGINAL

**Figure 50. Mean Supine DBP Across Visits during the Double-Blind Period (Pool 1)**



# subjects	BL	2	4	8	12	16	20	24	28	36	44	52
Placebo	654	652	645	637	631	523	415	378	251	232	214	210
Sarilumab 150 mg q2w	653	664	640	631	608	535	491	461	330	312	302	291
Sarilumab 200 mg q2w	657	649	644	639	619	531	490	472	328	304	297	282

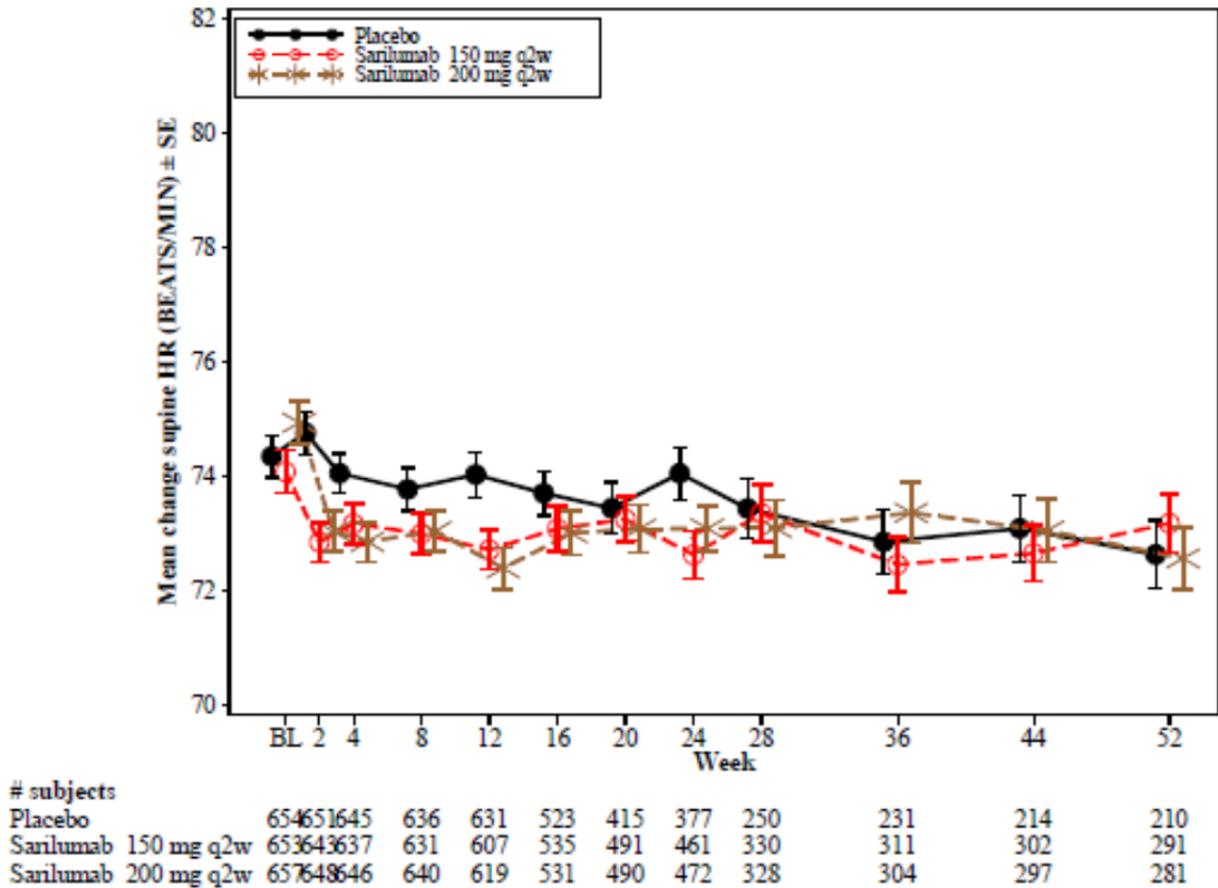
DBP = diastolic blood pressure

Source: Integrated Summary of Safety, Figure 40, dated October 6, 2015; page 310.

Similarly, the trend in heart rate was also similar across treatment arms (Figure 51) without a consistent change from baseline in any arm.

APPEARS THIS WAY ON ORIGINAL

**Figure 51. Mean Supine Heart Rate Across Visits during the Double Blind Period (Pool 1)**



Source: Integrated Summary of Safety, Figure 41, dated October 6, 2015; page 311.

In summary, based on the trend of vital signs during the treatment period, there was not concern regarding an association with sarilumab therapy. There did appear, though, to be a small increase in weight in subjects on sarilumab, but the reason for this weight increase is unclear.

#### 8.4.8. Electrocardiograms (ECGs)

A standard 12-lead ECG was recorded at screening and EOT (end-of-treatment) visits. Heart rate, QRS duration, PR interval, QT interval, ST deviation, T-wave morphology, and U-wave presence or absence were annotated by centralized automatic and manual readings. No notable differences were observed in the sarilumab treatment groups compared with placebo in the double-blind treatment period. No differences were noted in the long-term safety population either.

#### 8.4.9. QT

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

A formal QT study was not required. However, the QT interval was evaluated in the clinical trials that were part of the RA clinical development program. The QT interval was measured and corrected with both Bazett's formula (QTcB) and Fridericia's formula (QTcF). In the double-blind period, only 2 subjects total had a QT interval measured at >500 msec; both subjects were in the sarilumab 150mg treatment arm. Similarly, the incidence of potentially clinically significant abnormalities in QTcB and QTcF was very low and did not reveal any notable differences between the placebo and sarilumab arms (at either dose).

### 8.4.10. Immunogenicity

In the discussion of immunogenicity, terms such as ADA positivity (treatment-emergent and treatment-boosted), neutralizing and non-neutralizing antibodies, and persistent vs. transient positive response will be used. These terms are defined above in Section 8.3.2.

In the 52-week, placebo-controlled population (Pool 1), the proportion of subjects with ADA positivity was higher in the sarilumab arms compared to placebo. The incidence was 3.5% in placebo, 19.3% in the sarilumab 150mg q2w arm, and 14.0% in the sarilumab 200mg q2w arm. The majority of subjects with ADA positivity were positive based on the "treatment emergent" definition as well as the presence of non-neutralizing antibodies. In addition, most had a transient response. As a reminder, a persistent response was defined as positive detected at 2 or more consecutive sampling time points separated by a period of at least 16 weeks. The rate of a persistently positive response was 2.0% in the placebo group, 5.6% in the sarilumab 150mg q2w arm, and 4.0% in the sarilumab 200mg q2w arm. Table 80 is an overview of immunogenicity in the placebo-controlled population during the entire 52-week period.

APPEARS THIS WAY ON ORIGINAL

**Table 80. Overview of ADA during the Double-Blind Period (Pool 1)**

	Placebo + DMARD N=608	Sarilumab 150mg q2w + DMARD N=607	Sarilumab 200mg q2w + DMARD N=609
Number of patients with ADA assay results available	608/608 (100%)	607/607 (100%)	607/609 (99.7%)
Patients with an ADA positive sample at baseline	9/606 (1.5%)	14/599 (2.3%)	10/599 (1.7%)
<b>ADA positive<sup>a</sup> patients during the TEAE period</b>	<b>21/608 (3.5%)</b>	<b>117/607 (19.3%)</b>	<b>85/607 (14.0%)</b>
Neutralizing <sup>b</sup>	1/608 (0.2%)	20/607 (3.3%)	11/607 (1.8%)
Non-neutralizing	20/608 (3.3%)	97/607 (16.0%)	74/607 (12.2%)
Treatment-boosted ADA positive <sup>a</sup> patients	0/608	1/607 (0.2%)	1/607 (0.2%)
Treatment-emergent ADA positive <sup>a</sup> patients	21/608 (3.5%)	116/607 (19.1%)	84/607 (13.8%)
Patients with a persistent <sup>c</sup> positive response	12/608 (2.0%)	34/607 (5.6%)	24/607 (4.0%)
Neutralizing <sup>b</sup>	1/608 (0.2%)	10/607 (1.6%)	6/607 (1.0%)
Non-Neutralizing	11/608 (1.8%)	24/607 (4.0%)	18/607 (3.0%)
Patients with a transient <sup>d</sup> positive response	9/608 (1.5%)	82/607 (13.5%)	60/607 (9.9%)
Neutralizing <sup>b</sup>	0/608	9/607 (1.5%)	5/607 (0.8%)
Non-Neutralizing	9/608 (1.5%)	73/607 (12.0%)	55/607 (9.1%)

ADA = anti-sarilumab antibody; Negative = below the assay cut point or not drug specific; Positive = drug specific signal above the assay cut point

a ADA positive patients include “treatment-emergent positive” and “treatment-boosted positive”

Treatment-emergent positive: patients with no positive assay response at baseline but with a positive assay response during the TEAE period

Treatment-boosted positive: patients with a positive ADA assay response at baseline and also have at least 4-fold increase in titer during the TEAE period

b At least one post-baseline measurement classified as neutralizing positive

c Persistent positive response: treatment-emergent positive ADA detected at 2 or more consecutive sampling time points during the TEAE period, where the first and last ADA positive samples are separated by a period of at least 16 weeks. Also, persistent in case last sample analyzed is positive.

d Transient positive response is defined as any positive ADA assay response that is not considered persistent.

Source: ISS, Table 107, dated October 6, 2015; page 261.

In the long-term safety population, 21.6% of subjects in the 150mg q2w arm and 11.9% of subjects in the 200mg q2w arm developed anti-sarilumab antibodies. Like the double-blind period, more of the subjects were treatment-emergent as compared to treatment-boosted, and more subjects had non-neutralizing antibodies. The number of subjects with a persistently positive response was low: 7.0% in the 150mg q2w arm and 3.2% in the 200mg q2w arm. In both the placebo-controlled and long-term safety population, the number of subjects with ADA positivity decreased with time.

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

To assess the effect of ADA on safety, Sanofi evaluated ADA positivity in subjects who developed hypersensitivity. A more detailed review of hypersensitivity can be found in Section 8.5.6 with an explanation of Sanofi's search criteria for hypersensitivity. Table 81 presents the proportion of subjects with hypersensitivity by ADA status. Of the ADA positive subjects, 22 (5.3%) were identified with the SMQ Hypersensitivity. Five of the 22 subjects had injection site reactions such as a rash at the injection site. In the more general review of hypersensitivity (Section 8.5.6), it is noted that 27 subjects discontinued the study due to hypersensitivity (for the long-term safety population); of those, 2 were ADA positive (transient, titers 30-60). Thus, based on these data, there does not seem to be a correlation between ADA and hypersensitivity.

Of note, there were no cases of anaphylaxis through the entire sarilumab program (long-term safety population, Pool 2). Thus, an assessment of ADA positivity could not be made for cases of anaphylaxis.

**Table 81. Number of Patients with Hypersensitivity Events by ADA Status during the Entire TEAE Period (Pool 2)**

n (%)	ADA negative N=2138	ADA positive <sup>a</sup> N=417
Hypersensitivity reaction <sup>b</sup>	181 (8.5%)	22 (5.3%)
Anaphylaxis <sup>c</sup>	0	0

a ADA positive status is defined as (1) patients with no positive assay response at baseline but with a positive assay response during the TEAE period or (2) patients with a positive ADA assay response at baseline and also have at least 4-fold increase in titer during the TEAE period

b SMQ Hypersensitivity (narrow)

c SMQ Anaphylactic reaction (narrow)

Source: ISS, Table 111, dated October 6, 2015; page 265.

Sanofi used the terms "lack of efficacy" and "loss of efficacy" in determining any association between ADA status and efficacy. As a reminder, "lack of efficacy" was defined as treatment discontinuation due to lack of efficacy, whereas "loss of efficacy" was defined as treatment discontinuation due to lack of efficacy after achieving an ACR50 or EULAR Good response. Table 82 shows the ADA status of subjects who met Sanofi's criteria for lack of efficacy and loss of efficacy. The number of subjects who experienced a lack of efficacy or loss of efficacy was low. The proportion of subjects who were ADA negative or ADA positive and developed lack/loss of efficacy was similarly low. Approximately, 3.4% of ADA positive subjects had a lack of efficacy, compared to 2.8% of ADA negative subjects. Similarly, 1.7% of ADA positive subjects had a loss of efficacy, compared to 1.2% of ADA negative subjects. The majority of subjects who were ADA positive and experienced either lack or loss of efficacy had a transient response with non-neutralizing antibodies. Therefore, based on these data, there does not seem to be an effect of ADA on efficacy.

**Table 82. Number of Patients with Lack or Loss of Efficacy by ADA status (Neutralizing and Persistent) during the Entire TEAE Period (Pool 2)**

	Lack of Efficacy <sup>b</sup>	Loss of Efficacy <sup>c</sup>
<b>ADA negative (N=2138)</b>	<b>60 (2.8%)</b>	<b>26 (1.2%)</b>
<b>ADA positive<sup>a</sup> (N=417)</b>	<b>14 (3.4%)</b>	<b>7 (1.7%)</b>
<b>Neutralizing ADA Status</b>		
Neutralizing <sup>d</sup> (N=52)	0	0
Non-neutralizing (N=365)	14 (3.8%)	7 (1.9%)
<b>Persistent ADA Status</b>		
Persistent <sup>e</sup> (N=114)	1 (0.9%)	0
Transient <sup>f</sup> (N=300)	13 (4.3%)	7 (2.3%)
Treatment-boosted (N=3)	0	0

a ADA positive status are defined as (1) “treatment-emergent” (patients with no positive assay response at baseline but with a positive assay response during the TEAE period) or (2) “treatment-boosted” (patients with a positive ADA assay response at baseline and also have at least 4-fold increase in titer during the TEAE period)

b Lack of efficacy is defined as treatment discontinuation due to lack of efficacy

c Loss of efficacy is defined as treatment discontinuation due to lack of efficacy after achieving an ACR50 or EULAR Good Response

d Positive Neutralizing Antibody status is defined as patients who had at least 1 post-baseline ADA measurement classified as neutralizing positive during the entire TEAE period

e Persistent positive response: treatment emergent positive ADA detected at 2 or more consecutive sampling time points during the TEAE period where the first and last ADA positive samples are separated by a period of at least 16 weeks.

f Transient positive response is defined as any positive ADA assay response that is not considered persistent

Source: ISS, Table 112-3, dated October 6, 2015; page 265-6.

The effect of ADA on PK was also assessed by Sanofi. Please see the review by Dr. Jianmeng Chen (primary clinical pharmacology reviewer) for details of the impact of immunogenicity on PK. In brief, there was a 24% - 28% lower exposure in subjects with a positive ADA status. Concentrations in patients with a persistent response were lower than that in patients with a transient response. Additionally, sarilumab concentration in the small number of NAb positive patients appeared to be lower than in NAb negative patients; however, this did not appear to affect efficacy. Table 82 shows that no subjects with neutralizing antibodies had lack or loss of efficacy.

### **Immunogenicity and Monotherapy (Study EFC13752 and Pool 3)**

Study EFC13752 was conducted to evaluate immunogenicity with sarilumab monotherapy. In fact, the incidence of ADA from baseline to Week 24 was the primary endpoint. In addition, Pool 3 is the safety population which includes subjects from EFC13752 during the 24-week study period as well as those some subjects who rolled over into the open-label extension study (LTS11210). Therefore, Pool 3 represents all the monotherapy subjects through the long-term safety period. In the review of immunogenicity and monotherapy, the focus will be the results of study EFC13752. However, supportive data from the analyses of Pool 3 may also be presented.

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

Table 83 shows the incidence of ADA in study EFC13752. The incidence of ADA positivity was 24.6% in the sarilumab 150mg q2w arm and 18.2% in the sarilumab 200mg q2w arm. Therefore, the incidence is numerically higher for both doses of sarilumab monotherapy compared to sarilumab + DMARD. Even though the incidence was higher with monotherapy, the type of ADA response was similar to the sarilumab + DMARD trials in that the majority of ADA positivity was treatment-emergent and non-neutralizing antibodies. There was also a notable increase in neutralizing antibody (NAb), particularly for the lower dose, with an incidence of 10.8% in subjects on sarilumab 150mg q2w and 3.0% in subjects on sarilumab 200mg q2w. Numerically, there was a total of 9 subjects with NAb in the monotherapy study for both doses. As noted previously in Table 80, the proportion of subjects with NAb was 3.3% in the sarilumab 150mg q2w + DMARD arm and 1.8% in the sarilumab 200mg q2w + DMARD arm. Of the 9 subjects with NAb in study EFC13752, 7 subjects completed treatment and enrolled in LTS11210; 1 subject discontinued sarilumab due to worsening of RA; 1 subject discontinued due to injection site erythema.

Lastly, in regards to persistent vs. transient response, subjects on sarilumab 150mg q2w had an equal proportion of persistent and transient responses (12.3% for both). This pattern in sarilumab 150mg q2w was different than what was seen in the sarilumab + DMARD population for which there was a higher proportion of subjects on both doses of sarilumab who had a transient response. Subjects on sarilumab 200mg qw (monotherapy) continued to have more subjects with a transient response, compared to a persistent response.

APPEARS THIS WAY ON ORIGINAL

**Table 83. Overview of Incidence of Positive ADA in Study EFC13752**

	Sarilumab 150mg q2w N=65	Sarilumab 200mg q2w N=66
Number of patients with ADA assay results available	65/65 (100%)	66/66 (100%)
Patients with an ADA positive sample at baseline	1/65 (1.5%)	2/66 (3.0%)
<b>ADA positive<sup>a</sup> patients during the TEAE period</b>	<b>16/65 (24.6%)</b>	<b>12/66 (18.2%)</b>
Neutralizing <sup>b</sup>	7/65 (10.8%)	2/66 (3.0%)
Non-neutralizing	9/65 (13.8%)	10/66 (15.2%)
Treatment-boosted ADA positive <sup>a</sup> patients	0/65	0/66
Treatment-emergent ADA positive <sup>a</sup> patients	16/65 (24.6%)	12/66 (18.2%)
Patients with a persistent <sup>c</sup> positive response	8/65 (12.3%)	4/66 (6.1%)
Neutralizing <sup>b</sup>	7/65 (10.8%)	2/66 (3.0%)
Non-Neutralizing	1/65 (1.5%)	2/66 (3.0%)
Patients with a transient <sup>d</sup> positive response	8/65 (12.3%)	8/66 (12.1%)
Neutralizing <sup>b</sup>	0/65	0/66
Non-Neutralizing	8/65 (12.3%)	8/66 (12.1%)

ADA = anti-sarilumab antibody; Negative = below the assay cut point or not drug specific; Positive = drug specific signal above the assay cut point

a ADA positive patients include “treatment-emergent positive” and “treatment-boosted positive”

Treatment-emergent positive: patients with no positive assay response at baseline but with a positive assay response during the TEAE period

Treatment-boosted positive: patients with a positive ADA assay response at baseline and also have at least 4-fold increase in titer during the TEAE period

b At least one post-baseline measurement classified as neutralizing positive

c Persistent positive response: treatment-emergent positive ADA detected at 2 or more consecutive sampling time points during the TEAE period, where the first and last ADA positive samples are separated by a period of at least 16 weeks. Also, persistent in case last sample analyzed is positive.

d Transient positive response is defined as any positive ADA assay response that is not considered persistent.

Source: EFC13752 CSR, Table 11, dated August 18, 2015; page 65.

In the Pool 3 population, the percentage of ADA positive patients in each treatment arm was the same as that for study EFC13752. The overall rate of ADA positivity in the any dose group was 21.4%. Of the ADA positive patients in the any dose arm, 9.2% of patients had persistent ADA, and 6.9% had neutralizing antibodies.

As above, Sanofi correlated ADA status with events of hypersensitivity to evaluate the effect of immunogenicity on safety with sarilumab monotherapy. Again, the search criteria used to identify these events are described below in Section 8.5.6. The number of subjects with hypersensitivity events was low overall with only 4 subjects who were identified with the SMQ Hypersensitivity. Three of these subjects were ADA negative, and 1 was ADA positive. Thus, the proportion of ADA positive subjects who had a hypersensitivity reaction was roughly similar to the proportion of ADA negative subjects. Table 84 shows the number of ADA negative and ADA positive subjects who met the search criteria SMQ Hypersensitivity, as well as the specific

adverse events (by PT). As noted previously, no subjects had an event consistent with anaphylaxis, and, thus, a correlation with ADA status was not evaluated. Hypersensitivity events and ADA status were the same in Pool 3. The proportion of subjects who were ADA positive and had a hypersensitivity reaction was actually lower in the monotherapy population than in the sarilumab + DMARD population. However, because the number of hypersensitivity events was so low overall in the monotherapy population, it is difficult to make any conclusion.

**Table 84. Overview of ADA Status in Study EFC13752**

n (%)	ADA negative N=103	ADA positive <sup>a</sup> N=28
<b>Hypersensitivity reaction<sup>b</sup></b>	3 (2.9%)	1 (3.6%)
Drug eruption	0	1 (3.6%)
Injection site rash	1 (1.0%)	0
Rash	2 (1.9%)	0
Rash pruritic	1 (1.0%)	0
<b>Anaphylaxis<sup>c</sup></b>	0	0

a ADA positive status is defined as (1) patients with no positive assay response at baseline but with a positive assay response during the TEAE period or (2) patients with a positive ADA assay response at baseline and also have at least 4-fold increase in titer during the TEAE period

b SMQ Hypersensitivity (narrow)

c SMQ Anaphylactic reaction (narrow)

Source: EFC13752 CSR, Table 12, dated August 18, 2015; page 66.

Table 85 shows the number of subjects with AEs leading to discontinuation by ADA status. A total 10 subjects in study EFC13752 experienced AEs leading to discontinuation. Five subjects (17.9%) of ADA positive patients compared to 5 subjects (4.9%) of ADA negative patients had an AE leading to permanent discontinuation. Thus, although numerically similar, the proportion was higher in the ADA positive subjects. However, many of the specific AEs, such as OA and otitis media, may not be associated with the presence of ADA.

APPEARS THIS WAY ON ORIGINAL

**Table 85. Number of Patients with AEs Leading to Discontinuation by ADA Status in Study EFC13752**

n (%)	ADA negative N=103	ADA positive <sup>a</sup> N=28
<b>Permanent treatment discontinuation due to TEAEs</b>	5 (4.9%)	5 (17.9%)
Injection site erythema	1 (1.0%)	1 (3.6%)
Neutropenia	1 (1.0%)	1 (3.6%)
Osteoarthritis	0	1 (3.6%)
Otitis media	0	1 (3.6%)
Rheumatoid arthritis	1 (1.0%)	1 (3.6%)
Herpes zoster	1 (1.0%)	0
Transaminases increased	1 (1.0%)	0

a ADA positive status is defined as (1) patients with no positive assay response at baseline but with a positive assay response during the TEAE period or (2) patients with a positive ADA assay response at baseline and also have at least 4-fold increase in titer during the TEAE period

Source: EFC13752 CSR, Table 13, dated August 18, 2015; page 66.

To evaluate the effect of immunogenicity on efficacy with sarilumab monotherapy, Sanofi utilized “lack of efficacy” and “loss of efficacy,” as already defined above. Table 86 shows subjects who met the criteria for lack or loss of efficacy by ADA status. There were no subjects who met the criteria for loss of efficacy in this study. One ADA positive subject and one ADA negative subject each experienced a “lack of efficacy.” As above with AEs leading to discontinuation, numerically, the number of subjects was the same between ADA positive and negative, but the proportion was higher in the ADA positive group. With so few subjects with lack of efficacy, it is difficult to make any conclusions; however, generally, these results are comparable to what was seen in the sarilumab + DMARD safety population. In the subject who was ADA positive and showed lack of efficacy, the antibody status was transient and non-neutralizing. The effect of ADA on lack or loss of efficacy was the same through the entire TEAE period (Pool 3).

**Table 86. Number of Patients with Lack or Loss of Efficacy by ADA status in Study EFC13752**

n (%)	ADA negative N=103	ADA positive <sup>a</sup> N=28
<b>Lack of efficacy<sup>b</sup></b>	1 (1.0%)	1 (3.6%)
<b>Loss of efficacy<sup>c</sup></b>	0	0

a ADA positive status is defined as (1) patients with no positive assay response at baseline but with a positive assay response during the TEAE period or (2) patients with a positive ADA assay response at baseline and also have at least 4-fold increase in titer during the TEAE period

b Lack of efficacy is defined as permanent treatment discontinuation due to lack of efficacy

c Loss of efficacy is defined as permanent treatment discontinuation due to lack of efficacy after achieving an ACR50 or EULAR Good Response (defined as improvement of >1.2 and a present DAS28-CRP score ≤ 3.2)

Source: EFC13752 CSR, Table 14, dated August 18, 2015; page 69.

For study EFC13752, Sanofi also evaluated the proportion of subjects with an ACR20 response at Week 24 by ADA status, as shown in Table 87. What is notable is that the proportion of non-

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

responders is higher in the ADA positive patients compared to the ADA negative patients for both doses of sarilumab. In the sarilumab 150mg q2w arm, 56.3% of ADA positive subjects were non-responders versus 16.3% of ADA negative subjects. Similarly, in the sarilumab 200mg q2w arm, 41.7% of ADA positive subjects were non-responders compared to 24.1% of ADA negative subjects. Of the 9 subjects on sarilumab 150mg q2w, Sanofi noted that 4 never responded and had evidence of ADA positivity as early as Week 2. Additionally, 1 subject was an ACR20 responder at Week 4, developed ADA positivity (neutralizing AB), and continued to Week 24 as a non-responder. However, the other 4 subjects achieved an ACR20 response at different time points, but ADA onset did not necessarily correlate with ACR non-responder status. Similarly, 2 of the 5 ADA positive non-responders on sarilumab 200mg q2w monotherapy did not respond at all and were ADA positive early in the course of the study, and 1 subject had an ACR20 response, then developed ADA, and then became a non-responders. However, the other 2 subjects did have an ACR20 response earlier in the study with unclear association with ADA status. Thus, Sanofi concluded that, while the percentage of ACR20 non-responders among ADA positive patients in both treatment arms was higher compared to ADA negative patients, many of the non-reponder cases were due to early discontinuation for various reasons not necessarily associated with ADA status, such as degenerative arthritis and otitis media.

**Table 87. Incidence of ACR20 Response at Week 24 by ADA Status in Study EFC13752**

	Sarilumab 150mg q2w	Sarilumab 200mg q2w
ACR20 at Week 24 n (%)	N=65	N=67
<b>ADA status</b>		
<b>Positive<sup>a</sup></b>		
Number	16	12
Responders	7 (43.8%)	7 (58.3%)
Non-responders	9 (56.3%)	5 (41.7%)
<b>Negative</b>		
Number	49	54
Responders	41 (83.7%)	41 (75.9%)
Non-responders	8 (16.3%)	13 (24.1%)

a ADA positive status is defined as (1) patients with no positive assay response at baseline but with a positive assay response during the TEAE period or (2) patients with a positive ADA assay response at baseline and also have at least 4-fold increase in titer during the TEAE period

Source: EFC13752 CSR, Table 15, dated August 18, 2015; page 73.

In regards to immunogenicity and PK for the monotherapy population, again, please refer to the clinical pharmacology review. Overall, the mean serum functional sarilumab concentration was lower in ADA positive subjects for both doses of sarilumab. However, there was an overlap in concentrations between ADA positive and ADA negative subjects.

In conclusion, for sarilumab monotherapy, the proportion of subjects who developed ADA

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

positivity was higher for both doses of sarilumab, compared to that in the sarilumab + DMARD population. Subjects who were ADA positive had a lower functional sarilumab concentration. Utilizing Sanofi's definitions of hypersensitivity events and lack/loss of efficacy, there does not appear to be a signal based on ADA status in the monotherapy subjects. The overall number of events identified by Sanofi, though, was low. It should be noted that the proportion of subjects with AEs leading to discontinuation was higher in the ADA positive patients, but the reasons for discontinuation were not necessarily related to ADA status. Similarly, the proportion of ACR20 non-responders was higher in the ADA positive population. However, some of these non-responders were ACR20 responders at other time points but were discontinued for reasons that may not be clearly associated with ADA status. In summary, based on the data from EFC13752 and the Pool 3 safety population, the correlation of ADA status on safety and efficacy in the monotherapy population is not entirely clear.

### 8.5. Analysis of Submission-Specific Safety Issues

As described above, there were multiple adverse events of special interest (AESIs) that were anticipated based on known effects of IL-6 blockade in the RA population (that is, previous experience with tocilizumab), risks associated with other biologic use in RA, and some general adverse events noted in biologic products in general. The AESIs that were analyzed due to experience with IL-6 inhibition included neutropenia, thrombocytopenia, elevations in liver associated enzymes, elevations in lipids, cardiovascular events, and infections. The AESIs that were selected based on other biologic DMARDs included malignancy, autoimmunity/lupus-like syndrome, and demyelinating disorders. Lastly, the AESIs based on general biologic concerns included injection site reactions, hypersensitivity, and immunogenicity.

Elevation in liver enzymes, neutropenia, and thrombocytopenia are discussed in Section 8.4.6. Immunogenicity is reviewed in Section 8.4.10. Immunogenicity on monotherapy is presented in Section 8.7. The other AESIs are presented below.

#### 8.5.1. Infections

Most therapy for RA (conventional DMARDs, biologic DMARDs, corticosteroids) is immunomodulating to some extent. Therefore, therapy for RA is frequently associated with infection. Previous experience with IL-6 inhibition in RA (namely, with tocilizumab) noted an association with infection. With this in mind, patients were excluded if they had a fever, chronic/persistent/recurring infections within 4 weeks prior to screening, history of invasive opportunistic infection, active tuberculosis (TB), history of incompletely treated TB, or a positive QuantiFERON-TB Gold test.

This review will present an overview of all infections as well as serious and opportunistic infections in the different safety populations. Serious infections were those infections that

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

were also serious adverse events. Sanofi provided a non-exhaustive list of possible opportunistic infections: aspergillosis, blastomyces dermatitiidis, candidiasis (not cutaneous), coccidioides immitis, cryptococcus, cytomegalovirus, herpes simplex (severe/disseminated), herpes zoster, histoplasmosis (pulmonary or disseminated), listeriosis, malaria, mycobacterium avium, nontuberculosis mycobacteria, and pneumocystis pneumonia (PCP). Because of the concern for infection with IL-6 inhibition and the possible longer exposure required to develop a serious or opportunistic infection, a more detailed review of the types of infections in all safety populations will be discussed.

Table 88 provides an overview of all infections in the pre-rescue population (Pool 1a). The incidence rate of subjects with an infection was 17.3% in the placebo arm, 21.1% in the sarilumab 150mg q2w arm, and 22.3% in the sarilumab 200mg q2w arm. The rate difference between doses was 1.1% (95% CI: -4.3, 6.5), thus, including 0. For both serious infections and opportunistic infections, the overall number of subjects was low in the pre-rescue period. Numerically, there were more serious infections in the sarilumab arms, but there were no difference between doses. As for opportunistic infections, there were a total of 8 events in the pre-rescue period (2 in placebo arm, 2 in sarilumab 150mg q2w arm, and 4 in sarilumab 200 mg q2w arm). In summary, in the pre-rescue period, there does appear to be a higher risk of infection with sarilumab administration, but the dose response between the 2 doses is small. It is difficult to make any conclusions regarding the serious and opportunistic infections given the low numbers in the pre-rescue period.

APPEARS THIS WAY ON ORIGINAL

**Table 88. Summary of Overall Infections during the Pre-Rescue Period (Pool 1a)**

	Placebo + DMARD	Sarilumab 150mg q2w + DMARD	Sarilumab 200mg q2w + DMARD
<b>Infections</b>			
Raw incidence rate n/N (%)	100/579 (17.3%)	122/579 (21.1%)	130/582 (22.3%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	100/123.3 (81.1)	122/115.8 (105.4)	130/118.3 (109.8)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		5.0% (-0.1, 10.2)	6.1% (0.9, 11.3)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			1.1% (-4.3, 6.5)
<b>Serious Infections</b>			
Raw incidence rate n/N (%)	4/579 (0.7%)	6/579 (1.0%)	6/582 (1.0%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	4/158.8 (2.5)	6/157.5 (3.8)	6/156.9 (3.8)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		0.3% (-0.7, 1.4)	0.4% (-0.7, 1.4)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			0.0% (-1.2, 1.2)
<b>Opportunistic Infections</b>			
Raw incidence rate n/N (%)	2/579 (0.3%)	2/579 (0.3%)	4/582 (0.7%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	2/161.1 (1.2)	2/159.8 (1.3)	4/160.2 (2.5)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		-0.0% (-0.7, 0.7)	0.3% (-0.5, 1.2)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			0.3% (-0.5, 1.2)

n (%) = number and percentage of patients with at least one TEAE

a Number of patients with at least 1 event per 100 patient-years, where the exposure time for patients who have experienced the specific adverse event experience was defined as the time to first adverse experience of interest whereas the exposure time for those who have not had this adverse experience was total TEAE period duration

b The rate difference and its 95% confidence interval were estimated using the M&N method stratified by the study, using the CMH weight

Source: ISS Appendix 1.12.1.52, dated September 29, 2015, page 8287-8.

Data from the entire 52-week, double-blind period provided more details regarding the specific infections noted in the safety population. The incidence of infections was higher in the double-blind treatment period, but, like the pre-rescue period, there were more subjects with infections in the sarilumab arms, and there was not a significant difference between doses. Table 89 provides the summary of infections, along with the most common infections, in the placebo-controlled population for the entire 52-week, double-blind period (Pool 1). The most common infections in all treatment arms were upper respiratory tract infection, urinary tract infection, and nasopharyngitis.

**Table 89. Overview of Infections in the Entire Double-blind Treatment Period (Pool 1)**

	Placebo + DMARD	Sarilumab	
		150mg q2w + DMARD	200mg q2w + DMARD
Total number of patients	661	660	661
Total treatment duration in pt-yrs	382.3	440.7	441.4
Treatment duration up to the first event in pt-years <sup>a</sup>	305.5	339.6	339.5
<b>Total patients with ≥ 1 infection (%)</b>	<b>189 (28.6%)</b>	<b>227 (34.4%)</b>	<b>233 (35.2%)</b>
<b>Number of patients with ≥ 1 infection per 100 pt-yrs</b>	<b>61.9</b>	<b>66.8</b>	<b>68.6</b>
<b>Total number of infections (per 100 pt-yrs)</b>	<b>287 (75.1)</b>	<b>357 (81.0)</b>	<b>373 (84.5)</b>
<b>Number (%) of patients with ≥ 1 infection by PT with incidence of ≥2%</b>			
Upper respiratory tract infection	32 (4.8%)	42 (6.4%)	47 (7.1%)
Urinary tract infection	28 (4.2%)	29 (4.4%)	38 (5.7%)
Nasopharyngitis	31 (4.7%)	37 (5.6%)	28 (4.2%)
Bronchitis	19 (2.9%)	18 (2.7%)	25 (3.8%)
Influenza	19 (2.9%)	17 (2.6%)	16 (2.4%)
Pharyngitis	14 (2.1%)	15 (2.3%)	16 (2.4%)
Sinusitis	11 (1.7%)	14 (2.1%)	16 (2.4%)

SMQ or company-defined search criteria: Infections, SOC Infections and infestations

a For patients with no such event, the duration is up to the end of the treatment duration

Source: ISS, Table 50, page 138.

Serious infections are presented in more detail for the 52-week, placebo-controlled period in Table 90. The proportion of subjects with serious infections was essentially consistent with that in the pre-rescue period. Twelve subjects (1.8%) on placebo had a serious infection, compared to 12 subjects (1.8%) on sarilumab 150mg q2w and 19 subjects (2.9%) on sarilumab 200mg q2w. Therefore, for serious infections in the double blind period, there was not a difference between placebo and sarilumab 150mg q2w. However, there were more subjects with infections on the 200mg dose. The most common types of serious infections in the sarilumab arms included erysipelas, pneumonia, bronchitis, and cellulitis. Overall, there were no unusual or unexpected serious infections. There were no serious infections leading to death in placebo-controlled population during the 52-week, double-blind period.

**Table 90. Overview of Serious Infections in the Double-Blind Treatment Period (Pool 1)**

	Placebo + DMARD	Sarilumab	
		150mg q2w + DMARD	200mg q2w + DMARD
Total number of patients	661	660	661
Total treatment duration in pt-yrs	382.3	440.7	441.4
Treatment duration up to the first serious infection in pt-years <sup>a</sup>	378.9	438.0	436.2
<b>Total patients with ≥ 1 serious infection (%)</b>	<b>12 (1.8%)</b>	<b>12 (1.8%)</b>	<b>19 (2.9%)</b>
<b>Number of patients with ≥ 1 serious infection per 100 pt-yrs</b>	<b>3.2</b>	<b>2.7</b>	<b>4.4</b>
<b>Total number of serious infections (per 100 pt-yrs)</b>	<b>15 (3.9)</b>	<b>16 (3.6)</b>	<b>23 (5.2)</b>
<b>Number (%) of patients with ≥ 1 serious infection by PT</b>			
Erysipelas	0	0	3 (0.5%)
Pneumonia	1 (0.2%)	1 (0.2%)	3 (0.5%)
Bronchitis	3 (0.5%)	0	2 (0.3%)
Cellulitis	4 (0.6%)	1 (0.2%)	2 (0.3%)
Abscess limb	0	1 (0.2%)	1 (0.2%)
Bronchitis fungal	0	0	1 (0.2%)
Conjunctivitis	0	0	1 (0.2%)
Diverticulitis	0	0	1 (0.2%)
Herpes zoster	0	0	1 (0.2%)
Infected skin ulcer	0	0	1 (0.2%)
Necrotising fasciitis	0	0	1 (0.2%)
Osteomyelitis	0	1 (0.2%)	1 (0.2%)
Pelvic abscess	0	0	1 (0.2%)
Pharyngitis	0	0	1 (0.2%)
Pyelonephritis	0	1 (0.2%)	1 (0.2%)
Septic shock	0	0	1 (0.2%)
Sinusitis	0	1 (0.2%)	0
Appendicitis	2 (0.3%)	0	0
Arthritis bacterial	0	1 (0.2%)	0
Bacteraemia	1 (0.2%)	0	0
Clostridium difficile colitis	0	1 (0.2%)	0
Endometritis	0	1 (0.2%)	0
Gastroenteritis	0	1 (0.2%)	0
Localised infection	0	1 (0.2%)	0
Otitis media acute	0	1 (0.2%)	0
Otitis media chronic	1 (0.2%)	0	0
Pneumonia streptococcal	0	1 (0.2%)	0
Pyelonephritis chronic	1 (0.2%)	0	0
Subacute endocarditis	1 (0.2%)	0	0

Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

Tinea cruris	0	1 (0.2%)	0
Upper respiratory tract infection	0	1 (0.2%)	0
Urinary tract infection	1 (0.2%)	0	0
<b>Total patients with infection leading to death (%)</b>	<b>0</b>	<b>0</b>	<b>0</b>

SMQ or company-defined search criteria: Infections, SOC Infections and infestations

a For patients with no such event, the duration is up to the end of the treatment duration

Source: ISS, Table 51, dated October 6, 2015; page 139-40.

The incidence of opportunistic infections during the double-blind period was also generally consistent with that in the pre-rescue period. Like the pre-rescue period, the general numbers of opportunistic infections are low. There was a small difference between placebo and sarilumab arms, and there was a small difference between doses. The incidence rates were 0.5% in placebo, 0.6% in the 150mg q2w arm, and 0.9% in the 200mg q2w arm. Table 91 breaks down the types of opportunistic infections that occurred in the double-blind period. Herpes zoster was the most common opportunistic infection. Of note, there were no cases of TB in the double-blind period.

**Table 91. Overview of Opportunistic Infections in the Double-blind Treatment Period (Pool 1)**

	Placebo + DMARD	Sarilumab	
		150mg q2w + DMARD	200mg q2w + DMARD
Total number of patients	661	660	661
Total treatment duration in pt-yrs	382.3	440.7	441.4
<b>Total patients with ≥ 1 Opportunistic infection (%)</b>	<b>3 (0.5%)</b>	<b>4 (0.6%)</b>	<b>6 (0.9%)</b>
<b>Total number of Opportunistic infections (per 100 pt-yrs)</b>	<b>3 (0.8)</b>	<b>4 (0.9)</b>	<b>6 (1.4)</b>
<b>Total patients with ≥ 1 Herpes zoster (%)</b>	<b>3 (0.5%)</b>	<b>4 (0.6%)</b>	<b>5 (0.8%)</b>
<b>Total number of Herpes zoster (per 100 pt-yrs)</b>	<b>3 (0.8)</b>	<b>4 (0.9)</b>	<b>5 (1.1)</b>
<b>Number (%) of patients with ≥ 1 Herpes zoster by PT</b>			
Herpes zoster	3 (0.5%)	3 (0.5%)	5 (0.8%)
Ophthalmic herpes zoster	0	1 (0.2%)	0
<b>Total patients with ≥ 1 Tuberculosis (%)</b>	<b>0</b>	<b>0</b>	<b>0</b>
<b>Total number of Tuberculosis (per 100 pt-yrs)</b>	<b>0</b>	<b>0</b>	<b>0</b>
<b>Total patients with Other opportunistic infection (%)</b>	<b>0</b>	<b>0</b>	<b>1 (0.2%)</b>
<b>Total number of Other opportunistic infection (per 100 pt-yrs)<sup>a</sup></b>	<b>0</b>	<b>0</b>	<b>1 (0.2)</b>
<b>Number (%) of patients with ≥ 1 Other opportunistic infections by PT</b>			
Bronchitis fungal	0	0	1(0.2%)

For EFC11072 Part A, opportunistic infections were selected based on clinical review.

For other studies, opportunistic infections were selected based on the following: (1) "Opportunistic infection" selected on Suspected Infection Event CRF; (2) "Herpes zoster" selected on the CRF; (3) Tuberculosis based on "Mycobacterium

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

tuberculosis” selected on CRF; (4) Other opportunistic infection based on “opportunistic” selected on CRF, but not part of “herpes zoster” or “tuberculosis”

a Other opportunistic infection reported was a Candida infection

Source: ISS, Table 52, dated October 6, 2015; page 141.

The number of patients and the number of events per 100 patient-years in the long-term safety population are similar to the double-treatment period. Particularly, in the sarilumab 150mg group, the number of patients with  $\geq 1$  infection was 66.8 per 100 patient-years in the placebo-controlled population and 67.2 per 100 patient-years in the long-term safety population. The exposure-adjusted incidence rate is slightly lower in the 200mg treatment arm, but this may be secondary to the longer exposure. The exposure-adjusted incidence rates of subjects with serious infections were generally consistent (to slightly lower) with that in the pre-rescue and double-blind period. Serious infections will be discussed in more details below. There were, however, more opportunistic infections in the sarilumab 200mg q2w initial dose arm in the long-term safety population, which will also be detailed below. Table 92 presents the raw incidence rate, the exposure-adjusted incidence rate, and the exposure-adjusted event rates of infections, serious infections, and opportunistic infections in the long-term safety population (Pool 2).

APPEARS THIS WAY ON ORIGINAL

**Table 92. Overview of All Infections for the Entire TEAE Period (Pool 2)**

	Sarilumab		
	150mg q2w Initial Dose	200mg q2w Initial Dose	Any Dose
<b>Infections</b>			
Raw incidence rate n/N (%)	365/1155 (31.6%)	572/1351 (42.3%)	1313/2887 (45.5%)
Number of patients with ≥ 1 infection per 100 pt-yrs	67.2	50.6	48.0
Exposure adjusted event rate <sup>a</sup> n <sub>E</sub> /PY	565/701.9	1169/1758.6	2867/4481.8
Exposure adjusted event rate <sup>a</sup> Rate per 100 PYs (95% CI)	80.5 (73.99, 87.42)	66.5 (62.72, 70.40)	64.0 (61.65, 66.36)
<b>Serious Infections</b>			
Raw incidence rate n/N (%)	17/1155 (1.5%)	64/1351 (4.7%)	158/2887 (1.5%)
Number of patients with ≥ 1 serious infection per 100 pt-yrs	2.4	3.7	3.6
Exposure adjusted event rate <sup>a</sup> n <sub>E</sub> /PY	22/701.9	75/1758.6	190/4481.8
Exposure adjusted event rate <sup>a</sup> Rate per 100 PYs (95% CI)	3.1 (1.96, 4.75)	4.3 (3.35, 5.35)	4.2 (3.66, 4.89)
<b>Opportunistic Infections</b>			
Raw incidence rate n/N (%)	4/1155 (0.3%)	18/1351 (1.3%)	44/2887 (1.5%)
Exposure adjusted event rate <sup>a</sup> n <sub>E</sub> /PY	4/701.9	19/1758.6	46/4481.8
Exposure adjusted event rate <sup>a</sup> Rate per 100 PYs (95% CI)	0.6 (0.16, 1.46)	1.1 (0.65, 1.69)	1.0 (0.75, 1.37)

n (%) = number and percentage of patients with at least one TEAE

a For patients with no such event, the duration is up to the end of the treatment duration

Source: ISS, Table 54, dated October 6, 2015; page 143; ISS, Table 55, dated October 6, 2015; page 146; ISS Appendix 1.9.14, dated September 10, 2015; page 8035.

Overall, the most common infections in the long-term safety population and the placebo-controlled population are also similar. The three most common infections in the long-term safety population were upper respiratory tract infection (6.2% in 150mg q2w initial dose and 9.0% in 200mg q2w initial dose), nasopharyngitis (5.5% in 150mg q2w initial dose and 6.5% in 200mg q2w initial dose), and urinary tract infection (3.7% in 150mg q2w initial dose and 7.6% in 200mg q2w initial dose). These are the same top 3 common infections in the double-blind treatment period, as noted in Table 92.

Table 93 presents the serious infections for the long-term safety infection. The actual incidence rates were higher, particularly in the 200mg q2w initial dose arm, which can be attributed to longer exposure. Seventeen subjects (1.5%) in the sarilumab 150mg q2w arm, 64 subjects (4.7%) in the sarilumab 200mg q2w arm, and 158 subjects (5.5%) in the any dose arm had serious infections. As already noted, the overall exposure-adjusted incidence rates were

Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

consistent with the placebo-controlled and double-blind period. The most common serious infections were also generally consistent with the double-blind period, including pneumonia, cellulitis, bronchitis, diverticulitis, and erysipelas.

APPEARS THIS WAY ON ORIGINAL

**Table 93. Overview of Serious Infections in the Entire TEAE Period (Pool 2)**

	Sarilumab		
	150mg q2w Initial Dose	200mg q2w Initial Dose	Any Dose
Total number of patients	1155	1351	2887
Total treatment duration in pt-yrs	701.9	1758.6	4481.8
Treatment duration up to the first serious infection in pt-years <sup>a</sup>	698.3	1720.5	4369.6
<b>Total patients with ≥ 1 serious infection (%)</b>	<b>17 (1.5%)</b>	<b>64 (4.7%)</b>	<b>158 (5.5%)</b>
<b>Number of patients with ≥ 1 serious infection per 100 pt-yrs</b>	<b>2.4</b>	<b>3.7</b>	<b>3.6</b>
<b>Total number of serious infections (per 100 pt-yrs)</b>	<b>22 (3.1)</b>	<b>75 (4.3)</b>	<b>190 (4.2)</b>
<b>Number (%) of patients with ≥ 1 serious infection by PT with ≥ 0.1% (any dose)</b>			
Pneumonia	2 (0.2%)	11 (0.8%)	27 (0.9%)
Cellulitis	1 (<0.1%)	6 (0.4%)	12 (0.4%)
Bronchitis	1 (<0.1%)	3 (0.2%)	7 (0.2%)
Diverticulitis	1 (<0.1%)	3 (0.2%)	6 (0.2%)
Erysipelas	0	4 (0.3%)	6 (0.2%)
Herpes zoster	0	2 (0.1%)	5 (0.2%)
Osteomyelitis	1 (<0.1%)	2 (0.1%)	5 (0.2%)
Subcutaneous abscess	0	2 (0.1%)	4 (0.1%)
Abscess limb	1 (<0.1%)	1 (<0.1%)	4 (0.1%)
Arthritis bacterial	1 (<0.1%)	1 (<0.1%)	4 (0.1%)
Septic shock	0	2 (0.1%)	3 (0.1%)
Cellulitis staphylococcal	0	0	3 (0.1%)
Localised infection	1 (<0.1%)	1 (<0.1%)	3 (0.1%)
Pneumonia streptococcal	1 (<0.1%)	0	3 (0.1%)
Pyelonephritis	1 (<0.1%)	1 (<0.1%)	3 (0.1%)
Sinusitis	1 (<0.1%)	2 (0.1%)	3 (0.1%)
Urinary tract infection	0	2 (0.1%)	5 (0.2%)
<b>Total patients with infection leading to death (%)</b>			
	<b>0</b>	<b>2 (0.1%)</b>	<b>3 (0.1%)</b>
<b>Number of patients with infection leading to death per 100 pt-yrs</b>			
	<b>0</b>	<b>2 (0.1%)</b>	<b>5 (0.2%)</b>
<b>Number (%) of patients with infection leading to death by PT</b>			
	<b>0</b>	<b>0.1</b>	<b>0.1</b>
Pneumonia	0	0	2 (<0.1%)
Pneumonia viral	0	0	1 (<0.1%)
Sepsis <sup>b</sup>	0	1 (<0.1%)	1 (<0.1%)
Septic shock <sup>c</sup>	0	1 (<0.1%)	1 (<0.1%)

SMQ or company-defined search criteria: Infections, SOC Infections and infestations

a For patients with no such event, the duration is up to the end of the treatment duration

b Reported cutaneous infection

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

c Pneumonia

Source: ISS, Table 55, dated October 6, 2015; page 146-7.

The fatal serious infections are described in Section 8.4.1 (Deaths). There were 5 patients who had a fatal infection. All events occurred during the open-label study LTS11210 with 4 patients on 200mg q2w and 1 patient on 150mg q2w at the time of the event.

As noted in Table 93, there were 4 reports of non-fatal sepsis or septic shock. One of these events occurred in EFC11072, and the remaining events occurred in the open-label study LTS11210. All of these subjects were taking the 200mg q2w dose and are described briefly below.

- Patient 011072-170-002-201 was a 58 year-old male with rheumatoid arthritis on the IMP, methotrexate, and prednisolone. He experienced necrotizing fasciitis and septic shock after having punctured his hand with a barbed wire on Day 322 of the study.
- Patient 011072-036-003-104 was a 63 year-old male with rheumatoid arthritis on IMP, methotrexate, and prednisone. The patient had a non-healing wound and would frequently swim in saltwater environment. He was diagnosed with necrotizing fasciitis of his left leg secondary to *Vibrio vulnificus* on Day 624 of the study and subsequently developed septic shock. The patient recovered 1 week later but continued to require wound debridements of his left leg. Methotrexate was temporarily discontinued during treatment of his necrotizing fasciitis, but IMP was permanently discontinued with the last dose received 3 days prior to diagnosis. Of note, this subject later developed metastatic lung squamous cell carcinoma from which he died.
- Patient 013370-840-153-607 was a 77 year-old female with rheumatoid arthritis on the IMP and methotrexate. She was previously treated with infliximab. She developed a draining rectal wound and was admitted for further diagnostic evaluation for dyspnea on exertion and palpitations. Blood cultures on admission were positive for *Candida albicans*, and sepsis was reported as adverse event on Day 146 of the study. During this hospitalization, the subject suffered respiratory failure and a perforated pyloric ulcer. According to the patient narrative, the subject eventually recovered enough to be discharged from the hospital nearly over 2 months after the diagnosis of sepsis.
- Patient 011072-152-007-224 was a 70 y/o female with rheumatoid arthritis, diabetes, hypertension, hyperlipidemia, and left bundle branch block. For her RA, she was taking IMP, methotrexate (IM), methylprednisolone, and acetylsalicylic acid. This subject experienced multiple adverse events including uterine leiomyoma (Day 15 of the open-label study), diverticulitis (Day 54), pelvic abscess secondary to diverticulitis (Day 73), and then large intestine perforation secondary to diverticulitis (Day 92). The subject required corrective surgery and then developed post-operative septic shock (Day 93). The subject eventually recovered and was discharged approximately 2 months later. It should be noted that the IMP (sarilumab 200mg q2w) was permanently discontinued after her diagnosis of diverticulitis (Day 54). Although the subject was exposed to

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

approximately 55 days of sarilumab 200mg q2w, the subject received sarilumab 150mg q2w during the double-blind treatment period (EFC11072 Part B) for nearly 1 year.

*Reviewer Comment: These infections that led to septic shock appear reasonable given the circumstances surrounding the events. Three of the subjects suffered wounds that later became infected. One subject had complications after diverticulitis. Although their immunosuppressive therapy may have played a role, there were certainly other triggering factors.*

In the long-term safety population (Pool 2), the number of subjects with opportunistic infections did not change in the sarilumab 150mg treatment arm. There were 4 subjects for an incidence rate of 0.3%, and all cases were related to herpes zoster.

With the increased exposure in the 200mg treatment arm in the long-term safety population, the number of subjects with opportunistic infections was higher at 18 for an incidence of 1.3%. This included 16 subjects with herpes zoster (1.0 event per 100 patient-years) and no subjects with tuberculosis. Two subjects (0.1 events per 100 patient-years) did have other opportunistic infections: a fungal bronchitis and peritonitis, both secondary to *Candida*. Therefore, the event rates were consistent with the double-blind period.

Lastly, as noted in Table 92, 44 subjects in the any dose group had an opportunistic infection for an event rate of 1.0 event per 10 patient-years. 36 patients had herpes zoster for an event rate of 0.8 events per 10 patient years. Six patients had *Candida* infections for an event rate of 0.2 events per 100 patient-years. Also, 2 subjects in the any dose arm had tuberculosis (TB) for an event rate of 0.04 events per 100 patient-years. Descriptions of the 2 subjects with tuberculosis are described below. Both subjects were previously treated with tocilizumab and were taking concomitant immunosuppressants (MTX and steroids) at the time of the event. Sanofi relates that the incidence of tuberculosis in RA patients treated with biologics is between 0.01-2.6 per 100 patient-years. Therefore, the number of subjects with tuberculosis on sarilumab did not exceed what has been seen with other biologics.

- Subject 011072-076-005-209 (Brazil) was 38 year-old woman who was originally randomized to the sarilumab 150mg q2w treatment arm (study EFC11072 Part B Cohort 2) and then transitioned to the open-label long-term extension study (LTS11210). It appears that the subject remained on sarilumab 150mg q2w for the long-term extension. For her RA, she was treated with concomitant methotrexate and prednisone. Previously, the subject had received tocilizumab for 5 years with unknown reason for discontinuation. On Day 758 of LTS11210, the subject was diagnosed with tuberculosis based on multiple subcutaneous abscesses eventually cultured as *Mycobacterium tuberculosis* and *Enterobacter cloacae*. Subject did not have pulmonary TB.
- Subject 011072-710-009-201 (South Africa) was a 51 year-old male with RA who was being treated with the IMP, methotrexate, and prednisone. He was originally

Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

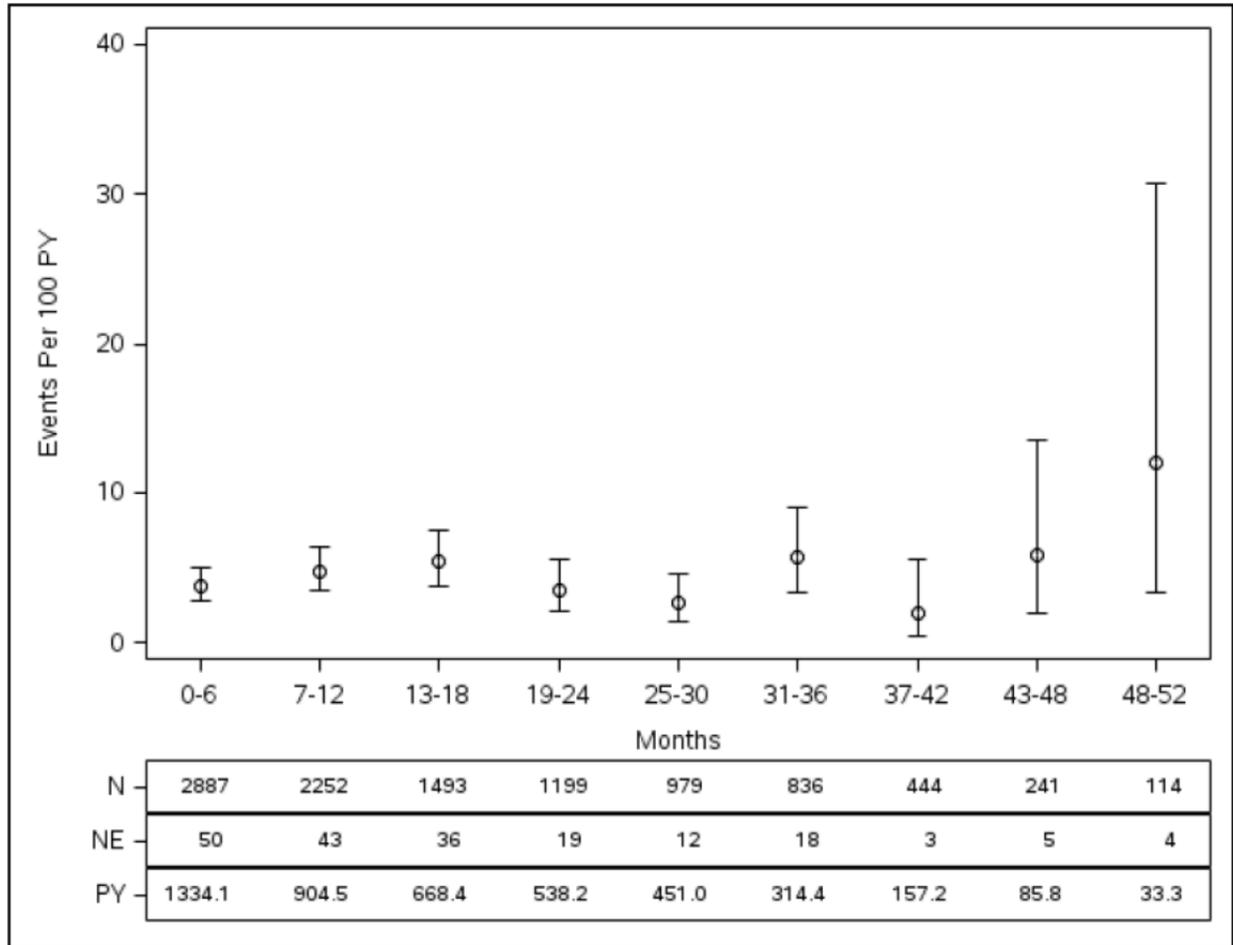
randomized to sarilumab 150mg q2w for approximately 50 weeks; he then entered LTS11210 and received sarilumab 200mg q2w. Of note, this subject was also previously treated with tocilizumab for over 6 years, and the tocilizumab was discontinued for unknown reasons. On Day 609 of LTS11210, the subject was diagnosed with pulmonary TB presenting with shortness of breath and cough productive of thick dark mucus. Sarilumab was discontinued after the diagnosis.

*Reviewer Comment: Both subjects who developed TB were originally randomized to the 150mg q2w arm. Both subjects were being treated with concomitant MTX and prednisone. Additionally, both previously received tocilizumab for >5 years. Both subjects were also living in endemic countries. Therefore, these cases of TB do not seem unreasonable.*

Although there were more infections in the 200mg q2w with longer exposure, the exposure-adjusted incidence rates over the entire TEAE period is relatively stable for subjects on sarilumab. Figure 52 shows the exposure-adjusted rates of serious infection by 6-month intervals. Although the incidence rate increases between 48-52 months, the confidence interval is much wider than the other intervals.

APPEARS THIS WAY ON ORIGINAL

**Figure 52. Exposure-Adjusted Rate of Serious Infections by 6-month Intervals During the Entire TEAE Period (Pool 2)**



N = sample size; NE = number of events in a 6-month period; PY = patient-years  
 95% confidence interval was calculated using the exact method  
 Source: ISS, Figure 10, dated October 6, 2015; page 148.

Sanofi further evaluates the infection risk with sensitivity and model-based analyses. Additionally, Sanofi provided a breakdown of the open-label period to clarify what treatments the subjects were actually taking at the time of the event.

As a reminder, the sensitivity analyses for Weeks 0-52 combined the number of events for subjects randomized and for the subjects who were rescued within the first 52 weeks of therapy. Table 94 shows the sensitivity analyses of serious infections for Weeks 0-52. With this analysis, there did appear to be a higher rate of overall infection in the sarilumab arms. Additionally, the rate was slightly higher in the sarilumab 200mg q2w dose. For serious infections and opportunistic infections, there was less of a difference between placebo and sarilumab 150mg q2w. Both serious and opportunistic infections were higher with the

sarilumab 200mg q2w dose.

**Table 94. Sensitivity Analyses of Infections during the TEAE Period (Week 0-52, Pool 1a)**

n(%)	PBO + DMARD		Sarilumab 150mg q2w + DMARD		Sarilumab 200mg q2w + DMARD <sup>a</sup>	
	Raw incidence rate	Exposure adjusted incidence rate <sup>b</sup>	Raw incidence rate	Exposure adjusted incidence rate <sup>b</sup>	Raw incidence rate	Exposure adjusted incidence rate <sup>b</sup>
	n/N (%)	n/PY (rate per 100 PYs)	n/N (%)	n/PY (rate per 100 PYs)	n/N (%)	n/PY (rate per 100 PYs)
<b>Infections</b>	176/579 (30.4%)	176/276.3 (63.7)	210/579 (36.3%)	210/307.0 (68.4)	316/881 (35.9%)	316/444.4 (71.1)
<b>Serious infections</b>	12/579 (2.1%)	12/345.2 (3.5)	12/579 (2.1%)	12/401.2 (3.0)	25/881 (2.8%)	25/573.8 (4.4)
<b>Opportunistic infections</b>	3/579 (0.5%)	3/348.3 (0.9)	2/579 (0.3%)	2/403.5 (0.5)	9/881 (1.0%)	9/580.0 (1.6)
<b>Tuberculosis</b>	0/579	0/348.7	0/579	0/403.9	0/881	0/581.5

n(%) = number and % of patients with at least 1 TEAE

a Includes randomized patients and patient who rescued and were within the first 52 weeks with this regimen

b Number of patients with at least 1 event per 100 patient-years, where the exposure time for patients who have experienced the specific adverse experience was defined as the time to first adverse experience of interest whereas the exposure time for those who have not had this adverse experience was total TEAE period duration

Source: ISS Appendix 1.12.2.9, page 8440.

Sanofi also performed a model-based analysis which essentially combined data for Pools 1 and 2. Table 95 shows the model-based analysis for serious infections. With this analysis, the rate of serious infections was actually lower in the sarilumab 150mg q2w arm compared to placebo. There was, however, a small increase in rate in the 200mg q2w arm compared to both placebo and sarilumab 150mg q2w. The rate ratio was 1.19 compared to placebo (95% CI: 0.64, 2.20) and 1.55 compared to 150mg q2w (95% CI: 0.91, 2.65).

APPEARS THIS WAY ON ORIGINAL

**Table 95. Model-based Analyses on Patients with at least one Serious Infection during the TEAE Period**

	Placebo + DMARD	Sarilumab 150mg q2w + DMARD	Sarilumab 200mg q2w + DMARD	Any Sarilumab + DMARD
<b>Serious infection</b>				
Raw incidence rate n/N (%)	12/661 (1.8)	17/1155 (1.5)	64/1351 (4.7)	158/2887 (5.5)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	12/378.9 (3.2)	17/698.3 (2.4)	64/1720.5 (3.7)	158/4369.6 (3.6)
Rate ratio vs. PBO + DMARD (95% CI)		0.77 (0.37, 1.60) <sup>b</sup>	1.19 (0.64, 2.20) <sup>b</sup>	1.17 (0.65, 2.10) <sup>c</sup>
Rate ratio vs. sarilumab 150mg + DMARD (95% CI)			1.55 (0.91, 2.65) <sup>b</sup>	

a Number of patients with at least one event per 100 patient-years (PYs), where the exposure time for patients who have experienced the specific adverse experience was defined as the time to first adverse experience of interest whereas the exposure time for those who have not had this adverse experience was total TEAE period duration

b The rate ratio and its 95% confidence interval (CI) were estimated using the GEE (Poisson distribution with exposure calculated based on the time to first event as an offset), adjusted for treatment and the important baseline factors (age, weight, RA duration of disease, diabetes), assuming an exchangeable covariance structure for the within-subject correlations

c The rate ratio and its 95% confidence interval (CI) were estimated using the GEE (Poisson distribution with exposure calculated based on the time to first event as an offset), adjusted for treatment and the important baseline factors (age, gender, weight, RA duration of disease, geographic region, diabetes), assuming an exchangeable covariance structure for the within-subject correlations

Source: Sanofi response to IR (June 10 and 13, 2016), Appendix B 1.12.3.1, dated June 15, 2016, page 8.

Table 96 is a similar model-based analysis of serious infections, except evaluating the number of events rather than the number of patients with events. In this analysis, the actual event rate of serious infections for both doses of sarilumab outnumbered that for placebo. Additionally, there was a small dose response with a rate ratio of 1.36 between both doses (95% CI: 0.77, 2.39).

APPEARS THIS WAY ON ORIGINAL

**Table 96. Model-based Analyses on Number of Serious Infections during the Entire TEAE Period**

	Placebo + DMARD	Sarilumab 150mg q2w + DMARD	Sarilumab 200mg q2w + DMARD	Any Sarilumab + DMARD
<b>Serious infection</b>				
Total sample size	661	1155	1351	2887
Total treatment exposure in PY	382.3	701.9	1758.6	4481.8
Number of the events per 100 PYs nE (nE/100 PY)	15 (3.9)	22 (3.1)	75 (4.3)	190 (4.2)
Rate ratio vs. PBO + DMARD (95% CI)		0.81 (0.36, 1.79) <sup>a</sup>	1.10 (0.56, 2.15) <sup>a</sup>	1.11 (0.58, 2.11) <sup>b</sup>
Rate ratio vs. sarilumab 150mg + DMARD (95% CI)			1.36 (0.77, 2.39) <sup>a</sup>	

a The rate ratio and its 95% confidence interval (CI) were estimated using the GEE (Poisson distribution with total treatment exposure as an offset) that adjusted for treatment and the important baseline factors (age, weight, RA duration of disease, diabetes), assuming an exchangeable covariance structure for the within-subject correlations

b The rate ratio and its 95% confidence interval (CI) were estimated using the GEE (Poisson distribution with total treatment exposure as an offset) that adjusted for treatment and the important baseline factors (age, gender, weight, RA duration of disease, geographic region, diabetes), assuming an exchangeable covariance structure for the within-subject correlations

Source: Sanofi response to IR (June 10 and 13, 2016), Appendix B 1.12.3.2, dated June 15, 2016, page 9.

Sanofi also provided a more granular analysis of the open-label period by providing the incidence and event rate for subjects with serious infections according to what treatment the subjects were actually taking, broken down into what treatments they were originally taking. Table 97 evaluates the serious infections according to these treatment arms: randomized treatments (placebo, 150mg q2w, 200mg q2w), rescue/open label (placebo → 200mg q2w, 150mg q2w → 200mg q2w, 200mg q2w → 200mg q2w), or dose reduction (PBO → 200mg q2w → 150mg q2w, 150mg q2w → 200mg q2w → 150mg q2w, 200mg q2w → 200mg q2w → 150mg q2w). With this analysis, one can evaluate whether longer exposure at 200mg q2w was associated with more serious infections. It appears that the raw incidence as well as exposure adjusted incidence and event rates were actually higher for subjects who transitioned from placebo or 150mg q2w to 200mg q2w in the open-label period. Therefore, the higher incidence of serious infections on the 200mg q2w dose was not likely related to the longer exposure at that particular dose. Rather, it may be related to the fact that all subjects were on 200mg q2w in the open-label study, and, therefore, there was a longer follow-up time at that dose.

**Table 97. Summary of Serious Infections in Pivotal Studies and OLE (EFC11072, EFC10832, LTS11210)**

Treatment	Raw incidence rate n/N (%)	Exposure adjusted incidence rate <sup>a</sup> n/PY (n/100 PY)	Exposure adjusted event rate <sup>b</sup> n <sub>E</sub> /PY (n <sub>E</sub> /100 PY)
Placebo initial dose	12/661 (1.8%)	12/380.4 (3.2)	15/383.9 (3.9)
Sarilumab 150mg q2w initial dose	12/660 (1.8%)	12/439.4 (2.7)	16/440.7 (3.6)
Sarilumab 200mg q2w initial dose	19/661 (2.9%)	19/437.6 (4.3)	23/441.4 (5.3)
PBO → sarilumab 200mg q2w (rescue/OL)	27/520 (5.2%)	27/651.4 (4.1)	31/660.3 (4.8)
Sarilumab 150mg q2w → 200mg q2w (rescue/OL)	28/483 (5.8%)	28/593.6 (4.7)	34/607.7 (5.7)
Sarilumab 200mg q2w → 200mg q2w (OL)	15/475 (3.2%)	15/568.7 (2.6)	18/579.0 (3.2)
PBO → sarilumab 200mg q2w (rescue/OL) → 150mg q2w (dose decrease)	2/96 (2.1%)	2/111.7 (1.8)	2/113.0 (1.8)
Sarilumab 150mg q2w → 200mg q2w (rescue/OL) → 150mg q2w (dose decrease)	3/68 (4.4%)	3/77.3 (3.9)	3/77.6 (3.9)
Sarilumab 200mg q2w → 200mg q2w (OL) → 150mg q2w (dose decrease)	1/71 (1.4%)	1/88.2 (1.1)	1/88.4 (1.1)

n (%) = number and % of patients with at least 1 TEAE

Search criteria: Infections: SOC Infections and infestations

a Number of patients with at least one event per 100 pt-yrs, where the exposure time for patients who have experienced the specific adverse experience was defined as the time to first adverse experience of interest whereas the exposure time for those who have not had this adverse experience was total TEAE period duration

b Number of events per 100 pt-yrs, where the exposure time was the total TEAE period duration

Source: Sanofi response to IR (May 27, 2016), Table 2, dated June 3, 2016, page 7.

In conclusion, infections were an expected adverse event with sarilumab administration. This was seen in all the safety populations for all infections. Additionally, for serious infections and opportunistic infections, there was a slight increase over placebo, particularly in the 200mg q2w dose. Overall, though, the number of serious and, particularly opportunistic infections was low in the pre-rescue and double-blind treatment period in the placebo-controlled population. The types of infections were not unusual or unexpected in the setting of immunosuppression. In the long-term safety population, the rate of overall infections, serious infections, and opportunistic infections did seem higher, particularly in the 200mg q2w dose. However, based on additional analyses, the higher number of infections in the 200mg q2w dose may be related to the longer follow-up period on this dose. It should be noted that there were 2 cases of tuberculosis.

### 8.5.2. Lipid Abnormalities

An elevation in lipids is known to occur with IL-6 inhibition in RA patients. Specifically, tocilizumab, which was approved by the FDA in January 2010, caused an increase in all lipid

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

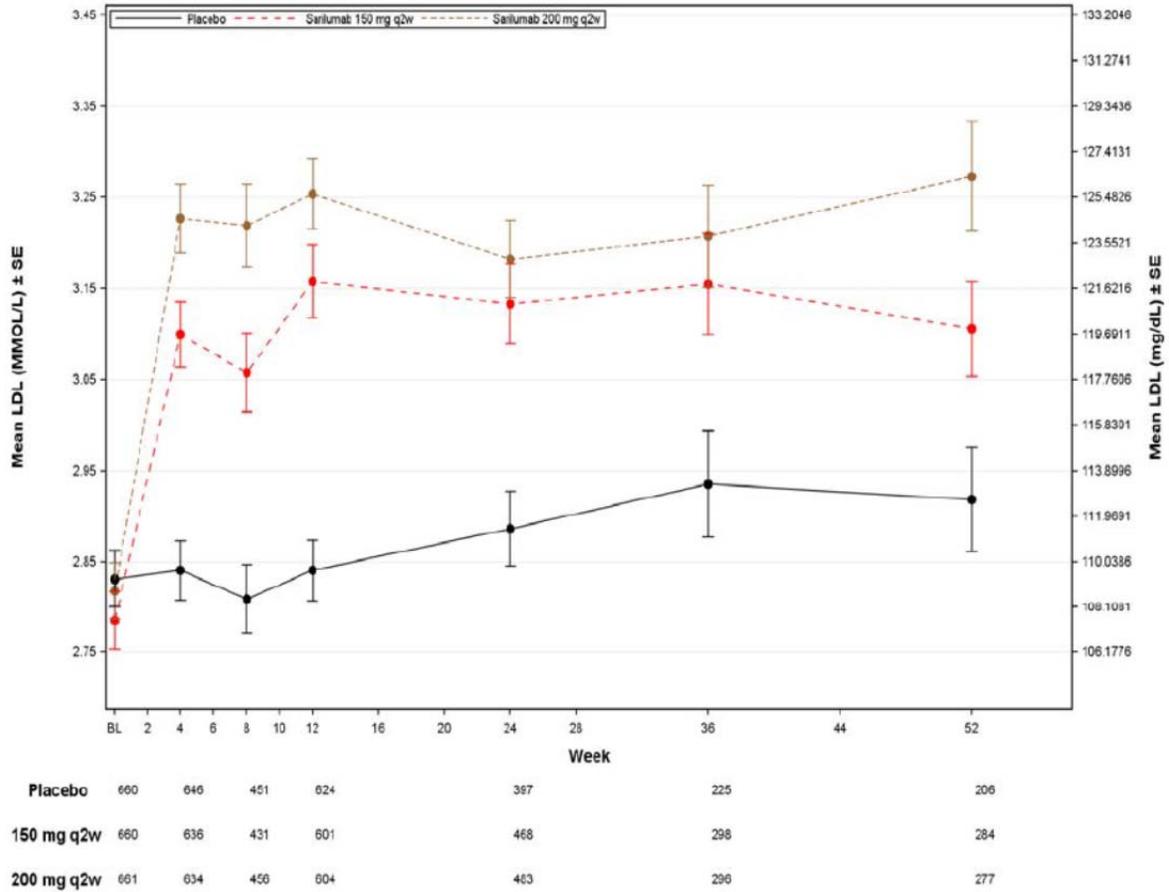
parameters. Therefore, an elevation in lipids was one of the AESIs and was monitored closely in the sarilumab clinical development.

As noted in Section 6, patients were excluded from the clinical studies if he/she had a severe uncontrolled hypercholesterolemia (>350 mg/dL, 9.1 mmol/L) or hypertriglyceridemia (>500 mg/dL, 5.6 mmol/L) at screening. In fact, at baseline, the majority of patient had a NCEP ATPIII classification of optimal (LDL <100 mg/dL) or near or above optimal (LDL 100 to <130 mg/dL). Across treatment arms in the placebo-controlled population, only 10% of subjects were taking statins at baseline.

The following 3 figures (Figure 53, Figure 54, and Figure 55) show the change in LDL, HDL, and triglycerides over time. Overall, the placebo group's entire lipid panel remained relatively stable. However, there was an elevation in all lipid parameters in the sarilumab treatment groups. The sarilumab treatment groups experienced elevations in LDL, HDL, and triglyceride within the first 4 weeks of treatment. For LDL and triglycerides, the elevation appeared to stabilize at Week 4. For HDL, the elevation also stabilized at Week 4 but then began to drop around Week 24. In the sarilumab + DMARD treatment groups, the mean increase in LDL was approximately 14 mg/dL (16%), the mean increase in triglycerides approximately 23 mg/dL (23%), and mean increase in HDL approximately 3 mg/dL (6%).

APPEARS THIS WAY ON ORIGINAL

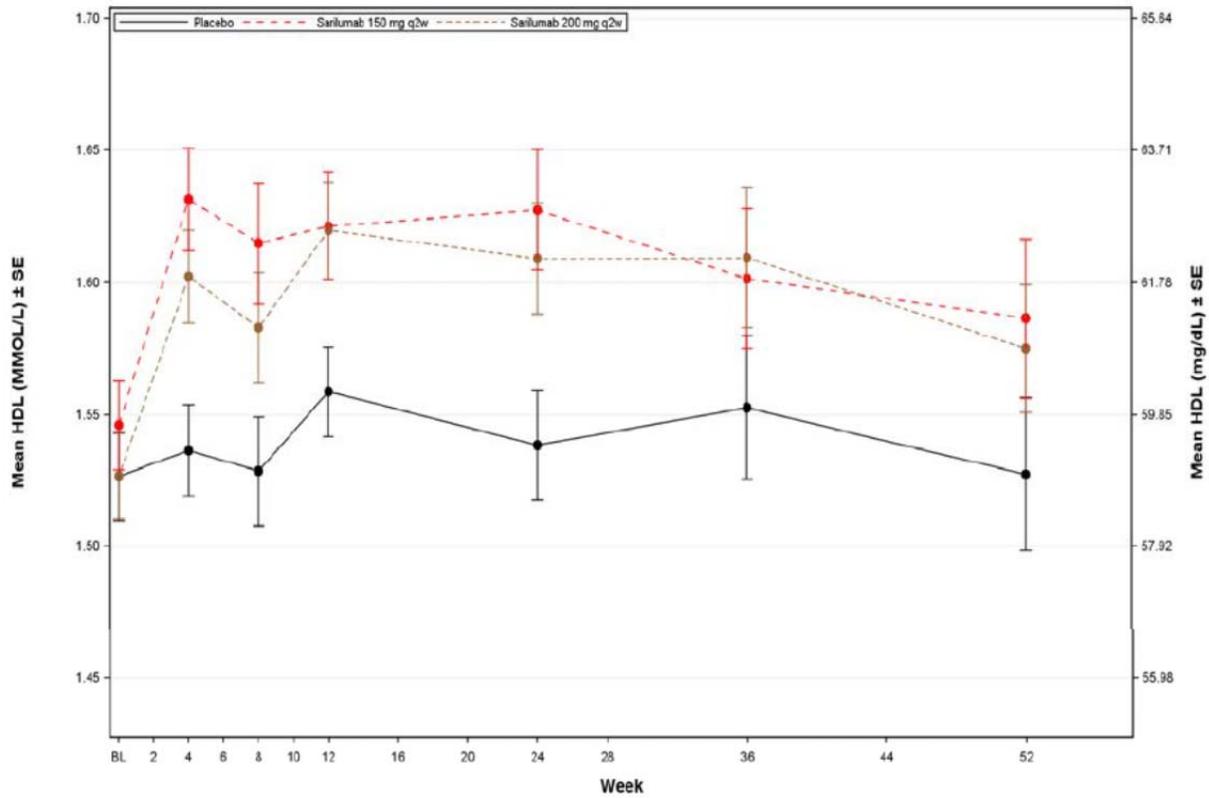
**Figure 53. Mean LDL across Visits during the Double-Blind Treatment Period (Pool 1)**



Normal range: 2.28-5.21 mmol/L (88-201 mg/dL)  
 Source: Integrated Summary of Safety, Figure 24, page 221.

APPEARS THIS WAY ON ORIGINAL

**Figure 54. Mean HDL across Visits during the Double-Blind Treatment Period (Pool 1)**

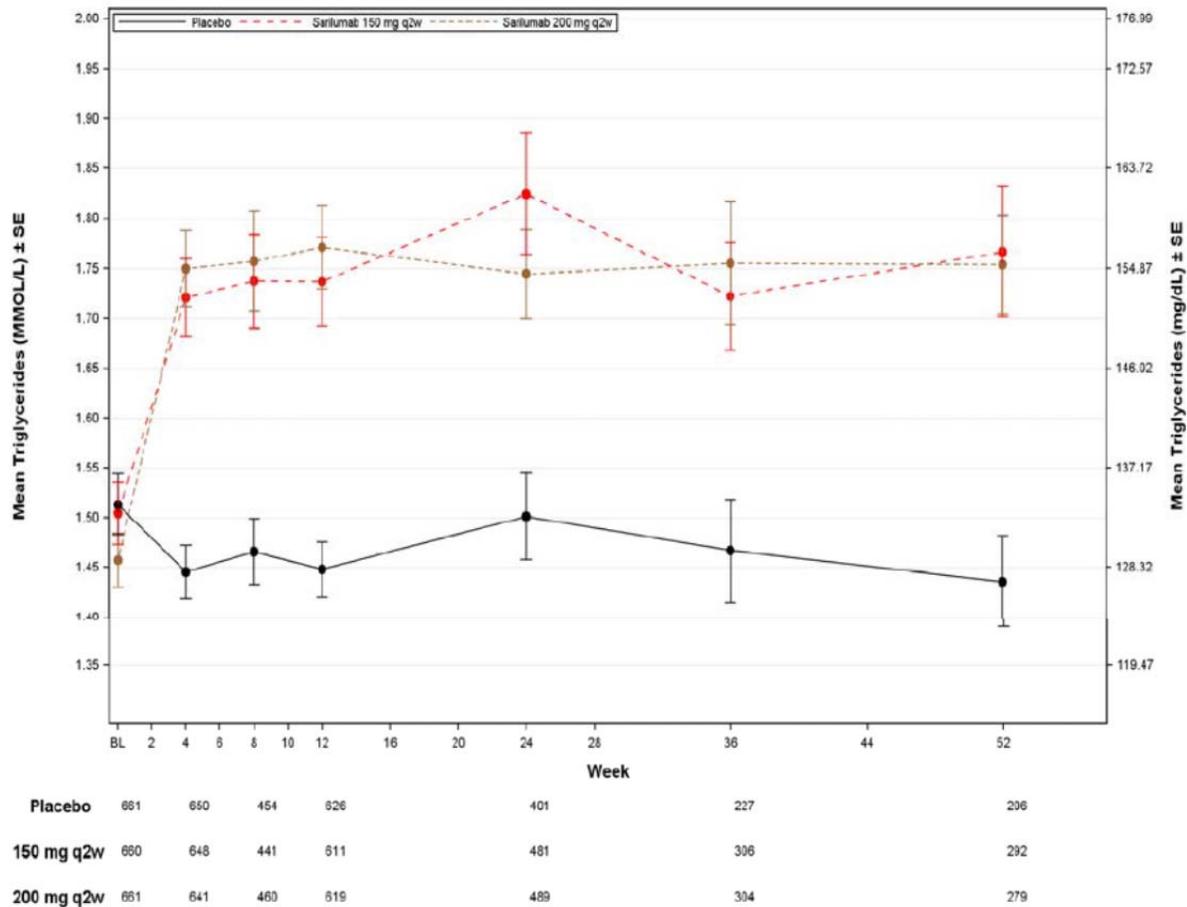


	BL	4	8	12	24	36	52
<b>Placebo</b>	661	649	453	625	401	226	206
<b>150 mg q2w</b>	660	648	441	610	481	303	292
<b>200 mg q2w</b>	661	641	460	619	489	304	276

Normal range: 0.96-2.38 mmol/L (37-92 mg/dL)  
 Source: Integrated Summary of Safety, Figure 25, page 222.

APPEARS THIS WAY ON ORIGINAL

**Figure 55. Mean Triglycerides across Visits during the Double-Blind Treatment Period (Pool 1)**



Normal range: 0.59-2.96 mmol/L (52-262 mg/dL)  
 Source: Integrated Summary of Safety, Figure 26, page 223.

Overall, the elevation appears similar for both doses of sarilumab although LDL elevations appeared slightly higher for the 200mg than the 150mg dose.

Reporting of “elevation in lipids” as an adverse event was left to the discretion of the investigator. “Elevation in lipids” is based on MedDRA SMQ Dyslipidemia. The Preferred Terms included hypertriglyceridemia, hypercholesterolemia, dyslipidemia, blood cholesterol increased, blood triglycerides increased, hyperlipidemia, low density lipoprotein increased, and high density lipoprotein increased. Table 98 shows the elevation of lipids in the pre-rescue period. As already shown in the figures above, more subjects on sarilumab experienced an elevation in lipids than those on placebo (raw incidence rate of 0.9% in placebo vs. 4.3% in sarilumab 150mg q2w vs. 3.6% in sarilumab 200mg q2w). No clinically meaningful difference is noted between the 2 sarilumab doses; in fact, sarilumab 200mg q2w actually has a numerically lower number of events.

**Table 98. Elevation in Lipids during Pre-Rescue Period (Pool 1a)**

	Placebo + DMARD	Sarilumab 150mg q2w + DMARD	Sarilumab 200mg q2w + DMARD
<b>Elevation in Lipids</b>			
Raw incidence rate n/N (%)	5/579 (0.9%)	25/579 (4.3%)	21/582 (3.6%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	5/158.9 (3.1)	25/152.8 (16.4)	21/155.4 (13.5)
Rate difference vs. PBO + DMARD (95% CI)		3.6% (1.7, 5.4)	2.8% (1.1, 4.5)
Rate difference vs. sarilumab 150mg + DMARD (95% CI)			-0.7% (-3.0, 1.5)

n (%) = number and percentage of patients with at least one TEAE

a Number of patients with at least 1 event per 100 patient-years, where the exposure time for patients who have experienced the specific adverse event experience was defined as the time to first adverse experience of interest whereas the exposure time for those who have not had this adverse experience was total TEAE period duration

Source: Integrated Summary of Safety Appendix 1.12, page 8290

In general, the elevation in lipids during the pre-rescue period was consistent with what was seen during the entire double-blind period. Table 99 provides an overview of the elevation in lipids for the entire double-blind treatment period. More subjects in the sarilumab treatment groups experienced an elevation in lipids than in the placebo group. As compared to the pre-rescue period, the raw incidence rates are slightly higher for both sarilumab doses (5.9% for 150mg q2w and 5.0% for 200mg q2w), but the exposure adjusted incidence rates are actually lower than the pre-rescue period (9.2 per 100 pt-yrs for 150mg q2w and 7.7 per 100 pt-yrs for 200mg q2w). Similar to the pre-rescue period, there is not a significant difference in number of patients with elevation in lipids between the 2 sarilumab doses. The sarilumab 200mg q2w actually had numerically lower numbers. The rate difference between sarilumab 200mg q2w and 150mg q2w is -0.9% (-3.4, 1.5). No elevations of lipids were reported as an SAE or were reported to lead to treatment discontinuation.

APPEARS THIS WAY ON ORIGINAL

**Table 99. Elevation in Lipids during the Double-Blind Treatment Period (Pool 1)**

	Placebo + DMARD	Sarilumab 150mg q2w + DMARD	Sarilumab 200mg q2w + DMARD
Total number of patients	661	660	661
Total treatment duration in pt-yrs	382.3	440.7	441.4
Treatment duration up to the first event in pt-yrs	377.7	424.5	427.6
Treatment duration up to the first serious event in pt-yrs	382.3	440.7	441.4
<b>Total patients with ≥ 1 Elevation in lipids (%)</b>	13 (2.0%)	39 (5.9%)	33 (5.0%)
<b>Number of patients with ≥ 1 Elevation in lipids per 100 pt-yrs</b>	3.4	9.2	7.7
Total number of Elevation in lipids (per 100 pt-yrs)	15 (3.9)	47 (10.7)	41 (9.3)
Total patients with ≥ 1 serious Elevation in lipids (%)	0	0	0
Total patients with Elevation in lipids leading to death (%)	0	0	0
Total patients with Elevation in lipids leading to permanent treatment discontinuation (%)	0	0	0

Source: Integrated Summary of Safety, Table 91, page 226

It should be noted that, although there were elevations in LDL, HDL, and triglycerides, the elevated lipid values during the double-blind treatment period remained within the normal range. In the case of LDL, the majority of subjects did not even shift NCEP ATP III classification category. The NCEP ATP III classification categories are < 100 mg/dL, 100 - <130 mg/dL, 130 - <160 mg/dL, 160 - <190 mg/DL, and ≥ 190 mg/dL. Of those who did experience a shift, the majority shifted up one classification. Table 100 presents the baseline and post-baseline LDL values (by NCEP ATP III LDL classification).

APPEARS THIS WAY ON ORIGINAL

**Table 100. Number of Patients by NCEP ATPIII LDL Classification according to Baseline Status and Post-Baseline Values during Double-Blind Treatment Period (Pool 1)**

Laboratory Parameter Baseline Post-baseline n/N(%)	Placebo + DMARD	Sarilumab 150mg q2w + DMARD	Sarilumab 200mg q2w + DMARD
<b>LDL</b>			
Total <sup>a</sup>			
< 100 mg/dL	255/660 (38.6%)	181/655 (27.6%)	152/655 (23.2%)
100 - < 130 mg/dL	240/660 (36.4%)	237/655 (36.2%)	232/655 (35.4%)
130 - < 160 mg/dL	133/660 (20.2%)	159/655 (24.3%)	167/655 (25.5%)
160 - < 190 mg/dL	27/660 (4.1%)	63/655 (9.6%)	80/655 (12.2%)
≥ 190 mg/dL	5/660 (0.8%)	15/65 (2.3%)	24/655 (3.7%)
< 100 mg/dL			
< 100 mg/dL	212/263 (80.6%)	164/280 (58.6%)	132/259 (51.0%)
100 - < 130 mg/dL	47/263 (17.9%)	95/280 (33.9%)	108/259 (41.7%)
130 - < 160 mg/dL	4/263 (1.5%)	20/280 (7.1%)	17/259 (6.6%)
160 - < 190 mg/dL	0/263	1/280 (0.5%)	2/259 (0.8%)
≥ 190 mg/dL	0/263	0/280	0/259
100 - < 130 mg/dL			
< 100 mg/dL	40/235 (17.0%)	16/223 (7.2%)	18/249 (7.2%)
100 - < 130 mg/dL	156/235 (66.4%)	112/223 (50.2%)	109/249(43.8%)
130 - < 160 mg/dL	35/235 (14.9%)	78/223 (35.0%)	95/249 (38.2%)
160 - < 190 mg/dL	4/235 (1.7%)	15/223 (6.7%)	26/249 (10.4%)
≥ 190 mg/dL	0/235	2/223 (0.9%)	1/249 (0.4%)
130 - < 160 mg/dL			
< 100 mg/dL	2/117 (1.7%)	0/110	2/104 (1.9%)
100 - < 130 mg/dL	34/117 (29.1%)	28/110 (25.5%)	12/104 (11.5%)
130 - < 160 mg/dL	71/117 (60.7%)	50/110 (45.5%)	48/104 (46.2%)
160 - < 190 mg/dL	10/117 (8.5%)	29/110 (26.4%)	35/104 (33.7%)
≥ 190 mg/dL	0/117	3/110 (2.7%)	7/104 (6.7%)
160 - < 190 mg/dL			
< 100 mg/dL	0/38	1/34 (2.9%)	0/38
100 - < 130 mg/dL	3/38 (7.9%)	2/34 (5.9%)	2/38 (5.3%)
130 - < 160 mg/dL	21/38 (55.3%)	10/34 (29.4%)	6/38 (15.8%)
160 - < 190 mg/dL	12/38 (31.6%)	14/34 (41.2%)	17/38 (44.7%)
≥ 190 mg/dL	2/38 (5.3%)	7/34 (20.6%)	13/38 (34.2%)
≥ 190 mg/dL			
< 100 mg/dL	0/6	0/8	0/5
100 - < 130 mg/dL	0/6	0/8	1/5 (20.0%)
130 - < 160 mg/dL	2/6 (33.3%)	1/8 (12.5%)	1/5 (20.0%)
160 - < 190 mg/dL	1/6 (16.7%)	4/8 (50.0%)	0/5
≥ 190 mg/dL	3/6 (50.0%)	3/8 (37.5%)	3/5 (60.0%)

a Regardless of baseline status

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

Note: The number (n) represents the subset of the total number of pts who met the criterion in question at least once during treatment. The denominator (/N1) for each parameter within a treatment group is the number of patients for the treatment group who had that parameter assessed post-baseline.

Source: Integrated Summary of Safety, Table 90, page 224-5.

Reflecting the lipid parameter changes, numerically higher number of patients on sarilumab initiated statins compared to placebo during the double-blind treatment period (0-52 weeks), but no difference in statin initiation was observed between the 2 doses of sarilumab. The rates of statin initiation were generally low: 16 patients (2.4%) in 200mg q2w; 16 patients (2.4%) in 150mg q2w; 3 patients (0.5%) in placebo.

Lipid elevations in the long-term safety population remained consistent with that in the double-blind, placebo-controlled population. Table 101 presents an overview of the elevation in lipids for the entire TEAE period, thus, the long-term safety population (Pool 2). With the increased exposure, both sarilumab doses show an increase in number of patients with at least one elevation in lipids. Over time, the increase appears to be greater in the 200mg q2w group, but the exposure is also much greater in the 200mg q2w group. The exposure-adjusted incidence rates of elevation in lipids, however, are similar to the placebo-controlled population, and there are no major difference between both doses of sarilumab (8.8 per 100 pt-yrs in 150mg q2w and 7.3 per 100 pt-yrs in 200mg q2w).

Also, similar to the placebo-controlled population, the majority of the patients did not have a shift in NCEP ATPIII LDL classification. Of those who did shift up, the majority shifted up one classification. One hundred nineteen subjects (4.1%) in the any dose group had a triglyceride value > 495.6 mg/dL, but none of these patients experienced pancreatitis. Initiation of statins occurred in 178 (6.2%) of subjects on any dose of sarilumab; the higher incidence compared to the placebo-controlled population reflects the longer observation period.

APPEARS THIS WAY ON ORIGINAL

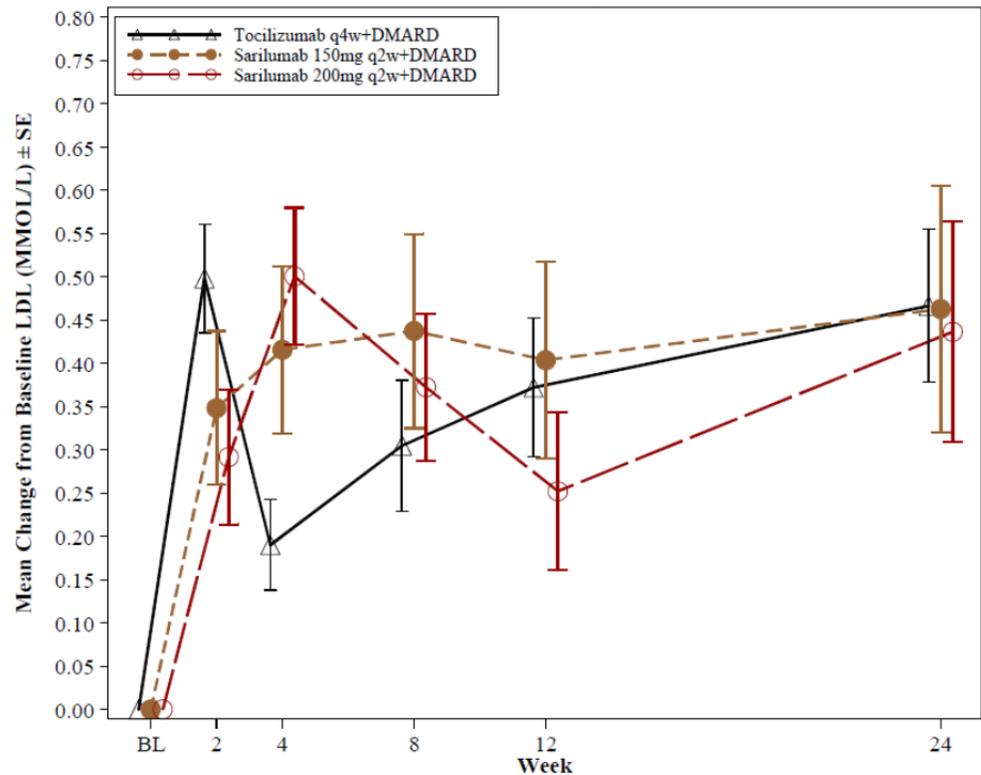
**Table 101. Elevation in Lipids in Long-Term Safety Population (Pool 2)**

	Sarilumab + DMARD		
	150mg q2w Initial dose	200mg q2w Initial dose	Any dose
Total number of patients	1155	1351	2887
Total treatment duration in pt-yrs	701.9	1758.6	4481.8
Treatment duration up to the first event in pt-yrs	678.9	1613.3	4144.0
Treatment duration up to the first serious event in pt-yrs	701.9	1758.6	4479.5
<b>Total patients with ≥ 1 Elevation in lipids (%)</b>	60 (5.2%)	118 (8.7%)	263 (9.1%)
<b>Number of patients with ≥ 1 Elevation in lipids per 100 pt-yrs</b>	8.8	7.3	6.3
Total number of Elevation in lipids (per 100 pt-yrs)	69 (9.8)	152 (8.6)	351 (7.8)
Total patients with ≥ 1 serious Elevation in lipids (%)	0	0	1 (<0.1%)
Number of patients with ≥ 1 serious Elevation in lipids per 100 pt-yrs	0	0	0.0
Total number of serious Elevation in lipids (per 100 pt-yrs)	0	0	1 (0.0)
Total patients with Elevation in lipids leading to death (%)	0	0	0
Total patients with Elevation in lipids leading to permanent treatment discontinuation (%)	0	0	0

Source: Integrated Summary of Safety, Table 93, page 229-230.

SFY13370 was the study designed to evaluate the safety of sarilumab and tocilizumab. The study is described in detail in Sections 6.4 and 8.7. However, as part of the analysis of elevation in lipids, the lipid data will also be presented here. Figure 56 displays the mean change from baseline in LDL for both doses of sarilumab and tocilizumab (IV dosing). There was an elevation in LDL in all treatment arms in a similar rate and patten. The trend in elevation of HDL and triglycerides was also similar across treatment arms. In the pre-rescue period (Pool 1a), there were actually more subjects with a PT of “elevation in lipids” in the tocilizumab arm compared to the sarilumab arms (13 [12.7%] in tocilizumab group vs. 2 [4.1%] in sarilumab 150mg q2w group vs. 3 [5.9%] in sarilumab 200mg q2w group). There were also more subjects in the tocilizumab arm who started a statin during the treatment period (8 [7.8%] in tocilizumab group, 2 [4.1%] in sarilumab 150mg q2w group, 2 [3.9%] in sarilumab 200mg q2w group).

**Figure 56. Mean Change from Baseline in LDL at Each Visit during the TEAE Period (SFY13370)**



# subjects	BL	2	4	8	12	24
Tocilizumab q4w+DMARD	102	98	98	96	97	93
Sarilumab 150mg q2w+DMARD	48	45	46	44	45	39
Sarilumab 200mg q2w+DMARD	51	49	49	48	43	41

LDL = low density lipoprotein

Source: SFY13370 Clinical Study Report, Figure 12, dated August 12, 2015; page 105.

In summary, based on the data in the sarilumab clinical program, it does appear that more subjects on sarilumab had an elevation in all lipid parameters compared to subjects on placebo. Most of these elevations were small, as, for example, the LDL elevation did not even shift the subjects into a higher NCEP ATP III LDL classification. In study SFY13370 when sarilumab was compared to tocilizumab, the elevation in lipid parameters was comparable, even lower when comparing adverse events. Therefore, this elevation in lipids is consistent with what was anticipated for IL-6 inhibition in RA patients.

*Reviewer Comment: As has been discussed earlier, tocilizumab has the same mechanism of action as sarilumab and was previously approved in 2010. At the time of tocilizumab's review for approval, tocilizumab was also noted to cause elevations in lipid parameters. Because elevated LDL has an established risk for CV disease (CVD), it was determined that a post-marketing cardiovascular outcomes trial would be necessary to assess whether the lipid abnormalities seen pre-marketing are associated with an increased risk of cardiovascular*

Clinical Review  
Reviewer: Suzette Peng, MD  
NME/BLA 761037  
Sarilumab/Kevzara

*thromboembolic events. With this regulatory background, the significance of the elevation in lipids in the sarilumab trials was also considered and discussed in great detail at multiple levels.*

*The Division of Metabolism and Endocrine Products (DMEP) was consulted to provide comments and recommendations on the lipid parameter changes. Specifically, they were asked to weigh in as to whether the lipid changes were significant, whether the elevation in lipids might be correlated with an increased risk of CV events, and if they feel that a post-marketing cardiovascular outcome trial (CVOT) should be recommended to address any possible concern. Mary Roberts, M.D., provided a very thorough and well-written discussion of the issues and questions posed to DMEP. I will review DMEP's consult as well as provided my own conclusion on significance of the elevation in lipids, particularly in association with the risk for CV events, at the end of the following section 8.5.3 (CV Events).*

### **8.5.3. Cardiovascular Events**

To aid in evaluating for cardiovascular risk, the applicant utilized an external cardiovascular adjudication committee (CAC), which included 2 cardiologists and 1 neurologist, to review and adjudicate all deaths and serious cardiovascular adverse events in a blinded fashion. The CAC identified the Major Adverse Cardiovascular Events (MACE). MACE was further defined as primary or narrow. MACE (primary) is defined as cardiovascular death (including undetermined cause of death), myocardial infarction, stroke, hospitalization for unstable angina, or hospitalization for transient ischemic attack. MACE (narrow) is defined as cardiovascular death (including undetermined cause of death), myocardial infarction, and stroke.

Approximately 38-39% of patients in the sarilumab trials had cardiovascular disease at baseline, as seen in Table 102. Hypertension was actually the most commonly reported medical history for all 3 safety pools and amongst treatment groups. The baseline CV disease was consistent in the long-term safety population (Pool 2), slightly numerically higher in both treatment arms (41.8% in sarilumab 150mg q2w and 41.1% in sarilumab 200mg q2w).

**Table 102. Cardiovascular History in the Placebo-Controlled Population (Pool 1)**

	Placebo + DMARD  N=661	Sarilumab	
		150mg q2w + DMARD N=660	200mg q2w + DMARD N=661
<b>Total number of patients with any CV history</b>	<b>252 (38.1%)</b>	<b>257 (38.9%)</b>	<b>258 (39.0%)</b>
Hypertension	211 (31.9%)	200 (30.3%)	205 (31.0%)
Diabetes	54 (8.2%)	47 (7.1%)	58 (8.8%)
Dyslipidemia	71 (10.7%)	81 (12.3%)	71 (10.7%)
Coronary artery disease	26 (3.9%)	25 (3.8%)	25 (3.8%)
Ischemic cerebrovascular disease	8 (1.2%)	9 (1.4%)	10 (1.5%)
Family history of CAD	19 (2.9%)	19 (2.9%)	22 (3.3%)

Hypertension: SMQ Hypertension; Diabetes: SMQ Hyperglycaemia/New onset Diabetes; Dyslipidemia: SMQ Dyslipidemia; Coronary artery disease: SMQ Ischemic heart disease; Cerebrovascular disease: Ischemic cerebrovascular conditions; Family history of CAD: CRF page

Source: ISS Appendix 1.2.2.1, dated September 10, 2015; page 108.

*Reviewer Comment: Cardiovascular risk associated with the study drug can be difficult to determine in RA clinical trials, as RA itself is a cardiovascular risk factor. RA increases the risk of CV mortality by up to 50% compared with the general population (Choy E, Ganeshalingham K, et al. 2143). The risk for cardiovascular disease is not only related to traditional risk factors (e.g., hypertension, smoking, type 2 diabetes) but also to chronic inflammation. The heightened systemic inflammation in RA is linked to “accelerated atherosclerosis” (2143).*

Table 103 presents the incidence rates of MACE (primary and narrow) for placebo, sarilumab 150mg q2w, and sarilumab 200mg q2w for the pre-rescue period. No events occurred in the placebo group. The incidence rate of MACE was the same for both doses of sarilumab at 0.2%. The exposure-adjusted incidence rate was also the same for both doses at 0.6 per 100 patient-years. The estimated risk difference between sarilumab 150mg q2w and placebo was 0.2% (95% CI: -0.2, 0.5). The same risk difference was calculated for sarilumab 200mg q2w.

APPEARS THIS WAY ON ORIGINAL

**Table 103. Summary of CV Events during Pre-Rescue Period (Pool 1a)**

	Placebo + DMARD	Sarilumab 150mg q2w + DMARD	Sarilumab 200mg q2w + DMARD
<b>MACE (primary)</b>			
Raw incidence rate n/N (%)	0/579	1/579 (0.2%)	1/582 (0.2%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	0/161.6 (0.0)	1/159.7 (0.6)	1/161.0 (0.6)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		0.2% (-0.2, 0.5)	0.2% (-0.2, 0.5)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			-0.0% (-0.5, 0.5)
<b>MACE (narrow)</b>			
Raw incidence rate n/N (%)	0/579	1/579 (0.2%)	1/582 (0.2%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	0/161.6 (0.0)	1/159.7 (0.6)	1/161.0 (0.6)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		0.2% (-0.2, 0.5)	0.2% (-0.2, 0.5)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			-0.0% (-0.5, 0.5)

n (%) = number and percentage of patients with at least one TEAE

a Number of patients with at least 1 event per 100 patient-years, where the exposure time for patients who have experienced the specific adverse event experience was defined as the time to first adverse experience of interest whereas the exposure time for those who have not had this adverse experience was total TEAE period duration

b The rate difference and its 95% confidence interval were estimated using the M&N method stratified by the study, using the CMH weight

Source: Sanofi Response to IR (June 10 and 13), Revision to ISS Appendix 1.12.1.53, dated June 15, 2016, page 7

For the entire double-blind treatment period, there were 2 events for each dose of sarilumab. No MACE events occurred in the placebo group. The incidence was, thus, similar to what was seen in the pre-rescue period: 0.3% for MACE events (primary and narrow) for both sarilumab treatment groups. The exposure-adjusted incidence rate of MACE events was 0.5 per 100 patient-years for both sarilumab 150 mg and 200 mg q2w. The estimated risk difference between sarilumab and placebo was 0.3% (95% CI: -0.1, 0.7).

The 4 events adjudicated as MACE in the sarilumab groups were 2 CV deaths and 2 non-fatal strokes.

#### CV deaths

- Patient 011072-643-008-215 was a 56 year-old woman without known CV disease on sarilumab 150mg q2w and concomitant MTX who was noted to have mild leukopenia, neutropenia, and anemia which worsened after her second dose of therapy. She died suddenly on her way to study site for further evaluation. The autopsy showed a principal diagnosis of chronic ischemic heart disease and atherosclerotic cardiosclerosis. There was also evidence of hypertensive disease with left ventricular hypertrophy and

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

arteriolar nephrosclerosis. Therefore, the CAC adjudicated this episode of sudden death as a CV death, specifically cardiogenic pulmonary edema.

- Patient 011072-032-009-212 was a 59 year-old man who had hypertension and obesity and was an active smoker. He received approximately 3 months of sarilumab 200mg q2w when he was hospitalized for left lower extremity paresis, cranial nerve abnormalities, and sensory impairment. Prior to undergoing a CT scan for possible CVA, the subject went into cardiac arrest. The CAC adjudicated this case as CV death given the “quite confusing report. Suggestion of stroke (no evidence). Could be pulmonary embolism or heart failure. CV death most probably due to rapid progression until respiratory and cardiac arrest.”

### Strokes

- Patient 011072-152-001-211 was a 49 year-old man who had COPD and was a smoker. After 6 months on sarilumab 150mg q2w (around Day 140), the subject developed abdominal/epigastric pain and vertigo. Imaging revealed renal/splenic infarcts and brain infarcts, and a CT angiogram confirmed an embolic focus in the distal SMA and in the posterior branch of splenic artery and left renal artery. TTE and TEE did not show thrombi, but the cardiologist felt the origin of the embolus was cardiogenic. The patient underwent a mesenteric artery embolectomy and received anticoagulation. The event of multiple arterial emboli was adjudicated by the CAC as stroke.
- Patient 010832-616-020-401 was a 67 year-old woman with hypertension and possible polycystic kidney disease. She was receiving sarilumab 200mg q2w and concomitant leflunomide, but, for her RA, she was previously treated with infliximab and rituximab. Around Day 150, she developed an ischemic stroke (CT scan) and non-ST elevation MI (NSTEMI) in the setting of non-infectious endocarditis (sterile mitral valve mass) which was attributed to her RA. As part of DMEP’s consult, the reviewer was able to find that the CAD adjudicated the ischemic stroke as a stroke and did not adjudicate the NSTEMI as a myocardial infarction. Additionally, the reviewer noted that the baseline LDL for this subject was 88 mg/dL but, prior to hospitalization, was 120 mg/dL. As part of her corrective treatment, atorvastatin 80mg was started.

Of note, there was one subject in the placebo group (Patient 011072-032-001-203, 58 year-old man with a history of hypertension, diabetes mellitus type 2, atrial fibrillation, and a history of an acute MI) who developed a transient ischemic attack (TIA) for which the IMP was temporarily delayed. Then, he suffered an acute myocardial infarction and ischemic stroke in the setting of infectious endocarditis; however, these occurred when the patient was off placebo for greater than 60 days. Therefore, based on the definition of the TEAE period in the ISS, it was not included in the analysis. (As noted in Section 8.3.2, the definition of the TEAE

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

period differed in study EFC11072 Part B, and, thus, this event was included in the analysis for this study alone.)

*Reviewer Comment: These 4 adjudicated MACE during the double-blind period occurred in subjects on sarilumab. However, each of the subjects had other CV risk factors including hypertension, active tobacco use, diabetes, and obesity. For the subject who suffered sudden death, this CV history was unknown but was revealed through the autopsy. Also, for the subject with stroke and non-infectious endocarditis, her valve abnormality was attributed to RA, but she also carried a diagnosis of “congenital cysts in the kidney.” I am unclear to what this is referring, but, if she had polycystic kidney disease, this would be a more likely risk factor. She did have an elevation in lipids after treatment with sarilumab, but appropriate doses of atorvastatin was initiated. Therefore, given the multiple CV risks in these subjects, a direct association with sarilumab use is not entirely clear.*

Sensitivity analyses done on Pool 1a also revealed similar findings for subjects based on exposure through Week 52. This analysis included patients who were randomized into a certain dose group as well as patients who were rescued into that dose group and were within the first 52 weeks of treatment. In this analysis, the placebo group’s incidence rate remained at 0. The exposure adjusted incidence rate of MACE was 0.5 for sarilumab 150mg per 100 pt-yrs and 0.3 for sarilumab 200mg per 100 pt-yrs.

**Table 104. Sensitivity Analyses of CV Events during TEAE Period (Weeks 0-52, Pool 1a)**

n(%)	Sarilumab 150mg q2w + DMARD		Sarilumab 200mg q2w + DMARD <sup>a</sup>	
	Raw incidence rate n/N (%)	Exposure adjusted incidence rate <sup>b</sup> n/PY (rate per 100 PYs)	Raw incidence rate n/N (%)	Exposure adjusted incidence rate <sup>b</sup> n/PY (rate per 100 PYs)
<b>MACE primary</b>	2/579 (0.3%)	2/403.7 (0.5)	2/881 (0.2%)	2/581.3 (0.3)
<b>MACE narrow</b>	2/579 (0.3%)	2/403.7 (0.5)	2/881 (0.2%)	2/581.3 (0.3)

n(%) = number and % of patients with at least 1 TEAE

a Includes randomized patients and patient who rescued and were within the first 52 weeks with this regimen

b Number of patients with at least 1 event per 100 patient-years, where the exposure time for patients who have experienced the specific adverse experience was defined as the time to first adverse experience of interest whereas the exposure time for those who have not had this adverse experience was total TEAE period duration

Source: ISS Appendix 1.12.2.12, page 8444.

Table 105 presents the CV events in the long-term safety population (Pool 2). The exposure-adjusted incidence rate for MACE (primary) was 0.3 per 100 pt-yrs for sarilumab 150mg q2w and 0.7 per 100 pt-yrs for sarilumab 200mg q2w. A similar difference was present for MACE (narrow). Given the longer exposure in the sarilumab 200mg q2w treatment group and complexities in the study design, the higher incidence rate for the 200mg dose group is difficult to interpret.

**Table 105. Number of CV Events (per 100 pt-yrs) in the Long-Term Safety Population (Pool 2)**

CV Events	Sarilumab + DMARD		
	150 mg q2w Initial Dose (PY=701.9) nE (nE/100 PY)	200 mg q2w Initial Dose (PY=1758.6) nE (nE/100 PY)	Any Dose (PY=4481.8) nE (nE/100 PY)
<b>MACE (primary)</b>	2 (0.3)	12 (0.7)	28 (0.6)
<b>MACE (narrow)</b>	2 (0.3)	11 (0.6)	24 (0.5)
CV Death	1 (0.1)	3 (0.2)	7 (0.2)
Myocardial infarction	0	0	1 (0.0)
Other cardiovascular causes	1 (0.1)	2 (0.1)	5 (0.1)
Undetermined cause of death	0	1 (0.1)	1 (0.0)
Myocardial infarction (non-fatal)	0	3 (0.2)	10 (0.2)
Hospitalization for unstable angina (non-fatal)	0	0	0
Stroke (non-fatal)	1 (0.1)	5 (0.3)	7 (0.2)
Hospitalization for transient ischemic attack (non-fatal)	0	1 (0.1)	4 (0.1)

Source: Integrated Summary of Safety, Table 97, page 238.

Sanofi also performed a model-based analysis of MACE, which showed a similarly increased risk of MACE with the sarilumab 200mg q2w arm. Table 106 shows the model-based analysis of MACE primary and narrow. As a reminder, all the safety data on placebo and sarilumab were included in these analyses. The exposure-adjusted incidence rate of sarilumab (0.6 per 100 patient-years for any sarilumab dose) exceeds that of placebo (0 per 100 patient-years). Additionally, in this analysis, the exposure-adjusted incidence rate for sarilumab 200mg (0.7 per 100 patient-years) was higher than that for sarilumab 150mg (0.3 per 100 patient-years); however, there were limitations to these analyses given the study design.

APPEARS THIS WAY ON ORIGINAL

**Table 106. Model-based Analyses on Patients with at least one MACE during the TEAE period**

	Placebo + DMARD	Sarilumab 150mg q2w + DMARD	Sarilumab 200mg q2w + DMARD	Any Sarilumab + DMARD
<b>MACE (primary)</b>				
Raw incidence rate n/N (%)	0/661 (0)	2/1155 (0.2)	12/1351 (0.9)	26/2887 (0.9)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	0/382.4 (0)	2/701.7 (0.3)	12/1756.3 (0.7)	26/4469.4 (0.6)
Rate ratio vs. PBO + DMARD (95% CI)		--	--	--
Rate ratio vs. sarilumab 150mg + DMARD (95% CI)			2.49 (0.54, 11.40) <sup>b</sup>	
<b>MACE (narrow)</b>				
Raw incidence rate n/N (%)	0/661 (0)	2/1155 (0.2)	11/1351 (0.8)	23/2887 (0.8)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	0/382.3 (0)	2/701.7 (0.3)	11/1757.1 (0.6)	23/4475.3 (0.5)
Rate ratio vs. PBO + DMARD (95% CI)		--	--	--
Rate ratio vs. sarilumab 150mg + DMARD (95% CI)			2.31 (0.50, 10.72) <sup>b</sup>	

a Number of patients with at least one event per 100 patient-years (PYs), where the exposure time for patients who have experienced the specific adverse experience was defined as the time to first adverse experience of interest whereas the exposure time for those who have not had this adverse experience was total TEAE period duration

b The rate ratio and its 95% confidence interval (CI) were estimated using the GEE (Poisson distribution with exposure calculated based on the time to first event as an offset), adjusted for treatment and the important baseline factors (age, gender, RA duration of disease), assuming an exchangeable covariance structure for the within-subject correlations

Source: Sanofi response to IR (July 12, 2016), Tables 1 and 2, dated July 14, 2016, pages 7-8.

However, Sanofi provided a more granular analysis of the long-term safety population, as described in Section 8.3.2. Table 107 presents the MACE (primary and narrow) for the phase 3 studies and the open-label extension study. The events are categorized separately into exactly what treatment the patient was receiving at the time of the event. The treatment categories are separated by the 3 randomized treatment groups, all treatment groups after rescue or open-label treatment, and then treatment groups who had to decrease down to 150mg q2w during the open-label period because of laboratory abnormalities. With this analysis of CV events, it is evident that most of the CV events occurred in the open-label period. The number of events all occurred in subjects on sarilumab 200mg, as this was the only dose given in the open-label period. However, it is important to note that a similar number of events occurred for all treatment groups regardless of the starting treatment (i.e., placebo, sarilumab 150mg q2w, and sarilumab 200mg q2w). Therefore, the duration that subjects were administered sarilumab 200mg q2w may not be a contributing factor. Overall, these data are difficult to interpret but may support that the increased incidence of events noted in the sarilumab 200mg

q2w group in the long-term safety population may not represent a true dose response, especially given that a dose response was not seen in the placebo-controlled period.

**Table 107. Summary of CV Events in Pivotal Studies and OLE (EFC11072, EFC10832, LTS11210)**

Treatment	Raw incidence rate n/N (%)	Exposure adjusted incidence rate <sup>a</sup> n/PY (n/100 PY)	Exposure adjusted event rate <sup>b</sup> n <sub>E</sub> /PY (n <sub>E</sub> /100 PY)
<b>MACE (primary)</b>			
Placebo initial dose	0/661	0/383.9	0/383.9
Sarilumab 150mg q2w initial dose	2/660 (0.3%)	2/442.0 (0.5)	2/442.2 (0.5)
Sarilumab 200mg q2w initial dose	2/661 (0.3%)	2/442.7 (0.5)	2/442.8 (0.5)
PBO → sarilumab 200mg q2w (rescue/OL)	5/520 (1.0%)	5/659.2 (0.8)	5/660.3 (0.8)
Sarilumab 150mg q2w → 200mg q2w (rescue/OL)	4/483 (0.8%)	4/605.1 (0.7)	4/607.7 (0.7)
Sarilumab 200mg q2w → 200mg q2w (OL)	5/475 (1.1%)	5/578.0 (0.9)	5/579.0 (0.9)
PBO → sarilumab 200mg q2w (rescue/OL) → 150mg q2w (dose decrease)	0/96	0/113.0	0/113.0
Sarilumab 150mg q2w → 200mg q2w (rescue/OL) → 150mg q2w (dose decrease)	0/68	0/77.6	0/77.6
Sarilumab 200mg q2w → 200mg q2w (OL) → 150mg q2w (dose decrease)	0/71	0/88.4	0/88.4
<b>MACE (narrow)</b>			
Placebo initial dose	0/661	0/383.9	0/383.9
Sarilumab 150mg q2w initial dose	2/660 (0.3%)	2/442.0 (0.5)	2/442.2 (0.5)
Sarilumab 200mg q2w initial dose	2/661 (0.3%)	2/442.7 (0.5)	2/442.8 (0.5)
PBO → sarilumab 200mg q2w (rescue/OL)	5/520 (1.0%)	5/659.2 (0.8)	5/660.3 (0.8)
Sarilumab 150mg q2w → 200mg q2w (rescue/OL)	4/483 (0.8%)	4/605.1 (0.7)	4/607.7 (0.7)
Sarilumab 200mg q2w → 200mg q2w (OL)	5/475 (1.1%)	5/578.0 (0.9)	5/579.0 (0.9)
PBO → sarilumab 200mg q2w (rescue/OL) → 150mg q2w (dose decrease)	0/96	0/113.0	0/113.0
Sarilumab 150mg q2w → 200mg q2w (rescue/OL) → 150mg q2w (dose decrease)	0/68	0/77.6	0/77.6
Sarilumab 200mg q2w → 200mg q2w (OL) → 150mg q2w (dose decrease)	0/71	0/88.4	0/88.4

n (%) = number and % of patients with at least 1 TEAE

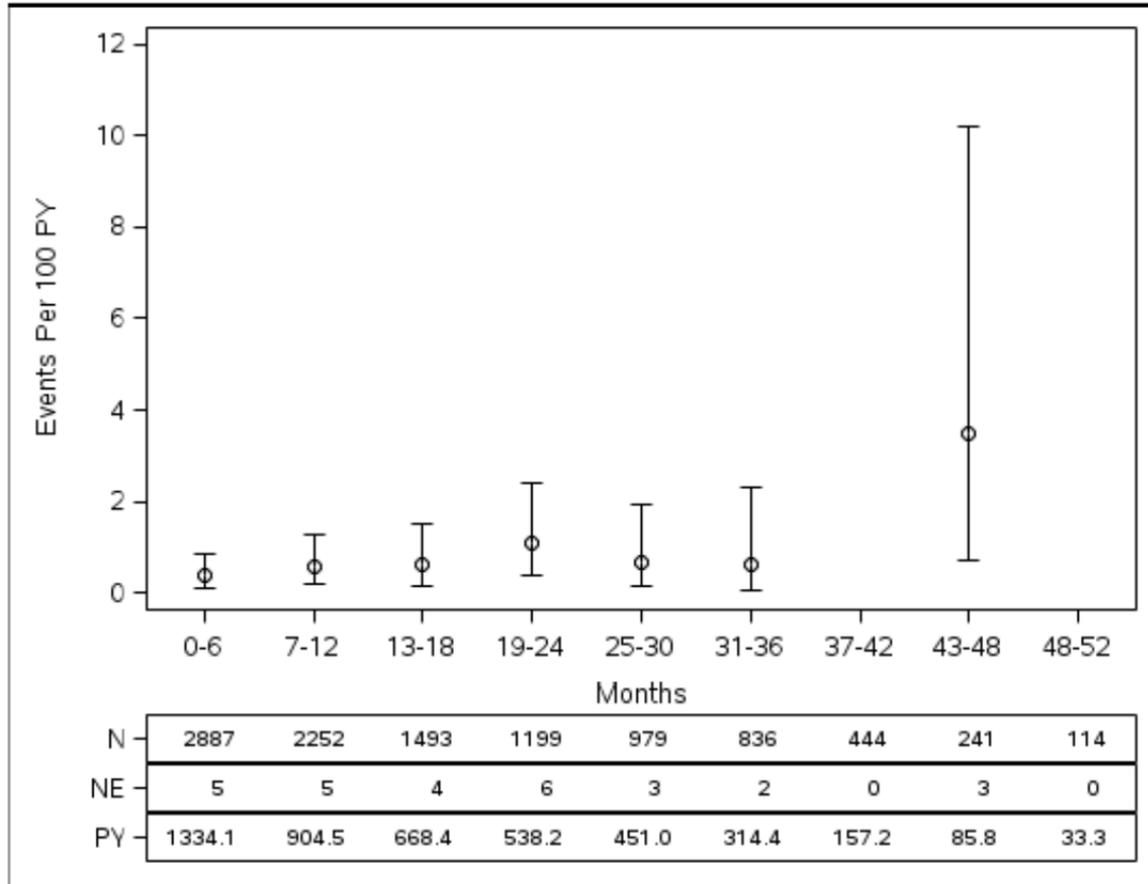
a Number of patients with at least one event per 100 pt-yrs, where the exposure time for patients who have experienced the specific adverse experience was defined as the time to first adverse experience of interest whereas the exposure time for those who have not had this adverse experience was total TEAE period duration

b Number of events per 100 pt-yrs, where the exposure time was the total TEAE period duration

Source: Sanofi response to IR (May 27, 2016), Table 1, dated June 3, 2016, page 6; Sanofi response to IR (June 10, 2016), Table C.1, dated June 15, 2016, page 15.

Lastly, the exposure-adjusted incidence rates for adjudicated MACE for any dose of sarilumab were stable over time in the long-term safety population (Figure 57). This further supports the conclusion that longer duration of exposure does not increase the risk of MACE.

**Figure 57. Exposure-adjusted Rate of MACE (primary) by 6-month Intervals During the Entire TEAE Period (Pool 2)**



N = sample size; NE = number of events in a 6-month period; PY = patient-years  
 95% confidence interval was calculated using the exact method  
 MACE (primary) = CV death, MI, stroke, hospitalization for unstable angina or hospitalization for TIA  
 Source: ISS, Figure 28, dated October 6, 2015; page 240.

In summary, during the entire double-blind period, there were 2 events in each sarilumab arm but no events in the placebo arm. With such low numbers, it is difficult to make any conclusion regarding risk of MACE with sarilumab. In particular, the subjects who developed MACE in the double-blind period had other CV risk factors. Although analysis of the long-term safety data might suggest a dose-response, which would support a possible relationship, the increase number of MACE in the sarilumab 200mg q2w may be more related to the complex study design and the increased exposure at that dose. Therefore, based on the clinical trial data alone, there does not appear to be a signal for MACE.

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

*Reviewer Comment: Although the risk of MACE does not appear to be increased in the sarilumab clinical development program, there is an association with lipid elevation. In turn, the possible association with MACE is still present given that elevation in lipids is an established CV risk factor.*

*As mentioned in Section 8.5.2 on elevation in lipids, DMEP was consulted with questions regarding the significance of the elevation in lipids and the possible association with CV events. The Division of Cardiovascular and Renal Products (DCaRP) was also consulted with the same questions. DCaRP subsequently deferred the consult to the Safety Outcome Trial (SOT) Subcommittee of the Medical Policy Committee. Therefore, a summary of the consult and subcommittee meeting will be provided below with a final conclusion from the reviewer.*

### **DMEP Consult**

The DMEP reviewer provided a thorough analysis of sarilumab's effect on lipid levels, effect on CRP, and the adjudicated MACE in the development program. Much of the reviewer's analysis was similar to what is presented above, but, for more details, please see Dr. Roberts' full consult.

The reviewer then made a few comments/recommendations:

- Patients with RA have an increased risk of CV disease. This risk is not fully explained by traditional risk factors, but the "chronic pro-inflammatory state" is a primary contributor. The reviewer noted that there are ongoing CV outcome trials testing the effects of anti-inflammatory therapy on CV risk.
- "Unlike the general population, where there is a linear correlation with LDL-C levels and CV risk, patients with RA, despite higher CV risk, tend to have lower total cholesterol and LDL-C in the setting of active inflammation. This relationship has been described as a 'lipid paradox.'"
- Therefore, the reviewer concludes that the interplay of inflammation, lipid levels, and CV risk is complex and "complicates conclusions about the clinical significance of the observed elevations in lipids with sarilumab, especially as they are occurring in tandem with reductions in the inflammatory biomarker, CRP."
- The reviewer noted that "in theory, if the statin-based relationship between LDL-C and CV risk were to hold for drug-induced increases in LDL-C and could be extrapolated to the RA population, the magnitude of change could be on the order of 8% compared to placebo. However, this quantification of risk is speculative, especially considering that sarilumab induces favorable changes in inflammation .... Furthermore, we note that sarilumab modestly increases HDL-C, which could be considered favorable since epidemiologic studies have observed an inverse relationship between HDL-C and CV risk ...."

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

- Dr. Roberts concluded that a CVOT may be necessary if it is critical to characterize the effect of sarilumab on CV risk. However, labeling could communicate that healthcare providers should follow lipid levels and treat accordingly.

### **SOT Subcommittee Meeting (July 28, 2016)**

After presenting the subcommittee with background on the sarilumab program and the analysis of MACE and lipids, the SOT subcommittee agreed that, given the low number of MACE, it is difficult to determine a risk for MACE based on the clinical trial data alone. However, based on the elevation in lipids, there is a biological plausibility for an increased CV risk. The discussion was then whether a post-marketing CVOT should be performed. The members acknowledged that tocilizumab, which has the same mechanism of action and also causes an elevation of lipids, was required to conduct a CVOT as a post-marketing requirement (PMR). Members of the committee also acknowledged that any trial that could adequately determine CV risk would require approximately 20,000 subjects. Members of the committee then voted on whether a post-marketing CVOT should be required. The committee was voted 9:2 against performing the CVOT, but some of these votes were qualified with discussion regarding study feasibility and tocilizumab's current PMR.

*Reviewer Comment: The discussions and recommendations of the DMEP consult and SOT subcommittee meeting are acknowledged and appreciated. With their recommendations alongside the Division's own analysis of the data, the Division made the following conclusions:*

- *Based on the safety data, there appears to be an association between sarilumab and an elevation in lipids. The elevation in lipids trends higher with the 200mg dose compared to the 150mg dose.*
- *The association between sarilumab and MACE is less clear. Given the small numbers during the double-blind period and the complexities of the long-term safety population, there does not appear to be an increased risk of MACE based on the safety data.*
- *Because of the elevation in lipids associated with sarilumab, this may theoretically convey a CV risk. However, it is now better understood that "while studies in the general population indicate a positive relationship between CV disease and cholesterol levels, in RA this relationship is different, likely as a result of a chronic inflammatory state, where inflammation as a CV risk factor seems to be inversely associated with cholesterol levels" (Urruela and Suarez-Almazor 430). It has been seen that untreated patient with RA may have lower lipid levels but an increased risk of CV disease that can be attributed instead to inflammation. This relationship between lipids and CV disease in RA patients has been called the "lipid paradox" (Urruela and Suarez-Almazor 428). Rather, inflammatory*

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

*markers are associated with an increased risk of CV death in RA patients, even when other CV risk factors are controlled (Urruela and Suarez-Almazor 430).*

- *An adequate CVOT would require approximately 20,000 subjects in order to determine a true CV risk.*
- *At this time, the Division does not feel that a post-marketing CVOT would add any further information. The elevation in lipids will be placed in the label, as this was the finding from the sarilumab clinical development program. The label will advise healthcare providers to monitor and treat the patients' lipid parameters appropriately. However, the Division also acknowledges that a CVOT is currently being performed for tocilizumab, an approved medication with the same mechanism of action as sarilumab. Dependent on the findings, the results from tocilizumab's CVOT may have labeling ramifications for sarilumab.*

### 8.5.4. Malignancy

Malignancy was an AESI based on previous experience with other biologic DMARDs in the treatment of RA. Table 108 presents the rates of malignancies in the pre-rescue period (Pool 1a). For this patient population, the number of malignancies was low and similar across treatment arms. In fact, the 2 malignancies that occurred in the 200mg q2w arm were both non-melanomatous skin cancers (NMSC). Given that the pre-rescue period was just 16 and 12 weeks for studies EFC 11072 Part B and EFC10832, respectively, the low numbers are not entirely unexpected.

APPEARS THIS WAY ON ORIGINAL

**Table 108. Summary of Malignancies in the Pre-Rescue Period (Pool 1a)**

	Placebo + DMARD	Sarilumab 150mg q2w + DMARD	Sarilumab 200mg q2w + DMARD
<b>Malignancy</b>			
Raw incidence rate n/N (%)	2/579 (0.3%)	3/579 (0.5%)	2/582 (0.3%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	2/161.2 (1.2)	3/159.2 (1.9)	2/160.4 (1.2)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		0.2% (-0.6, 0.9)	0.0% (-0.7, 0.7)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			-0.2% (-0.9, 0.6)
<b>Malignancy excluding NMSC</b>			
Raw incidence rate n/N (%)	1/579 (0.2%)	3/579 (0.5%)	0/582
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	1/161.4 (0.6)	3/159.2 (1.2)	0/160.6 (0.0)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		0.3% (-0.3, 1.0)	-0.2% (-0.5, 0.2)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			-0.5% (-1.1, 0.1)

n (%) = number and percentage of patients with at least one TEAE

a Number of patients with at least 1 event per 100 patient-years, where the exposure time for patients who have experienced the specific adverse event experience was defined as the time to first adverse experience of interest whereas the exposure time for those who have not had this adverse experience was total TEAE period duration

b The rate difference and its 95% confidence interval were estimated using the M&N method stratified by the study, using the CMH weight

Source: ISS Appendix 1.12.1.52, page 8291-8292.

For the entire 52-week, double-blind treatment period, the placebo-controlled, safety population (Pool 1) showed similarly low numbers of malignancies. The incidence rates remained roughly equivalent across treatment arms, 0.5% in the placebo arm, 0.8% in the 150mg q2w arm, and 0.6% in the 200mg q2w arm. Table 109 presents the raw incidence and exposure-adjusted incidence rates of all malignancies, non-melanomatous skin cancers, and solid tumors excluding NMSC. The table also lists the types of malignancies that occurred during this period.

**Table 109. Overview of Malignancy TEAEs in Entire Double-Blind Treatment Period (Pool 1)**

	Placebo + DMARD	Sarilumab	
		150mg q2w + DMARD	200mg q2w + DMARD
Total number of patients	661	660	661
Total treatment duration in pt-yrs	382.3	440.7	441.4
Treatment duration up to the first event in pt-years <sup>a</sup>	380.8	440.0	439.6
<b>Total patients with ≥ 1 malignancy (%)</b>	<b>3 (0.5%)</b>	<b>5 (0.8%)</b>	<b>4 (0.6%)</b>
<b>Number of patients with ≥ 1 malignancy per 100 pt-yrs</b>	<b>0.8</b>	<b>1.1</b>	<b>0.9</b>
<b>Total number of malignancy (per 100 pt-yrs)</b>	<b>4 (1.0)</b>	<b>5 (1.1)</b>	<b>4 (0.9)</b>
<b>Non-melanoma skin cancer –</b>			
Total number of events (events/100 pt-yrs)	3 (0.8)	0	2 (0.5)
Basal cell carcinoma	1 (0.3)	0	1 (0.2)
Squamous cell carcinoma of skin	2 (0.5)	0	1 (0.2)
<b>Total patients with ≥ 1 malignancy excluding NMSC (%)</b>			
	1 (0.2%)	5 (0.8%)	2 (0.3%)
<b>Number of patients with ≥ 1 malignancy excluding NMSC per 100 pt-yrs</b>			
	0.3	1.1	0.5
<b>Total number of malignancy excluding NMSC (per 100 pt-yrs)</b>			
	1 (0.3)	5 (1.1)	2 (0.5)
<b>Solid tumors excluding NMSC –</b>			
Total number of events (events/100 pt-yrs)	1 (0.3)	5 (1.1)	2 (0.5)
Breast cancer	0	2 (0.5)	1 (0.2)
Malignant melanoma	0	1 (0.2)	1 (0.2)
Appendiceal cancer	0	1 (0.2)	0
Renal and renal pelvic cancer	1 (0.3)	1 (0.2)	0
<b>Hematologic – total number of events (events/100 pt-yrs)</b>			
	0	0	0

Search criteria: SMQ Malignant or unspecified tumors

a For patients with no such event, the duration is up to the end of the treatment duration

Source: ISS, Table 118, page 271.

In general, the types of cancers are typical given the patient population (based on age, gender, and underlying RA). However, there were a few uncommon malignancies, namely the appendiceal cancer and renal cancers. The patient narratives are described briefly below.

- Patient 011072-554-001-204 (New Zealand) was a 59 year-old woman with RA on MTX (since 2011) and prednisone (since 2011). She was randomized to sarilumab 150mg q2w. During the study, the patient had multiple UTIs (11 days prior to study, Day 29, Day 55), and the IMP was continued without interruption. On Day 309, she was noted to be neutropenic (0.86 Giga/L, Grade 3 neutropenia). This was the lowest her

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

neutrophil count had been. On Day 313, a CT scan was done as “follow-up for recurrent UTIs,” and it revealed a focal dilatation at the tip of the retrocecal appendix. On Day 360 (9 days after her last dose of IMP), she had a laproscopic appendectomy for which the histology revealed a low grade appendiceal mucinous neoplasm. She recovered and did roll over into LTS11210. It is unclear, however, whether she continued to receive sarilumab.

- Patient 010832-840-129-410 (USA) was a 65 year-old woman with RA, a history of a “benign neoplasm” of the thyroid, and large intestine polyps. For her RA, she was previously treated with golimumab which was discontinued due to lack of efficacy. At baseline, she was receiving treatment with methotrexate. She was randomized to sarilumab 150mg q2w. On Day 1 (screening) of the study, she had a mild decline in neutrophils as well as a UTI (*Klebsiella pneumonia*). On Day 10 of the study, the patient was diagnosed with renal cell carcinoma of the right kidney. She subsequently underwent right partial nephrectomy. In total, she only received 1 dose of sarilumab.
- Patient 010832-840-137-409 (USA) was a 71 year-old woman with RA and history of a “large intestine benign neoplasm.” She had previous treatment for her RA with etanercept and infliximab; both of which were discontinued due to lack of efficacy. She was randomized to placebo. She was also taking concomitant MTX and prednisone (5mg). On Day 29 of the study, she had hematuria. She did have an episode of hypercalcemia about 6 weeks prior to this event. For her hematuria, the IMP was temporarily discontinued but restarted. However, 2 months later, she underwent first a cystoscopy (normal) and then a CT scan (left ureteral stone and focal lesion of the left kidney). About 1 month after that scan, the patient had another episode of hematuria and hypercalcemia. IMP was again temporarily interrupted. Another cystoscopy 1 week later confirmed the diagnosis of non-invasive low-grade papillary urothelial carcinoma of the left ureter. The IMP was discontinued about 1 month later.

*Reviewer Comment: Of these 3 unusual malignancies, one of the renal cancers occurred in a subject on placebo. The other case of renal cancer occurred in a subject who only received 1 dose of sarilumab, and it occurred on Day 10 of the study. Therefore, it is unlikely to be related. The third malignancy was the appendiceal cancer which was an incidental finding in the subject’s work-up of recurrent UTIs. The relationship to sarilumab therapy is unclear.*

Sanofi provided sensitivity analysis of the Pool 1a safety data. Table 110 shows the sensitivity analysis for Weeks 0-52, thus, including both the randomized and rescued subjects in their first 52 weeks of therapy. In this analysis, both the raw incidence rate and the exposure-adjusted incidence rate are slightly lower in the placebo arm. However, the rates are essentially the same for both sarilumab doses.

**Table 110. Sensitivity Analyses of Malignancies during TEAE period (Week 0-52, Pool 1a)**

n(%)	PBO + DMARD		Sarilumab 150mg q2w + DMARD		Sarilumab 200mg q2w + DMARD <sup>a</sup>	
	Raw incidence rate	Exposure adjusted incidence rate <sup>b</sup>	Raw incidence rate	Exposure adjusted incidence rate <sup>b</sup>	Raw incidence rate	Exposure adjusted incidence rate <sup>b</sup>
	n/N (%)	n/PY (rate per 100 PYs)	n/N (%)	n/PY (rate per 100 PYs)	n/N (%)	n/PY (rate per 100 PYs)
<b>Malignancy</b>	2/579 (0.3%)	2/347.3 (0.6)	5/579 (0.9%)	5/403.2 (1.2)	6/881 (0.7%)	6/579.2 (1.0)
<b>Malignancy excluding NMSC</b>	1/579 (0.2%)	1/348.1 (0.3)	5/579 (0.9%)	5/403.2 (1.2)	4/881 (0.5%)	4/580.5 (0.7)

n(%) = number and % of patients with at least 1 TEAE

a Includes randomized patients and patient who rescued and were within the first 52 weeks with this regimen

b Number of patients with at least 1 event per 100 patient-years, where the exposure time for patients who have experienced the specific adverse experience was defined as the time to first adverse experience of interest whereas the exposure time for those who have not had this adverse experience was total TEAE period duration

Source: ISS Appendix 1.12.2.9, page 8441.

Given the latency in malignancy development, it is worthwhile to evaluate the long-term safety population for malignancies in a little more detail. As would be expected, there were more cases of malignancies in the long-term safety population (Pool 2). However, the incidence rate was about the same in the sarilumab 150mg q2w initial dose arm at 0.8%. For the 200mg q2w initial dose arm, the incidence rate was slightly higher at 1.0%, but the exposure-adjusted incidence rate was about the same at 0.8 patients per 100 patient-years. Table 111 presents a summary of malignancies for the long-term safety population (Pool 2). Out of all subjects who received sarilumab, 33 (1.1%) patients developed a malignancy for an exposure-adjusted rate of 0.7 per 100 patient-years. Sanofi noted that the event rate of malignancies in the any dose arm by 6-month intervals over time was constant.

APPEARS THIS WAY ON ORIGINAL

**Table 111. Overview of Malignancy TEAEs in the Long-Term Safety Population (Pool 2)**

	Sarilumab		
	150mg Q2W Initial Dose	200mg Q2W Initial Dose	Any Dose
Total number of patients	1155	1351	2887
Total treatment duration in pt-yrs <sup>a</sup>	701.9	1758.6	4481.8
Treatment duration up to the first serious infection in pt-yrs	700.5	1749.0	4466.6
<b>Total patients with ≥ 1 malignancy (%)</b>	<b>9 (0.8%)</b>	<b>14 (1.0%)</b>	<b>33 (1.1%)</b>
<b>Number of patients with ≥ 1 malignancy per 100 pt-yrs</b>	<b>1.3</b>	<b>0.8</b>	<b>0.7</b>
<b>Total number of malignancy (per 100 pt-yrs)</b>	<b>9 (1.3)</b>	<b>15 (0.9)</b>	<b>34 (0.8)</b>
<b>Non-melanoma skin cancer –</b>			
Total number of events (events/100 pt-yrs)	1 (0.1)	7 (0.4)	11 (0.2)
Basal cell carcinoma	0	3 (0.2)	6 (0.1)
Squamous cell carcinoma of skin	1 (0.1)	4 (0.2)	5 (0.1)
<b>Total patients with ≥ 1 malignancy excluding NMSC (%)</b>			
	8 (0.7%)	8 (0.6%)	23 (0.8%)
<b>Number of patients with ≥ 1 malignancy excluding NMSC per 100 pt-yrs</b>			
	1.1	0.5	0.5
<b>Total number of malignancy excluding NMSC (per 100 pt-yrs)</b>			
	8 (1.1)	8 (0.5)	23 (0.5)
<b>Solid tumor excluding NMSC –</b>			
Total number of events (events/100 pt-yrs)	8 (1.1)	8 (0.5)	22 (0.5)
Breast cancer	3 (0.4)	2 (0.1)	6 (0.1)
Malignant melanoma	1 (0.1)	2 (0.1)	3 (0.1)
Renal and renal pelvic cancer	1 (0.1)	0	3 (0.1)
Colorectal cancer	0	0	2 (0.0)
Appendiceal cancer	1 (0.1)	0	1 (0.0)
Bladder	1 (0.1)	0	1 (0.0)
Cervical cancer	0	0	1 (0.0)
Lung cancer	0	1 (0.1)	1 (0.0)
Pancreatic cancer	0	1 (0.1)	1 (0.0)
Small intestinal cancer	0	1 (0.1)	1 (0.0)
Thyroid cancer	0	1 (0.1)	1 (0.0)
Tumour of unspecified malignancy	1 (0.1)	0	1 (0.0)
<b>Hematologic – total number of events (events/100 pt-yrs)</b>			
Plasmacytoma	0	0	1 (0.0)

Search criteria: SMQ Malignant or unspecified tumors

a For patients with no such event, the duration is up to the end of the treatment duration

Source: ISS, Table 119, page 273.

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

In general, like the double-blind population, the types of cancers in the long-term safety population are consistent with the types of cancers seen in the underlying patient population (based on age, gender, and underlying RA). In addition to the more uncommon cancers that were already discussed, there were 2 more cases of renal cell cancer, 1 case of small intestinal cancer, and 1 case of plasmacytoma. The patient narratives are presented below.

- Patient 011072-840-012-104 (USA) was a 63 year-old black woman with RA (since 2008) and HTN. For her RA, she was being treated with ASA and MTX at baseline. She was enrolled in the phase 2 study EFC11072 Part A and was randomized to receive sarilumab 100mg qw. She was diagnosed with clear cell renal cell carcinoma of the kidney on Day 58 of the study after about 1 month of shortness of breath and peripheral edema. She underwent a right partial nephrectomy. Her hospital course was complicated by a pulmonary embolism (Day 122 of the study).
- Patient 011072-840-013-204 (USA) was a 67 year-old man with RA, congestive heart failure (CHF), left bundle branch block (LBBB), history of pacemaker, hyperlipidemia, and hypertension. For his RA, he was previously treated with adalimumab, which was discontinued due to cost. He was originally enrolled in study EFC11072 Part B Cohort 1 and was randomized to sarilumab 100mg q2w. He was also taking MTX and prednisone (2.5mg) for his RA. He rolled over into LTS11210 about 3 months after original randomization and then began receiving open-label sarilumab 200mg q2w. On Day 809 of LTS11210, he developed a spontaneous pathologic fracture of the left distal humerus (lytic lesion). About 1 month later, a CT chest/abdomen/pelvis revealed an exophytic mass of the right upper kidney. On Day 848 of the study, the patient underwent surgery for his pathologic fracture, and biopsy of the humeral lesions confirmed metastatic renal cell carcinoma. Further imaging also confirmed other boney metastases to the right acetabulum and 5<sup>th</sup> lumbar spine. IMP was permanently discontinued.
- Patient 011072-152-009-201 (Chile) was a 42 year-old woman with RA (since 2006), former smoker, and history of cholecystectomy. For her RA, she was treated with MTX and diclofenac at baseline. She was originally randomized to placebo. After 52 weeks of therapy, she entered study LTS11210 and started to receive sarilumab 200mg q2w. While on the open-label study, she was diagnosed with cervical dysplasia (Day 44) and later choledocolithiasis (Day 379). IMP was discontinued around that time. Subsequently, the patient underwent MRI and ERCP, which showed a periampullary tumor (small intestinal cancer). On Day 419, the patient was diagnosed with a perimampullar carcinoma (next to the ampulla of vater). She underwent cholecystectomy, choledocostomy, and pancreatoduodenectomy. Her subsequent course was complicated by peritonitis and portal vein thrombosis. By Day 467, she was noted to have recovered from both the bile duct stone and small intestine carcinoma.
- Patient 011072-616-002-115 (Poland) was a 60 year-old man with RA. He was also enrolled in the phase 2 study and was randomized to receive sarilumab 100mg q2w.

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

Along with his RA, the patient's medical history was notable for COPD, BPH, and hepatic steatosis. For his RA, he was also receiving MTX and a COX-2 inhibitor. On Day 29, the patient presented with polyarthralgias/arthritis. A WBC count at the time revealed 15.8% plasmacytes. About 1 month later, the patient re-presented with polyarthritis. A bone marrow biopsy was performed consistent with 15% plasma cells with microscopy consistent with a plasmacytoma. IMP was permanently discontinued.

*Reviewer Comment: Of these 4 additional unusual malignancies, only 2 could possibly have an association with sarilumab use. Patient 011072-840-012-104 (renal cell carcinoma) and patient 011072-616-002-115 (plasmacytoma) each developed their cancers less than 2 months after initiation of sarilumab. Thus, the association with sarilumab is less likely. The cases of metastatic renal cell carcinoma and small intestinal cancer are less clear. It should be noted that the subject with metastatic renal cell cancer had previous treatment with another biologic and also had multiple co-morbid conditions. The subject with small intestinal cancer was a smoker and also had some notable co-morbidities such as cervical dysplasia (early in the course of the study).*

Sanofi performed a model-based analysis on malignancies (Table 112). Combining the data from Pools 1 and 2, the overall incidence of malignancies in any arm remained low with only small differences between sarilumab and placebo as well as between sarilumab doses. The rate ratio between the 150mg q2w and placebo was 1.51 (95% CI: 0.35, 6.49) and between the 200mg q2w and placebo was 1.14 (95% CI: 0.31, 4.28). The rate ratio between any dose of sarilumab and placebo was 0.76 (95% CI: 0.32, 1.81). The rate ratio between doses was 0.96 (95% CI 0.29, 3.26).

APPEARS THIS WAY ON ORIGINAL

**Table 112. Model-based Analyses on Patients with at least one Malignancy during the TEAE Period**

	Placebo + DMARD	Sarilumab 150mg q2w + DMARD	Sarilumab 200mg q2w + DMARD	Any Sarilumab + DMARD
<b>Malignancy</b>				
Raw incidence rate n/N (%)	3/661 (0.5)	9/1155 (0.8)	14/1351 (1.0)	33/2887 (1.1)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	3/380.8 (0.8)	9/700.5 (1.3)	14/1749.0 (0.8)	33/4466.6 (0.7)
Rate ratio vs. PBO + DMARD (95% CI)		1.51 (0.35, 6.49) <sup>b</sup>	1.14 (0.31, 4.28) <sup>b</sup>	0.76 (0.32, 1.81) <sup>c</sup>
Rate ratio vs. sarilumab 150mg + DMARD (95% CI)			0.96 (0.29, 3.26) <sup>b</sup>	

a Number of patients with at least one event per 100 patient-years (PYs), where the exposure time for patients who have experienced the specific adverse experience was defined as the time to first adverse experience of interest whereas the exposure time for those who have not had this adverse experience was total TEAE period duration

b The rate ratio and its 95% confidence interval (CI) were estimated using the GEE (Poisson distribution with exposure calculated based on the time to first event as an offset), adjusted for treatment and the important baseline factors (age, gender, geographic region, prior biologic use, medical history of malignancy), assuming an exchangeable covariance structure for the within-subject correlations

c The rate ratio and its 95% confidence interval (CI) were estimated using the GEE (Poisson distribution with exposure calculated based on the time to first event as an offset), adjusted for treatment and the important baseline factors (age, gender, geographic region, prior biologic use, medical history of malignancy), assuming an exchangeable covariance structure for the within-subject correlations

Source: Sanofi response to IR (July 12, 2016), Table 3, dated July 14, 2016, page 9.

As with cardiovascular events and serious infections, Sanofi provided a break down of the open-label period based on the originally randomized treatment and then categorized the number of malignancies based on this more granular analysis (Table 113). The different treatment arms in this analysis were the 3 randomized treatments (placebo, sarilumab 150mg q2w, sarilumab 200mg q2w), open-label therapy based on previous treatments (placebo → sarilumab 200mg q2w, sarilumab 150mg q2w → sarilumab 200mg q2w, sarilumab 200mg q2w → sarilumab 200mg q2w), and then dose reduction during the open-label study (placebo → sarilumab 200mg q2w → sarilumab 150mg q2w, sarilumab 150mg q2w → sarilumab 200mg q2w → sarilumab 150mg q2w, sarilumab 200mg q2w → sarilumab 200mg q2w → sarilumab 150mg q2w). Based on this more granular analysis, the incidence rate of malignancies during the double-blind period is consistent with what has already been discussed. Also, during the open-label period, the incidence rate was the same no matter if placebo → 200mg q2w arm and the 200mg q2w → 200mg q2w arm (4 events in each of these arms, 0.8%). There was only 1 additional event in subjects who started on 150mg q2w and then transitioned to 200mg q2w during the open-label period. No malignancies occurred in subjects who required further dose reduction in the open-label study.

**Table 113. Summary of Malignancies in Pivotal Studies and OLE (EFC11072, EFC10832, LTS11210)**

Treatment	Raw incidence rate n/N (%)	Exposure adjusted incidence rate <sup>a</sup> n/PY (n/100 PY)	Exposure adjusted event rate <sup>b</sup> n <sub>E</sub> /PY (n <sub>E</sub> /100 PY)
<b>Malignancy (all)</b>			
Placebo initial dose	3/661 (0.5%)	3/382.4 (0.8)	4/383.9 (1.0)
Sarilumab 150mg q2w initial dose	5/660 (0.8%)	5/441.4 (1.1)	5/442.2 (1.1)
Sarilumab 200mg q2w initial dose	4/661 (0.6%)	4/441.0 (0.9)	4/442.8 (0.9)
PBO → sarilumab 200mg q2w (rescue/OL)	4/520 (0.8%)	4/658.5 (0.6)	4/660.3 (0.6)
Sarilumab 150mg q2w → 200mg q2w (rescue/OL)	1/483 (0.2%)	1/607.6 (0.2)	1/607.7 (0.2)
Sarilumab 200mg q2w → 200mg q2w (OL)	4/475 (0.8%)	4/576.5 (0.7)	5/579.0 (0.9)
PBO → sarilumab 200mg q2w (rescue/OL) → 150mg q2w (dose decrease)	0/96	0/113.0	0/113.0
Sarilumab 150mg q2w → 200mg q2w (rescue/OL) → 150mg q2w (dose decrease)	0/68	0/77.6	0/77.6
Sarilumab 200mg q2w → 200mg q2w (OL) → 150mg q2w (dose decrease)	0/71	0/88.4	0/88.4
<b>Malignancy excluding NMSC</b>			
Placebo initial dose	1/661 (0.2%)	1/383.4 (0.3)	1/383.9 (0.3)
Sarilumab 150mg q2w initial dose	5/660 (0.8%)	5/441.4 (1.1)	5/442.2 (1.1)
Sarilumab 200mg q2w initial dose	2/661 (0.3%)	2/442.3 (0.5)	2/442.8 (0.5)
PBO → sarilumab 200mg q2w (rescue/OL)	3/520 (0.6%)	3/658.8 (0.5)	3/660.3 (0.5)
Sarilumab 150mg q2w → 200mg q2w (rescue/OL)	1/483 (0.2%)	1/607.6 (0.2)	1/607.7 (0.2)
Sarilumab 200mg q2w → 200mg q2w (OL)	3/475 (0.6%)	3/577.3 (0.5)	3/579.0 (0.5)
PBO → sarilumab 200mg q2w (rescue/OL) → 150mg q2w (dose decrease)	0/96	0/113.0	0/113.0
Sarilumab 150mg q2w → 200mg q2w (rescue/OL) → 150mg q2w (dose decrease)	0/68	0/77.6	0/77.6
Sarilumab 200mg q2w → 200mg q2w (OL) → 150mg q2w (dose decrease)	0/71	0/88.4	0/88.4

n (%) = number and % of patients with at least 1 TEAE

Search criteria: SMQ Malignant or unspecified tumours

a Number of patients with at least one event per 100 pt-yrs, where the exposure time for patients who have experienced the specific adverse experience was defined as the time to first adverse experience of interest whereas the exposure time for those who have not had this adverse experience was total TEAE period duration

b Number of events per 100 pt-yrs, where the exposure time was the total TEAE period duration

Source: Sanofi response to IR (May 27, 2016), Table 1, dated June 3, 2016, page 6.

Lastly, Sanofi did provide 2 comparisons with existing databases: the SEER datable and the Clinformatic Data Mart database. The Surveillance, Epidemiology, and End Results (SEER)

Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

program of the National Cancer Institute (NCI) collects and publishes cancer incidence and survival data from population-based cancer registries covering approximately 30% of the US population. Clinformatics Data Mart database allows for longitudinal data analysis based on medical claims, pharmacy claims, etc. Therefore, utilizing the SEER database, Sanofi noted that the number of events with sarilumab (any dose arm) was generally comparable to the expected number in the general population. For some of the rarer cancers (such as renal cancer and small intestinal cancer), it is difficult to make any conclusions. Table 114 compares the rates of malignancies in the sarilumab “any dose” arm to the expected number of events in RA patients in the Clinformatics Data Mart database. Utilizing standard incidence ratios, there were generally fewer events in the sarilumab trial. The malignancies highlighted in yellow in Table 114 represent types of cancers that exceeded what was expected in the general RA population in this particular database. Most of these were for the rarer cancers that have been briefly summarized above. However, it is unclear why it appears that NMSC was higher in the sarilumab trials. Sanofi noted that, based on a large US observational study in RA patients, the incidence rate of NMSC was 1342 patients/100,000 patient-years. Thus, this number seems to far exceed the Clinformatics database. In summary, database comparisons provide very limited information. Generally, though, what was seen in the sarilumab trials in regards to malignancy does not seem to exceed what is expected.

APPEARS THIS WAY ON ORIGINAL

**Table 114. Standard Incidence Ratios for Malignancies in the Sarilumab + DMARD (any dose) Long-Term Safety Population (Pool 2): Rheumatoid Arthritis Patients (Clinformatics 2000-2014)**

Malignancy	Observed Number of Events in Sarilumab + DMARD (any dose)	Expected Number of Events Based on the Incidence Rates in RA patients in Clinformatics*	SIR* (95% Confidence Interval)
Any malignancy	34	56.58	0.60 (0.43-0.84)
Any malignancy excluding NMSC	23	55.45	0.61 (0.44-0.86)
NMSC	11	4.74	2.32 (1.28-4.19)
Breast cancer	6	14.30	0.42 (0.19-0.93)
Malignant melanoma	3	1.08	2.78 (0.90-8.62)
Renal and renal pelvic cancer	3	1.67	1.80 (0.58-5.57)
Colorectal cancer	2	3.84	0.52 (0.13-2.08)
Appendiceal cancer	1	0.16	6.11 (0.86-43.49)
Bladder cancer	1	1.24	0.81 (0.11-5.73)
Cervical cancer	1	1.30	0.77 (0.11-5.48)
Lung cancer	1	5.15	0.19 (0.03-1.38)
Pancreatic cancer	1	0.90	1.11 (0.16-7.85)
Small intestinal cancer	1	0.48	2.06 (0.29-14.65)
Thyroid cancer	1	1.69	0.59 (0.08-4.20)
Tumor of unspecified malignancy	1	3.74	0.27 (0.04-1.90)
Hematologic	1	5.56	0.18 (0.03-1.28)

Reference population: Clinformatics Data Mart, 2000-2014

NMSC = non-melanoma skin cancer

\* SIR adjusted for age and gender

Source: Integrated Summary of Safety, Table 121, page 276.

In conclusion, the overall number of malignancies was low in all safety populations. In the 52-week, double-blind period, the incidence of malignancies was generally similar across treatment arms. In the long-term safety population, the exposure-adjusted incidence rates of malignancies did not change. The types of cancers noted were generally consistent with what would be expected in the underlying patient population. There was no signal for any typical type of cancer. There were a few uncommon cancers, but the narratives for these cases did not seem to support an association with sarilumab use for many of them. Therefore, based on the sarilumab safety data alone, it is difficult to draw a conclusion on the risk of malignancy with sarilumab use.

### 8.5.5. Gastrointestinal (GI) Perforations

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

In the clinical trial of tocilizumab, there were cases of GI perforation. Most of these occurred as a complication to diverticulitis. Therefore, GI perforation was an AESI in the sarilumab trials. Patients with a history of inflammatory bowel disease, severe diverticulitis, or previous GI perforation were excluded from the sarilumab program.

Sanofi utilized multiple search criteria to evaluate for possible adverse events that could encompass diverticulitis or potential GI perforations. The search criteria included MedDRA HLT diverticulum inflammation and SMQ gastrointestinal perforation, which included PTs such as diverticulitis, anal abscess, duodenal ulcer perforation, peritonitis, anal abscess, anal fistula, colonic abscess, diverticular perforation, duodenal perforation, gastric ulcer perforation, large intestine perforation. However, since the SMQ included events such as fistula and rectal abscess which may not be associated with GI perforation, Sanofi reviewed the clinical details of the events identified with these search criteria. For example, diverticulitis events were reviewed to assess if it was a case of complicated diverticulitis (abscess, perforation) or uncomplicated diverticulitis. Cases of complicated diverticulitis were considered to be cases of lower GI perforation. In addition to the above search terms, Sanofi also performed an alternate search with the MedDRA SMQ GI ulceration which included PTs such as colitis ulcerative, erosive esophagitis, gastric ulcer hemorrhage, duodenal ulcer, duodenal ulcer hemorrhage, duodenal ulcer perforation, erosive duodenitis, gastric ulcer, gastritis erosive, hemorrhagic erosive gastritis, peptic ulcer Helicobacter, and rectal ulcer. Some of these PTs under SMQ GI ulceration were the same as what would have been identified with the search SMQ GI perforation.

Table 115 is an overview of all 3 search criteria listed above (HLT diverticulum inflammation, SMQ GI perforation, and SMQ GI ulcerations) for the pre-rescue period (Pool 1a). For this population, there were no events meeting the criteria for diverticulitis and GI perforation. For GI ulcerations, the events were low and evenly distributed across treatment arms, 0.3% in the placebo arm, 0.3% in the 150mg q2w arm, and 0.2% in the 200mg q2w arm.

APPEARS THIS WAY ON ORIGINAL

**Table 115. Summary of GI Perforations and Ulcerations in the Pre-Rescue Period (Pool 1a)**

	Placebo + DMARD	Sarilumab 150mg q2w + DMARD	Sarilumab 200mg q2w + DMARD
<b>Diverticulitis/potential GI perforations</b>			
Raw incidence rate n/N (%)	0/579	0/579	0/582
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	0/161.6 (0.0)	0/159.4 (0.0)	0/161.2 (0.0)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		0	0
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			0
<b>GI ulcerations</b>			
Raw incidence rate n/N (%)	2/579 (0.3%)	2/579 (0.3%)	1/582 (0.2%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	2/161.5 (1.2)	2/158.3 (1.3)	1/160.6 (0.6)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		0.0% (-0.7, 0.7)	-0.2% (-0.8, 0.4)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			-0.2% (-0.8, 0.4)

n (%) = number and percentage of patients with at least one TEAE

a Number of patients with at least 1 event per 100 patient-years, where the exposure time for patients who have experienced the specific adverse event experience was defined as the time to first adverse experience of interest whereas the exposure time for those who have not had this adverse experience was total TEAE period duration

b The rate difference and its 95% confidence interval were estimated using the M&N method stratified by the study, using the CMH weight

Source: ISS Appendix 1.12.1.52, dated September 29, 2015, page 8289.

In the 52-week, double-blind period, the placebo group continued to have no patients with diverticulitis/potential GI perforation. However, there were 3 patients (out of 660, 0.5%) in the sarilumab 150mg treatment arm and 1 patient (out of 661, 0.2%) in the sarilumab 200mg treatment arm. The event rate was 1.8 per 100 patient years for sarilumab 150mg q2w and 0.7 per 100 patient-years for sarilumab 200mg q2w.

For GI ulcerations, the number of subjects with events in the double-blind period was 2/661 (0.3%) in the placebo group, 7/660 (1.1%) in the sarilumab 150mg group, and 3/661 (0.5%) in the sarilumab 200mg group. One of the subjects in the 150mg group had a duodenal ulcer perforation. Of the total 12 subjects with events, 10 subjects (1 in the 200mg arm, 7 in the 150mg arm, and 2 in the placebo arm) were also taking either concomitant steroids or concomitant NSAIDs.

Sanofi provided sensitivity analyses utilizing the search criteria for diverticulitis/potential GI perforation and GI ulcerations. Table 116 shows the sensitivity analysis for Week 0-52, thus including randomized and rescued patients within the first 52 weeks of treatment from Pool 1a. With this sensitivity analysis, there continued to be no events of diverticulitis and potential UI

perforation in the placebo and sarilumab 200mg arms. For GI ulcerations, the exposure adjusted incidence rate was highest in the sarilumab 150mg q2w arm at 1.7 per 100 patient-years and equally low in the placebo and sarilumab 200mg q2w arm (0.6 per 100 PYs and 0.5 per 100 PYs, respectively).

**Table 116. Sensitivity Analyses of GI Perforations and Ulcerations during TEAE period (Week 0-52, Pool 1a)**

n(%)	PBO + DMARD		Sarilumab 150mg q2w + DMARD		Sarilumab 200mg q2w + DMARD <sup>a</sup>	
	Raw incidence rate	Exposure adjusted incidence rate <sup>b</sup>	Raw incidence rate	Exposure adjusted incidence rate <sup>b</sup>	Raw incidence rate	Exposure adjusted incidence rate <sup>b</sup>
	n/N (%)	n/PY (rate per 100 PYs)	n/N (%)	n/PY (rate per 100 PYs)	n/N (%)	n/PY (rate per 100 PYs)
<b>Diverticulitis/ potential GI perforations</b>	0/579	0/348.7 (0.0)	2/579 (0.3%)	2/403.2 (0.5)	0/881	0/581.5 (0.0)
<b>GI ulcerations</b>	2/579 (0.3%)	2/348.5 (0.6)	7/579 (1.2%)	7/402.7 (1.7)	3/881 (0.3%)	3/580.2 (0.5)

n(%) = number and % of patients with at least 1 TEAE

a Includes randomized patients and patient who rescued and were within the first 52 weeks with this regimen

b Number of patients with at least 1 event per 100 patient-years, where the exposure time for patients who have experienced the specific adverse experience was defined as the time to first adverse experience of interest whereas the exposure time for those who have not had this adverse experience was total TEAE period duration

Source: ISS Appendix 1.12.2.9, page 8440.

Table 117 shows the actual summary of events consistent with diverticulitis and GI perforations in the long-term safety population (Pool 2). As with the double-blind period, the numbers remained low. Four subjects (0.3%) had events consistent with diverticulitis or potential GI perforation in the sarilumab 150mg q2w initial dose arm, and there were 5 subjects (0.4%) in the sarilumab 200mg q2w arm and 15 subjects (0.5%) in the any dose arm. The exposure-adjusted incidence in the sarilumab any dose arm was 0.3 per 100 patient-years.

APPEARS THIS WAY ON ORIGINAL

**Table 117. Overview of Diverticulitis/GI perforations in the Entire TEAE Period (Pool 2)**

	Sarilumab		
	150mg Q2W Initial Dose	200mg Q2W Initial Dose	Any Dose
Total number of patients	1155	1351	2887
Total treatment duration in pt-yrs <sup>a</sup>	701.9	1758.6	4481.8
Treatment duration up to the first event in pt-years	700.9	1757.9	4473.2
Treatment duration up to the first serious event in pt-years	701.7	1757.9	4480.5
<b>Total patients with ≥ 1 Diverticulitis/potential GI perforations (%)</b>	<b>4 (0.3%)</b>	<b>5 (0.4%)</b>	<b>15 (0.5%)</b>
<b>Number of patients with ≥ 1 Diverticulitis/potential GI perforations (per 100 pt-yrs)</b>	<b>0.6</b>	<b>0.3</b>	<b>0.3</b>
<b>Total number of Diverticulitis/potential GI perforations (per 100 pt-yrs)</b>	<b>5 (0.7)</b>	<b>6 (0.3)</b>	<b>18 (0.4)</b>
Total patients with ≥ 1 serious Diverticulitis/potential GI perforations (%)	2 (0.2%)	5 (0.4%)	11 (0.4%)
Number of patients with ≥ 1 serious Diverticulitis/potential GI perforations per 100 pt-yrs	0.3	0.3	0.2
Total number of serious Diverticulitis/potential GI perforations (per 100 pt-yrs)	3 (0.4)	6 (0.3)	14 (0.3)
Total patients with Diverticulitis/potential GI perforations leading to death (%)	0	0	0
Total patients with Diverticulitis/potential GI perforations leading to permanent treatment discontinuation (%)	3 (0.3%)	2 (0.1%)	9 (0.3%)
Number of patients with Diverticulitis/potential GI perforations leading to permanent treatment discontinuation per 100 pt-yrs	0.4	0.1	0.2

Search criteria: Diverticulitis: HLT Diverticulum inflammations; GI perforations: SMQ Gastrointestinal perforation.

a For patients with no such event, the duration is up to the end of the treatment duration

Source: ISS, Table 87, page 213.

Of the 15 subjects in the any dose arm, 8 subjects had diverticulitis (4 complicated, 4 uncomplicated), and 4 had GI perforations. One of the 4 GI perforations occurred as a surgical complication during appendectomy. Three additional subjects met the search criteria but did not have evidence of either diverticulitis or GI perforation after Sanofi's review of their narratives (peritonitis after surgery for small intestinal cancer, anal fistula, and anal abscess). Therefore, based on Sanofi's review of the individual events, there were 7 subjects with GI perforations not related to surgery: 4 had complicated diverticulitis (classified as lower GI perforations), and 3 had upper GI perforations. Of the 4 complicated diverticulitis cases, 3 out of the 4 were taking concomitant NSAIDs or steroids. One subject with the upper GI perforation was taking concomitant steroids, and one subject was taking a baby aspirin.

Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

Utilizing this revised sum of 7 subjects with “GI perforation,” the event rate was 0.16 per 100 patient-years (95% CI: 0.06, 0.32). Sanofi noted that the rate of GI perforation for RA patients receiving steroids is 0.39 events per 100 patient-years (95% CI: 0.31, 0.48).

For GI ulcers, the incidence rates were similar for the double-blind treatment population (Pool 1) and the long-term safety population (Pool 2). Table 118 is an overview of subjects with events that were identified with the SMQ GI ulceration. Of the multiple PTs that were identified with this search criterion in the long-term safety population, there remained only 1 event truly consistent with GI perforation, that is, the event of duodenal ulcer perforation that was already counted in Pool 1 and also identified with the SMQ GI perforation presented above. Therefore, the additional search utilizing the SMQ GI ulceration did not necessarily add anything to the search done with diverticulitis and potential GI perforation. It should be noted, however, that 25 of the 28 subjects in the any dose arm, who did meet criterion for SMQ GI ulceration, were taking a concomitant steroid or NSAID.

**Table 118. Overview of GI Ulcerations in the Entire TEAE Period (Pool 2)**

	Sarilumab		
	150mg Q2W Initial Dose	200mg Q2W Initial Dose	Any Dose
Total number of patients	1155	1351	2887
Total treatment duration in pt-yrs <sup>a</sup>	701.9	1758.6	4481.8
Treatment duration up to the first event in pt-years	700.9	17571.5	4451.7
Treatment duration up to the first serious event in pt-years	701.8	1757.1	4477.8
<b>Total patients with ≥ 1 GI ulcerations (%)</b>	<b>7 (0.6%)</b>	<b>7 (0.5%)</b>	<b>28 (1.0%)</b>
<b>Number of patients with ≥ 1 GI ulcerations (per 100 pt-yrs)</b>	<b>1.0</b>	<b>0.4</b>	<b>0.6</b>
<b>Total number of GI ulcerations (per 100 pt-yrs)</b>	<b>8 (1.1)</b>	<b>8 (0.5)</b>	<b>33 (0.7)</b>
Total patients with ≥ 1 serious GI ulcerations (%)	2 (0.2%)	2 (0.1%)	5 (0.2%)
Number of patients with ≥ 1 serious GI ulcerations per 100 pt-yrs	0.3	0.1	0.1
Total number of serious GI ulcerations (per 100 pt-yrs)	3 (0.4)	2 (0.1)	6 (0.1)
Total patients with GI ulcerations leading to death (%)	0	0	0
Total patients with GI ulcerations leading to permanent treatment discontinuation (%)	1 (<0.1%)	0	2 (<0.1%)
Number of patients with GI ulcerations leading to permanent treatment discontinuation per 100 pt-yrs	0.1	0	0

Search criteria: GI Ulceration: SMQ Gastrointestinal ulceration

a For patients with no such event, the duration is up to the end of the treatment duration

Source: ISS, Table 89, page 217-8.

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

Lastly, as described in Section 6.4 study SFY13370 compares tocilizumab (IV) and sarilumab with the objective comparing safety. Much of the safety comparisons are presented below in Section 8.7. However, to further evaluate potential GI perforations with sarilumab, the results utilizing the same search criteria (HLT diverticulum inflammations, SMQ GI perforation, and SMQ GI ulceration) for study SFY13370 are presented in Table 119. No events were identified in any arm as being consistent with diverticulitis or potential GI perforations. However, there was 1 event of GI ulceration in the tocilizumab arms, compared to none for either dose of sarilumab.

**Table 119. Number (%) of Patients with Potential GI Perforation and GI Ulcerations**

	<b>Tocilizumab q4w + DMARD (N=102) n(%)</b>	<b>Sarilumab 150mg q2w + DMARD (N=49) n(%)</b>	<b>Sarilumab 200mg q2w + DMARD (N=51) n(%)</b>
<b>Diverticulitis/potential GI perforations<sup>a</sup></b>	0	0	0
<b>GI ulcerations</b>	1 (1.0%)	0	0

Search criteria: GI Ulceration: SMQ Gastrointestinal ulceration

a Cases were medically reviewed to identify cases of GI perforation

Source: SFY13370 CSR, Table 21, dated August 12, 2015; page 82.

In conclusion, the numbers of events that could be considered GI perforation or complicated diverticulitis were low in the sarilumab trials. Utilizing the search criteria for diverticulitis and potential GI perforation, the event rate was 0.4 per 100 patient-years in the sarilumab any dose arm in the long-term safety population. However, after Sanofi reviewed all these events in the sarilumab any dose arm and excluded events that were not consistent, the event rate was 0.16 per 100 patient-years. This revised rate is lower than the event rate of GI perforations in the tocilizumab clinical trials (IV therapy), which was 0.26 events per 100 patient-years. It is difficult to compare across trials, but the lower event rate may be due to the exclusion criteria that were in place for the sarilumab trials. In study SFY13370, which directly compared tocilizumab and sarilumab, no subjects in any arms met criteria for diverticulitis and GI perforation, and only 1 subject in the tocilizumab arm met criteria for GI ulceration. In summary, given the low numbers, it is difficult to determine the exact risk of GI perforation with sarilumab use.

### 8.5.6. Hypersensitivity

Hypersensitivity and anaphylaxis are adverse events that have been identified with all biologic DMARDs in the treatment of rheumatoid arthritis, and, thus, these were AESIs in the sarilumab clinical development program. Sanofi used the MedDRA SMQ hypersensitivity and SMQ anaphylactic reaction to identify investigator-reported adverse events indicative of hypersensitivity and anaphylaxis. The search criterion SMQ Hypersensitivity included multiple PTs such as injection site rash, rash, urticarial, eczema, rash generalized, rash erythematous,

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

injection site urticarial, and hypersensitivity. As described in the protocols, investigators utilized the criteria described by Sampson et al. to capture all possible cases of anaphylaxis (Sampson et al. 391-7). Injection site reactions were analyzed by searching for the HLT injection site reactions. Lastly, Sanofi defined a “severe systemic hypersensitivity reaction” with the following criteria:

- Anaphylaxis that led to permanent treatment discontinuation and with no alternative etiology
- Any case of laryngeal, uvula, or tongue edema that occurred within 24 hours (i.e., onset within 1 day) of dose which led to permanent discontinuation and with no clear etiology
- Occurrence of significant respiratory (cyanosis or SpO<sub>2</sub> ≤ 92%), cardiovascular (SBP < 90 mmHg in adults), or neurologic (confusion, collapse, loss of consciousness, incontinence) symptoms that occurred within 24 hours (i.e., onset within 1 day) of dose which led to permanent discontinuation
- Any case of Stevens Johnson Syndrome (SJS)/Toxic Epidermal Necrolysis (TEN)

This portion of the review will present hypersensitivity and anaphylaxis together and then injection site reactions separately. However, in some tables (such as those for the pre-rescue period), all of these AEs will be presented together.

Table 120 presents an overview of subjects who were identified with the 3 search criteria, SMQ Hypersensitivity, SMQ Anaphylactic reaction, and HLT injection site reaction in the pre-rescue period (Pool 1a). First, it is important to note that there were no cases of anaphylaxis in any of the treatment arms. Greater proportions of subjects in the sarilumab arms compared to the placebo arm experienced both hypersensitivity events and injection site reactions. There was little difference, however, between the doses.

APPEARS THIS WAY ON ORIGINAL

**Table 120. Overview of Hypersensitivity Events in the Pre-Rescue Period (Pool 1a)**

	Placebo + DMARD	Sarilumab 150mg q2w + DMARD	Sarilumab 200mg q2w + DMARD
<b>Hypersensitivity</b>			
Raw incidence rate n/N (%)	14/579 (2.4%)	24/579 (4.1%)	24/582 (4.1%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	14/157.0 (8.9)	24/153.3 (15.7)	24/151.9 (15.8)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		1.8% (-0.3, 3.9)	1.8% (-0.3, 3.9)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			0.0% (-2.3, 2.3)
<b>Anaphylaxis</b>			
Raw incidence rate n/N (%)	0/579	0/579	0/582
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	0/161.6 (0)	0/160.0 (0)	0/161.2 (0)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		0	0
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			0
<b>Injection Site Reactions</b>			
Raw incidence rate n/N (%)	6/579 (1.0%)	33/579 (5.7%)	40/582 (6.9%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	6/159.6 (3.8)	33/151.5 (21.8)	40/150.1 (26.6)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		4.8% (2.7, 6.9)	6.0% (3.8, 8.3)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			1.3% (-1.6, 4.1)

n (%) = number and percentage of patients with at least one TEAE

a Number of patients with at least 1 event per 100 patient-years, where the exposure time for patients who have experienced the specific adverse event experience was defined as the time to first adverse experience of interest whereas the exposure time for those who have not had this adverse experience was total TEAE period duration

b The rate difference and its 95% confidence interval were estimated using the M&N method stratified by the study, using the CMH weight

Source: ISS Appendix 1.12.1.52, dated September 29, 2015, page 8290-91.

Before moving onto a more detailed look at the double-blind and long-term safety populations, I will present Sanofi's sensitivity analysis of Pool 1a. Table 121 shows the sensitivity analysis of hypersensitivity events for Weeks 0-52, thus, including both randomized and rescued subjects within the first 52 weeks of treatment. With this analysis, the numbers of subjects with hypersensitivity events looked generally the same as that for the pre-rescue period. More subjects on sarilumab compared to placebo were identified with the search criteria SMQ Hypersensitivity and HLT Injection site reactions, and the differences between doses was small for both the raw and exposure-adjusted incidence rate.

**Table 121. Sensitivity Analyses of Hypersensitivity Events during the TEAE Period (Weeks 0-52, Pool 1a)**

n (%)	PBO + DMARD		Sarilumab 150mg q2w + DMARD		Sarilumab 200mg q2w + DMARD <sup>a</sup>	
	Raw incidence rate	Exposure adjusted incidence rate <sup>b</sup>	Raw incidence rate	Exposure adjusted incidence rate <sup>b</sup>	Raw incidence rate	Exposure adjusted incidence rate <sup>b</sup>
	n/N (%)	n/PY (rate per 100 PYs)	n/N (%)	n/PY (rate per 100 PYs)	n/N (%)	n/PY (rate per 100 PYs)
<b>Hypersensitivity</b>	24/579 (4.1%)	24/340.9 (7.0)	36/579 (6.2%)	36/389.1 (9.3)	52/881 (5.9%)	52/559.5 (9.3)
<b>Anaphylaxis</b>	0/579	0/348.7 (0)	0/579	0/403.9 (0)	0/881	0/581.5 (0)
<b>Injection site reactions</b>	8/579 (1.4%)	8/344.5 (2.3)	44/579 (7.6%)	44/381.1 (11.4)	76/81 (8.6%)	76/541.7 (14.0)

n(%) = number and % of patients with at least 1 TEAE

a Includes randomized patients and patient who rescued and were within the first 52 weeks with this regimen

b Number of patients with at least 1 event per 100 patient-years, where the exposure time for patients who have experienced the specific adverse experience was defined as the time to first adverse experience of interest whereas the exposure time for those who have not had this adverse experience was total TEAE period duration

Source: ISS Appendix 1.12.2.9, page 8440-1.

### Hypersensitivity and anaphylaxis

Table 122 presents the subjects who met the search criteria SMQ Hypersensitivity and SMQ Anaphylaxis for the 52-week, placebo-controlled population (Pool 1). By the end of the double-blind period, there were more hypersensitivity events in all treatment arms. As in the pre-rescue period, more subjects on sarilumab experienced hypersensitivity events than subjects on placebo. The incidence rates were 3.9% in the placebo arm, 6.8% in the sarilumab 150mg q2w arm, and 7.3% in the sarilumab 200mg q2w arm.

APPEARS THIS WAY ON ORIGINAL

**Table 122. Overview of Hypersensitivity in the Double-Blind Period (Pool 1)**

	Placebo + DMARD	Sarilumab	
		150mg q2w + DMARD	200mg q2w + DMARD
Total number of patients	661	660	661
Total treatment duration in pt-yrs <sup>a</sup>	382.3	440.7	441.4
Treatment duration up to the first event in pt-years	373.1	422.4	421.2
Treatment duration up to the first serious event in pt-years	382.3	440.7	441.2
<b>Total patients with ≥ 1 Hypersensitivity (%)</b>	<b>26 (3.9%)</b>	<b>45 (6.8%)</b>	<b>48 (7.3%)</b>
<b>Number of patients with ≥ 1 Hypersensitivity (per 100 pt-yrs)</b>	<b>7.0</b>	<b>10.7</b>	<b>11.4</b>
<b>Total number of Hypersensitivity (per 100 pt-yrs)</b>	<b>27 (7.1)</b>	<b>60 (13.6)</b>	<b>55 (12.5)</b>
<hr/>			
Total patients with ≥ 1 serious Hypersensitivity (%)	0	0	1 (0.2%)
Number of patients with ≥ 1 serious Hypersensitivity per 100 pt-yrs	0	0	0.2
Total number of serious Hypersensitivity (per 100 pt-yrs)	0	0	1 (0.2)
Total patients with Hypersensitivity leading to death (%)	0	0	0
Total patients with Hypersensitivity leading to permanent treatment discontinuation (%)	1 (0.2%)	3 (0.5%)	6 (0.9%)
Number of patients with Hypersensitivity leading to permanent treatment discontinuation per 100 pt-yrs	0.3	0.7	1.4

Search criteria: SMQ Hypersensitivity

a For patients with no such event, the duration is up to the end of the treatment duration

Source: ISS, Table 98, page 243-4.

The most common PTs under “hypersensitivity” were essentially different kinds of skin reactions with the top 5 being injection site rash, rash, urticaria, eczema, and rash generalised. There was one 1 case of angioedema in the sarilumab 200mg arm. There was 1 serious hypersensitivity event also in the sarilumab 200mg arm; the PT for this event was immediate post-injection reaction. Lastly, the hypersensitivity PTs that led to discontinuation included 1 event in placebo (hypersensitivity vasculitis), 3 events in the sarilumab 150mg arm (rash erythematous, rash generalized, dermatitis allergic), and 6 events in the sarilumab 200mg arm (rash erythematous, rash generalized, angioedema, injection site urticarial).

In the long-term safety population, the overall incidence rates were similar to the double-blind period. The exposure-adjusted incidence rate was actually slightly lower in the sarilumab 200mg arm. The overall exposure-adjusted incidence of hypersensitivity events in the sarilumab any dose arm was 5.8 per 100 patient-years. There were no cases of anaphylaxis in any treatment arm for the entire long-term safety population.

**Table 123. Overview of Hypersensitivity in the Entire TEAE Period (Pool 2)**

	Sarilumab		
	150mg q2w Initial Dose	200mg q2w Initial Dose	Any Dose
Total number of patients	1155	1351	2887
Total treatment duration in pt-yrs <sup>a</sup>	701.9	1758.6	4481.8
Treatment duration up to the first event in pt-years	668.3	1662.9	4219.5
Treatment duration up to first serious event in pt-years	701.7	1758.4	4481.3
<b>Total patients with ≥ 1 Hypersensitivity (%)</b>	<b>78 (6.8%)</b>	<b>99 (7.3%)</b>	<b>243 (8.4%)</b>
<b>Number of patients with ≥ 1 Hypersensitivity (per 100 pt-yrs)</b>	<b>11.7</b>	<b>6.0</b>	<b>5.8</b>
<b>Total number of Hypersensitivity (per 100 pt-yrs)</b>	<b>101 (14.4)</b>	<b>120 (6.8)</b>	<b>317 (7.1)</b>
Total patients with ≥ 1 serious Hypersensitivity (%)	1 (<0.1%)	1 (<0.1%)	4 (0.1%)
Number of patients with ≥ 1 serious Hypersensitivity per 100 pt-yrs	0.1	0.1	0.1
Total number of serious Hypersensitivity (per 100 pt-yrs)	1 (0.1)	1 (0.1)	4 (0.1)
Total patients with Hypersensitivity leading to death (%)	0	0	0
Total patients with Hypersensitivity leading to permanent treatment discontinuation (%)	7 (0.6%)	11 (0.8%)	27 (0.9%)
Number of patients with Hypersensitivity leading to permanent treatment discontinuation per 100 pt-yrs	1.0	0.6	0.6

Search criteria: SMQ Hypersensitivity

a For patients with no such event, the duration is up to the end of the treatment duration

Source: ISS, Table 99-101, page 245, 247, 249.

In the long-term safety population, the most common PTs that met the SMQ Hypersensitivity reaction was injection site rash, rash, and urticarial. There were 4 serious hypersensitivity AEs: angioedema (sarilumab 150mg q2w initial dose), hypersensitivity (sarilumab any dose), immediate post-injection reaction (sarilumab 200mg q2w initial dose, already counted above in the double-blind period), and skin necrosis (sarilumab any dose). Notably, all 4 of these subjects with serious hypersensitivity events were ADA negative.

### **Injection site reactions**

As noted above in Table 120, there were more injection site reactions in subjects who received sarilumab as compared to subjects who received placebo in the pre-rescue period. During the double-blind period, this trend continued but with a higher incidence in the sarilumab arms. Table 124 shows the number of subjects who met the HLT Injection site reaction in the 52-week, placebo-controlled population (Pool 1). For both the exposure-adjusted incidence rate and exposure-adjusted event rate, the rates were much higher in the sarilumab arms. The event rate was 46.5 per 100 patient-years for sarilumab 150mg q2w, 46.7 per 100 patient-years for sarilumab 200mg q2w, and 3.4 per 100 patient-years for placebo. Therefore, the difference

between doses was minimal. The most common PTs were injection site erythema, injection site pruritus, and injection site rash. There were no serious injection site reactions in the double-blind period, but there were 3 events in the sarilumab treatment arms that led to treatment discontinuation.

**Table 124. Overview of Injection Site Reactions in the Double-Blind Period (Pool 1)**

	Placebo + DMARD	Sarilumab	
		150mg q2w + DMARD	200mg q2w + DMARD
Total number of patients	661	660	661
Total treatment duration in pt-yrs <sup>a</sup>	382.3	440.7	441.4
Treatment duration up to the first event in pt-years	373.1	422.4	421.2
Treatment duration up to the first serious event in pt-years	382.3	440.7	441.2
<b>Total patients with ≥ 1 Injection site reaction (%)</b>	<b>9 (1.4%)</b>	<b>53 (8.0%)</b>	<b>63 (9.5%)</b>
<b>Number of patients with ≥ 1 Injection site reaction (per 100 pt-yrs)</b>	<b>2.4</b>	<b>12.9</b>	<b>15.4</b>
<b>Total number of Injection site reaction (per 100 pt-yrs)</b>	<b>13 (3.4)</b>	<b>205 (46.5)</b>	<b>206 (46.7)</b>
Number (%) of patients with ≥1 Injection site reaction by PT with incidence ≥ 0.5%			
Injection site erythema	6 (0.9%)	36 (5.5%)	35 (5.3%)
Injection site pruritus	1 (0.2%)	17 (2.6%)	16 (2.4%)
Injection site rash	1 (0.2%)	7 (1.1%)	7 (1.1%)
Injection site haematoma	0	0	4 (0.6%)
Injection site haemorrhage	1 (0.2%)	1 (0.2%)	4 (0.6%)
Injection site swelling	0	0	4 (0.6%)
Injection site pain	0	4 (0.6%)	2 (0.3%)
Total patients with ≥ 1 serious Injection site reaction (%)			
	0	0	0
Total patients with Injection site reaction leading to permanent treatment discontinuation (%)	0	1 (0.2%)	2 (0.3%)
Number of patients with Injection site reaction leading to permanent treatment discontinuation per 100 pt-yrs	0	0.2	0.5
Number of patients with Injection site reaction by PT leading to permanent treatment discontinuation			
Injection site erythema	0	1 (0.2%)	1 (0.2%)
Injection site urticaria	0	0	1 (0.2%)
Injection site pruritus	0	1 (0.2%)	0

Search criteria: HLT Injection site reactions.

a For patients with no such event, the duration is up to the end of the treatment duration

Source: ISS, Table 98, page 243-4.

Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

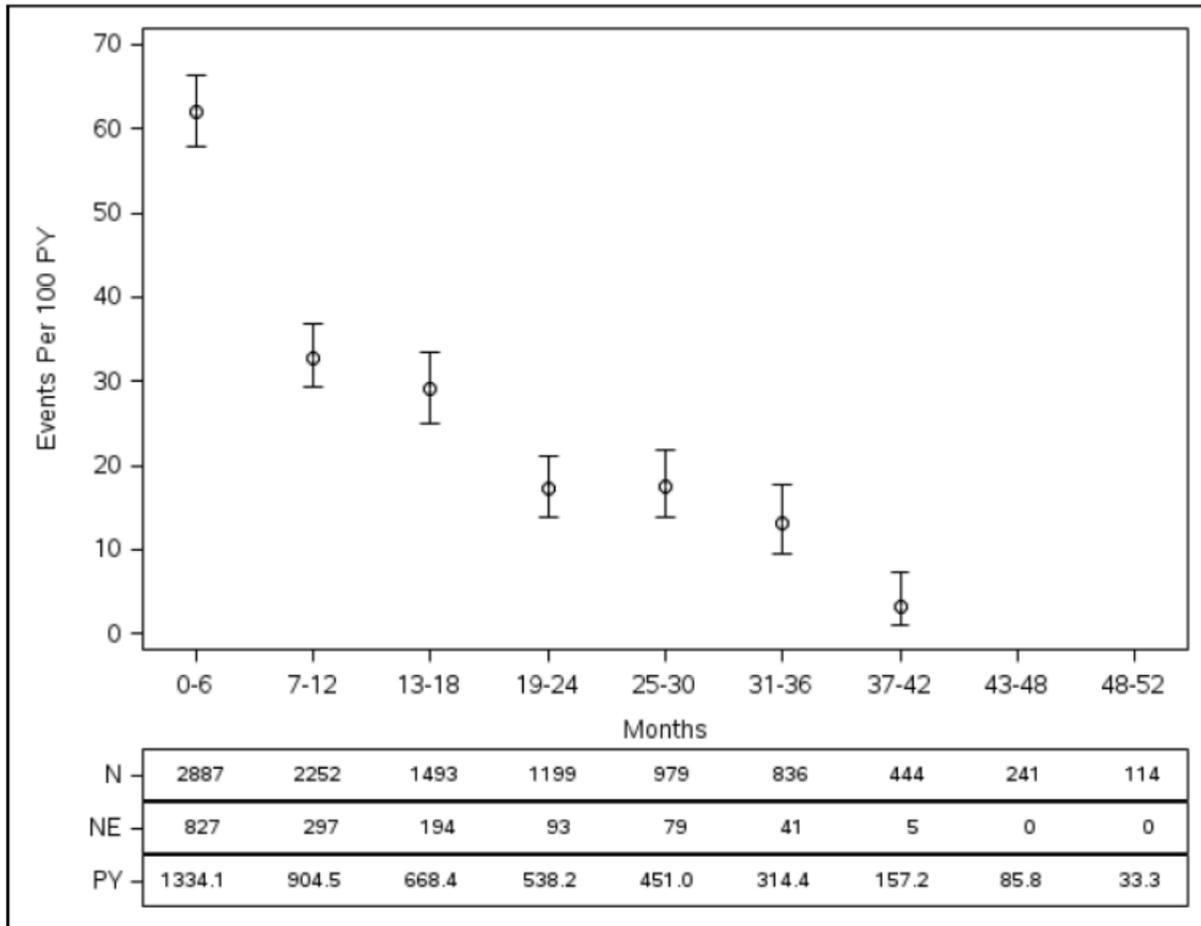
Sarilumab/Kevzara

The long-term safety population showed similar incidence rates for the sarilumab doses with 8.0% patients with  $\geq 1$  injection site reaction in the sarilumab 150mg arm and 9.9% in the sarilumab 200mg arm. The event rate was 46.4 injection site reactions per 100 patient-years in the sarilumab 150mg arm and 36.8 injection site reactions per 100 patient-years in the sarilumab 200mg arm. The overall event rate for any dose of sarilumab was 34.3 events per 100 patient-years. The most common injection site reactions were the same as the double blind period: injection site erythema, injection site pruritus, and injection site rash. As in the double-blind period, no serious injection site reactions occurred in the long-term safety population.

By analyzing the number of injection site reactions by 6-months intervals, the incidence of injection site reactions appears to decrease over time (Figure 58).

APPEARS THIS WAY ON ORIGINAL

**Figure 58. Exposure-adjusted Rate of Injection Site Reactions by 6-month Interval during the Entire TEAE Period (Pool 2)**



N = sample size; NE = number of events in a 6-month period; PY = patient-years  
 95% confidence interval was calculated using the exact method  
 Source: ISS, Figure 29, dated October 6, 2015; page 257.

As a biologic DMARD, hypersensitivity is an anticipated adverse event. In conclusion, there are 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.”

### 8.5.7. Lupus-like Disorders/Autoimmunity

Some biologic DMARDs have been associated with development of a lupus-like syndrome. This has specifically been seen with TNF $\alpha$  blockers. Therefore, Sanofi designated lupus-like

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

syndrome as an AESI. Sanofi utilized the search criteria MedDRA SMQ systemic lupus erythematosus to identify lupus-like disorders. Sanofi also assessed autoantibodies such as anti-nuclear antibody (ANA) and double-stranded DNA (dsDNA).

There were no lupus-like disorders in any treatment arm during the pre-rescue period (Pool 1a). In the double-blind treatment period (Pool 1), one subject in the sarilumab 150mg developed a lupus-like syndrome. The subject developed a skin rash which was biopsied and showed perivascular dermatitis associated with vacuolar interface (thus, with the differential of erythema multiforme, lupus erythematosus, or dermatomyositis) in the setting of a very low titer ANA (1:40 and 1:80). The subject was diagnosed with cutaneous lupus.

In evaluating autoantibodies during the double-blind period, a similar percentage of subjects (who had a negative ANA at baseline) developed a positive ANA across all treatment arms: placebo 126/289 (43.6%), sarilumab 150mg q2w 108/291 (37.1%), and sarilumab 200mg q2w 114/302 (37.7%). One subject on the placebo arm and 1 subject on the sarilumab 200mg q2w arm had a negative dsDNA at baseline but developed a positive test during the study.

In the long-term safety population, there were a total of 4 subjects (including the one already described above) who developed a lupus-like syndrome. Two of these subjects were taking sarilumab 150mg, and one subject, whose event was considered serious, was in the sarilumab 200mg treatment arm. Two of the subjects (including the one with the serious event) had facial rashes in the setting of a positive ANA. Neither of these rashes was biopsied. One subject on sarilumab 150mg q2w had an ear lesion that was biopsied and consistent with discoid lupus, along with a positive ANA. This last subject continued to receive sarilumab.

As for autoantibodies in the long-term safety population, the overall rates of conversions to ANA positivity were similar between both doses, numerically higher in the 200mg arm: 29.5% for sarilumab 150mg q2w, 39.0% for sarilumab 200mg q2w, and 42.1% for sarilumab any dose. Similar to the double-blind period, only subject in the sarilumab 200mg q2w group developed a positive dsDNA although there were 2 in the any dose arm.

In conclusion, the number of "lupus-like disorders" was very low. No events occurred in the placebo arm although some subjects on placebo did develop a positive ANA. All 4 events that did occur in the sarilumab arms were rashes. Two were biopsied to be consistent with a lupus rash. The other 2 rashes were transient but in the setting of a positive ANA. Therefore, the cases of lupus-like disorders themselves might be questionable. Therefore, there does not seem to be a signal for development of autoimmunity/lupus-like disorders based on the safety data from the sarilumab clinical development program.

### 8.5.8. Demyelinating disorders

Like lupus-like disorders, demyelinating disorders have been associated with other biologic DMARDs, namely anti-TNF $\alpha$  therapy. Therefore, one of the AESIs was demyelinating disorders. Sanofi utilized the search criteria MedDRA SMQ Demyelination.

In the pre-rescue period (Table 125), only 1 subject was identified with the SMQ Demyelination, and this subject was on placebo and met the search criterion with the diagnosis of benign monoclonal hypergammaglobunemia.

**Table 125. Overview of Demyelinating Disorders in the Pre-Rescue Period (Pool 1a)**

	Placebo + DMARD	Sarilumab 150mg q2w + DMARD	Sarilumab 200mg q2w + DMARD
<b>Demyelinating disorders</b>			
Raw incidence rate n/N (%)	1/579 (0.2%)	0/579	0/582
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	1/161.5 (0.6)	0/160.0 (0)	0/161.2 (0)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		-0.2% (-0.5, 0.2)	-0.2% (-0.5, 0.2)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			0

n (%) = number and percentage of patients with at least one TEAE

a Number of patients with at least 1 event per 100 patient-years, where the exposure time for patients who have experienced the specific adverse event experience was defined as the time to first adverse experience of interest whereas the exposure time for those who have not had this adverse experience was total TEAE period duration

b The rate difference and its 95% confidence interval were estimated using the M&N method stratified by the study, using the CMH weight

Source: ISS Appendix 1.12.1.52, dated September 29, 2015, page 8292.

By the end of the double blind period, there was an additional subject who was identified with the SMQ Demyelination. The subject was in the sarilumab 200mg q2w arm but discontinued due to lack of efficacy. She developed transverse myelitis 7 months after the last dose of sarilumab. Of note, this subject was previously treated with TNF $\alpha$  inhibitors and re-initiated TNF $\alpha$  therapy 6 months after discontinuing sarilumab. Sanofi noted that there was another subject who was not captured by the SMQ Demyelination but had a multifocal motor neuropathy (around Day 575). This subject was originally randomized to placebo but was rescued with open-label 200mg q2w.

In conclusion, the number of demyelinating disorders was very low. The cases that did occur were not necessarily associated with sarilumab use. One subject was on placebo, and one subject was off sarilumab for 7 months but was taking a TNF inhibitor. Based on the sarilumab safety data, there does not appear to be a signal for demyelinating disorders.

## 8.6. Safety Analyses by Demographic Subgroups

Sanofi provided subgroup analyses of the safety data. This review will focus on the analyses of Pool 1 by age, weight, MTX dose, and race. Specifically, the analyses of SAEs and AESIs (serious infections, neutropenia, and elevated liver enzymes) are presented.

Table 126 shows an overview of SAEs, serious infections, neutropenia (ANC <1.0 Giga/L), and elevated liver enzymes (ALT >3x ULN) by age. Overall, the number of subjects over the age of 75 is small, so it is difficult to make any conclusions about this age group. In comparing the patients <65 years of age and between 65 and 75 years of age, there does seem to be a slightly higher incidence of SAEs, serious infections, and neutropenia in the older age group. This finding may be related to the general increased likelihood of comorbidities and infections in the elderly population. It is important to note that the numerical increase in incidence was noted in all treatment arms, including placebo.

APPEARS THIS WAY ON ORIGINAL

**Table 126. Overview of Adverse Events by Age during the Double-Blind Period (Pool 1)**

	Age <65 years			Age ≥65 and <75 years			Age ≥75 years		
	PBO + DMARD	Sarilumab		PBO + DMARD	Sarilumab		PBO + DMARD	Sarilumab	
		150mg q2w + DMARD	200mg q2w + DMARD		150mg q2w + DMARD	200mg q2w + DMARD		150mg q2w + DMARD	200mg q2w + DMARD
<b>SAEs</b>	24/573 (4.2%)	35/574 (6.1%)	42/569 (7.4%)	7/84 (8.3%)	7/79 (8.9%)	16/82 (19.5%)	0/4	0/7	1/10 (10.0%)
<b>Serious infections</b>	10/573 (1.7%)	8/574 (1.4%)	15/569 (2.6%)	2/84 (2.4%)	4/79 (5.1%)	4/82 (4.9%)	0/4	0/7	0/10
<b>ANC &lt; 1.0 Giga/L</b>	0/573	34/574 (5.9%)	50/569 (8.8%)	0/84	6/79 (7.6%)	8/82 (9.8%)	1/4 (25.0%)	0/7	3/10 (30.0%)
<b>ALT &gt; 3x ULN</b>	10/573 (1.7%)	46/574 (8.0%)	41/569 (7.2%)	1/84 (1.2%)	3/79 (3.8%)	1/82 (1.2%)	0/4	0/7	1/10 (10.0%)

Source: ISS, Tables 159, 161, 163, dated Oct 6, 2015; pages 347-8, 349, 351. ISS Appendix 1.8.1, dated Sep 10, 2015, pages 7950-1.

Table 127 presents these same adverse events by weight. What is notable in this subgroup analysis is how neutropenia (ANC<1.0 Giga/L) occurs more frequently in the lower weight population. As in the patient population as a whole, the rates of neutropenia in the placebo group was low in all weight categories. However, the proportion was 14.1% in the 150mg q2w arm and 17.6% in the 200mg q2w in subjects <60 kg, compared to 4.3% in the 150mg q2w arm and 7.1% in the 200mg q2w arm in the subjects between 60-100kg. The proportions were even lower in the subjects >100kg. Despite this trend in neutropenia, the proportion of serious infections was low and similar in the subjects <60kg and between 60-100 kg. In fact, the higher proportion of serious infections occurred in subjects ≥100kg. Thus, there may not be a clinical correlation between neutropenia and infection. This was similar to what was seen in the general analyses of safety. Other than neutropenia, there did not appear to be an association between weight and other adverse events.

*Reviewer Comment: Please see the primary clinical pharmacology review by Dr.Jianmeng Chen for details regarding weight and PK. Weight was noted to be a factor on PK with higher drug exposure at lower body weights. Therefore, the neutropenia results may reflect the drug exposure. However, as noted, the presence of neutropenia did not necessarily correlate with the risk of infection. Further, the proposed labeling will indicate that the dose should be reduced for neutropenia. Thus, if patients of lower weights develop neutropenia, the dose can be reduced.*

**Table 127. Overview of Adverse Events by Weight during the Double-Blind Period (Pool 1)**

	Weight <60 kg			Weight ≥60 and <100 kg			Weight ≥100 kg		
	PBO + DMARD	Sarilumab		PBO + DMARD	Sarilumab		PBO + DMARD	Sarilumab	
		150mg q2w + DMARD	200mg q2w + DMARD		150mg q2w + DMARD	200mg q2w + DMARD		150mg q2w + DMARD	200mg q2w + DMARD
<b>SAEs</b>	2/135 (4.4%)	7/128 (5.5%)	14/136 (10.3%)	25/454 (5.5%)	28/467 (6.0%)	37/451 (8.2%)	4/72 (5.6%)	7/65 (10.8%)	8/74 (10.8%)
<b>Serious infections</b>	2/135 (1.5%)	2/128 (1.6%)	3/136 (2.2%)	9/454 (2.0%)	8/467 (1.75%)	11/451 (2.4%)	1/72 (1.4%)	2/65 (3.1%)	5/74 (6.8%)
<b>ANC &lt; 1.0 Giga/L</b>	1/135 (0.7%)	18/128 (14.1%)	24/136 (17.6%)	0/454	20/467 (4.3%)	32/451 (7.1%)	0/72	2/65 (3.1%)	5/74 (6.8%)
<b>ALT &gt; 3x ULN</b>	2/135 (1.5%)	7/128 (5.5%)	9/136 (6.6%)	7/454 (1.5%)	38/467 (8.1%)	33/451 (7.3%)	2/72 (2.8%)	4/65 (6.2%)	1/74 (1.4%)

Source: ISS, Tables 159, 161, 163, dated Oct 6, 2015; pages 347-8, 349, 351. ISS Appendix 1.8.1, dated Sep 10, 2015, pages 7955-6.

Table 128 presents the subgroup analysis of concomitant MTX dose. A MTX dose less than 15mg per week is considered low; a dose between 15-20mg per week is considered moderate; and a dose greater than 20mg is considered high. A low number of subjects was on high dose MTX. However, in comparing the dose categories, there does not appear to be an association between concomitant MTX dose with various AESIs, including elevated liver enzymes. The proportions of events were similar in each MTX category to the overall patient population.

**Table 128. Overview of Adverse Events by MTX Dose during the Double-Blind Period (Pool 1)**

	MTX LOW Dose			MTX MODERATE Dose			MTX HIGH Dose		
	PBO + DMARD	Sarilumab		PBO + DMARD	Sarilumab		PBO + DMARD	Sarilumab	
		150mg q2w + DMARD	200mg q2w + DMARD		150mg q2w + DMARD	200mg q2w + DMARD		150mg q2w + DMARD	200mg q2w + DMARD
<b>Serious infections</b>	5/167 (3.0%)	3/167 (1.8%)	6/173 (3.5%)	7/420 (1.7%)	6/403 (1.5%)	11/420 (2.6%)	0	2/62 (3.2%)	2/40 (5.0%)
<b>ANC &lt; 1.0 Giga/L</b>	0/167	18/167 (10.8%)	16/173 (9.2%)	1/420 (0.2%)	19/403 (4.7%)	36/420 (8.6%)	0/50	0/62	3/40 (7.5%)
<b>ALT &gt; 3x ULN</b>	2/167 (1.2%)	16/167 (9.6%)	8/173 (4.6%)	8/420 (1.9%)	31/403 (7.7%)	29/420 (6.9%)	1/50 (2.0%)	2/62 (3.2%)	4/40 (10.0%)

MTX weekly dose: Low <15 mg, Moderate ≥15 and ≤20mg, High >20mg

Source: ISS, Tables 159, 161, 163, dated Oct 6, 2015; pages 347-8, 349, 351. ISS Appendix 1.8.1, dated Sep 10, 2015, pages 7950-1.

Lastly, Table 129 shows these same adverse events by race (Caucasian vs. non-Caucasian). There were fewer non-Caucasian subjects in the sarilumab clinical development program. As discussed in Section 6 and Section 8.2.2, this appropriately represented the general RA population in the US. However, there has been some discussion in the literature that non-Caucasian subjects (specifically, black or Latino patients) may have higher disease activity. With this in mind, the subgroup analysis by race did not show any major trends. Interestingly, the proportion of subjects with ANC <1.0 Giga/L was slightly higher for both doses of sariluman in the non-Caucasian population. However, the clinical significance is unclear, as the incidence of SAEs, serious infections, and elevated liver enzymes was higher in the Caucasian population.

**Table 129. Overview of Adverse Events by Race during the Double-Blind Period (Pool 1)**

	Caucasian			Non-Caucasian		
	PBO + DMARD	Sarilumab		PBO + DMARD	Sarilumab	
		150mg q2w + DMARD	200mg q2w + DMARD		150mg q2w + DMARD	200mg q2w + DMARD
<b>SAEs</b>	26/543 (4.8%)	37/553 (6.7%)	52/545 (9.5%)	5/118 (4.2%)	5/107 (4.7%)	6/116 (5.2%)
<b>Serious infections</b>	10/543 (1.8%)	11/553 (2.0%)	17/545 (3.1%)	2/118 (1.7%)	1/107 (0.9%)	2/116 (1.7%)
<b>ANC &lt; 1.0 Giga/L</b>	1/543 (0.2%)	31/553 (5.6%)	48/545 (8.8%)	0/118	9/107 (8.4%)	13/116 (11.2%)
<b>ALT &gt; 3x ULN</b>	9/543 (1.7%)	47/553 (8.5%)	35/545 (6.4%)	2/118 (1.7%)	2/107 (1.9%)	8/116 (6.9%)

Source: ISS Appendix 1.8.1, 1.8.2, 1.8.4, 1.8.6, dated Sep 10, 2015; pages 7951-3, 7957, 7968, 7982.

Overall, the subgroup analyses are limited, but they do support the safety findings in the general patient population in the sarilumab clinical development program. Based on the subgroup analyses, there does not appear to be a safety signal in any particular subgroup.

APPEARS THIS WAY ON ORIGINAL

## 8.7. Specific Safety Studies/Clinical Trials

Two studies were performed primarily for the purpose of completing the safety assessment of sarilumab. SFY13370 was conducted to compare the safety of sarilumab with the only FDA-approved IL-6 inhibitor. EFC13752 was conducted to assess the safety and immunogenicity of sarilumab monotherapy. Both studies will be reviewed here from a safety perspective.

### **SFY13370: Sarilumab vs. Tocilizumab**

Study SFY13370 is discussed in detail in Section 6.4. The objective of study SFY13370 was to assess safety of sarilumab and tocilizumab in the same study since tocilizumab is the approved IL-6 inhibitor. In Section 6.4, the protocol and exploratory efficacy results are reviewed. This section will review the available safety data.

Table 130 presents the extent of exposure in study SFY13370. The cumulative exposure to active treatment was 45.6 patient-years for the tocilizumab group, 19.9 patient-years for the sarilumab 150mg q2w group, and 20.0 patient-years for the sarilumab 200mg q2w group. Generally, the proportion of subjects in each arm was similar across arms through >4 weeks of therapy. However, after >8 weeks of therapy, the proportion of subjects in the sarilumab arms began to decrease. At >24 weeks of study treatment, the proportion of subjects who remained on treatment in the tocilizumab group (34.3%) was higher compared to the sarilumab arms (18.4% in 150mg q2w arm and 15.7% in the 200mg q2w arm).

APPEARS THIS WAY ON ORIGINAL

**Table 130. SFY13370 Exposure to Investigational Medicinal Product**

	Tocilizumab q4w + DMARD  N=102 n (%)	Sarilumab	
		150mg q2w + DMARD N=49 n (%)	200mg q2w + DMARD N=51 n (%)
Cumulative exposure to treatment (pt-yrs)	45.6	19.9	20.0
Duration of study treatment			
Number	102	49	51
Mean (SD)	163.2 (26.0)	148.6 (44.6)	143.4 (47.0)
Median	168.0	168.0	168.0
Min : Max	28:183	14:196	42:187
Number of pts with duration of study treatment by category [n(%)]			
≥ 1 day	102 (100%)	49 (100%)	51 (100%)
> 4 weeks	99 (97.1%)	47 (95.9%)	51 (100%)
> 8 weeks	99 (97.1%)	44 (89.8%)	44 (86.3%)
> 12 weeks	99 (97.1%)	43 (87.8%)	41 (80.4%)
> 16 weeks	97 (95.1%)	40 (81.6%)	40 (78.4%)
> 20 weeks	96 (94.1%)	40 (81.6%)	39 (76.5%)
> 24 weeks	35 (34.3%)	9 (18.4%)	8 (15.7%)

Source: SFY13370 Clinical Study Report, Table 14, dated August 12, 2015, page 72-3.

Of note, all patients in the tocilizumab group started at 4mg/kg, and subjects could increase to 8mg/kg at any time based on Investigator’s judgment. A total of 60.8% of subjects on tocilizumab increased the dose during the treatment period, and 42.4% of the subjects up-titrated as early as Week 4. Subjects in the sarilumab arms did not have an option to modify dose. Four patients who up-titrated to 8 mg/kg later had to reduce their dose to 4 mg/kg due to adverse safety findings.

Table 131 presents an overview of adverse events in study SFY13370. The incidence of all adverse events was similar across treatment arms. The proportion of SAEs was similar between the tocilizumab arm and the sarilumab 200mg q2w arm but was lower in the sarilumab 150mg q2w arm.

There was 1 death in study in the tocilizumab group, involving a 64 year-old female who experienced bloody diarrhea and abdominal pain and then “septic shock” around Day 18 of the study. It is unclear what was the patient’s infectious source. The patient died the day after presentation in shock. Given that the subject received only 1 dose of tocilizumab, it is unlikely that this death was related to tocilizumab.

In this overview of adverse events, the greatest difference was in the AEs leading to permanent discontinuation. There were more discontinuations in the sarilumab compared to the

tocilizumab group. This was first noted in the table of patient disposition in study SFY13370 (Table 16). The discontinuations secondary to adverse events are described further below in Table 133.

**Table 131. Overview of Adverse Events in SFY13370**

	Tocilizumab q4w + DMARD  N=102 n (%)	Sarilumab	
		150mg q2w + DMARD N=49 n (%)	200mg q2w + DMARD N=51 n (%)
Patients with any TEAE	68 (66.7%)	33 (67.3%)	36 (70.6%)
Patients with SAEs	7 (6.9%)	1 (2.0%)	3 (5.9%)
Patients with any TEAE leading death	1 (1.0%)	0	0
Patients with any TEAE leading to permanent treatment discontinuation	4 (3.9%)	6 (12.2%)	8 (15.7%)

Source: SFY13370 Clinical Study Report, Table 17, dated August 12, 2015, page 75.

### **Common AEs**

The Infections and infestations SOC was the most common SOC for all treatment arms (31.4% in tocilizumab arm, 40.8% in the sarilumab 150mg q2w arm, and 21.6% in the sarilumab 200mg q2w arm). The 3 most common PTs in the tocilizumab arm different from the most common PTs in the sarilumab arms. For tocilizumab, the most common PTs were accidental overdose (8.8%), nausea (6.9%), and upper respiratory tract infection (6.9%). For sarilumab, the 3 most common PTs were similar to what was seen in the pivotal trials: neutropenia (12.2% in 150mg q2w, 15.7% in 200mg q2w), nasopharyngitis (12.2% in 150mg q2w, 5.9% in 200mg q2w), and injection site erythema (8.2% in 150mg q2w and 7.8% in 200mg q2w).

As described in the protocol, an overdose was defined as the administration of 2 or more sarilumab doses in less than 11 calendar days or at least twice the tocilizumab dose in less than 21 calendar days or at least twice of the intended dose within the intended therapeutic interval for sarilumab or tocilizumab. No symptomatic overdoses were reported.

The other common PTs (infections, neutropenia, and hypersensitivity) will be discussed below under AESIs.

### **Serious AEs**

Table 132 presents the SAEs in study SFY13370. In this study, the overall numbers of SAEs was very low. There was only 1 subject with SAEs in the sarilumab 150mg q2w arm. The proportion of subjects with SAEs was similar between the tocilizumab and sarilumab 200mg q2w arm. All the PTs occurred as single events, and there was no overlap between treatment arms. Thus, no safety signal was evident.

**Table 132. Number (%) of Patients with SAEs by SOC and PT in study SFY13370**

	Tocilizumab q4w + DMARD  N=102 n (%)	Sarilumab	
		150mg q2w + DMARD N=49 n (%)	200mg q2w + DMARD N=51 n (%)
Any class	7 (6.9%)	1 (2.0%)	3 (5.9%)
Infections and infestations	2 (2.0%)	0	1 (2.0%)
Urinary tract infection	0	0	1 (2.0%)
Erysipelas	1 (1.0%)	0	0
Septic shock	1 (1.0%)	0	0
Blood and lymphatic system disorders	1 (1.0%)	0	0
Neutropenia	1 (1.0%)	0	0
Nervous system disorders	1 (1.0%)	0	0
Tremor	1 (1.0%)	0	0
Cardiac disorders	0	0	1 (2.0%)
Atrial fibrillation	0	0	1 (2.0%)
Vascular disorders	0	1 (2.0%)	0
Deep vein thrombosis	0	1 (2.0%)	0
Respiratory, thoracic, and mediastinal disorders	0	1 (2.0%)	0
Idiopathic pulmonary fibrosis	0	1 (2.0%)	0
Pulmonary embolism	0	1 (2.0%)	0
Musculoskeletal and connective tissue disorders	2 (2.0%)	0	0
Osteochondrosis	1 (1.0%)	0	0
Pseudoarthrosis	1 (1.0%)	0	0
Renal and urinary disorders	1 (1.0%)	0	0
Renal failure acute	1 (1.0%)	0	0
Investigations	0	0	1 (2.0%)
Transaminases increased	0	0	1 (2.0%)

Source: SFY13370 Clinical Study Report, Table 19, dated August 12, 2015, page 77-78.

### **AEs Leading to Treatment Discontinuation**

As already noted in the overview of safety events in study SFY13370, there were more AEs leading to discontinuation in the sarilumab arms compared to the tocilizumab arm. Table 133 displays the AEs by SOC and PT that led to discontinuation.

**Table 133. SFY13370 Number of Patients with AEs Leading to Permanent Discontinuation**

	Tocilizumab q4w + DMARD  N=102 n (%)	Sarilumab	
		150mg q2w + DMARD N=49 n (%)	200mg q2w + DMARD N=51 n (%)
Any class	4 (3.9%)	6 (12.2%)	8 (15.7%)
Infections and infestations	1 (1.0%)	2 (4.1%)	2 (3.9%)
Skin infection	0	0	1 (2.0%)
Urinary tract infection	0	1 (2.0%)	1 (2.0%)
Pneumonia	0	1 (2.0%)	0
Septic shock	1 (1.0%)	0	0
Blood and lymphatic system disorders	0	1 (2.0%)	0
Leukopenia	0	1 (2.0%)	0
Neutropenia	0	1 (2.0%)	0
Nervous system disorders	1 (1.0%)	0	0
Tremor	1 (1.0%)	0	0
Cardiac disorders	0	0	1 (2.0%)
Atrial fibrillation	0	0	1 (2.0%)
Respiratory, thoracic, and mediastinal disorders	0	1 (2.0%)	0
Idiopathic pulmonary fibrosis	0	1 (2.0%)	0
Skin and subcutaneous tissue disorders	0	0	1 (2.0%)
Pruritus generalized	0	0	1 (2.0%)
Musculoskeletal and connective tissue disorders	1 (1.0%)	0	0
Rheumatoid arthritis	1 (1.0%)	0	0
Renal and urinary disorders	1 (1.0%)	0	0
Renal failure acute	1 (1.0%)	0	0
General disorders and administration site conditions	0	0	2 (3.9%)
Injection site erythema	0	0	1 (2.0%)
Injection site rash	0	0	1 (2.0%)
Investigations	0	2 (4.1%)	2 (3.9%)
Neutrophil count decreased	0	0	1 (2.0%)
Transaminases increased	0	1 (2.0%)	1 (2.0%)
Alanine aminotransferase increased	0	1 (2.0%)	0
Injury, poisoning, and procedural complications	0	0	1 (2.0%)
Infusion related reaction	0	0	1 (2.0%)

Source: SFY13370 Clinical Study Report, Table 20, date August 12, 2015, page 80.

In the sarilumab treatment groups, there were 6 discontinuations from laboratory abnormalities in 5 patients. There were no discontinuations from laboratory abnormalities in

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

the tocilizumab group. Per the applicant, many of these discontinuations were related to the protocol-defined criteria for permanent treatment discontinuation. The laboratory abnormalities included neutropenia, leukopenia, and elevated liver associated enzymes (specifically, elevated ALT). Three of the 5 subjects temporarily interrupted IMP because of laboratory abnormalities but were able to re-initiate IMP. However, because IMP was not administered for 42 days, these subjects had to be permanently discontinued.

Some subjects on sarilumab also developed injection or infusion related events. Two subjects on sarilumab 200 mg q2w discontinued due to injection site reactions. One subjects, also on sarilumab 200 mg q2w, developed an infusion-related reaction (thus, a reaction to IV placebo).

The other adverse events leading to permanent discontinuation were low and were generally single occurrences.

### **AEs of Special Interest**

The AESIs in study SFY13370 were the same pre-specified adverse events described for the rest of the safety evaluation. Table 134 presents the AESIs for study SFY13370. What is notable is that the vast majority of the same AESIs were experienced by subjects on both tocilizumab and sarilumab. These included infections, leukopenia, hepatic disorders, elevation in lipids, hypersensitivity, and injection site reactions. Thus, this confirms that these were appropriate AESIs based on what was expected with IL-6 inhibition in the RA population. Hepatic disorders and hypersensitivity occurred in similar proportions in the tocilizumab and sarilumab arms. However, for leukopenia and injection site reactions, the proportion of subjects with events was higher in the sarilumab arms. The incidence of subjects with elevation in lipids was higher in the tocilizumab group. Infections seemed to vary with the highest proportion in sarilumab 150mg q2w (40.8%) and then in tocilizumab arm (31.4%) and lastly in the sarilumab 200mg q2w arm (21.6%).

APPEARS THIS WAY ON ORIGINAL

**Table 134. SFY13370 Number of Patients with AEs of Special Interest (AESI)**

	Tocilizumab q4w + DMARD  N=102 n (%)	Sarilumab	
		150mg q2w + DMARD N=49 n (%)	200mg q2w + DMARD N=51 n (%)
Infections	32 (31.4%)	20 (40.8%)	11 (21.6%)
Serious infections	2 (2.0%)	0	1 (2.0%)
Opportunistic infections	0	0	0
Tuberculosis	0	0	0
Leukopenia	7 (6.9%)	6 (12.2%)	9 (17.6%)
Thrombocytopenia	0	1 (2.0%)	0
Hepatic disorders	7 (6.9%)	3 (6.1%)	3 (5.9%)
Diverticulitis/potential GI perforations	0	0	0
GI ulcerations	1 (1.0%)	0	0
Elevation in lipids	13 (12.7%)	2 (4.1%)	3 (5.9%)
Hypersensitivity	4 (3.9%)	1 (2.0%)	2 (3.9%)
Anaphylaxis	0	0	0
Injection site reactions	4 (3.9%)	5 (10.2%)	5 (9.8%)
Malignancy	0	0	0
Malignancy excluding NMSC	0	0	0
Lupus-like syndrome	0	0	0
Demyelinating disorders	0	0	0

Source: SFY13370 Clinical Study Report, Table 21, date August 12, 2015, page 82.

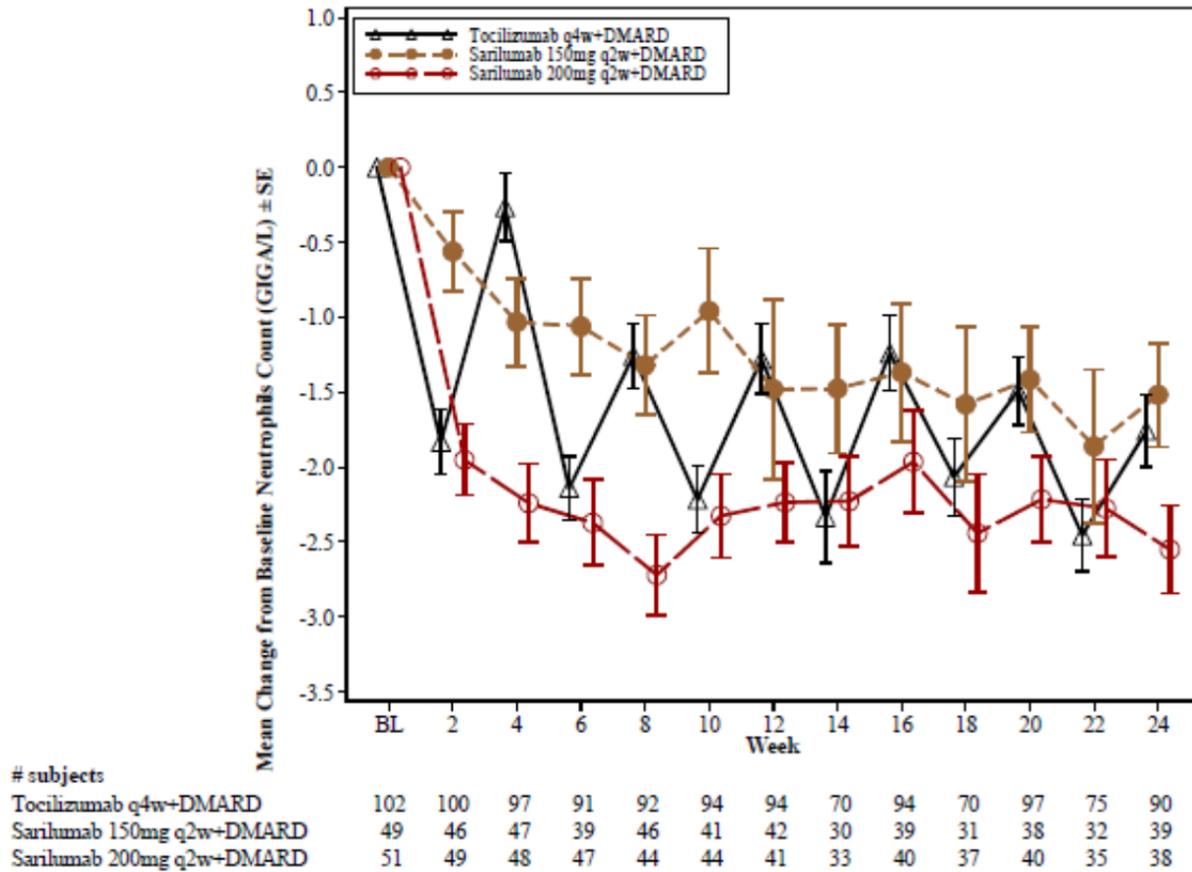
The assessment of Elevation in lipids, Diverticulitis/potential GI perforations, and GI ulcerations in study SFY13370 are reviewed as part of the safety sections for the respective AESIs, Sections 8.5.2 and 8.5.5. The other AESIs will be reviewed briefly here.

In regards to infections, the proportions of subjects with infections differed in the treatment arms as described above with the highest proportion in the subjects on sarilumab 150mg q2w. However, there were no subjects with serious infections in this arm. The incidence of serious infections was the same for the tocilizumab and sarilumab 200mg q2w arm at 2.0% with an event rate of 4.2 and 4.5 per 100 patient-years, respectively. Overall, the differences between treatment arms did not appear to be clinically meaningful.

For leukopenia/neutropenia, Figure 59 shows the trend in absolute neutrophil count over the course of study SFY13370. In general, the neutrophil count in the tocilizumab arm reflected the PK with greater changes from baseline about 2 weeks after the tocilizumab was dosed. The change in neutrophil counts in the tocilizumab arm essentially varied between both doses of sarilumab. More subjects on sarilumab had an ANC <1 Giga/L than subjects on tocilizumab. Only 1 subject (1.0%) on tocilizumab had an ANC <1 Giga/L, compared to 3 subjects on sarilumab 150mg q2w (6.3%) and 5 subjects on sarilumab 200mg q2w (9.8%). Sanofi noted

that all 9 subjects with ANC <1.0 Giga/L recovered their neutrophil counts and were able to reinstate IMP. There were also more subjects identified from the sarilumab arms who met the search criterion SMQ Hematopoietic leukopenia. There was an incidence rate of 6.9% in the tocilizumab arm versus 12.2% in the sarilumab 150mg q2w arm and 17.6% in the sarilumab 200mg q2w. Similarly, the exposure-adjusted event rate was higher in the sarilumab arms: 14.8 per 100 patient-years in tocilizumab, 78.1 per 100 patient-years in sarilumab 150mg q2w, and 58.7 per 100 patient-years in sarilumab 200mg q2w.

**Figure 59. Mean Change from Baseline in ANC at Each Visit for Study SFY13370**

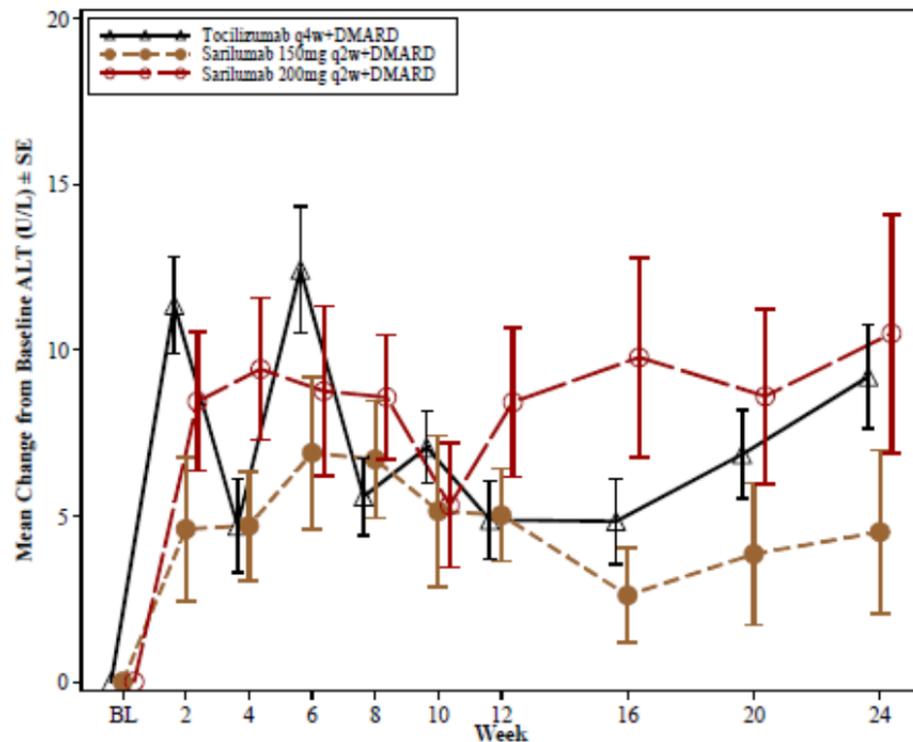


ANC = absolute neutrophil count  
 Source: SFY13370 Clinical Study Report, Figure 4, date August 12, 2015, page 89.

Similar to neutrophil counts, elevations in liver enzymes in the tocilizumab arm correlated with PK with an increased elevation about 2 weeks after dosing. In general, the trend in ALT elevation for subjects on tocilizumab seemed to be more consistent with subjects on sarilumab 200mgq2w. It should be noted that the liver enzymes values roughly stayed within normal range for all treatment arms. Similar proportion of subjects in each treatment arm had an ALT elevation between 3-5x ULN. The incidence was 3.0% in the tocilizumab arm, 4.3% in the sarilumab 150mg q2w arm, and 3.9% in the sarilumab 200mg q2w arm. One subject in the trial

had an ALT between >5X ULN, and this subject was in the sarilumab 200mg q2w arm. Five of the 8 subjects with an ALT >3x ULN was able to reinstate therapy. Of these 5 subjects, 3 subjects completed the study, but 2 subjects on sarilumab had to discontinue again because of elevation in ALT. The number of subjects who were identified with the search criterion SMQ Drug-related hepatic disorders was similar across treatment arms: 6.9% on placebo, 6.1% on sarilumab 150mg q2w, and 5.9% on sarilumab 200mg q2w. The exposure-adjusted event rates were also similar.

**Figure 60. Mean Change from Baseline in ALT at Each Visit for Study SFY13370**



# subjects	BL	2	4	6	8	10	12	16	20	24
Tocilizumab q4w+DMARD	102	99	95	92	93	95	98	97	91	95
Sarilumab 150mg q2w+DMARD	49	45	47	40	44	41	43	43	40	39
Sarilumab 200mg q2w+DMARD	51	47	47	46	45	44	42	41	41	38

ALT = alanine aminotransferase

Source: SFY13370 Clinical Study Report, Figure 7, date August 12, 2015, page 95.

Lastly, a brief discussion of hypersensitivity events will be provided. Utilizing the SMQ Hypersensitivity, there was a similar proportion of subjects identified from each treatment arm (3.9% on tocilizumab, 2.0% on sarilumab 150mg q2w, 3.9% on sarilumab 200mg q2w). However, there were more subjects in the sarilumab arms who met the search criteria HLT Injection site reactions. Since tocilizumab was given IV, the “tocilizumab” arm was actually injection site reaction observed with SC injection of placebo. Most of the reactions in the sarilumab arms were secondary to injection site erythema with 8.2% in the 150mg q2w arm

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

and 7.8% in the 200mg q2w arm. No Investigator categorized any of these injection site reactions as being “severe” in intensity. Of note, there were 2 infusion reactions, 1 in the tocilizumab arm and 1 in the “sarilumab 200mg q2w” arm (which was infusion of placebo).

Of note, ADA response was not evaluated in the tocilizumab arm, so a comparison of ADA could not be conducted. Therefore, a discussion on immunogenicity will be deferred in this section. Instead, refer to the general discussion of immunogenicity in the Safety Section 8.4.10.

In conclusion, SFY13370 provided a unique opportunity to compare sarilumab with the approved IL-6 inhibitor (tocilizumab) in the same trial. As such, there were no new safety signals, as the safety events were consistent with what was expected. In regards to differences, there were more subjects with the adverse event of neutropenia in the sarilumab arms, and there were more subjects with the adverse event of “elevation in lipids” in the tocilizumab arm. However, when actually trending these laboratory values, the values were overlapping/similar amongst treatment arms. Another difference was that there were more subjects in the sarilumab arms who discontinued because of AEs, and most of the AEs were related to interruptions in therapy because of laboratory abnormalities which later recovered. Otherwise, the review of safety was actually quite similar between treatment arms. Based on the safety data, it is difficult to determine if there is a truly clinically meaningful difference in safety between tocilizumab and sarilumab.

### **EFC13752: Sarilumab Monotherapy**

Study EFC13752 was the open-label study assessing the immunogenicity and safety of sarilumab administered as monotherapy for a 24-week treatment period. The review of the protocol is located in Section 6.5 along with a brief presentation of efficacy. The primary endpoint was immunogenicity, and that was discussed above in Section 8.4.10. Here, I will present the safety analyses of EFC13752. Additionally, an overview of safety of Pool 3 will be presented alongside the safety results from EFC13752. A brief description of Pool 3 is provided in Section 8.1, and, as a reminder, it will be presented again here. Pool 3 consisted of subjects who received sarilumab as monotherapy in study EFC13752 from the first dose to the end of study. Additionally, subjects from EFC1372 who continued to receive monotherapy in LTS11210 were included. Therefore, Pool 3 was essentially the long-term safety population for the monotherapy regimen. Safety data were summarized and categorized by the 3 treatment groups utilized in Pool 2: sarilumab 150mg q2w initial dose, sarilumab 200mg q2w initial dose, and any sarilumab dose. The review of Pool 3 safety will be brief and, mainly, used to support the safety data from study EFC13752, all in an effort to assess the safety of sarilumab monotherapy.

Table 135 is an overview of the adverse event profile for study EFC13752. The proportion of subjects with TEAEs was similar for both doses (63.1% in sarilumab 150mg q2w arm and 68.7%

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

in the sarilumab 200mg q2w arm). Generally, the incidence of any TEAEs were similar (perhaps, slightly higher) than what was seen in the pre-rescue period (54.2% for sarilumab 150mg q2w + DMARD and 57.2% for sarilumab 200mg q2w + DMARD). It was, however, lower than the incidence of TEAEs through the 52-week, double-blind period (70.5% for sarilumab 150mg q2w + DMARD and 73.8% for sarilumab 200mg q2w + DMARD).

The number of subjects with SAEs was very low with just 1 subject on the lower dose and 2 subjects on the higher dose. There were no deaths. There were equally low numbers of subjects who had AEs leading to permanent treatment discontinuation (5 on each dose).

**Table 135. Overview of Adverse Events in Study EFC13752**

	Sarilumab 150mg q2w N=65	Sarilumab 200mg q2w N=67
Patients with any TEAE	41 (63.1%)	46 (68.7%)
Patients with any treatment-emergent SAE	1 (1.5%)	2 (3.0%)
Patients with any TEAE leading to death	0	0
Patients with any TEAE leading to permanent treatment discontinuation	5 (7.7%)	5 (7.5%)

n (%) = number and percentage of patients with at least one TEAE

Source: EFC13752 CSR, Table 16, dated August 18, 2015; page 74.

The overview of AEs for Pool 3 was similar to what has been reviewed in Table 135. There was 1 death that occurred during the open label study on a subject who was originally randomized to the 150mg q2w arm of study EFC13752. This subject was a 73 year-old woman who had completed 24 weeks of sarilumab 150mg q2w and then received 1 dose of sarilumab 200mg q2w. On Day 30 of LTS11210, she developed pneumonia and heart failure. She then developed *Clostridium Difficile* which led to multi-organ failure and death. This subject was counted amongst deaths previously reviewed. As this subject only received 1 dose of sarilumab 200mg, she was counted amongst subjects who died on sarilumab 150mg q2w. See Section 8.4.1 for a review of deaths in the sarilumab clinical development program. Other than this death, the proportion of AEs, SAEs, and AEs leading to discontinuation were generally similar to what was presented here. The exposure-adjusted incidence rates were also similar to what was seen for the long-term safety population (Pool 2). The exposure-adjusted incidence of SAEs for the any dose group was 10.2 per 100 patient-years for Pool 3 versus 10.5 per 100 patient-years for Pool 2, and the exposure-adjusted incidence of AEs leading to discontinuation for the any dose group was 16.1 per 100 patient-years for Pool 3 versus 12.3 per 100 patient-years for Pool 2.

### **Common TEAEs**

The most frequently reported TEAEs by SOC in study EFC13752 were the following, listed by highest frequency:

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

- Infections and infestations SOC with most frequent PTs of upper respiratory tract infection (4.6% for sarilumab 150mg q2w and 6.0% for sarilumab 200mg q2w) and urinary infections (3.1% for sarilumab 150mg q2w and 6.0% for sarilumab 200mg q2w)
- Blood and lymphatic system disorders SOC with most frequent PT of neutropenia (12.3% for sarilumab 150mg q2w and 17.9% for sarilumab 200mg q2w)
- General site and administration site disorders with most frequent PT of injection site erythema (7.7% for sarilumab 150mg q2w and 3.0% for sarilumab 200mg q2w)

The common TEAEs (by PT) for Pool 3 were the same. Thus, the common TEAEs in the sarilumab monotherapy population were generally similar to what was reported for the sarilumab + DMARD population.

### **Serious AEs**

There were only 3 patients with SAEs, which included osteoarthritis (requiring total knee replacement), finger laceration from a knife, and Grade 4 neutropenia. The subjects with osteoarthritis was on the sarilumab 150mg q2w dose, and the other 2 subjects were randomized to the 200mg q2w dose. For Pool 3, the overall numbers in the 150mg q2w and 200mg q2w arms did not change. However, there was a total of 7 subjects with SAEs in the any dose arm. The exposure-adjusted event rate in the any dose arm was 11.5 per 100 patient-years. The only event to occur in more than single digits was osteoarthritis with 2 events in the any dose arm. Thus, in the sarilumab monotherapy population, no conclusions can be drawn given the low numbers.

### **AEs leading to treatment discontinuation**

There were a total of 10 subjects with AEs leading to discontinuation, 5 in each dose, for study EFC13752. The AEs included otitis media, herpes zoster, neutropenia, osteoarthritis, rheumatoid arthritis, injection site erythema, and transaminases increased. Evaluation of Pool 3 showed the same events with the addition of 1 subject with pneumonia in the any dose arm. Overall, the numbers of subjects of AEs leading to discontinuation was low, and the reasons for discontinuation were consistent with what was reported for the sarilumab + DMARD population. In Section 8.4.10, these AEs leading to discontinuation are reviewed in the setting of immunogenicity.

### **AEs of Special Interest**

AESIs were assessed in the monotherapy population, as displayed in Table 136. Generally, the number of subjects with AESIs in study EFC13752 was low. Given the low numbers, only the AEs of overall infections, neutropenia/leukopenia, and injection site reaction will be reviewed briefly below. Subjects identified with the search criteria for hypersensitivity was already discussed in the setting of immunogenicity in Section 8.4.10.

**Table 136. Number of Patients with AESI in Study EFC13752**

	Sarilumab 150mg q2w	Sarilumab 200mg q2w
	N=65	N=67
Infections	18 (27.7%)	22 (32.8%)
Serious infections	0	0
Opportunistic infections	1 (1.5%)	0
Tuberculosis	0	0
Leukopenia	9 (13.8%)	13 (19.4%)
Thrombocytopenia	0	0
Hepatic disorders	0	2 (3.0%)
Diverticulitis/potential GI perforations	0	0
GI ulcerations	0	0
Elevations in lipids	0	2 (3.0%)
Hypersensitivity	2 (3.1%)	2 (3.0%)
Anaphylaxis	0	0
Injection site reactions	6 (9.2%)	2 (3.0%)
Malignancy	0	1 (1.5%)
Malignancy excluding NMSC	0	0
Lupus-like syndrome	0	0
Demyelinating disorders	0	0

AESI = adverse events of special interest

n (%) = number and percentage of patients with at least one AESI

Source: EFC13752 CSR, Table 20, dated August 18, 2015; page 80.

Numerically, there were slightly more infections on the higher dose than the lower dose (32.8% for sarilumab 200mg q2w vs. 27.7% for sarilumab 150mg q2w). Generally, the proportion of subjects with infections in study EFC13752 was similar to that in the sarilumab + DMARD safety population (Pool 1a pre-rescue period and Pool 1 double-blind period). The incidence of subjects with infections was actually a little higher in the 52-week, placebo-controlled population (Pool 1). Pool 3 also had similar proportions of infections with 27.7% in the 150mg q2w arm, 34.3% in the 200mg q2w arm, and 36.4% in the any dose arm. In study EFC13752, the most AEs reported were upper respiratory tract infection and urinary tract infection. There were no serious infections in this study. A total of 2 subjects discontinued treatment because of an infection. One patient on sarilumab 150mg q2w discontinued treatment because of herpes zoster, and one patient on sarilumab 200mg q2w discontinued treatment because of otitis media.

As already mentioned, leukopenia (specifically, neutropenia) was one of the most common AEs in study EFC13752. Based on the SMQ hematopoietic leukopenia, the proportion of subjects identified with the adverse event of leukopenia was 13.8% for sarilumab 150mg q2w and 19.4% for sarilumab 200mg q2w. These proportions are slightly higher than what was reported for the sarilumab + DMARD safety population. For both Pool1a (pre-rescue), the SMQ leukopenia

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

identified 7.6% for sarilumab 150mg q2w and 11.0% for sarilumab 200mg q2w. The number of subjects, though, with an ANC <1.0 Giga/L was low for the sarilumab monotherapy population and consistent with the sarilumab + DMARD safety population. In study EFC13752, 4.6% of subjects on sarilumab 150mg q2w and 7.5% of subjects on sarilumab 200mg q2w had an ANC <1.0 Giga/L. Of note, the assessment of Pool 3 was generally consistent with study EFC13752.

Lastly, as with the safety assessment of the pivotal studies, injection site reactions were identified in study EFC13752 with the HLT Injection site reactions. There were 6 subjects (9.2%) on sarilumab 150mg q2w and 2 subjects (3.0%) on sarilumab 200mg q2w who were identified as having injection site reactions. The most frequent reaction was injection site erythema. No patient had a severe injection site reaction. One patient on each dose of sarilumab discontinued study treatment because of an injection site reaction. Of these 2 subjects, the one on sarilumab 200mg q2w was also ADA positive. The analyses of Pool 3 data supported the analyses of study EFC13752. Overall, these proportions of subjects with injection site reactions in the monotherapy population were consistent (to slightly lower) to what was reported in the sarilumab + DMARD population.

In conclusion, for the sarilumab monotherapy safety population (based on study EFC13752 and Pool 3), there was no major difference in safety findings when compared to the sarilumab + DMARD safety population. It is difficult to make direct comparisons between studies, but the SAEs, AEs leading to discontinuation, and AESIs were consistent with what was expected from IL-6 inhibition in the RA population. Additionally, the types of AEs, such as the common AEs, were similar to those in the sarilumab + DMARD population.

## 8.8. Additional Safety Explorations

### 8.8.1. Human Carcinogenicity or Tumor Development

Malignancy is a concern for most biologic therapy for the treatment of RA. Therefore, malignancy was one of the AESIs. Please refer to Section 8.5.4 for a review of sarilumab and malignancy.

### 8.8.2. Human Reproduction and Pregnancy

In the long-term safety population (Pool 2), there were a total of 9 subjects who became pregnant and 1 male subject whose partner became pregnant. Table 137 lists all 9 subjects who became pregnant in the sarilumab RA development program. Of these 9 subjects, 4 experienced first-trimester miscarriages. (b) (4)

**Table 137. Patient Pregnancies in the Long-Term Safety Population (Pool 2)**

Study	Patient ID Age	Treatment (Sarilumab + DMARD)	LMP Date of last sarilumab dose	Pregnancy Outcome
LTS11210	840013106 24 y/o female	150mg qw MTX	LMP: Jul 24, 2011 Last dose: Aug 4, 2011	Healthy full-term child
LTS11210	484003101 28 y/o female	150mg qw MTX	LMP: May 8, 2012 Last dose: Jun 8, 2013	Healthy full-term child
LTS11210	484035601 30 y/o female	200mg q2w MTX	LMP: Apr 15, 2012 Last dose: Apr 29, 2014	Healthy full-term child
LTS11210	76013216 31 y/o female	200mg q2w MTX	LMP: Nov 2013 Last dose: Dec 26, 2012	<ul style="list-style-type: none"> <li>Spontaneous abortion (Jan 17, 2014)</li> <li>History of 2 prior healthy pregnancies</li> </ul>
EFC11072	484009220 38 y/o female	200mg q2w MTX	LMP: Feb 24, 2013 Last dose: Mar 28, 2013	<ul style="list-style-type: none"> <li>Spontaneous abortion (Apr 24, 2014)</li> <li>History of 3 spontaneous abortions</li> </ul>
LTS11210	643001613 40 y/o female	200mg q2w Leflunomide	LMP: Jan 2015 (last week) Last dose: Feb 3, 2015	<ul style="list-style-type: none"> <li>Missed abortion (Mar 14, 2015)</li> <li>History of 1 prior healthy pregnancy</li> </ul>
EFC11574	484013502 24 y/o female		LMP: Jun 11, 2014 Last dose: Jun 26, 2014	<ul style="list-style-type: none"> <li>Blighted ovum (Sep 1, 2015)</li> <li>History of prior abortion</li> </ul>
LTS11210	616005208 34 y/o female		LMP: Sep 30, 2014 Last dose: Oct 20, 2014	Estimated due date Jul 2015
MSC12665	710007708 35 y/o female		LMP: Dec 8, 2014 Last dose: Dec 24, 2014	Estimated due date Aug 2015

Source: ISS, Table 165, dated October 6, 2015; pages 354-355.

*Reviewer Comment: Given the low number of pregnancies as well as the low number of events (i.e., miscarriages), it is difficult to make any conclusions regarding sarilumab exposure and*

Clinical Review  
Reviewer: Suzette Peng, MD  
NME/BLA 761037  
Sarilumab/Kevzara

*effect on pregnancy outcomes based on clinical data. Of note, the non-clinical data did not show effects on fertility and reproduction.*

### 8.8.3. Pediatrics and Assessment of Effects on Growth

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 adult 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 until studies in adults are complete and ready for approval.

The applicant proposes to perform the following pJIA studies to fulfill PREA requirements. These studies were first submitted on August 12, 2013 as part of the initial Pediatric Study Plan (iPSP). The Agency agreed to the iPSP on January 10, 2014.

- Study DRI13925 is a (b) (4) dose study in patients (b) (4) who are 2 to 17 years of age. (b) (4) The goal of this study is to assess the PK profile of sarilumab in patients with pJIA in order to identify the dose (b) (4) in this population. At the time of BLA submission, the protocol for this study was already submitted.
- Study EFC11783 is a (b) (4) study (b) (4) in patients (b) (4) who are 2 to 17 years of age. The goal of EFC11783 is to evaluate the efficacy and safety of sarilumab in patients with pJIA.

Both studies include an extension phase. These studies will be performed as post-marketing requirements (PMRs). The sarilumab pediatric program was discussed at the Pediatric Review Committee (PeRC) meeting on June 15, 2016. The PeRC agreed with the requested waiver, deferral, and proposed pJIA studies.

(b) (4)

### 8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

**Overdose:** In the sarilumab clinical development program, 2 subjects were documented and

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

confirmed to have received 2 doses of sarilumab 200mg within a 24-hour period. It was noted that neither of these subjects experienced any adverse events or laboratory abnormalities as a consequence of this “overdose.”

**Drug abuse potential:** Sanofi argues that the likelihood that sarilumab has any potential for abuse liability is very limited. Sanofi bases this argument on a few features of sarilumab.

- First, sarilumab is a recombinant human monoclonal antibody IgG1 isotype binding the IL-6R $\alpha$  with a molecular weight of approximately 150 kDa. In general, brain penetration may occur when a therapeutic molecule is lipid soluble with a molecular weight of less than 400-600 Da. Therefore, it is unlikely that sarilumab can cross the blood brain barrier.
- Additionally, monoclonal antibodies do not have active metabolites and are not precursors of identified controlled drug substances.
- Sanofi also notes that there is no evidence in the literature to support an association between IL-6 inhibition and abuse/dependence.
- Tocilizumab has not had evidence of abuse/dependence.
- The non-clinical studies do not suggest a potential for dependence or abuse.
- Sanofi also reviewed the safety data for AEs related to activation/stimulation, sedation, mood elevation/euphoria, or psychomotor effects, and the overall numbers were small and similar across all treatment arms, including placebo.

**Withdrawal and rebound:** Based on PK data, Sanofi reviewed any AEs that occurred or worsened 28 days after the last dose of IMP was administered. Sanofi noted that the number of events were small and were consistent with AEs that occurred during the treatment period. Thus, Sanofi concluded that these AEs were not likely to be related to rebound or withdrawal.

## 8.9. Safety in the Postmarket Setting

### 8.9.1. Safety Concerns Identified Through Postmarket Experience

As sarilumab is a new molecular entity (NME) and has not been approved in the US or elsewhere, there is no postmarket experience. Therefore, no safety concerns have been identified from this perspective.

### 8.9.2. Expectations on Safety in the Postmarket Setting

At this time, there are no potential safety concerns in the postmarket setting. No specific REMS or postmarket study for the purposes of evaluating safety are currently being recommended. See the previous discussion of cardiovascular risk in Section 8.5.3 in regards to decision not to recommend a cardiovascular outcome trial.

### 8.10. Additional Safety Issues From Other Disciplines

There are no additional safety issues from other disciplines that have not already been captured in other sections of this review.

### 8.11. Integrated Assessment of Safety

Sarilumab is a recombinant human IgG1 monoclonal antibody that binds to IL-6R. As such, there were many adverse events that were expected with treatment with sarilumab in the RA population.

In terms of safety, there were more of the following adverse events in the sarilumab treatment groups compared to the placebo group: deaths, serious adverse events, adverse events leading to discontinuation, specific laboratory abnormalities (neutropenia, thrombocytopenia, elevated liver enzymes, elevation in lipids), overall and serious infections, and hypersensitivity events/injection site reactions. Some events occurred too infrequently to make a conclusion regarding risk, namely, GI perforations, cardiovascular events, and malignancy.

- **Deaths**

Out of the 24 deaths in the sarilumab clinical development program, 3 occurred on placebo, and 20 occurred in subjects on sarilumab. The causes of deaths included infection, cardiovascular events, and malignancy; thus, the causes were consistent with those of the general RA population. It was notable that 17 of the deaths occurred in subjects on the higher dose of sarilumab, but most of these deaths occurred in the open-label study when 200mg q2w was the only permitted therapy. Therefore, the deaths may not be related to the higher dose but the increased exposure in the sarilumab 200mg q2w arm.

- **Serious adverse events**

In both the pre-rescue period (Pool 1a) and the double-blind, 52-week treatment period (Pool 1), more serious adverse events occurred in the sarilumab arms compared to the placebo arm. Additionally, there were numerically more subjects with SAEs on the higher dose compared to the lower dose. Infections and Blood and Lymphatic Disorders (due to neutropenia) were the most common SOC. These will be discussed below, but these adverse events are what are expected with treatment with IL-6 inhibitors. Over time, the exposure-adjusted incidence rate of SAEs remained relatively stable.

- **Infections**

For overall infections in the pre-rescue period (Pool 1a) and the double-blind, 52-week treatment period (Pool 1), 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

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

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.

- **Neutropenia**

Neutropenia was one of the most common adverse events to occur in the sarilumab clinical development program. There was a clear association with sarilumab use and a decline in neutrophil counts. In the pre-rescue period, no subjects in the placebo arm developed an ANC <1.0 Giga/L, whereas 25 (4.3%) of subjects on sarilumab 150mg q2w and 35 (6.0%) of subjects on 200mg q2w developed an ANC <1.0 Giga/L. There was a dose-response in both the pre-rescue period (Pool 1a) and the double-blind, 52-week treatment period (Pool 1) with more subjects on the higher dose experiencing a decrease in neutrophils. It does appear that the neutropenia is generally reversible. Additionally, in LTS11210, it was shown that dose reduction (from 200mg q2w to 150mg q2w) can improve neutrophil counts. Lastly, it was unclear if the drop in neutrophil counts was clinically significant, as there did not appear to be an association between infections and neutropenia, even with an ANC <1.0 Giga/L.

- **Elevation in lipids and potential cardiovascular risk**

More subjects on sarilumab had an elevation in lipid parameters compared to subjects on placebo. This was seen in both the pre-rescue period (Pool 1a) and the double-blind, 52-week treatment period (Pool 1). Most of the elevations were small, as the LDL elevation did not shift subjects into a higher NCEP ATP III LDL classification. The elevation in lipids trended higher in subjects on the higher dose of sarilumab. Notably, in study SFY13370, the elevation in lipid parameters in subjects on sarilumab was comparable to what was seen in subjects on tocilizumab. The association of these lipid elevations to cardiovascular events was reviewed in detail in Sections 8.5.2 and 8.5.3. As noted, there were too few MACE to make a conclusion regarding a CV signal based on the safety data alone. The lipid elevation in itself may theoretically convey a CV risk to subjects on sarilumab. However, there appears to be a “lipid paradox” in subjects with RA. Untreated patients with RA may have lower lipid levels but an increased CV risk attributed to inflammation. Once the inflammation is controlled, lipid levels may actually elevate. The Division considered whether a cardiovascular outcome trial (CVOT) should be performed to better assess the CV risk with sarilumab, but, as discussed in Section 8.5.3, the Division decided against the CVOT.

- **Elevation in lipid enzymes**

The safety data supports an association between elevation in liver enzymes and treatment with sarilumab. The dose response was small. There were no cases of Hy's law. Follow-up safety data showed that, for the majority of subjects, the elevation in liver enzymes was reversible. Additionally, in the open-label study, dose reduction improved the elevation in liver enzymes.

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

- **Hypersensitivity events**

Hypersensitivity events and injection site reactions were more common in subjects on sarilumab compared to subjects on placebo in the pre-rescue period (Pool 1a) and double-blind, 52-week treatment period (Pool 1). There was only a small difference between doses of sarilumab. Of note, there were no cases of anaphylaxis in the sarilumab clinical development program.

- **Immunogenicity**

More subjects on sarilumab developed anti-drug antibodies (ADA) compared to subjects on placebo. There did not appear to be a difference between doses. ADA positivity was most frequently treatment-emergent and transient and consisted of non-neutralizing antibodies. ADA positivity did not seem to lead to a significant effect on safety (hypersensitivity events) or lack or loss of efficacy.

For many of the safety events (specifically, neutropenia, infections, serious adverse events), there appeared to be a dose response in that more subjects on sarilumab 200mg q2w had such events compared to subjects on sarilumab 150mg q2w. In general, the numerical difference appeared to be small. Additionally, for the laboratory abnormalities (neutropenia, thrombocytopenia, and elevated liver enzymes), it was noted in study LTS11210 that dose reduction from 200mg q2w to 150mg q2w led to improvement/correction in the laboratory abnormalities. These increased safety events with the higher dose were reviewed in detailed and weighed against efficacy in determining the most appropriate dose for therapy. Please see Section 1 for discussion of benefit-risk assessment in dose selection.

In terms of sarilumab monotherapy, please see the review Sections 6.5 and 8.7 for the review of EFC13752, a study that evaluated the immunogenicity and safety of monotherapy. Overall, the safety findings were comparable to that of the sarilumab + DMARD pivotal trials. Section 8.4.10 specifically reviews immunogenicity and monotherapy. The incidence of ADA was higher with monotherapy compared to sarilumab + DMARD combination therapy. There also was greater proportion of subjects with neutralizing antibody in the sarilumab monotherapy study. Subjects who were ADA positive had a lower functional sarilumab concentration. However, even in the monotherapy study, there does not appear to be a correlation between ADA status and hypersensitivity events or lack/loss of efficacy.

Lastly, Sanofi also performed a study to compare the safety of sarilumab and the currently approved IL-6 inhibitor, tocilizumab. See Sections 6.4 and 8.7 for the detailed review of study SFY13370. The safety events were generally consistent between tocilizumab and sarilumab. More subjects on sarilumab developed neutropenia, but more subjects on tocilizumab developed an elevation in lipids. However, when comparing actual laboratory values, they were overlapping between sarilumab and tocilizumab. More subjects on sarilumab seemed to experience AEs leading to discontinuation, but this may have been related to the protocol criteria. Overall, there did not appear to be any clinically meaningful difference in the safety

findings between tocilizumab and sarilumab.

In conclusion, based on the safety data from the pivotal trials, the risks associated with use of sarilumab were consistent with what is expected from a biologic and, specifically, from an IL-6 inhibitor. There were no new safety signals. The label should convey these known safety risks that were seen in the clinical development program. Please see Section 10 for details on labeling for safety associated with sarilumab. The labeling should be sufficient to describe all safety concerns, and no other REMS or PMRs/PMCs are recommended at this time in regards to safety.

## 9 Advisory Committee Meeting and Other External Consultations

---

An advisory committee meeting was not recommended for sarilumab. The data from the pivotal trials support efficacy. There were no unexpected safety signals; that is, safety was similar to that of tocilizumab.

## 10 Labeling Recommendations

---

### 10.1. Prescribing Information

- **Section 2: Dosage and Administration**

Sanofi proposes that “KEVZARA may be used as monotherapy or in combination with methotrexate or other (b) (4) DMARDs.” The Agency recommends the use of “conventional DMARDs” instead of “(b) (4) DMARDs.”

*Reviewer Comment:*

(b) (4)  
It is the Agency’s preference to use “conventional DMARDs.”

Sanofi also proposes, “The recommended dose of KEVZARA is 200mg once every two weeks.”

*Reviewer Comment: Based on the efficacy and safety assessments (already discussed above), the Agency is in agreement with the proposed dose. The Agency also agrees with the initial dosing prohibition and later dose modification based on laboratory monitoring, as these are supported by inclusion/exclusion criteria of the pivotal trials as well as dose modification criteria in study LTS11210.*

- **Boxed Warning**

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

The originally submitted prescribing information included a BOXED WARNING related to risk of serious infections, including bacterial, viral, fungal, and other opportunistic infections. The Agency recommends more description of the reported infections, such as more details on TB, and invasive fungal infections.

*Reviewer Comment: This recommendation would make this BOXED WARNING more consistent with other biologics with similar BOXED WARNINGS for serious infections.*

- **Section 5: Warnings and Precautions**

The Agency recommends adding a bullet related to Hypersensitivity.

*Reviewer Comment: As discussed in Section 8.5.6, there was a greater number of hypersensitivity events and injection site reactions in subjects on sarilumab compared to subjects on placebo. There were no cases of anaphylaxis. Given these findings and the fact that hypersensitivity is a predicated adverse event with biologics, the Agency recommends the addition of hypersensitivity to this section.*

- **Section 6: Adverse Reactions**

For most of the adverse events, the Agency recommends the use of the safety data from Pool 1a, pre-rescue period. For rarer event (such as malignancy, GI perforation, CV events), it is reasonable to use the double-blind, 52-week safety population (Pool 1).

*Reviewer Comment: As described in Section 8.1, the safety data for the Pool 1a pre-rescue period were least influenced by the various dose modifications that could be made in the clinical trials. Therefore, for purposes of labeling, this would also be the appropriate patient population for more common safety events.*

- **Section 8: Use in Specific Populations**

The Agency recommends multiple modifications to this section on pregnancy and lactation to make the formatting and language more in line with the Pregnancy and Lactation Labeling Rule (PLLR). Please see Dr. Eleni Salicru's review for more details on the exact changes based on non-clinical data.

- **Section 14: Clinical Studies**

The Agency recommends the following modifications to this section based on input from the statistical and clinical teams.

- A description of the escape options and escape criteria should be added to both studies described since the opportunity to escape/rescue was an important aspect of the study design and interpretation of the results.
- Since the response curves for ACR20 over time are similar for both phase 3 studies, the Agency recommends that only one response curve be included.
- Modifications are recommended to the text and table regarding DAS28-CRP<2.6. The goal of these modifications is to clarify what was originally proposed by the Applicant and to indicated that, while both doses of sarilumab had a significantly

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

- greater proportion of subjects achieve “DAS28 remission” compared to placebo, the majority of patients with DAS28-CRP<2.6 still had at least one active joint.
- For the radiographic data, it is recommended that the results be displayed for analyses including data collected after escape/rescue and treatment discontinuation, rather than analyses based on linear extrapolation.
  - The Agency recommends that information (b) (4) be removed since the labeling will reflect efficacy information at earlier time points, and it is reasonable to assume that efficacy would be maintained.
  - Data related to SF-36 should be shown for each of the domains.

### 10.2. Patient Labeling

The patient labeling is still under review by the patient labeling teams at this time.

### 10.3. Nonprescription Labeling

Not applicable

## 11 Risk Evaluation and Mitigation Strategies (REMS)

---

### 11.1. Safety Issue(s) that Warrant Consideration of a REMS

Based on the review of data, there are no safety issues that warrant consideration of a REMS. See Section 11.3 below.

### 11.2. Conditions of Use to Address Safety Issue(s)

Not applicable

### 11.3. Recommendations on REMS

Sanofi proposed the following Risk Evaluation and Management Strategies (REMS): a

(b) (4)  
Based on the review of safety and efficacy data submitted, a REMS are not recommended. Product labeling will be adequate to ensure that the product’s benefit outweigh its risk in the postmarket setting. Review by the Division of Risk Management (DRISK) has not been finalized, but, at this point, DRISK agrees that a REMS is not required.

## 12 Postmarketing Requirements and Commitments

---

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

As already discussed elsewhere in this review, Sanofi will have a PREA postmarketing requirement (PMR). The studies that will comprise this PMR are described in Section 8.8.3.

Additionally, there was discussion regarding a possible cardiovascular outcome trial as a postmarketing commitment. However, as reviewed in Section 8.5.3, this was deemed to be unnecessary at this time.

Lastly, there are currently ongoing discussions (b) (4) Please see the Product Quality review for more details.

## 13 Appendices

---

### 13.1. References

1. Aletaha D, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Ann Rheum Dis*. 2010; 69: 1580-8.
2. Birnbaum H, et al. Societal cost of rheumatoid arthritis patients in the US. *Curr Med Res Opin*. 2010; 26(1): 77-90.
3. Choy E, Ganeshalingham K, Semb AG, et al. Cardiovascular risk in rheumatoid arthritis: recent advances in the understanding of the pivotal role of inflammation, risk predictors, and the impact of treatment. *Rheumatology*. 2014; 53: 2143-54.
4. Gabriel SE, et al. Epidemiological studies in incidence, prevalence, mortality, and comorbidity of the rheumatic diseases. *Arthritis Res Ther*. 2009; 11 (3): 229.
5. Greenberg JD, Spruill T, Shan Y, et al. Racial and Ethnic Disparities in Disease Activity in Rheumatoid Arthritis. *Am J Med*. 2013; 126: 1089-1098.
6. Katchamart W, et al. Methotrexate monotherapy versus methotrexate combination therapy with non-biologic disease modifying anti-rheumatic drugs for rheumatoid arthritis. *Cochrane Database Syst Rev*. 2010; 4: CD008495.
7. Kawatkar AA, Portugal C, Chu L, Iyer R. Racial/Ethnic Trends in Incidence and Prevalence of Rheumatoid Arthritis in a Large Multi-Ethnic Managed Care Population [abstract]. *Arthritis Rheumatol*. 2012; 64 Suppl 10: 2514.

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

8. Madhok R, et al. Serum interleukin 6 levels in rheumatoid arthritis: correlations with clinical and laboratory indices of disease activity. *Ann Rheum Dis*. 1993; 52(3): 232-4.
9. Mitchell DM, et al. Survival, prognosis, and causes of death in rheumatoid arthritis. *Arthritis Rheum*. 1986; 29: 706-14.
10. Nielen MM, et al. Specific autoantibodies precede the symptoms of rheumatoid arthritis: a study of serial measurements in blood donors. *Arthritis Rheum*. 2004; 50: 380-6.
11. Nyhall-Wahlin BM, et al. High disease activity disability burden and smoking predict severe extra-articular manifestations in early rheumatoid arthritis. *Rheumatology (Oxford)*. 2009; 48 (4): 416-20.
12. Sampson HA, Munoz-Furlong A, Campbell RL, et al. Second Symposium on the definition and management of anaphylaxis: summary report-Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol*. 2006; 117: 391-397.
13. Scott DL, et al. Joint damage and disability in rheumatoid arthritis: an updated systematic review. *Clin Exp Rheumatol*. 2003; 21 (5 Suppl 21): S20-27.
14. Scott DL, et al. Long-term outcome of treating rheumatoid arthritis: results after 20 years. *Lancet*. 1987; 1: 1108-11.
15. Scott DL. Radiographic progression in established rheumatoid arthritis. *J Rheumatol Suppl*. 2004; 69: 55-65.
16. Sheehy C, Evans V, Hasthorpe H, Mukhtyar C. Brief report: revising DAS28 scores for remission in rheumatoid arthritis. *Clin Rheumatol*. 2014; 33: 269-272.
17. Singh JA, et al. 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. *Arthritis Care Res (Hoboken)*. 2012; 64(5): 625-39.
18. Singh JA, Saag KG, Bridges SL, et al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. *Arthritis Rheumatol*. 2016; 68: 1-26.
19. Smolen JS, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. *Ann*

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

*Rheum Dis.* 2014; 73(3): 492-509.

20. Smolen JS, et al. Rheumatoid arthritis therapy reappraisal: strategies, opportunities and challenges. *Nat Rev Rheumatol.* 2015; 11(5): 276-89.
21. Smolen JS, Breedveld FC, Burmester GR, et al. Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force. *Ann Rheum Dis.* 2015; 0: 1-13.
22. Turesson C, et al. Extra-articular disease manifestations in rheumatoid arthritis: incidence trends and risk factors over 46 years. *Ann Rheum Dis.* 2003; 62 (8): 722-7.
23. Urruela MA and Suarez-Almazor ME. Lipid paradox in rheumatoid arthritis: changes with rheumatoid arthritis therapies. *Curr Rheumatol Rep.* 2012; 14: 428-437.
24. West SG and O'Dell JR. "Rheumatoid Arthritis." Ed. Sterling West. *Rheumatology Secrets.* 3<sup>rd</sup> Ed., Elsevier Mosby, 2015.
25. Wolfe F, et al. The mortality of rheumatoid arthritis. *Arthritis Rheum.* 1994; 37(4): 481.

### 13.2. Financial Disclosure

Three studies (EFC11072, EFC10832, and SFY13370) were considered covered clinical studies that required financial disclosure. Table 138 presents the financial disclosure information for all 3 studies.

Of the 2455 unique clinical investigators, Sanofi provided a list of one clinical investigator with disclosable financial interests, including equity interests in the sponsor as defined by 21 CFR 54.2(b) and significant payments of other sorts as defined by 21 CFR 54.2(f). Sanofi certified that it did not enter into any financial arrangement with the clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). Sanofi provided a description of specific steps to minimize bias, intentional or unintentional, that could be introduced by these arrangements. The steps implemented to protect studies from potential bias included the following measures:

- All of the covered studies employed double-blind masking for the collection of pivotal safety and efficacy data.
- Primary endpoints for the pivotal trials were handled in the following ways
  - Signs and symptoms: TJC and SJC were evaluated by an independent assessor at the sites, and the sites were blinded to CRP and IL-6 levels.
  - HAQ was assessed by the patient.

Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

- mTSS was assessed by blinded central readers.
- Patients were randomly assigned to treatment arms via an IVRS system.
- Recruitment threshold was set up for each study site, and further recruitment was authorized upon careful review of the quality of data.
- Quality of data reported by investigators and adherence to the protocol were followed during the course of the studies by a central clinical team blinded to the treatment arm.

In conclusion, it is unlikely the one clinical investigator with disclosable financial interests would impact the study results given that the study was large, international, and multicenter.

APPEARS THIS WAY ON ORIGINAL

Clinical Review  
 Reviewer: Suzette Peng, MD  
 NME/BLA 761037  
 Sarilumab/Kevzara

**Table 138. Financial Disclosure for Covered Clinical Studies: EFC11072 (MOBILITY), EFC10832 (TARGET), SFY13370 (ASCERTAIN)**

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from Applicant)
Total number of investigators identified: <u>2455</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>None</u> EFC11072: 1347 investigators EFC10832: 1167 investigators SFY13370: 354 investigators		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>1</u> (b) (6) was a principal investigator for EFC11072. He received an honoraria (USD \$46,119) for attendance in conferences from October 2011 until June 2015.		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u> Significant payments of other sorts: <u>1 (see above)</u> Proprietary interest in the product tested held by investigator: <u>0</u> Significant equity interest held by investigator: <u>1 (see above)</u> Sponsor of covered study: <u>0</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>1</u> Reason: Investigator left the clinical trial site prior to obtaining the required information, and attempts to locate and contact the investigator were unsuccessful. Per Sanofi, several attempts were made to contact the investigator, at in first in contacting the site by e-mail and then by sending 2 letters to the Investigator (b) (6) without a response.		

Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

Is an attachment provided with the reason:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request explanation from Applicant)
--	---	--

APPEARS THIS WAY ON ORIGINAL

Clinical Review  
 Reviewer: Suzette Peng, MD  
 NME/BLA 761037  
 Sarilumab/Kevzara

### 13.3. Schedule of Assessments

**Table 139. EFC11072 Part A Study Flow Chart**

Part A	Screening phase		Study phase						
	Evaluation	Screening	Treatment					EOT	Post-treatment FU /Exit <sup>e</sup>
Visit	V1	V2	V3	V4	V5 <sup>a</sup>	V6	V7 <sup>a</sup>	V8	V9
DAY	D-28 to D-1	D1	D15 (±3)	D29 (±3)	D43 (±3)	D57 (±3)	D71 (±3)	D85 (±3)	D127 (±3) <sup>f</sup>
Week		Wk 0	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Wk 18
<b>Design</b>									
Inclusion/exclusion criteria	X	X							
Previous medical/surgical history	X								
Informed consent /patient demography, height	X								
Prior medication history	X	X							
Clinical examination	X	X						X	
Confirm eligibility		X							
Randomization		X							
<b>Treatment</b>									
Treatment kit assignment / Diary <sup>b</sup>		X	X	X		X			
Investigational medicinal product administration		←-----	-----	-----	-----	-----	-----	-----→	
Concomitant medication <sup>h</sup>	←-----	-----	-----	-----	-----	-----	-----	-----→	
Compliance			X	X		X		X	
<b>Vital signs</b>									
Temperature, heart rate, blood pressure	X	X	X	X		X		X	
Weight	X	X	X	X		X		X	
<b>Efficacy</b>									
ACR score <sup>c</sup>	X	X	X	X		X		X	
<b>Safety</b>									
AE/SAE recording (if any)	←-----	-----	-----	-----	-----	-----	-----	-----→	-----→
Tuberculosis assessment	X	X	X	X		X		X	
QuantiferON / PPD skin test <sup>d</sup>	X								
Chest X-ray (if not available within past 3 months) <sup>d</sup>	X								
<b>Health economic</b>									

Source: EFC11072 Part A Clinical Study Report, dated January 16, 2012, Table 1, page 38-40.

Clinical Review  
 Reviewer: Suzette Peng, MD  
 NME/BLA 761037  
 Sarilumab/Kevzara

**Table XX (cont). EFC11072 Part A Study Flow Chart**

Part A Evaluation	Screening phase	Study phase							EOT	Post-treatment FU /Exit <sup>e</sup>
	Screening	Treatment								
Visit	V1	V2	V3	V4	V5 <sup>a</sup>	V6	V7 <sup>a</sup>	V8	V9	
DAY	D-28 to D-1	D1	D15 (±3)	D29 (±3)	D43 (±3)	D57 (±3)	D71 (±3)	D85 (±3)	D127 (±3) <sup>f</sup>	
Week		Wk 0	Wk 2	Wk 4	Wk6	Wk 8	Wk 10	Wk 12	Wk18	
Sleep questionnaire		X	X	X		X		X		
FACIT-Fatigue		X	X	X		X		X		
WPAI		X						X		
<u>Laboratory testing</u>										
Rheumatoid factor	X							X		
ANA / anti-ds DNA		X						X		
Anticyclic citrullinated peptides (anti-CCP) antibody	X							X		
Hematology <sup>j</sup> , LFTs <sup>j</sup>	X	X	X	X	X	X	X	X		
Other chemistry <sup>k</sup> , fasting glucose	X	X		X				X		
Lipids <sup>l</sup>	X	X		X		X		X		
Hb1Ac (screening) – CPK	X							X		
Urinalysis <sup>g</sup>	X	X	X	X		X		X		
Hepatitis B and C, HCVAb, HbsAg, total hepatitis B core Ab	X									
Serum pregnancy test <sup>m</sup>	X									
Urine pregnancy test <sup>n</sup>		X		X		X		X		
hs-CRP <sup>o</sup> , SAA, IL6 <sup>o</sup> , fibrinogen	X	X	X	X		X		X		
12-lead ECG	X							X		
<u>Pharmacokinetic and genotyping &amp; biomarkers</u>										
DNA (at V2 only) and genetic RNA (for specifically consented patients only)		X	X							
AB to SAR153191		X		X		X		X		
sIL-6R (soluble IL6 R)		X	X	X		X		X		
RNA expression		X	X							
Biomarkers (protein/serum), protein/urine		X	X					X		
PK		X	X	X		X		X		

Source: EFC11072 Part A Clinical Study Report, dated January 16, 2012, Table 1, page 38-40.

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

### Table XX (cont). EFC11072 Part A Study Flow Chart

*a* This visit could be a Home Visit

*b* Diary given to the patient for recording of IMP injection tolerability and reviewed by the Investigator at every clinic visit.

*c* ACR score included joint examination (Swollen Joint Count, 66 joints, Tender Joint Count, 68 joints assessed by a third party), Patient Global Assessment, Physician Global Assessment, Pain Intensity, Health Assessment Questionnaire-Disability Index (HAQ-DI)

*d* Can be performed at any time during the study if needed

*e* Schedule visit (all patients) and screen for LTS11210 (long term safety study) eligibility. If eligible for LTS11210, this visit is not completed by the patient

*f* Or 6 weeks after last intake

*g* Urinalysis dipstick: specific gravity, pH, glucose, blood, ketones, protein, bilirubin, urobilinogen, nitrate, leukocytes.

*h* Methotrexate + folic acid + any other concomitant medication

*i* Hemoglobin, hematocrit, RBC morphology (if RBC count is abnormal), WBC, WBC differential, platelet count

*j* Albumin, ALT (SGPT), AST (SGOT), alkaline phosphatase (ALP), prothrombin time (PT), total bilirubin, conjugated bilirubin, unconjugated bilirubin.

*k* Sodium, potassium, calcium, chloride, bicarbonate, total protein, creatinine and clearance, BUN, uric acid, LDH (lactate dehydrogenase)

*l* TG, total cholesterol, HDL cholesterol, LDL cholesterol. In addition Apolipoprotein B and Apolipoprotein A will be tested at baseline and end of treatment visit.

*m* Serum  $\beta$ -HCG for women of childbearing potential

*n* Urine  $\beta$ -HCG for women of childbearing potential

*o* hs-CRP, IL6 assessment will be blinded to both Investigator and sponsor (except screening and baseline)

EOT = end-of-treatment

Source: EFC11072 Part A Clinical Study Report, dated January 16, 2012, Table 1, page 38-40.

Clinical Review  
 Reviewer: Suzette Peng, MD  
 NME/BLA 761037  
 Sarilumab/Kevzara

**Table 140. EFC11072 Part B Study Flow Chart**

PART B	Screening	Study phase														
Treatment	Screening	Treatment												End of treatment	Posttreatment FU/Exit <sup>e</sup>	
Visit	V1	V2	V3	V4	V4.1 <sup>a</sup>	V5	V5.1 <sup>a</sup>	V6	V7	V8	V9	V10	V11	V12	V13	V14
DAY	D-28 to D-1	D1	D15 (±3)	D29 (±3)	D43 (±3)	D57 (±3)	D71 (±3)	D85 (±3)	D113 (±3)	D141 (±3)	D169 (±3)	D197 (±3)	D253 (±3)	D309 (±3)	D365 (±3) or immediately after double-blind treatment stop	D406 (±3) <sup>f</sup>
Week		Wk 0	Wk 2	Wk 4	W6	Wk 8	W10	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 36	Wk 44	Wk 52	Wk58
<b>Design</b>																
Inclusion/exclusion criteria	X	X														
Previous medical/surgical history	X	X														
Family history	X															
Informed consent/patient demography/height	X															
Prior medication history	X	X														
Clinical examination	X	X						X			X		X		X	
Confirm eligibility (including bone erosion)		X														
Review V2 laboratory results before IMP administration <sup>s</sup>			X													
Randomization		X														
<b>Treatment</b>																
Treatment kit assignment / Diary <sup>a</sup>		X		X		X		X	X	X	X	X	X	X		
Investigational medicinal product administration		←												→		
Concomitant medication <sup>h</sup>	←															→
Compliance			X	X		X		X	X	X	X	X	X	X	X	

Source: EFC11072 Part B Clinical Study Report, dated August 20, 2015, Table 3, page 39-42.

Clinical Review  
 Reviewer: Suzette Peng, MD  
 NME/BLA 761037  
 Sarilumab/Kevzara

**Table XX (cont). EFC11072 Part B Study Flow Chart**

PART B	Screening	Study phase														
Treatment	Screening	Treatment													End of treatment	Posttreatment FU / Exit <sup>e</sup>
Visit	V1	V2	V3	V4	V4.1 <sup>a</sup>	V5	V5.1 <sup>a</sup>	V6	V7	V8	V9	V10	V11	V12	V13	V14
DAY	D <sub>-28</sub> to D <sub>-1</sub>	D1	D15 (±3)	D29 (±3)	D43 (±3)	D57 (±3)	D71 (±3)	D85 (±3)	D113 (±3)	D141 (±3)	D169 (±3)	D197 (±3)	D253 (±3)	D309 (±3)	D365 (±3) or immediately after double-blind treatment stop	D406 (±3) <sup>f</sup>
Week		Wk 0	Wk 2	Wk 4	W6	Wk 8	W10	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 36	Wk 44	Wk 52	Wk58
<b>Vital signs</b>																
Temperature, heart rate, blood pressure, weight	X	X	X	X		X		X	X	X	X	X	X	X	X	
<b>Efficacy</b>																
ACR score <sup>b</sup>	X	X	X	X		X		X	X	X	X	X	X	X	X	
X-ray (hand, feet)	X <sup>r</sup>	X									X				X <sup>q</sup>	
<b>Health economic</b>																
SF-36		X									X				X	
WPAI		X						X							X	
FACIT-Fatigue, sleep questionnaire		X	X	X				X			X		X		X	
<b>Safety</b>																
AE /SAE recording (if any)	←															→
Tuberculosis assessment	X	X	X	X		X		X	X	X	X	X	X	X	X	
QuantIFERON / PPD skin test <sup>d</sup>	X															
Chest X-ray (if not available within past 3 months) <sup>d</sup>	X															
<b>Laboratory testing</b>																
Rheumatoid factor	X										X				X	
ANA / Anti-ds DNA		X									X				X	
Anticyclic citrullinated peptides antibody	X										X				X	
Hematology <sup>j</sup> , LFTs <sup>j</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Other chemistry <sup>k</sup> , fasting glucose	X	X		X				X			X		X		X	
Lipids <sup>l</sup>	X	X		X		X		X			X		X		X	

Source: EFC11072 Part B Clinical Study Report, dated August 20, 2015, Table 3, page 39-42.

Clinical Review  
 Reviewer: Suzette Peng, MD  
 NME/BLA 761037  
 Sarilumab/Kevzara

**Table XX (cont). EFC11072 Part B Study Flow Chart**

PART B Treatment	Screening	Study phase														
	Screening	Treatment													End of treatment	Posttreatment FU / Exit <sup>e</sup>
Visit	V1	V2	V3	V4	V4.1 <sup>a</sup>	V5	V5.1 <sup>a</sup>	V6	V7	V8	V9	V10	V11	V12	V13	V14
DAY	D-28 to D-1	D1	D15 (±3)	D29 (±3)	D43 (±3)	D57 (±3)	D71 (±3)	D85 (±3)	D113 (±3)	D141 (±3)	D169 (±3)	D197 (±3)	D253 (±3)	D309 (±3)	D365 (±3) or immediately after double-blind treatment stop	D406 (±3) <sup>f</sup>
Week		Wk 0	Wk 2	Wk 4	W6	Wk 8	W10	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 36	Wk 44	Wk 52	Wk58
HbA1C (screening) – CPK	X														X	
Urinalysis <sup>g</sup>	X	X	X	X		X		X	X	X	X	X	X	X	X	
Hepatitis B and C, HCVAb, HbsAg, total hepatitis B core Ab	X															
Serum pregnancy test <sup>m</sup>	X															
Urine pregnancy test <sup>n</sup>		X		X		X		X	X	X	X	X	X	X	X	
hs-CRP <sup>n</sup> , SAA, IL-6 <sup>n</sup> , Fibrinogen	X	X	X	X		X		X	X	X	X	X	X	X	X	
12-lead ECG	X														X	
<b>Pharmacokinetic and genotyping biomarkers:</b>																
DNA (for specifically consented patients only)		X														
PK		X	X <sup>f</sup>	X				X			X				X	
AB to sarilumab		X		X				X			X				X	X
sIL-6R (soluble IL-6 R)		X	X	X				X			X				X	
RNA expression for all patients and genetic RNA (for specifically consented patients only)		X	X													
Biomarkers (protein/serum), protein/urine		X	X								X				X <sup>p</sup>	

Source: EFC11072 Part B Clinical Study Report, dated August 20, 2015, Table 3, page 39-42.

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

### Table XX (cont). EFC11072 Part B Study Flow Chart

- a* This visit can be Home Visit. Note the following exception: Under circumstances where the neutrophil count and/or platelet count(s) are below lower limits of normal, based on Covance Laboratory CBC results at the previous visit, Visit 4.1 and V5.1 must be conducted at the site and not as a home visit.
- b* Diary given to the patient for recording of IMP injection tolerability and reviewed by the Investigator at every clinic visit.
- c* ACR score includes joint examination (Swollen Joint Count, 66 joints, Tender Joint Count, 68 joints assessed by a third party), Patient Global Assessment, Physician Global Assessment, Pain Intensity, HAQ-DI
- d* Can be performed at any time during the study if needed
- e* Schedule visit (all patients). If continuing in LTS11210, this visit is not completed by the patient
- f* Or 6 weeks after last intake
- g* Urinalysis dipstick: specific gravity, pH, glucose, blood, ketones, protein, bilirubin, urobilinogen, nitrate, leukocytes.
- h* Methotrexate + folic acid + any other concomitant medication
- i* Hemoglobin, hematocrit, RBC morphology (if RBC count is abnormal), WBC, WBC differential, platelet count. For all patients, a CBC test must be performed before or at Visit 3 (using either Covance or local laboratory facility) within a few days before the administration of the 2<sup>nd</sup> dose of study drug in order to confirm that the ANC and platelet count are not within the protocol-defined limits for temporary, or permanent discontinuation of study drug.
- j* Albumin, ALT (SGPT), AST (SGOT), alkaline phosphatase (ALP), prothrombin time (PT), total bilirubin, conjugated bilirubin, unconjugated bilirubin.
- k* Sodium, potassium, calcium, chloride, bicarbonate, total protein, creatinine and clearance, BUN, uric acid, LDH (lactate dehydrogenase)
- l* TG, total cholesterol, HDL cholesterol, LDL cholesterol. In addition Apolipoprotein B and Apolipoprotein A will be tested at baseline and end of treatment visit.
- m* Serum  $\beta$ -HCG for women of childbearing potential
- n* Urine  $\beta$ -HCG for women of childbearing potential
- o* hs-CRP, IL-6 assessment will be blinded to both Investigator and sponsor (except screening and baseline)
- p* Only in the case of study completion or premature withdrawal >8 weeks since Week 2 collection
- q* Except for patients discontinued because randomization to nonselected arms
- r* Ensure that the Visit 2 (baseline) X-ray has been taken within V2  $\pm$  14 days. If it is necessary to perform an X-ray at screening for confirmation of bone erosion eligibility by central reader (see 16-1-1-protocol [12.1.2.1]), then this screening assessment will be considered as the baseline measurement and will replace the V2 assessment.
- s* If any V2 laboratory result meets the values defined in exclusion criteria E34 or E38, the 2<sup>nd</sup> dose of IMP should not be administered and the patient should be withdrawn from study treatment
- t* PK samples collected at V3 may be also used to analyze AB to sarilumab

Source: EFC11072 Part B Clinical Study Report, dated August 20, 2015, Table 3, page 39-42.

Clinical Review  
 Reviewer: Suzette Peng, MD  
 NME/BLA 761037  
 Sarilumab/Kevzara

**Table 141. EFC10832 Study Flow Chart**

	Screening phase	Study phase										
	Screening	Treatment										End of Treatment/early term
VISIT	V1	V2	V3 <sup>n</sup>	V4	V5	V6	V7	V8	V9	V10	V11	V12
DAY	D -28 to D -1	D1	D15(±3)	D29(±3)	D43(±3)	D57(±3)	D71(±3)	D85(±3)	D113(±3)	D141(±3)	D169(±3)	D211(±3) <sup>b</sup>
WEEK	Wk -4 to -1	Wk0	Wk 2	Wk 4	Wk6 <sup>c</sup>	Wk 8	Wk10 <sup>c</sup>	Wk 12	Wk 16	Wk 20	Wk 24	Wk 30
<b>Eligibility</b>												
Written informed consent	X											
Inclusion/exclusion criteria	X	X										
Patient demography	X											
Medical/surgical history	X											
Prior medication history	X											
Full physical examination	X										X	
Targeted physical examination		X						X				
Confirm eligibility		X										
Review V2 lab results before IMP administrations <sup>o</sup>			X									
Randomization		X										
Call IVRS	X	X		X		X		X	X	X	X	X
<b>Treatment</b>												
Initial treatment kit assignment (IVRS)		X										
Investigational medicinal product administration		<---	----	----	----	----	----	----	----	----	----> <sup>d</sup>	
Investigational medicinal product dispensed <sup>e</sup>		X		X		X		X	X	X		
Concomitant medication		X	X	X		X		X	X	X	X	X
Dispense patient diary		X	X	X		X		X	X	X		
Compliance/review patient diary			X	X		X		X	X	X	X	

Source: EFC10832 Clinical Study Report, dated July 24, 2015, Table 1, page 33-36.

Clinical Review  
 Reviewer: Suzette Peng, MD  
 NME/BLA 761037  
 Sarilumab/Kevzara

**Table XX (cont). EFC10832 Study Flow Chart**

	Screening phase	Study phase										
	Screening	Treatment									End of Treatment/early term	Posttreatment Follow-up <sup>a,b</sup>
VISIT	V1	V2	V3 <sup>n</sup>	V4	V5	V6	V7	V8	V9	V10	V11	V12
DAY	D -28 to D -1	D1	D15(±3)	D29(±3)	D43(±3)	D57(±3)	D71(±3)	D85(±3)	D113(±3)	D141(±3)	D169(±3)	D211(±3) <sup>b</sup>
WEEK	Wk -4 to -1	Wk0	Wk 2	Wk 4	Wk6 <sup>c</sup>	Wk 8	Wk10 <sup>c</sup>	Wk 12	Wk 16	Wk 20	Wk 24	Wk 30
<b>Vital signs</b>												
Temperature, heart rate, blood pressure	X	X	X	X		X		X	X	X	X	
Weight	X	X		X		X		X	X	X	X	
Height	X											
<b>Efficacy</b>												
ACR disease core set <sup>f</sup>	X	X	X	X		X		X	X	X	X	
<b>Safety</b>												
AE/SAE recording		-----X-----										X
Tuberculosis risk assessment	X	X	X	X		X		X	X	X	X	X
QuantiFERON®	X											
Chest X-ray (when indicated)	X											
<b>Patient reported outcomes</b>												
SF-36		X		X				X			X	
WPS-RA		X		X				X			X	
FACIT-Fatigue		X	X	X				X			X	
EQ-5D-3L		X	X	X				X			X	
RAID score		X	X	X				X			X	
Morning stiffness VAS		X	X	X				X			X	
<b>Laboratory testing</b>												
Rheumatoid factor / anti CCP		X						X			X	
ANA/Anti-ds DNA antibody		X						X			X	
Hematology <sup>g</sup>	X	X	X	X	X	X	X	X	X	X	X	
Chemistry <sup>h</sup>	X	X	X	X	X	X	X	X	X	X	X	
Fasting lipids <sup>i</sup> , fasting glucose	X	X	X	X		X		X			X	
HbA1c	X							X			X	

Source: EFC10832 Clinical Study Report, dated July 24, 2015, Table 1, page 33-36.

Clinical Review  
 Reviewer: Suzette Peng, MD  
 NME/BLA 761037  
 Sarilumab/Kevzara

**Table XX (cont). EFC10832 Study Flow Chart**

	Screening phase	Study phase										
	Screening	Treatment									End of Treatment/early term	Posttreatment Follow-up <sup>a,b</sup>
VISIT	V1	V2	V3 <sup>n</sup>	V4	V5	V6	V7	V8	V9	V10	V11	V12
DAY	D -28 to D -1	D1	D15(±3)	D29(±3)	D43(±3)	D57(±3)	D71(±3)	D85(±3)	D113(±3)	D141(±3)	D169(±3)	D211(±3) <sup>b</sup>
WEEK	Wk -4 to -1	Wk0	Wk 2	Wk 4	Wk6 <sup>c</sup>	Wk 8	Wk10 <sup>c</sup>	Wk 12	Wk 16	Wk 20	Wk 24	Wk 30
Urinalysis <sup>j</sup>	X	X	X	X		X		X	X	X	X	
Human immunodeficiency virus; Hepatitis B and C: HBsAg, total Hepatitis B core Ab, HCV Ab	X											
Serum pregnancy test <sup>k</sup>	X											
Urine pregnancy test <sup>k</sup>		X		X		X		X	X	X	X	
Hs-CRP <sup>l</sup>	X	X	X	X		X		X	X	X	X	
12-lead ECG	X										X	
<b>Pharmacokinetics, genotyping, and biomarkers</b>												
Serum sarilumab / Antibodies to sarilumab <sup>l</sup>		X	X	X				X			X	X
Biomarkers – Biosampling (serum / urine <sup>p</sup> )		X	X					X			X	
DNA <sup>m</sup>		X										
RNA for sequencing <sup>m</sup>		X										
RNA expression		X	X									

- a. For patients unwilling or unable to continue in the long term extension study
- b. Or 6 weeks after last drug intake for patients not agreeing to remain in the study
- c. Visit could be a home visit or clinic visit, note the following exception: Under circumstances where the neutrophil count and/or platelet count(s) are below lower limits of normal (LLN), based on Covance laboratory hematology results at the previous visit, Visits 5, and 7 had to be conducted at the site and not as a home visit. Only hematology and limited chemistry tests (only albumin, ALT, AST, ALP, PT, total bilirubin, conjugated bilirubin and unconjugated bilirubin) were assessed.
- d. Last injection Week 22
- e. The number of treatment kits allocated to the patient provided sufficient medication until the next dispensation visit, non-investigational medicinal product (eg, non-biologic DMARDs) should be dispensed according to the local practice (starting as early as Week 12/Visit 8, patient with lack of efficacy as defined in protocol may be eligible for open-label treatment with sarilumab)
- f. ACR core set includes: swollen joint count (SJC), 66 joints, tender joint count (TJC), 68 joints, Patient's Global Assessment, Patient's Assessment of Pain, HAQ-DI, hs-CRP and Physician's Global Assessment; DAS28 components include selected 28 SJC, 28 TJC, Patient Global Assessment, CRP
- g. Hematology (blood should be drawn BEFORE drug administration): Hemoglobin, hematocrit, red blood cell (RBC) count and morphology (if RBC count is abnormal), white blood cell (WBC) differential, platelet count, absolute neutrophil count.

Source: EFC10832 Clinical Study Report, dated July 24, 2015, Table 1, page 33-36.

Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

**Table XX (cont). EFC10832 Study Flow Chart**

- h. Complete Chemistry (blood should be drawn BEFORE drug administration): Sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN), creatinine and creatinine clearance, calcium, phosphate, total protein, albumin, ALT (SGPT), AST (SGOT), alkaline phosphatase (ALP), total bilirubin, conjugated bilirubin, unconjugated bilirubin, lactate dehydrogenase (LDH), uric acid and prothrombin time (PT). At Weeks 6 and 10, limited chemistry that includes albumin, ALT, AST, ALP, PT, total bilirubin, conjugated bilirubin and unconjugated bilirubin were assessed.
- i. Lipids: Triglycerides (TG), total cholesterol, HDL cholesterol, LDL cholesterol; In addition, apolipoprotein A and apolipoprotein B were tested at baseline and end of treatment visit
- j. Urinalysis dipstick: specific gravity, pH, glucose, blood, protein, nitrites, leukocyte esterase, bilirubin
- k. In women of child-bearing potential
- l. blood should be drawn BEFORE drug administration; hs-CRP, serum sarilumab levels, and anti sarilumab antibodies results were blinded to both Investigator and Sponsor (except screening and baseline)
- m. Pharmacogenetic Research Informed Consent for DNA and RNA for sequencing has to be signed before any sampling. Only 1 DNA (at baseline or any treatment or follow up visit) and 1 RNA for sequencing sampling time point is needed (at baseline, predose).
- n. For all patients, a CBC must be performed a few days before or at Visit 3, but not earlier than the 12<sup>th</sup> day after the first dose of study drug administration, and prior to the administration of the Visit 3 study drug, to confirm that the neutrophil count is not within the protocol-defined limits for temporary or permanent discontinuation of study drug.
- o. V2 laboratory results should be reviewed before administration of the second dose of IMP. If any V2 laboratory result meets the values defined in exclusion criteria E21, E37 or E38, the second dose of IMP should not be administered and the patient should be permanently withdrawn from study treatment. Laboratory results obtained after V2 must remain within the range required for continuation of study treatment as defined in 16-1-1 protocol [10.6], [Appendix P], [Appendix Q], [Appendix R] and [Appendix S].
- p. Biomarkers will be analyzed later and presented in a separate report

Source: EFC10832 Clinical Study Report, dated July 24, 2015, Table 1, page 33-36.

APPEARS THIS WAY ON ORIGINAL

Clinical Review  
 Reviewer: Suzette Peng, MD  
 NME/BLA 761037  
 Sarilumab/Kevzara

**Table 142. LTS11210 Study Flow Chart (Subjects from ACT11575, EFC11072 Part A and B Cohort 1)**

Evaluation	Screening	Open Label Treatment										Post Treatment follow-up
	Day -7 to D-1	Day 1 Wk0	Day 15 Wk 2	Day 29 Wk 4	Day 43 Wk 6	Day 57 Wk 8	Day 71 Wk 10	D85 Wk 12	Wk 24-96 (every 12 wks) Wk24, 36, 48, 60, 72, 84, 96	Wk 108-252 IMP dispensing visits (every 24 weeks) Wk108, 132, 156, 180, 204, 228, 252 <sup>a</sup>	Wk120 – 260 (EOT) (every 24 weeks) Wk120, 144, 168, 192, 216, 240 and 260 (EOT) <sup>a</sup>	6 weeks after end of treatment <sup>a</sup> Post treatment follow-up
Visit no.	V 1 D-7 to D-1	V 2	HV 3 <sup>c</sup> (± 3 days)	V 4 (±3 days)	HV 5 <sup>c</sup> (±3 days)	V 6 (±3 days)	HV 6.1 <sup>c</sup> (±3 days)	V 7 (±3 days)	V 8 to V 14 (±3 days)	V15, V17, V19, V21, V23, V25, V27 (±3 days)	V16, V18, V20, V22, V24, V26, V28 (±3 days)	V 29 (±3 days)
<b>Design</b>												
Inclusion/exclusion criteria	X	X										
Previous medical/surgical history	X											
Informed consent	X											
Patient demography	X											
Prior medication history	X											
Smoking, alcohol, and illicit drug use history	X											
Detail history for tuberculosis and opportunistic infection	X											
Physical examination <sup>e</sup>	X <sup>d</sup>								X		X	
Confirm eligibility	X	X										
<b>Treatment</b>												
Study drug dispensing		X		X		X		X	X	X	X <sup>f</sup>	
Study drug compliance				X		X		X	X	X	X	
Concomitant medications	X	X		X		X		X	X	X	X	X
<b>Vital signs</b>												
Temperature, heart rate, blood pressure	X <sup>d</sup>	X		X		X		X	X		X	X
Weight in Kg	X <sup>d</sup>	X		X		X		X	X		X	X

Source: LTS11210 Clinical Study Report, dated August 24, 2015, Table 1, page 31-34.



Clinical Review  
 Reviewer: Suzette Peng, MD  
 NME/BLA 761037  
 Sarilumab/Kevzara

**Table XX (cont). LTS11210 Study Flow Chart (Subjects from ACT11575, EFC11072 Part A and B Cohort 1)**

Evaluation	Screening	Open Label Treatment											Post Treatment follow-up					
		Day -7 to D-1	Day 1	Day 15	Day 29	Day 43	Day 57	Day 71	D85	Wk 24-96 (every 12 wks)	Wk 108-252 IMP dispensing visits (every 24 weeks)	Wk120 – 260 (EOT) (every 24 weeks)						
DAY																		
Week		Wk0	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12		Wk24, 36, 48, 60, 72, 84, 96	Wk108, 132, 156, 180, 204, 228, 252 <sup>d</sup>	Wk120, 144, 168, 192, 216, 240 and 260 (EOT) <sup>d</sup>					6 weeks after end of treatment <sup>d</sup> Post treatment follow-up	
Visit no.	V 1 D-7 to D-1	V 2	HV 3 <sup>c</sup> (± 3 days)	V 4 (±3 days)	HV 5 <sup>c</sup> (±3 days)	V 6 (±3 days)	HV 6.1 <sup>c</sup> (±3 days)	V 7 (±3 days)	V 8 to V 14 (±3 days)	V15, V17, V19, V21, V23, V25, V27 (±3 days)	V16, V18, V20, V22, V24, V26, V28 (±3 days)						V 29 (±3 days)	
Dipstick urinalysis <sup>n</sup>	X <sup>d</sup>					X		X	X			X						
Urine pregnancy test (for women of childbearing potential) <sup>o</sup>	X <sup>d</sup>			X		X		X	X			X					X	
Dispense urine pregnancy kits <sup>o</sup>								X	X			X						
12-lead electrocardiogram <sup>p</sup>	X <sup>d</sup>								X			X						
Other analysis																		
Rheumatoid factor <sup>q</sup>		X							X			X						
Serum IL-6 <sup>v</sup>	X <sup>d</sup>			X				X	X									
Pharmacokinetics (including functional and/or bound sarilumab) <sup>r</sup>	X <sup>d</sup>			X				X	X			X					X	
Anti-sarilumab antibody	X <sup>d</sup>							X	X			X					X	
Serum sample to be stored for future biomarkers <sup>s</sup>	X <sup>d</sup>		X					X	X									
Expression RNA <sup>t</sup>		X <sup>d</sup>	X															

<sup>a</sup> EOT visit (V28 Week260) and follow up visit (V29) 6 weeks later are completed for all patients at the end of treatment, regardless of the length of the treatment period (It depended on duration of the treatment in the initial study). After Week 96, there are visits at 24 week intervals in between regular study visits for IMP allocation through IVRS/IWRS call, IMP dispensation and recording of AEs only). In case of permanent discontinuation of treatment, the patients are assessed using the procedures normally planned for the EOT visit (V28 Week 260) and the 6 week follow up visit (V29) 6 weeks later.

<sup>b</sup> Deleted

<sup>c</sup> HV: Visit could be a home visit or clinic visit to draw and collect the blood sample only for hematology and LFTs using the designated central laboratory.

Source: LTS11210 Clinical Study Report, dated August 24, 2015, Table 1, page 31-34.

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

### Table XX (cont). LTS11210 Study Flow Chart (Subjects from ACT11575, EFC11072 Part A and B Cohort 1)

- d* Last treatment visit from the study EFC11072 or ACT11575. Please note that the SF-36 is completed at the screening visit of the LTS11210 study for patients rolled over from EFC11072 Part A and ACT11575 studies. Please note that the RNA sample is collected at V2 of the LTS11210 study for patients rolled over from EFC11072.
- e* Physical examination is done at Weeks 48, 96, 144, 192, 260
- f* At Week 260 no study drug is dispensed or administered
- g* X-rays of hands and feet (only for patients who completed Part B of the study EFC11072 (not performed for Part A patients, or patients from Part B non-selected dose arms) are done at Weeks 48, 96, 144 ( $\pm 14$  days for each assessment), and 260 (EOT); this last time point is done within 12 weeks prior to the end of treatment visit. Required X-ray is done after confirmation of negative urine pregnancy test in women of child bearing potential.
- h* Deleted
- i* Hematology: Hemoglobin, hematocrit, red blood cell (RBC) morphology (if blood cell count is abnormal), white blood cell (WBC) with differential, platelets count. For all patients, a complete blood count (CBC) test is performed before or at Visit 3 (using either designated central lab or a local laboratory facility), but not earlier than the 12th day after the first dose of IMP administration in order to confirm that the neutrophil count and platelet count are not within the protocol-defined limits for temporary or permanent discontinuation of study drug.
- j* Liver Function Tests (LFTs): Prothrombin Time, Albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin, conjugated bilirubin, unconjugated bilirubin.
- k* Lipids (fasting): Total cholesterol, High-Density Lipoprotein cholesterol, Low-Density Lipoprotein (LDL) cholesterol, triglycerides, Apolipoprotein A, and Apolipoprotein B.
- l* Clinical chemistry (fasting): fasting glucose, total proteins, calcium, sodium, potassium, Lactate Dehydrogenase, (LDH) and creatinine. Creatinine clearance is calculated during the study if clinical indicated.
- m* ANA titer is done at screening, at Week 48, 96, 144, 192, 260, or sooner if clinical indicated (Anti-ds-DNA only if ANA titer is  $>1:160$ )
- n* Dipstick urinalysis for: specific gravity, pH, glucose, blood, ketones, proteins, bilirubin, urobilinogen, nitrite, leukocytes. If any parameter is abnormal, a urinalysis sample is sent to central laboratory for testing. If positive for proteins, microscopic analysis is performed by central laboratory.
- o* After Visit 7 (Week 12) between study visits the patient has a urine pregnancy test at home on a monthly basis. Patients are given sufficient urine pregnancy kits to take home at each successive visit for monthly testing up until the final treatment visit. When the testing coincides with a clinical visit as indicated in the flow chart, the results are reported in the eCRF. No pregnancy test kits are dispensed at V28 Week 260.
- p* ECG is done at Weeks 48, 96, 144, 192, and 260
- q* Rheumatoid factor only at LTS11210 Visit 2 (Week 0) and at Weeks 48, 96, 144, 192, and 260
- r* If throughout the study a serious adverse event (SAE) occurs in a patient, blood samples are collected for functional and/or bound sarilumab at or near the onset and completion of the occurrence of the event, if possible. The exact date of sample collection and last dose is recorded on the eCRF.
- s* Serum sample for biomarkers is collected at screening (ie, the last treatment visit from the EFC11072 or ACT11575), Week 2, Week 12, and Week 48.
- t* Blood sample for RNA is collected at Week 0 (prior to administration of study drug in LTS11210) and Week 2 (at site visit only; cancel RNA collection if home visit).
- u* Deleted
- v* Samples for IL-6 are collected at Screening (ie the last treatment visit from EFC11072 or ACT11575) and at V4 (Week 4), V7 (Week 12), V8 (Week 24), V9 (Week 36), and V10 (Week 48).

Source: LTS11210 Clinical Study Report, dated August 24, 2015, Table 1, page 31-34.

Clinical Review  
 Reviewer: Suzette Peng, MD  
 NME/BLA 761037  
 Sarilumab/Kevzara

**Table 143. LTS11210 Study Flow Chart (Subjects from EFC10832, EFC11072 Part B Cohort 2, SFY13370, EFC13752)**

Evaluation	Open Label Treatment										Post Treatment follow-up
	Day 1	Day 15	Day 29	Day 43	Day 57	Day 71	D85	Wk 24-96	Wk 108-252 IMP dispensing visits	Wk120 – 260 (EOT)	
DAY and/or WEEK	WK0	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	(every 12 wks) Wk 24, 36, 48, 60, 72, 84, 96	(every 24 weeks) Wk 108, 132, 156, 180, 204, 228, 252 <sup>a</sup>	(every 24 weeks) Wk120, 144, 168, 192, 216, 240 and 260 (EOT) <sup>a</sup>	6 weeks after end of treatment <sup>a</sup>  Post treatment follow-up
Visit no.	V1/V 2	HV 3 <sup>c</sup> (± 3 days)	V 4 (±3 days)	HV 5 <sup>c</sup> (±3 days)	V 6 (±3 days)	HV 6.1 <sup>c</sup> (±3 days)	V 7 (±3 days)	V 8 to V14 (±3 days)	V15, V17, V19, V21, V23, V25, V27(±3 days)	V16, V18, V20, V22, V24, V26, V28 (±3 days)	V29 (±3 days)
<b>Design</b>											
Inclusion/exclusion criteria	X										
Previous medical/surgical history	X										
Informed consent	X										
Patient demography	X										
Prior medication history	X										
Smoking, alcohol, and illicit drug use history	X										
Detail history for tuberculosis and opportunistic infection	X										
Physical examination <sup>e</sup>	X <sup>d</sup>							X		X	
Confirm eligibility	X										
<b>Treatment</b>											
Study drug dispensing	X		X		X		X	X	X	X <sup>f</sup>	
Study drug compliance			X		X		X	X	X	X	
Concomitant medications	X		X		X		X	X	X	X	X
<b>Vital signs</b>											
Temperature, heart rate, blood pressure	X <sup>d</sup>		X		X		X	X		X	X
Weight in Kg	X <sup>d</sup>		X		X		X	X		X	X

Source: LTS11210 Clinical Study Report, dated August 24, 2015, Table 2, page 35-38.

Clinical Review  
 Reviewer: Suzette Peng, MD  
 NME/BLA 761037  
 Sarilumab/Kevzara

**Table XX (cont). LTS11210 Study Flow Chart (Subjects from EFC10832, EFC11072 Part B Cohort 2, SFY13370, EFC13752)**

Evaluation	Open Label Treatment										Post Treatment follow-up
	Day 1  WK0	Day 15  Wk 2	Day 29  Wk 4	Day 43  Wk 6	Day 57  Wk 8	Day 71  Wk 10	D85  Wk 12	Wk 24-96  (every 12 wks) Wk 24, 36, 48, 60, 72, 84, 96	Wk 108-252 IMP dispensing visits  (every 24 weeks) Wk 108, 132, 156, 180, 204, 228, 252 <sup>a</sup>	Wk120 – 260 (EOT)  (every 24 weeks) Wk120, 144, 168, 192, 216, 240 and 260 (EOT) <sup>a</sup>	6 weeks after end of treatment <sup>a</sup>  Post treatment follow-up
Visit no.	V1/V 2	HV 3 <sup>c</sup> (± 3 days)	V 4 (±3 days)	HV 5 <sup>c</sup> (±3 days)	V 6 (±3 days)	HV 6.1 <sup>c</sup> (±3 days)	V 7 (±3 days)	V 8 to V14 (±3 days)	V15, V17, V19, V21, V23, V25, V27(±3 days)	V16, V18, V20, V22, V24, V26, V28 (±3 days)	V29 (±3 days)
<b>Efficacy</b>											
ACR disease core set	X <sup>d</sup>		X		X		X	X		X	
X-ray (hand, feet) <sup>g</sup>	X <sup>d</sup>							X		X	
<b>Health Economic</b>											
SF-36 (EFC11072, EFC10832)	X <sup>d</sup>						X	X		X	
WPAI (EFC11072)	X <sup>d</sup>						X	X		X	
FACIT-Fatigue (EFC11072, EFC10832)	X <sup>d</sup>						X	X		X	
Sleep questionnaire (EFC11072)	X <sup>d</sup>						X	X		X	
WPS-RA (EFC10832)	X <sup>d</sup>						X	X		X	
<b>Safety</b>											
Tuberculosis assessments	X <sup>d</sup>		X		X		X	X		X	X
AE/SAE recording (if any)	←										→
<b>Laboratory Testing</b>											
High sensitive- C- Reactive protein (hs-CRP)	X <sup>d</sup>		X		X		X	X		X	
Hematology: CBC and differential <sup>i</sup>	X <sup>d</sup>	X	X	X	X	X	X	X		X	
Liver Function Tests (LFTs) <sup>j</sup>	X <sup>d</sup>	X	X	X	X	X	X	X		X	
Lipids (fasting) <sup>k</sup>	X <sup>d</sup>		X		X		X	X		X	
Clinical chemistry (fasting) <sup>l</sup>	X <sup>d</sup>				X		X	X		X	
ANA/Anti-ds-DNA <sup>n</sup>	X <sup>d</sup>							X		X	

Source: LTS11210 Clinical Study Report, dated August 24, 2015, Table 2, page 35-38.

**Table XX (cont). LTS11210 Study Flow Chart (Subjects from EFC10832, EFC11072 Part B Cohort 2, SFY13370, EFC13752)**

Evaluation	Open Label Treatment										Post Treatment follow-up
	Day 1	Day 15	Day 29	Day 43	Day 57	Day 71	D85	Wk 24-96	Wk 108-252 IMP dispensing visits	Wk120 – 260 (EOT)	
DAY and/or WEEK	WK0	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	(every 12 wks) Wk 24, 36, 48, 60, 72, 84, 96	(every 24 weeks) Wk 108, 132, 156, 180, 204, 228, 252 <sup>a</sup>	(every 24 weeks) Wk120, 144, 168, 192, 216, 240 and 260 (EOT) <sup>a</sup>	6 weeks after end of treatment <sup>a</sup>  Post treatment follow-up
Visit no.	V1/V 2	HV 3 <sup>c</sup> (± 3 days)	V 4 (±3 days)	HV 5 <sup>c</sup> (±3 days)	V 6 (±3 days)	HV 6.1 <sup>c</sup> (±3 days)	V 7 (±3 days)	V 8 to V14 (±3 days)	V15, V17, V19, V21, V23, V25, V27(±3 days)	V16, V18, V20, V22, V24, V26, V28 (±3 days)	V29 (±3 days)
Dipstick urinalysis <sup>o</sup>	X <sup>d</sup>				X		X	X		X	
Urine pregnancy test (for women of childbearing potential) <sup>p</sup>	X <sup>d</sup>		X		X		X	X		X	X
Dispense urine pregnancy kits <sup>p</sup>							X	X		X	
12-lead electrocardiogram <sup>q</sup>	X <sup>d</sup>							X		X	
<b>Other analysis</b>											
Rheumatoid factor <sup>r</sup>	X <sup>d</sup>							X		X	
Serum IL-6 <sup>w</sup>	X		X				X	X			
Pharmacokinetics (including functional and/or bound sarilumab) <sup>s</sup>	X <sup>d</sup>		X				X	X		X	X
Anti-sarilumab antibody	X <sup>d</sup>						X	X		X	X
Serum sample to be stored for future biomarkers <sup>t</sup>	X <sup>d</sup>	X					X	X			
Expression RNA <sup>u</sup>	X	X									

<sup>a</sup> EOT visit (V28 Week260) and follow up visit (V29) 6 weeks later are completed for all patients at the end of treatment, regardless of the length of the treatment period (depending on duration of the treatment in the initial study). (In UK, the duration of treatment is 220 weeks from the first study drug administration in the initial study). After Week 96, there are visits at 24-week intervals in between regular study visits for IMP allocation through IVRS/IWRS call, IMP dispensation and recording of AEs only (in Portugal and Sweden, hematology and liver function test evaluations are performed at all IMP dispensing visits until end of treatment). In case of permanent discontinuation of treatment, the patients are assessed using the procedures normally planned for the EOT visit (V28 Week 260) and the 6 week follow up visit (V29) 6 weeks later.

<sup>b</sup> Deleted

<sup>c</sup> HV: Visit could be a home visit or clinic visit to draw and collect the blood sample only for hematology and LFTs using the designated central laboratory.

Source: LTS11210 Clinical Study Report, dated August 24, 2015, Table 2, page 35-38.

## Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

### Table XX (cont). LTS11210 Study Flow Chart (Subjects from EFC10832, EFC11072 Part B Cohort 2, SFY13370, EFC13752)

- d* Last treatment visit from the study EFC11072, EFC10832, SFY13370, or EFC13752.
- e* Physical examination is done at Weeks 48, 96, 144, 192, 260
- f* At Week 260 Visit no study drug is dispensed or administered.
- g* X-rays of hands and feet (only for patients who completed Part B of the study EFC11072 are done at Weeks 48, 96, 144 ( $\pm 14$  days for each assessment), and 260 (EOT) this last time point is done within 12 weeks prior to the end of treatment visit. Required X-ray is done after confirmation of negative urine pregnancy test in women of child bearing potential.
- h* Deleted
- i* Hematology: Hemoglobin, hematocrit, red blood cell (RBC) morphology (if blood cell count is abnormal), white blood cell (WBC) with differential, platelets count. For all patients, a CBC test is performed before or at Visit 3 (using either designated central or a local laboratory facility) but not earlier than the 12th day after the first dose of IMP administration in order to confirm that the neutrophil count and platelet count are not within the protocol-defined limits for temporary or permanent discontinuation of study drug.
- j* Liver Function Tests (LFTs): Albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin, conjugated bilirubin, unconjugated bilirubin, prothrombin time
- k* Lipids (fasting): Total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, tryglicerides, Apolipoprotein A, and Apolipoprotein B. (Apolipoprotein A and B are not done at initial visit for SFY13370 or EFC13752 patients).
- l* Clinical chemistry (fasting): fasting glucose, total proteins, calcium, sodium, potassium, lactate dehydrogenase, (LDH) and creatinine. Creatinine clearance is calculated during the study if clinical indicated.
- m* Deleted
- n* ANA titer is done at V1/V2 (ie the last treatment visit from the initial study) and at Week 48, 96, 144, 192, 260, or sooner if clinical indicated (Anti-ds-DNA only if ANA titer is  $>1:160$ )
- o* Dipstick urinalysis for: specific gravity, pH, glucose, blood, ketones, proteins, bilirubin, urobilinogen, nitrite, leukocytes. If any parameter is abnormal, a urinalysis sample is sent to central laboratory for testing. If positive for proteins, microscopic analysis is performed by central laboratory.
- p* After Visit 7 (Week 12) between study visits the patient had a urine pregnancy test at home on a monthly basis. Patients are given sufficient urine pregnancy kits to take home at each successive visit for monthly testing up until the final treatment visit. When the testing coincides with a clinical visit as indicated in the flow chart, the results are reported in the eCRF. No pregnancy test kits are dispensed at V28 Week 260.
- q* ECG is done at Weeks 48, 96, 144, 192, and 260
- r* Rheumatoid factor only at Weeks 48, 96, 144, 192, and 260
- s* If throughout the study a serious adverse event (SAE) occurred in a patient, blood samples are collected for functional and/or bound sarilumab at or near the onset and completion of the occurrence of the event, if possible. The exact date of sample collection and last dose is recorded on the eCRF.
- t* Serum sample for biomarkers is collected for all patients except EFC13752: at V1/V2 (ie, the last treatment visit from the initial study), as well as Week 2, Week 12, and Week 48.
- u* Blood sample for RNA except for SFY13370 and EFC13752 patients: is collected at V1/V2 (Week 0) (prior to administration of study drug) and V3 (Week 2) at site visit only (cancel RNA collection if home visit).
- v* Deleted
- w* Samples for IL-6 are collected at V1/V2 for EFC11072 patients only (ie the last treatment visit) and for all patients at V4 (Week 4), V7 (Week 12), V8 (Week 24), V9 (Week 36), and V10 (Week 48).

Source: LTS11210 Clinical Study Report, dated August 24, 2015, Table 2, page 35-38.

Clinical Review  
 Reviewer: Suzette Peng, MD  
 NME/BLA 761037  
 Sarilumab/Kevzara

**Table 144. SFY13370 Study Flow Chart**

	Screening		Treatment phase											EOT	FU
VISIT	V1	V2	V3	V4	V5	V6	V7	V8	V8.1	V9	V9.1	V10	V10.1	V11	V12
DAY	D -28 to D -1	D1	D15(±3)	D29(±3)	D43(±3)	D57(±3)	D71(±3)	D85(±3)	D99(±3)	D113(±3)	D127(±3)	141(±3)	D155(±3)	D169(±3)	D211(±3) <sup>a</sup>
WEEK		Wk 0	Wk 2 <sup>b</sup>	Wk 4	Wk6 <sup>c</sup>	Wk 8	Wk10 <sup>c</sup>	Wk 12	Wk14 <sup>c</sup>	Wk 16	Wk18 <sup>c</sup>	Wk 20	Wk22 <sup>c</sup>	Wk 24 <sup>g</sup>	Wk 30
<b>Eligibility</b>															
Written informed consent	X														
Inclusion/exclusion criteria	X	X													
Patient demography	X														
Medical/surgical/smoking-alcohol history	X														
Prior medication history	X														
Family cardiovascular history	X														
Full physical examination	X													X	
Targeted physical examination <sup>d</sup>		X						X							
Confirm eligibility		X													
Randomization		X													
Call IVRS	X	X		X		X		X		X		X		X	X
<b>Treatment</b>															
Initial treatment kit assignment (IVRS)		X													
Sarilumab/placebo administration <sup>e</sup>		X	X <sup>b</sup>	X	X	X	X	X	X	X	X	X	X		
Tocilizumab/placebo administration <sup>f</sup>		X		X		X		X		X		X			
Concomitant medication <sup>g</sup>		X	X	X		X		X		X		X		X	X
Dispense patient diary		X	X	X		X		X		X		X			
Compliance/review patient diary				X		X		X		X		X		X	

Source: SFY13370 Clinical Study Report, dated August 12, 2015, Table 1, page 34-37.

Clinical Review  
 Reviewer: Suzette Peng, MD  
 NME/BLA 761037  
 Sarilumab/Kevzara

**Table XX (cont). SFY13370 Study Flow Chart**

	Screening		Treatment phase												EOT	FU
VISIT	V1	V2	V3	V4	V5	V6	V7	V8	V8.1	V9	V9.1	V10	V10.1	V11	V12	
DAY	D -28 to D -1	D1	D15(±3)	D29(±3)	D43(±3)	D57(±3)	D71(±3)	D85(±3)	D99(±3)	D113(±3)	D127(±3)	141(±3)	D155(±3)	D169(±3)	D211(±3) <sup>a</sup>	
WEEK		Wk 0	Wk 2 <sup>b</sup>	Wk 4	Wk 6 <sup>c</sup>	Wk 8	Wk10 <sup>c</sup>	Wk 12	Wk14 <sup>c</sup>	Wk 16	Wk18 <sup>c</sup>	Wk 20	Wk22 <sup>c</sup>	Wk 24 <sup>q</sup>	Wk 30	
<b>Vital signs</b>																
Temperature, heart rate, blood pressure	X	X	X	X		X		X		X		X		X		
Weight	X	X		X		X		X		X		X		X		
Height	X															
<b>Efficacy</b>																
ACR disease core set <sup>h</sup>	X	X		X		X		X						X		
<b>Safety</b>																
AE/SAE recording	X															
Tuberculosis assessment	X	X	X	X		X		X		X		X		X	X	
QuantiFERON®	X															
Chest X-ray (when indicated)	X															
Review of V2 lab results before IMP administration <sup>i</sup>			X													
<b>Laboratory testing</b>																
Rheumatoid factor / anti-CCP		X						X						X		
ANA/Anti-ds DNA antibody		X						X						X		
Hematology <sup>j</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Chemistry <sup>k</sup>	X	X	X	X	X	X	X	X		X		X		X		
Fasting lipids <sup>l</sup> , fasting glucose <sup>m</sup>	X	X	X	X		X		X						X		
HbA1c	X							X						X		
Urinalysis <sup>n</sup>	X	X						X						X		
Human immunodeficiency virus antibodies (ab); Hepatitis B and C: HBsAg, total HBcore Ab, HCVAb	X															
Serum pregnancy test <sup>o</sup>	X															
Urine pregnancy test <sup>o</sup>		X		X		X		X		X		X		X		
Hs-CRP	X	X		X		X		X						X		

Source: SFY13370 Clinical Study Report, dated August 12, 2015, Table 1, page 34-37.

**Table XX (cont). SFY13370 Study Flow Chart**

	Screening		Treatment phase											EOT	FU
VISIT	V1	V2	V3	V4	V5	V6	V7	V8	V8.1	V9	V9.1	V10	V10.1	V11	V12
DAY	D -28 to D -1	D1	D15(±3)	D29(±3)	D43(±3)	D57(±3)	D71(±3)	D85(±3)	D99(±3)	D113(±3)	D127(±3)	141(±3)	D155(±3)	D169(±3)	D211(±3) <sup>a</sup>
WEEK		Wk 0	Wk 2 <sup>b</sup>	Wk 4	Wk6 <sup>c</sup>	Wk 8	Wk10 <sup>c</sup>	Wk 12	Wk14 <sup>c</sup>	Wk 16	Wk18 <sup>c</sup>	Wk 20	Wk22 <sup>c</sup>	Wk 24 <sup>g</sup>	Wk 30
12-lead ECG	X													X	
Antibodies to sarilumab <sup>m</sup> /serum sarilumab <sup>f</sup>		X	X	X				X						X	X
<b>Genotyping and biomarkers</b>															
Biomarkers – Biosampling (serum/ urine)		X	X					X						X	
DNA <sup>p</sup>		X													

- a For patients unwilling or unable to continue in the long term extension study (week 30) or 6 weeks after last IMP intake for patients prematurely leaving the main study.
- b For all patients, the Visit 2 hematology laboratory assessment must be available before the administration of the 2nd dose of study drug to confirm that the absolute neutrophil count (ANC) and platelet count are not within the protocol-defined limits for temporary or permanent discontinuation of study drug. A CBC must be performed a few days before or at Visit 3, but not earlier than the 12th day after the first dose of study drug administration and the results must be reviewed prior to the administration of the Visit 3 study drug.
- c This visit can be performed as a lab visit only and can be performed at home, except under circumstances where the neutrophil and/or platelet count(s) are below lower limits of normal, based on Covance laboratory (or designated central lab) complete blood count (CBC) results at the previous visit. In that case the visit (ie, the visit following the abnormal value) must be conducted by the investigator and not as a home/laboratory visit.
- d Targeted physical examination: skin, respiratory, cardiovascular, neurologic, lymphatic examinations and abdominal examination.
- e Last administration of sarilumab at Week 22.
- f Last administration of tocilizumab at Week 20.
- g Non-investigational medicinal product (eg, disease modifying anti-rheumatic drugs [DMARDs]) should be dispensed according to local practice and will not be dispensed nor supplied by the Sponsor.
- h American College of Rheumatology (ACR) core set includes: swollen joint count (SJC), 66 joints, tender joint count (TJC), 68 joints, Patient Global Assessment of Disease Activity, Pain Intensity, Patient's assessment of physical function (Health Assessment Questionnaire-Disease Index [HAQ-DI]), hs-CRP, and Physician Global Assessment of Disease Activity.
- i If any Visit 2 laboratory result meets the values defined in exclusion criterion E37 the 2nd dose of investigational medicinal product (IMP) should not be administered and the patient should be withdrawn from study treatment.

Source: SFY13370 Clinical Study Report, dated August 12, 2015, Table 1, page 34-37.

Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

**Table XX (cont). SFY13370 Study Flow Chart**

- j* Hematology (blood should be drawn before drug administration): Hemoglobin, hematocrit, red blood cell (RBC) count and morphology (if RBC count is abnormal), white blood cell (WBC) differential, platelet count, absolute neutrophil count (ANC).
- k* Chemistry(blood should be drawn before drug administration): Sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN), creatinine and creatinine clearance, calcium, phosphate, total protein, albumin, alanine aminotransferase (ALT) (SGPT), aspartate aminotransferase (AST) (SGOT), alkaline phosphatase (ALP), total bilirubin, conjugated bilirubin, unconjugated bilirubin, lactate dehydrogenase (LDH), uric acid and prothrombin time. At Week 6 and 10 only albumin, ALT, AST, ALP, PT, total bilirubin, conjugated bilirubin and unconjugated bilirubin will be assessed.
- l* Lipids (blood should be drawn before drug administration): Triglycerides (TG), total cholesterol, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol.
- m* Blood should be drawn before drug administration.
- n* Urinalysis dipstick: specific gravity, pH, glucose, hemoglobin, protein, nitrates, leukocyte esterase, bilirubin. If any parameter on the dipstick is abnormal, a urine sample should be sent to the central laboratory for testing. If positive for proteins, microscopic analysis is performed by central laboratory.
- o* In women of child-bearing potential.
- p* Pharmacogenomics informed consent form must be signed before DNA sample is collected at any visit from the randomization visit on.
- q* If the patient has fully completed the study treatment, the Investigator may offer the long-term extension study to the patient. If the patient agrees to enter the sarilumab open-label long-term extension study, LTS11210, and is confirmed to be eligible, the post-treatment follow-up visit will not be completed, and after completion of all study assessment, this end of treatment visit for SFY13370 serves as the baseline visit for the LTS11210 study.
- r* If an SAE occurs in a patient, blood samples should be collected for determination of sarilumab concentration (bound and functional), and antidrug antibody (ADA) assessment at or near the onset and completion of the occurrence of the event, if possible.

Source: SFY13370 Clinical Study Report, dated August 12, 2015, Table 1, page 34-37.

APPEARS THIS WAY ON ORIGINAL

Clinical Review  
 Reviewer: Suzette Peng, MD  
 NME/BLA 761037  
 Sarilumab/Kevzara

**Table 145. EFC13752 Study Flow Chart**

	Screening Phase	Study Phase										
	Screening <sup>a</sup>	Treatment										Post-treatment Follow-up
VISIT	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11 (EOT) <sup>p</sup>	V12 (EOS) <sup>p</sup>
DAY	D-28 to D-1	D1	D15(±3)	D29(±3)	D43(±3)	D57(±3)	D71(±3)	D85(±3)	D113(±3)	141(±3)	D169(±3)	D211(±3)
WEEK		Wk 0	Wk 2	Wk 4	Wk 6 <sup>o</sup>	Wk 8	Wk10 <sup>o</sup>	Wk 12	Wk 16	Wk 20	Wk 24 <sup>p</sup>	Wk 30
<b>Eligibility</b>												
Written informed consent	X											
Inclusion/exclusion criteria	X	X										
Patient demography	X											
Medical & surgical/smoking/alcohol history	X											
Prior medication history	X											
Family cardiovascular history	X											
Full physical examination	X										X	
Targeted physical examination <sup>b</sup>		X						X				
Confirm eligibility		X										
Randomization		X										
Call IVRS	X	X		X		X		X	X	X	X	X

Source: EFC13752 Clinical Study Report, dated August 18, 2015, page 28-32.

Clinical Review  
 Reviewer: Suzette Peng, MD  
 NME/BLA 761037  
 Sarilumab/Kevzara

**Table XX (cont). EFC13752 Study Flow Chart**

	Screening Phase	Study Phase										
	Screening <sup>a</sup>	Treatment										Post-treatment Follow-up
VISIT	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11 (EOT) <sup>p</sup>	V12 (EOS) <sup>p</sup>
DAY	D-28 to D-1	D1	D15(±3)	D29(±3)	D43(±3)	D57(±3)	D71(±3)	D85(±3)	D113(±3)	141(±3)	D169(±3)	D211(±3)
WEEK		Wk 0	Wk 2	Wk 4	Wk 6 <sup>o</sup>	Wk 8	Wk10 <sup>o</sup>	Wk 12	Wk 16	Wk 20	Wk 24 <sup>p</sup>	Wk 30
<b>Treatment</b>												
Initial treatment kit assignment (IVRS)		X										
IMP administration <sup>c</sup>		X	X <sup>d</sup>	X	X	X	X	X	X	X <sup>q</sup>		
Concomitant medication review		X	X	X		X		X	X	X	X	X
Dispense patient diary		X	X	X		X		X	X	X		
Compliance/review patient diary			X	X		X		X	X	X	X	
Dispense IMP				X		X		X	X	X		
<b>Vital signs</b>												
Temperature, heart rate, blood pressure	X	X	X	X		X		X	X	X	X	
Weight	X	X						X			X	
Height	X											
<b>Efficacy</b>												
ACR disease core set <sup>e</sup>	X	X		X		X		X			X	
<b>Safety</b>												
AE/SAE recording	X	X	X	X	X	X	X	X	X	X	X	X

Source: EFC13752 Clinical Study Report, dated August 18, 2015, page 28-32.

Clinical Review  
 Reviewer: Suzette Peng, MD  
 NME/BLA 761037  
 Sarilumab/Kevzara

**Table XX (cont). EFC13752 Study Flow Chart**

	Screening Phase	Study Phase										
	Screening <sup>a</sup>	Treatment										Post-treatment Follow-up
VISIT	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11 (EOT) <sup>p</sup>	V12 (EOS) <sup>p</sup>
DAY	D-28 to D-1	D1	D15(±3)	D29(±3)	D43(±3)	D57(±3)	D71(±3)	D85(±3)	D113(±3)	141(±3)	D169(±3)	D211(±3)
WEEK		Wk 0	Wk 2	Wk 4	Wk 6 <sup>o</sup>	Wk 8	Wk10 <sup>o</sup>	Wk 12	Wk 16	Wk 20	Wk 24 <sup>p</sup>	Wk 30
Tuberculosis assessment	X	X	X	X		X		X	X	X	X	X
QuantiFERON®	X											
Chest X-ray (when indicated)	X											
Laboratory testing												
Hematology <sup>f</sup>	X	X	X	X	X	X	X	X	X	X	X	
Chemistry <sup>g</sup>	X	X	X	X	X	X	X	X	X	X	X	
Fasting lipids <sup>h</sup> /fasting glucose <sup>i</sup>	X		X	X		X		X			X	
HbA1c	X							X			X	
hs-CRP <sup>j</sup>	X	X		X		X		X			X	
Rheumatoid factor / anti-CCP		X						X			X	
ANA/Anti-ds DNA antibody		X						X			X	
Urinalysis <sup>k</sup>	X	X						X			X	
Virology <sup>l</sup>	X											
Serum pregnancy test <sup>m</sup>	X											
Urine pregnancy test <sup>m</sup>		X		X		X		X	X	X	X	
12-lead ECG	X										X	
Serum sarilumab <sup>n</sup>		X	X	X				X	X	X	X	X

Source: EFC13752 Clinical Study Report, dated August 18, 2015, page 28-32.

**Table XX (cont). EFC13752 Study Flow Chart**

	Screening Phase	Study Phase										
	Screening <sup>a</sup>	Treatment										Post-treatment Follow-up
VISIT	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11 (EOT) <sup>p</sup>	V12 (EOS) <sup>p</sup>
DAY	D-28 to D-1	D1	D15(±3)	D29(±3)	D43(±3)	D57(±3)	D71(±3)	D85(±3)	D113(±3)	141(±3)	D169(±3)	D211(±3)
WEEK		Wk 0	Wk 2	Wk 4	Wk 6 <sup>o</sup>	Wk 8	Wk10 <sup>o</sup>	Wk 12	Wk 16	Wk 20	Wk 24 <sup>p</sup>	Wk 30
Antibodies to sarilumab <sup>n</sup>		X	X	X				X			X	X

- a. Patients who fail screening may be rescreened for study eligibility 1 additional time (see 16-1-1-protocol [10.1.1] and [8.4] for rescreening)
- b. Targeted physical examination: skin, respiratory, cardiovascular, neurologic, lymphatic examinations and abdominal examination
- c. The number of treatment kits allocated to the patient contained sufficient medication until the next visit at which IMP will be dispensed. Additional treatment kits, to provide medication to randomized patients under circumstances, such as a damaged kit, will be allocated by IVRS when a "replacement treatment call" is made to IVRS.
- d. For all patients, the Visit 2 hematology laboratory assessment must be reviewed before the administration of IMP at Visit 3. If any Visit 2 laboratory result meets the values defined in exclusion criterion E36, the 2nd dose of IMP should not be administered and the patient should be withdrawn from study treatment. In addition, a CBC must be performed a few days before or at Visit 3 but not earlier than the 12th day after first dose of IMP administration and the results must be reviewed prior to the administration of the Visit 3 IMP to confirm that the neutrophil count and platelet count are not within the protocol-defined limits for temporary or permanent discontinuation of IMP.
- e. American College of Rheumatology (ACR) core set includes: swollen joint count (SJC), 66 joints, tender joint count (TJC), 68 joints, Patient Global Assessment of Disease Activity, Patients Assessment of Pain, Patient's assessment of physical function (Health Assessment Questionnaire-Disease Index [HAQ-DI]), hs-CRP, and Physician Global Assessment of Disease Activity.
- f. Hematology (blood should be drawn prior to IMP administration): Hemoglobin, hematocrit, red blood cell (RBC) count and morphology (if RBC count is abnormal), white blood cell (WBC) differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils), platelet count.
- g. Chemistry (blood should be drawn prior to IMP administration): Sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN), creatinine and creatinine clearance, calcium, phosphate, total protein, albumin, alanine aminotransferase (ALT) (SGPT), aspartate aminotransferase (AST) (SGOT), alkaline phosphatase (ALP), total bilirubin, conjugated bilirubin, unconjugated bilirubin, lactate dehydrogenase (LDH), uric acid and prothrombin time. At Visit 5, Visit 7, only hematology and limited chemistry will be performed (see footnote o)
- h. Lipids (Prior to IMP administration): Triglycerides (TG), total cholesterol, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol.
- i. Blood should be drawn prior to IMP administration
- j. Blood should be drawn prior to IMP administration

Source: EFC13752 Clinical Study Report, dated August 18, 2015, page 28-32.

Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

**Table XX (cont). EFC13752 Study Flow Chart**

- k. Urinalysis dipstick: specific gravity, pH, glucose, blood, protein, nitrates, leukocyte esterase, bilirubin. If any parameter on the dipstick is abnormal, a urine sample should be sent to the central laboratory for testing. If positive for proteins, microscopic analysis is performed by central laboratory.
- l. Human immunodeficiency virus (HIV) antibodies; Hepatitis B: HBsAg, total HBcore Ab, Hepatitis C: HCV-antibodies
- m. In women of child-bearing potential. The serum pregnancy test should be completed prior to chest X-ray at the screening visit.
- n. Samples will be collected prior to IMP administration. Both functional and bound sarilumab serum concentration will be measured. There are two additional measurements at Week 16 and Week 20 for sarilumab serum concentrations. If an SAE occurs in a patient, blood samples should be collected for determination of sarilumab concentration (bound and functional) and antidrug antibody (ADA) assessment at or near the onset and completion of the occurrence of the event, if possible.
- o. Only hematology and limited chemistry tests (only albumin, ALT, AST, ALP, PT, total bilirubin, conjugated bilirubin and unconjugated bilirubin) will be assessed. The visit can be performed as a lab visit only and can be performed at home, except under circumstances where the neutrophil and/or platelet count(s) are below lower limits of normal, based on designated central lab results for complete blood count (CBC) from the previous visit. In this case, these visits must be conducted at the study site and not as a home/laboratory visit.
- p. Eligible patients who complete the 24-week treatment period will be offered to enter into the sarilumab open-label long-term extension study (LTS11210). EFC13752 EOT visit11 (Week 24) will be combined with LTS11210 screening visit (Visit 1) and LTS11210 enrollment visit/baseline visit (Visit 2). The post-treatment follow-up Visit 12 (Week 30) will not be completed. The EOT Visit 11 (Week 24) for EFC13752 serves as the baseline visit for the LTS11210 study. Patients who complete the 24-week treatment period and do not enter into the LTS11210 study will have a follow-up visit 6 weeks after the EOT visit. Patients with premature discontinuation will be assessed using the procedure normally planned for the EOT visit, followed by the End-of-Study visit in 6 weeks.
- q. The last IMP administration will occur at Week 22.

Source: EFC13752 Clinical Study Report, dated August 18, 2015, page 28-32.

APPEARS THIS WAY ON ORIGINAL

Clinical Review  
 Reviewer: Suzette Peng, MD  
 NME/BLA 761037  
 Sarilumab/Kevzara

**Table 146. EFC11574 Study Flow Chart (Open Label Phase)**

Evaluation	Screening					End of Treatment	Post-treatment FU/Exit
VISIT	OL1	OL2	OL3	OL4	OL5	OL6	FU1 <sup>c</sup>
DAY	Wk -4 to Wk -1	D1	D29(±3)	D57(±3)	D85(±3)	D113 (±3)	D155(±3)
WEEK		Wk 0	Wk 4	Wk 8	Wk 12	Wk16	Wk22
<b>Eligibility</b>							
Written informed consent	X						
Inclusion/exclusion criteria (Confirm eligibility)	X	X					
Patient demography	X						
Medical/surgical history	X						
Prior medication history	X						
Complete physical examination	X					X	
Targeted physical examination		X					
Confirm ACR responder status for substudy <sup>a</sup>						X	
Confirm ACR responder status/DAS28-CRP score for randomized phase <sup>b</sup>						X	
<b>Treatment</b>							
Call IVRS	X	X	X	X	X	X	X
Adalimumab administration <sup>d</sup>		X	X	X	X		
Adalimumab dispensed <sup>e</sup>		X	X	X	X		
Concomitant medication		X	X	X	X	X	X
Dispense Home Dosing Diary		X	X	X	X		
Compliance/review Dosing Diary			X	X	X	X	

Source: EFC11574 Clinical Study Report, Table 1, dated June 11, 2015, page 18-20.

Clinical Review  
 Reviewer: Suzette Peng, MD  
 NME/BLA 761037  
 Sarilumab/Kevzara

**Table XX (cont). EFC11574 Study Flow Chart (Open Label Phase)**

Evaluation	Screening					End of Treatment	Post-treatment FU/Exit
VISIT	OL1	OL2	OL3	OL4	OL5	OL6	FU1 <sup>c</sup>
DAY	Wk -4 to Wk -1	D1	D29(±3)	D57(±3)	D85(±3)	D113 (±3)	D155(±3)
WEEK		Wk 0	Wk 4	Wk 8	Wk 12	Wk16	Wk22
<b>Vital signs</b>							
Temperature, heart rate, blood pressure	X	X	X	X	X	X	
Weight	X					X	
Height	X						
<b>Efficacy</b>							
ACR disease core set <sup>f</sup>	X	X	X	X	X	X	
<b>Safety</b>							
AE/SAE recording	X	X	X	X	X	X	X
Tuberculosis risk assessment	X	X	X	X	X	X	X
QuantiFERON®	X						
Chest x-ray (when indicated)	X						
<b>Laboratory testing</b>							
Hematology <sup>g</sup>	X	X				X	
Chemistry <sup>h</sup>	X	X				X	
Fasting lipids <sup>i</sup> /fasting glucose	X						
HbA1c	X						
Urinalysis <sup>j</sup>	X					X	
Hepatitis B and C: HBsAg, total HBcore Ab, HCVAb, HIV-1/HIV-2 Ab	X						
Serum pregnancy test <sup>k</sup>	X						
Urine pregnancy test <sup>k</sup>		X	X	X	X	X	
hs-CRP	X	X	X	X	X	X	
DNA and RNA for sequencing sampling <sup>l</sup>		X					

Source: EFC11574 Clinical Study Report, Table 1, dated June 11, 2015, page 18-20.

**Table XX (cont). EFC11574 Study Flow Chart (Open Label Phase)**

Evaluation	Screening					End of Treatment	Post-treatment FU/Exit
VISIT	OL1	OL2	OL3	OL4	OL5	OL6	FU1 <sup>c</sup>
DAY	Wk -4 to Wk -1	D1	D29(±3)	D57(±3)	D85(±3)	D113 (±3)	D155(±3)
WEEK		Wk 0	Wk 4	Wk 8	Wk 12	Wk16	Wk22
RNA expression <sup>m</sup>		X	X				
12-lead ECG	X						

Abbreviations: Ab=antibody; ACR=American College of Rheumatology; AE=adverse event; ALP=alkaline phosphatase; ALT(SGPT)=alanine aminotransferase (serum glutamic-pyruvic transaminase); AST (SGOT)=aspartate aminotransferase (serum glutamic-oxaloacetic transaminase); BUN=blood urea nitrogen; CRP=C-reactive protein; D=day; DAS28=Disease Activity Score for 28 joints; DAS28-CRP= Disease Activity Score for 28 joints - C-reactive protein; DNA=deoxyribonucleic acid; ECG=electrocardiogram; EOT=end of treatment; FU=follow-up; HbA1c=hemoglobin A1c; HAQ-DI= Health Assessment Questionnaire - Disability Index; HBcore Ab=hepatitis B core antibody; HBsAg=hepatitis B surface antigen; HCVAb=hepatitis C virus antibody; HDL=high-density lipoprotein; HIV=human immunodeficiency virus; hs-CRP=high-sensitivity C-reactive protein; IVRS=interactive voice response system; LDH=lactate dehydrogenase; LDL=low-density lipoprotein; MTX=methotrexate; OL=open-label; PT=prothrombin time; q2w=every 2 weeks; R=randomization; RBC=red blood cell; RNA=ribonucleic acid; S=substudy; SAE=serious adverse event; SC=subcutaneous; SJC=swollen joint count; TG=triglycerides; TJC=tender joint count; WBC=white blood cell; Wk=week

- a Site calculated ACR20 response rate based on Week 4, 8, 12 and Week 16 ACR core set measurements. If response ≥ACR20 at any Week 4, 8, 12 and/or Week 16 time point, the patient was offered the opportunity to enroll in the uncontrolled 1-year sarilumab long-term safety substudy. If the patient agreed to screen for the substudy, the post-treatment follow-up visit was not scheduled; the patient was contacted and S1 scheduled 2 weeks after EOT Visit OL6. Visit S1 may have been scheduled within 4 weeks of the EOT Visit OL6 if patient had a scheduling difficulty or unresolved AE expected to end prior to S1. Alternatively, for patients unwilling or unsuitable to screen for the substudy, the post-treatment follow-up Visit F1 was scheduled.
- b Site calculated ACR20 response at Week 4, 8, 12, and Week 16 using ACR core set measurements at each visit, and DAS28-CRP score using the Week 16 DAS28-applicable core set measurements. If response <ACR20 at Weeks 4-16 (inclusive) and DAS28-CRP score >3.5 at Week 16, the patient was contacted and R1 was scheduled 2 weeks after EOT visit OL6. Visit R1 may have been scheduled within 4 weeks of the EOT Visit OL6 if patient had a scheduling difficulty or unresolved AE expected to end prior to R1.
- c For patients unwilling or not eligible to continue in randomized phase of EFC11574, and patients unwilling or unsuitable to screen for the uncontrolled 1-year sarilumab long-term safety substudy.
- d At Visit OL2, all patients were prescribed adalimumab 40 mg SC q2w and the initial dose is administered. Patients received adalimumab through Week 14.
- e MTX was to be dispensed according to local practice.
- f ACR core set included: swollen joint count, 66 joints, tender joint count, 68 joints, Patient's Global Assessments of Disease Activity, Patient's Assessment of Pain, HAQ-DI, hs-CRP and Physician's Global Assessments of Disease Activity; DAS28 components included selected 28 SJC, 28 TJC, Patient Global Assessment, and CRP.
- g Hematology (blood was to be drawn before dosing): Hemoglobin, hematocrit, RBC count and morphology (if RBC count was abnormal), WBC differential, platelet count, absolute neutrophil count.
- h Chemistry (blood was to be drawn before dosing): Sodium, potassium, chloride, bicarbonate, BUN, creatinine and creatinine clearance, calcium, phosphate, total protein, albumin, ALT (SGPT), AST (SGOT), ALP, total bilirubin, conjugated bilirubin, unconjugated bilirubin, LDH, uric acid and PT.
- i Fasting lipids (blood was to be drawn before dosing): TG, total cholesterol, HDL cholesterol, LDL cholesterol.
- j Urinalysis dipstick: specific gravity, pH, glucose, blood, ketones, protein, bilirubin, urobilinogen, nitrates and leukocyte esterase.
- k In women of child-bearing potential.
- l Genetic Informed Consent for DNA and RNA for sequencing had to be signed before any sampling. Only one DNA sampling time point was needed (at baseline or any treatment or follow up visit) and one RNA for sequencing sampling time point: at OL2 (Day 1).
- m Blood was to be drawn before dosing.

Source: EFC11574 Clinical Study Report, Table 1, dated June 11, 2015, page 18-20.

Clinical Review  
 Reviewer: Suzette Peng, MD  
 NME/BLA 761037  
 Sarilumab/Kevzara

**Table 147. EFC11574 Study Flow Chart (Randomized Control Phase)**

Evaluation	Randomized controlled treatment									End of Treatment	Post-treatment FU / exit
	R1	R2	R3	R4	R5	R6	R7	R8	R9		
VISIT	D1	D15 (±3)	D 29 (±3)	D43 (±3)	D 57 (±3)	D71(±3)	D85(±3)	D113(±3)	141(±3)	D169(±3)	D211 (±3)
WEEK	Wk0	Wk2 <sup>a</sup>	Wk4	Wk6 <sup>a</sup>	Wk8	Wk10 <sup>a</sup>	WK12	Wk16	Wk20	Wk24	Wk30
Eligibility											
Written informed consent (confirm signature)	X										
Inclusion/exclusion criteria (confirm eligibility) <sup>o</sup>	X										
Full physical examination										X	
Targeted physical examination	X						X				
Randomization	X										
Call IVRS	X		X		X		X	X	X	X	X
<b>Treatment</b>											
Initial treatment kit assignment (IVRS)	X										
Investigational medicinal product administration <sup>b</sup>	X	X	X	X	X	X	X	X	X		
Investigational medicinal product dispensed <sup>c</sup>	X		X		X		X	X	X		
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X
Dispense Home Dosing Diary	X	X	X		X		X	X	X		
Compliance/review Dosing Diary		X	X		X		X	X	X	X	
<b>Vital signs</b>											
Temperature, heart rate, blood pressure	X	X	X		X		X	X	X	X	
Weight							X			X	
<b>Efficacy</b>											
ACR disease core set <sup>d</sup>	X	X	X		X		X	X	X	X	

Source: EFC11574 Clinical Study Report, Table 2, dated June 11, 2015, page 21-23.

Clinical Review  
 Reviewer: Suzette Peng, MD  
 NME/BLA 761037  
 Sarilumab/Kevzara

**Table XX (cont). EFC11574 Study Flow Chart (Randomized Control Phase)**

Evaluation	Randomized controlled treatment									End of Treatment	Post-treatment FU / exit
	R1	R2	R3	R4	R5	R6	R7	R8	R9	R10	FU2
VISIT	D1	D15 (±3)	D 29 (±3)	D43 (±3)	D 57 (±3)	D71(±3)	D85(±3)	D113(±3)	141(±3)	D169(±3)	D211 (±3)
WEEK	Wk0	Wk2 <sup>a</sup>	Wk4	Wk6 <sup>a</sup>	Wk8	Wk10 <sup>a</sup>	WK12	Wk16	Wk20	Wk24	Wk30
<b>Safety</b>											
AE/SAE recording	X	X	X	X	X	X	X	X	X	X	X
Tuberculosis risk assessment	X	X	X		X		X	X	X	X	X
<b>Patient reported outcomes</b>											
EQ-5D-3L	X						X			X	
FACIT-F	X						X			X	
RAID	X						X			X	
Morning stiffness VAS	X						X			X	
<b>Laboratory testing</b>											
Rheumatoid factor / anti CCP	X						X			X	
ANA/Anti-ds DNA antibody	X						X			X	
Hematology <sup>e</sup>	X	X	X	X	X	X	X	X	X	X	
Chemistry <sup>f</sup>	X	X	X	X	X	X	X	X	X	X	
Fasting lipids <sup>g</sup> , fasting glucose	X	X	X		X		X			X	
HbA1c	X						X			X	
Urinalysis <sup>h</sup>	X	X	X		X		X	X	X	X	
Urine pregnancy test <sup>i</sup>	X		X		X		X	X	X	X	
Hs-CRP <sup>j</sup>	X	X	X		X		X	X	X	X	
Erythrocyte sedimentation rate <sup>j</sup>	X						X			X	
Serum Sarilumab PK <sup>k</sup> /anti-sarilumab antibodies	X	X	X				X			X	X
DNA and RNA for sequencing sampling <sup>l,m</sup>	X										
RNA expression <sup>n</sup>	X	X									
Serum/urine biomarkers	X	X								X	

Source: EFC11574 Clinical Study Report, Table 2, dated June 11, 2015, page 21-23.

**Table XX (cont). EFC11574 Study Flow Chart (Randomized Control Phase)**

Evaluation	Randomized controlled treatment									End of Treatment	Post-treatment FU / exit	
	R1	R2	R3	R4	R5	R6	R7	R8	R9			
VISIT												
DAY	D1	D15 (±3)	D 29 (±3)	D43 (±3)	D 57 (±3)	D71(±3)	D85(±3)	D113(±3)	141(±3)	D169(±3)	D211 (±3)	
WEEK	Wk0	Wk2 <sup>a</sup>	Wk4	Wk6 <sup>a</sup>	Wk8	Wk10 <sup>a</sup>	WK12	Wk16	Wk20	Wk24	Wk30	
12-lead ECG	X									X		

ACR=American College of Rheumatology; AE=adverse event; ALT(SGPT)=alanine aminotransferase (serum glutamic-pyruvic transaminase); ALP=alkaline phosphatase; ANA=anti-nuclear antibody; Anti-ds DNA=anti-double-stranded deoxyribonucleic acid; AST(SGOT)=aspartate aminotransferase (serum glutamic-oxaloacetic transaminase); BUN=blood urea nitrogen; CBC=complete blood count; CCP=citrullinated peptides; D=day; DAS28=Disease Activity Score for 28 joints; DNA=deoxyribonucleic acid; ECG=electrocardiogram; ESR=erythrocyte sedimentation rate; EQ-5D-3L=Euro-Qol Five-dimensional 3 Levels; FACIT-F=Functional Assessment of Chronic Illness Therapy-Fatigue; FU=follow-up; HAQ-DI= Health Assessment Questionnaire - Disability Index; HbA1c=hemoglobin A1c; HDL=high-density lipoprotein; hs-CRP=high-sensitivity C-reactive protein; IMP=investigational medicinal product; IVRS=interactive voice response system; LDH=lactate dehydrogenase; LDL=low-density lipoprotein; LLN=lower limit of normal; MTX=methotrexate; OL=open-label; PK=pharmacokinetic; PT=prothrombin time; R=randomization; RAID=Rheumatoid Arthritis Impact of Disease; RBC= red blood cell; RNA=ribonucleic acid; SAE=serious adverse event; SJC=swollen joint count; TG=triglycerides; TJC=tender joint count; VAS=visual analog scale; WBC=white blood cell; Wk=week

- a For all patients, CBC was drawn up to 3 days before, or at Visit R2 (using Covance or local laboratory facility). Verified before dosing at Visit R2 that the absolute neutrophil count and platelet count were above the protocol-defined limits for temporary or permanent discontinuation of IMP. Visits R4 and R6 could have been home visit or clinic visit to draw and collect the blood sample only for hematology and LFTs. Note the following exception: Under circumstances where the neutrophil count and/or platelet count(s) are below the LLN based on Covance laboratory complete blood count (CBC) results at the previous visit, Visits R4, and R6 must have been conducted at the site and not as a home visit.
- b At Visit R1, the initial dose of IMP was administered and then every week through Week 23.
- c MTX was to be dispensed according to local practice. The last date of IMP (sarilumab/matched placebo) was Week 22; the last date of IMP (etanercept/matched placebo) was Week 23.
- d ACR core set included: SJC 66 joints, TJC 68 joints, Patient's Global Assessments of Disease Activity, Patient's Assessment of Pain, HAQ-DI, hs-CRP, and Physician's Global Assessments of Disease Activity; DAS28 components included selected 28 SJC, 28 TJC, Patient Global Assessment, and ESR or hs-CRP.
- e Hematology (blood was to be drawn before drug administration): Hemoglobin, hematocrit, RBC count and morphology (if RBC count was abnormal), WBC differential, platelet count, absolute neutrophil count.
- f Chemistry (blood was to be drawn BEFORE drug administration): sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN), creatinine and creatinine clearance, calcium, phosphate, total protein, albumin, ALT (SGPT), AST (SGOT), ALP, total bilirubin, conjugated bilirubin, unconjugated bilirubin, LDH, uric acid and PT.
- g Fasting lipids: TG, total cholesterol, HDL cholesterol, LDL cholesterol.
- h Urinalysis dipstick: specific gravity, pH, glucose, blood, ketones, proteins, bilirubin, urobilinogen, nitrate and leukocyte esterase.
- i In women of child-bearing potential.
- j Blood was to be drawn BEFORE drug administration. Hs-CRP was blinded to both Investigator and Sponsor (except screening and randomization visit (R1) for the randomized controlled phase).
- k Blood was to be drawn BEFORE drug administration. Serum sarilumab PK and anti-sarilumab antibody results were blinded to both Investigator and Sponsor.
- l In consenting patients only; RNA for sequencing was collected for all patients and DNA sample was collected only in patients if not collected in OL phase.
- m Genetic Informed Consent for DNA and RNA for sequencing had to be signed before any sampling. If the DNA sampling time point at the baseline visit was inadvertently missed, the DNA sample could have been collected at any treatment or follow up visit.
- n Blood was to be drawn before dosing.
- o Study Investigator was to review AEs and laboratory results recorded at the open-label end of treatment visit (OL6) to determine, based on Investigator judgment, that the patient would not be adversely affected by participation in the substudy (see exclusion criterion E42, 16-1-1-protocol [7.4.3]). Furthermore, if any OL6 laboratory result(s) falls within the values defined in exclusion criteria E37 or E38, the patient was to be permanently withdrawn from the randomized study treatment period ([7.4.2]).

Source: EFC11574 Clinical Study Report, Table 2, dated June 11, 2015, page 21-23.

Clinical Review  
 Reviewer: Suzette Peng, MD  
 NME/BLA 761037  
 Sarilumab/Kevzara

**Table 148. EFC11574 Substudy Flow Chart (1-year OL Study)**

Evaluation	Sarilumab treatment									End of Treatment	Post-treatment FU / exit
	S1	S2	S3	S4	S5	S6	S7	S8	S9	S10	FU3
VISIT	D1	D15 (±3)	D 29 (±3)	D43 (±3)	D 57 (±3)	D71(±3)	D85(±3)	D169(±3)	D253(±3)	D365(±3)	D408 (±3)
DAY	Wk0	Wk2 <sup>a</sup>	Wk4	Wk6 <sup>a</sup>	Wk8	Wk10 <sup>a</sup>	WK12	Wk24	Wk36	Wk52	Wk58
WEEK											
Eligibility											
Written informed consent	X										
Inclusion/exclusion criteria (confirm eligibility) <sup>f</sup>	X										
Full physical examination										X	
Targeted physical examination	X						X				
Enrollment	X										
Call IVRS	X		X		X		X	X	X	X	X
<b>Treatment</b>											
Initial treatment kit assignment (IVRS)	X										
Investigational medicinal product administration <sup>b</sup>	X	X	X	X	X	X	X	X	X		
Investigational medicinal product dispensed <sup>c</sup>	X		X		X		X	X	X		
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X
Dispense Home Dosing Diary	X	X	X		X		X	X	X		
Compliance/review Dosing Diary			X		X		X	X	X	X	

Source: EFC11574 Clinical Study Report, Table 3, dated June 11, 2015, page 24-26.

Clinical Review  
 Reviewer: Suzette Peng, MD  
 NME/BLA 761037  
 Sarilumab/Kevzara

**Table XX (cont). EFC11574 Substudy Flow Chart (1-year OL Study)**

Evaluation	Sarilumab treatment									End of Treatment	Post-treatment FU / exit
	S1	S2	S3	S4	S5	S6	S7	S8	S9		
VISIT	D1	D15 (±3)	D 29 (±3)	D43 (±3)	D 57 (±3)	D71(±3)	D85(±3)	D169(±3)	D253(±3)	D365(±3)	FU3
DAY	D1	D15 (±3)	D 29 (±3)	D43 (±3)	D 57 (±3)	D71(±3)	D85(±3)	D169(±3)	D253(±3)	D365(±3)	D408 (±3)
WEEK	Wk0	Wk2 <sup>a</sup>	Wk4	Wk6 <sup>a</sup>	Wk8	Wk10 <sup>a</sup>	WK12	Wk24	Wk36	Wk52	Wk58
<b>Vital signs</b>											
Temperature, heart rate, blood pressure	X	X	X		X		X	X	X	X	
Weight							X			X	
<b>Disease assessment</b>											
ACR disease core set <sup>d</sup>	X		X		X		X	X	X	X	
<b>Safety</b>											
AE/SAE recording	X	X	X	X	X	X	X	X	X	X	X
Tuberculosis risk assessment	X	X	X		X		X	X	X	X	X
<b>Laboratory testing</b>											
Rheumatoid factor / anti CCP	X						X			X	
ANA/Anti-ds DNA antibody	X						X			X	
Hematology <sup>e</sup>	X	X	X	X	X	X	X	X	X	X	
Chemistry <sup>f</sup>	X	X	X	X	X	X	X	X	X	X	
Fasting lipids <sup>g</sup> , fasting glucose	X		X		X		X	X	X	X	
HbA1c	X						X			X	
Urinalysis <sup>h</sup>	X				X		X	X	X	X	
Urine pregnancy test <sup>i</sup>	X		X		X		X	X	X	X	
Hs-CRP <sup>j</sup>	X		X		X		X	X	X	X	
Serum Sarilumab PK/anti-sarilumab antibodies <sup>k</sup>	X	X	X				X	X	X	X	X

Source: EFC11574 Clinical Study Report, Table 3, dated June 11, 2015, page 24-26.

**Table XX (cont). EFC11574 Substudy Flow Chart (1-year OL Study)**

Evaluation	Sarilumab treatment									End of Treatment	Post-treatment FU / exit
	S1	S2	S3	S4	S5	S6	S7	S8	S9		
VISIT	S1	S2	S3	S4	S5	S6	S7	S8	S9	S10	FU3
DAY	D1	D15 (±3)	D 29 (±3)	D43 (±3)	D 57 (±3)	D71(±3)	D85(±3)	D169(±3)	D253(±3)	D365(±3)	D408 (±3)
WEEK	Wk0	Wk2 <sup>a</sup>	Wk4	Wk6 <sup>a</sup>	Wk8	Wk10 <sup>a</sup>	WK12	Wk24	Wk36	Wk52	Wk58
12-lead ECG	X									X	

ACR=American College of Rheumatology; AE=adverse event; ALT(SGPT)=alanine aminotransferase (serum glutamic-pyruvic transaminase); ALP=alkaline phosphatase; anti-ds DNA=anti-double stranded deoxyribonucleic acid; ANA=antinuclear antibody; AST(SGOT)=aspartate aminotransferase (serum glutamic-oxaloacetic transaminase); BUN=blood urea nitrogen; CBC=complete blood count; CCP=citrullinated peptides; CRP=C-reactive protein; D=day; DAS28=Disease Activity Score for 28 joints; DNA=deoxyribonucleic acid; ECG=electrocardiogram; FU=follow-up; HAQ-DI= Health Assessment Questionnaire - Disability Index; HbA1c=hemoglobin A1c; HDL=high-density lipoprotein; hs-CRP=high-sensitivity C-reactive protein; IMP=investigational medicinal product; IVRS=interactive voice response system; LDH=lactate dehydrogenase; LDL=low-density lipoprotein; LFTs=liver function tests; LLN=lower limit of normal; MTX=methotrexate; PK=pharmacokinetic; PT=prothrombin time; RBC= red blood cell; RNA=ribonucleic acid; S=Substudy; SAE=serious adverse event; SJC=swollen joint count; TG=triglycerides; TJC=tender joint count; WBC=white blood cell; Wk=week

- a For all patients, CBC was to be drawn up to 3 days before, or at Visit S2 (using Covance or local laboratory facility) before IMP administration. Verified before dosing at Visit S2 that the absolute neutrophil count and platelet count were above the protocol-defined limits for temporary or permanent discontinuation of IMP. Visits S4 and S6 could have been home visit or clinic visit to draw and collect the blood sample only for hematology and LFTs. Note the following exception: Under circumstances where the neutrophil count and/or platelet count(s) were below LLN, based on Covance laboratory CBC results at the previous visit, Visits S4, and S6 were to be conducted at the site and not as a home visit.
- b At Visit S1, the initial dose of IMP was administered and then every 2 weeks through Week 50. Last date of sarilumab administration was Week 50.
- c MTX was to be dispensed according to local practice.
- d ACR core set included SJC, 66 joints, TJC 68 joints, Patient's Global Assessments of Disease Activity, Patient's Assessment of Pain, HAQ-DI, hs-CRP, and Physician's Global Assessments of Disease Activity; DAS28 components included selected 28 SJC, 28 TJC, Patient Global Assessment, and CRP.
- e Hematology (blood was to be drawn before drug administration): Hemoglobin, hematocrit, RBC count and morphology (if RBC count is abnormal), WBC differential, platelet count, absolute neutrophil count.
- f Chemistry (blood was to be drawn BEFORE drug administration): sodium, potassium, chloride, bicarbonate, BUN, creatinine and creatinine clearance, calcium, phosphate, total protein, albumin, ALT (SGPT), AST (SGOT), ALP, total bilirubin, conjugated bilirubin, unconjugated bilirubin, LDH, uric acid and PT.
- g Fasting lipids: triglycerides (TG), total cholesterol, HDL cholesterol, LDL cholesterol.
- h Urinalysis dipstick: specific gravity, pH, glucose, blood, ketones, proteins, bilirubin, urobilinogen, nitrate and leukocyte esterase.
- i In women of child-bearing potential. After Visit S7 (Week 12) between study visits the patient was to have a urine pregnancy test at home on a monthly basis. Patients were to be given sufficient urine pregnancy kits to take home at each successive visit for monthly testing up until the final treatment visit.
- j Blood was to be drawn BEFORE drug administration for hs-CRP.
- k Serum sarilumab PK and anti-sarilumab antibodies (blood was to be drawn BEFORE drug administration).
- l Study Investigator was to review AEs and laboratory results recorded at the open-label end of treatment visit (OL6) to determine, based on Investigator judgment, that the patient would not be adversely affected by participation in the randomized treatment phase. Furthermore, if any OL6 laboratory result(s) that fell within the values defined in exclusion criteria E37 or E38, the patient was to be permanently withdrawn from the study treatment period (see 16-1-1-protocol [7.4.2]).

Source: EFC11574 Clinical Study Report, Table 3, dated June 11, 2015, page 24-26.

Clinical Review  
 Reviewer: Suzette Peng, MD  
 NME/BLA 761037  
 Sarilumab/Kevzara

**Table 149. MSC12665 Study Flow Chart**

	Screening		Baseline		AI assessment											EOT	Posttreatment follow-up / exit <sup>a</sup>
VISIT	V1	V2	V3 <sup>b,c</sup>	V4 <sup>b,c</sup>	V5 <sup>b,c</sup>	V6 <sup>b,f</sup>	V7	V8	V9 <sup>b</sup>	V10	V11 <sup>b</sup>	V12 <sup>b,c</sup>	V13 <sup>b,c</sup>	V14 <sup>b,c</sup>	V15 <sup>b,c</sup>	V16	V17
DAY	D -28 to D -1	D1	D3 (±1)	D5 (±1)	D8 (±1)	D12 (±1)	D15	D29	D43 (±3)	D57 (±3)	D71	D73 (±1)	D75 (±1)	D78 (±1)	D82 (±1)	D85 (±1)	D127 (±1)
WEEK		Wk 0					Wk 2	Wk 4	Wk 6	Wk 8	Wk 10					Wk 12	Wk 18
<b>Eligibility</b>																	
Written informed consent	X																
Inclusion/exclusion criteria	X	X															
Patient demography	X																
Medical/surgical/ cardiovascular family history	X																
Prior medication history	X																
Full physical examination	X															X	
Targeted physical examination		X							X								

Source: MSC12665 Clinical Study Report, Table 1, dated July 31, 2015, page 30-35.

Clinical Review  
 Reviewer: Suzette Peng, MD  
 NME/BLA 761037  
 Sarilumab/Kevzara

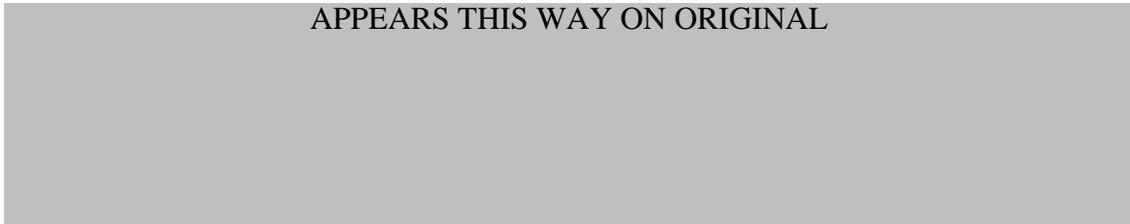
**Table XX (cont). MSC12665 Study Flow Chart**

	Screening	Baseline	AI assessment													EOT	Posttreatment follow-up / exit <sup>a</sup>
VISIT	V1	V2	V3 <sup>b,c</sup>	V4 <sup>b,c</sup>	V5 <sup>b,c</sup>	V6 <sup>b,f</sup>	V7	V8	V9 <sup>b</sup>	V10	V11 <sup>b</sup>	V12 <sup>b,c</sup>	V13 <sup>b,c</sup>	V14 <sup>b,c</sup>	V15 <sup>b,c</sup>	V16	V17
DAY	D -28 to D -1	D1	D3 (±1)	D5 (±1)	D8 (±1)	D12 (±1)	D15	D29	D43 (±3)	D57 (±3)	D71	D73 (±1)	D75 (±1)	D78 (±1)	D82 (±1)	D85 (±1)	D127 (±1)
WEEK		Wk 0					Wk 2	Wk 4	Wk 6	Wk 8	Wk 10					Wk 12	Wk 18
Hepatitis B and C: HBsAg, total HBcore Ab, HCVAb, HIV	X																
Hb A1c	X															X	
Serum pregnancy test <sup>d</sup>	X																
QuantiFERON®	X																
Chest X-ray (when indicated)	X																
Confirm eligibility		X															
Randomization		X															
Call IVRS	X	X						X		X						X	X
<b>Treatment</b>																	
IMP administration <sup>e</sup>		X					X <sup>f</sup>	X	X	X	X						
Patient training PFS/AI		X															
IMP dispensed <sup>g</sup>		X						X		X							
Concomitant medication recording		X					X	X		X						X	X
IMP compliance <sup>h</sup>								X		X						X	

Source: MSC12665 Clinical Study Report, Table 1, dated July 31, 2015, page 30-35.

Clinical Review  
Reviewer: Suzette Peng, MD  
NME/BLA 761037  
Sarilumab/Kevzara

APPEARS THIS WAY ON ORIGINAL



Clinical Review  
 Reviewer: Suzette Peng, MD  
 NME/BLA 761037  
 Sarilumab/Kevzara

**Table XX (cont). MSC12665 Study Flow Chart**

	Screening	Baseline	AI assessment													EOT	Posttreatment follow-up / exit <sup>a</sup>
VISIT	V1	V2	V3 <sup>b,c</sup>	V4 <sup>b,c</sup>	V5 <sup>b,c</sup>	V6 <sup>b,f</sup>	V7	V8	V9 <sup>b</sup>	V10	V11 <sup>b</sup>	V12 <sup>b,c</sup>	V13 <sup>b,c</sup>	V14 <sup>b,c</sup>	V15 <sup>b,c</sup>	V16	V17
DAY	D -28 to D -1	D1	D3 (±1)	D5 (±1)	D8 (±1)	D12 (±1)	D15	D29	D43 (±3)	D57 (±3)	D71	D73 (±1)	D75 (±1)	D78 (±1)	D82 (±1)	D85 (±1)	D127 (±1)
WEEK		Wk 0					Wk 2	Wk 4	Wk 6	Wk 8	Wk 10					Wk 12	Wk 18
Dispense patient diary		X						X	X	X	X						
Collect/review patient diary		X						X	X	X	X					X	
Efficacy																	
ACR disease core set <sup>i</sup>		X														X	
AI user assessment																	
Product Technical Complaints		X						X	X	X	X					X	
Patient satisfaction (from patients who were using AI s)		X														X	
Safety																	
Adverse event / SAE recording	X																X
Tuberculosis risk assessment	X	X					X	X		X						X	X
Review of Day 12 laboratory results before IMP administration <sup>j</sup>							X										
Vital signs																	

Source: MSC12665 Clinical Study Report, Table 1, dated July 31, 2015, page 30-35.

Clinical Review  
 Reviewer: Suzette Peng, MD  
 NME/BLA 761037  
 Sarilumab/Kevzara

**Table XX (cont). MSC12665 Study Flow Chart**

	Screening	Baseline	AI assessment													EOT	Posttreatment follow-up / exit <sup>a</sup>
VISIT	V1	V2	V3 <sup>b,c</sup>	V4 <sup>b,c</sup>	V5 <sup>b,c</sup>	V6 <sup>b,f</sup>	V7	V8	V9 <sup>b</sup>	V10	V11 <sup>b</sup>	V12 <sup>b,c</sup>	V13 <sup>b,c</sup>	V14 <sup>b,c</sup>	V15 <sup>b,c</sup>	V16	V17
DAY	D -28 to D -1	D1	D3 (±1)	D5 (±1)	D8 (±1)	D12 (±1)	D15	D29	D43 (±3)	D57 (±3)	D71	D73 (±1)	D75 (±1)	D78 (±1)	D82 (±1)	D85 (±1)	D127 (±1)
WEEK		Wk 0					Wk 2	Wk 4	Wk 6	Wk 8	Wk 10					Wk 12	Wk 18
Temperature, heart rate, blood pressure	X	X					X	X	X <sup>b</sup>	X	X <sup>b</sup>						X
Weight	X																X
Height	X																
Laboratory testing																	
Rheumatoid factor / anti-CCP		X															X
ANA/Anti-dsDNA antibody		X															X
Hematology <sup>k</sup>	X	X				X	X	X	X	X	X						X
Chemistry <sup>l</sup>	X	X					X <sup>m</sup>	X	X <sup>m</sup>	X	X <sup>m</sup>						X
Fasting lipids <sup>n</sup> , fasting glucose <sup>o</sup>	X																X
Urine pregnancy test <sup>d</sup>		X						X		X							X
Hs-CRP	X	X															X
12-lead electrocardiogram	X																X
Urinalysis <sup>p</sup>	X	X															X
Pharmacokinetics																	

Source: MSC12665 Clinical Study Report, Table 1, dated July 31, 2015, page 30-35.

**Table XX (cont). MSC12665 Study Flow Chart**

	Screening		Baseline				AI assessment										EOT	Posttreatment follow-up / exit <sup>a</sup>
VISIT	V1	V2	V3 <sup>b,c</sup>	V4 <sup>b,c</sup>	V5 <sup>b,c</sup>	V6 <sup>b,f</sup>	V7	V8	V9 <sup>b</sup>	V10	V11 <sup>b</sup>	V12 <sup>b,c</sup>	V13 <sup>b,c</sup>	V14 <sup>b,c</sup>	V15 <sup>b,c</sup>	V16	V17	
DAY	D -28 to D -1		D3 (±1)	D5 (±1)	D8 (±1)	D12 (±1)	D15	D29	D43 (±3)	D57 (±3)	D71	D73 (±1)	D75 (±1)	D78 (±1)	D82 (±1)	D85 (±1)	D127 (±1)	
WEEK	Wk 0						Wk 2	Wk 4	Wk 6	Wk 8	Wk 10					Wk 12	Wk 18	
Serum sarilumab <sup>g</sup>		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	
Antibodies to sarilumab <sup>g</sup>		X					X	X		X						X	X	

ACR = American College of Rheumatology; AI = autoinjector device; ALT = alanine aminotransferase; ALP = alkaline phosphatase; ANA = antinuclear antibody; ANC = absolute neutrophil count; anti-CCP = anti-citrullinated peptide antibody; Anti-dsDNA = anti double-stranded deoxyribonucleic acid; AST = aspartate aminotransferase; CBC = complete blood count; DAS28 = Disease Activity Score 28; DMARDs = Disease-modifying antirheumatic drugs; EOT = end of treatment; HAQ-DI = Health Assessment Questionnaire-Disability Index; Hb A1c = glycosylated hemoglobin; HBsAg = hepatitis B surface antigen; HBcore AB = hepatitis B core antibody; HCVAb = hepatitis C virus antibody; hs-CRP = high sensitivity C-reactive protein; INR = International normalized ratio; IMP = Investigational Medicinal Product; IVRS = Interactive Voice Response System; LLN = lower limit of normal; PFS = prefilled syringe; RBC = red blood cell; SAE = serious adverse event; SJC = swollen joint count; TJC = tender joint count; WBC = white blood cell

- a For patients who were unwilling or unable to continue in the long-term extension phase or those patients who prematurely discontinue from the study
- b Pharmacokinetic and/or laboratory sampling visits only. **Note the following exception:** Under circumstances where the neutrophil and/or platelet count(s) were below LLN, based on CBC results from central laboratory at Visits 8 and 10, Visit 9, which was a laboratory visit only and Visit 11, which was a laboratory and PK visit only, must have been conducted as standard site visits.
- c These visits could have been home visits
- d In women of child-bearing potential only
- e After instructions at Baseline (Visit 2, D1) patients self-administered all remaining doses at home.
- f For all patients, the Visit 6 hematology laboratory assessment was available to confirm that the ANC and platelet count were not within the protocol-defined limits for temporary or permanent discontinuation of the IMP, before the administration of the second dose of study drug at Visit 7.
- g Noninvestigational medicinal product (eg, nonbiological DMARDs) was dispensed according to the local practice
- h This includes collection of AI treatment kits (used and unused)
- i ACR core set included: SJC - 66 joints, TJC - 68 joints, Patient Global Assessment, Pain Intensity, HAQ-DI, hs-CRP and Physician Global Assessment; DAS28 components include selected 28 SJC, 28 TJC, Patient Global Assessment and hsCRP
- j If any Visit 2 laboratory result met the values defined in exclusion criterion E34, the second dose of investigational medicinal product (IMP) should not have been administered and the patient should have been withdrawn from study treatment
- k Hematology (blood should have been drawn BEFORE IMP administration): Hemoglobin, hematocrit, RBC count and morphology (if RBC count is abnormal), WBC differential, platelet count, absolute neutrophil count.

Source: MSC12665 Clinical Study Report, Table 1, dated July 31, 2015, page 30-35.

Clinical Review

Reviewer: Suzette Peng, MD

NME/BLA 761037

Sarilumab/Kevzara

**Table XX (cont). MSC12665 Study Flow Chart**

- l* Chemistry (blood should have been drawn BEFORE IMP administration): Sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, creatinine clearance, calcium, phosphate, total protein, albumin, ALT, AST, ALP, total bilirubin, conjugated bilirubin, unconjugated bilirubin, lactate dehydrogenase, uric acid, INR (prothrombin time), and hs-CRP
- m* Only ALT, AST, ALP, total bilirubin, conjugated bilirubin, unconjugated bilirubin, and INR (prothrombin time)
- n* Lipids (blood should have been drawn BEFORE IMP administration): triglycerides, total cholesterol, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol. In addition, Apolipoprotein A and Apolipoprotein B were to be tested at Screening and Visit 16 (Week 12).
- o* Blood should have been drawn BEFORE IMP administration
- p* Urinalysis dipstick: specific gravity, pH, glucose, blood, ketones, proteins, bilirubin, urobilinogen, nitrate, and leukocyte esterase
- q* Samples must have been taken within 24 hours prior to the next IMP administration.

Source: MSC12665 Clinical Study Report, Table 1, dated July 31, 2015, page 30-35.

APPEARS THIS WAY ON ORIGINAL

Clinical Review  
Reviewer: Suzette Peng, MD  
NME/BLA 761037  
Sarilumab/Kevzara

APPEARS THIS WAY ON ORIGINAL

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

SUZETTE W PENG

10/04/2016

This submission incorporates minor revisions made to the original review submitted on 9/22/16.

JANET W MAYNARD

10/04/2016

## Cross-Discipline Team Leader Review

<b>Date</b>	September 16, 2016
<b>From</b>	Janet Maynard, MD, MHS
<b>Subject</b>	Cross-Discipline Team Leader Review
<b>NDA/BLA # Supplement#</b>	761037
<b>Applicant</b>	sanofi-aventis U.S. LLC
<b>Date of Submission</b>	October 30, 2015
<b>PDUFA Goal Date</b>	October 30, 2016
<b>Proprietary Name / Non-Proprietary Name</b>	KEVZARA / Sarilumab
<b>Dosage form(s) / Strength(s)</b>	200 mg/1.14 mL or 150 mg/1.14 mL solution in a single-dose pre-filled syringe
<b>Applicant Proposed Indication(s)/Population(s)</b>	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
<b>Recommendation on Regulatory Action</b>	<i>Approval if able to resolve issues related to site for manufacture of the drug product</i>
<b>Recommended Indication(s)/Population(s) (if applicable)</b>	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)

## 1. Benefit-Risk Assessment

### **Benefit-Risk Summary and Assessment**

Rheumatoid arthritis (RA) is a serious disease that can cause pain, stiffness, and functional impairment. The majority of patients with RA have a chronic, progressive disease that is associated with increased morbidity and mortality. There are multiple approved drugs to treat RA, but another biologic therapy would add another therapeutic option for RA.

Sarilumab is a human monoclonal antibody of the IgG1 kappa isotype that binds to human interleukin-6 receptor (IL-6R). The efficacy of sarilumab (150 mg and 200 mg) was established in two phase 3 trials in patients with RA. These trials were adequate and well-controlled, and provided corroborating evidence of the efficacy of sarilumab for reducing signs and symptoms of RA, based on the proportion of patients experiencing an American College of Rheumatology (ACR) response criteria and reduction in DAS28-CRP. Comparison of the two sarilumab doses indicates that the proportion of patients experiencing improvement in the sarilumab 200 mg once every two week group was numerically higher than the 150 mg group. Both of the phase 3 trials provided corroborating evidence of sarilumab for improving physical function, as measured by Health Assessment Questionnaire-Disability Index (HAQ-DI). The level of improvement was similar for the 150 mg and 200 mg dose groups. The effect of sarilumab on structural damage progression was assessed by radiographs in one study, which provided evidence of efficacy of sarilumab on structural damage progression and suggested trends towards more inhibition of radiographic progression with the 200 mg dose as compared to the 150 mg dose. Although there was only a single study assessing radiographic progression, the evidence is sufficient due to the highly statistically significant p-values and the consistency of the results across the two doses and with different analysis techniques.

The safety profile of sarilumab is well-characterized within the clinical trials. Based on this profile, the major toxicities of concern with sarilumab are related to significant immunosuppression and are consistent with the safety concerns of tocilizumab, which has the same mechanism of action. Sarilumab was associated with an increased risk of serious infections, including opportunistic infections and tuberculosis. While no imbalance in malignancy was seen in the clinical trials, treatment with an immunosuppressant may increase the risk of malignancies. Sarilumab treatment was associated with laboratory abnormalities including decreases in neutrophils and platelets and increases in liver function tests and lipid parameters. In general, laboratory abnormalities appeared to be dose-related. Notably, there did not appear to be an association between neutropenia and the development of infections. There were elevations in LDL, HDL, and triglycerides on sarilumab, but there was no clear increase in the risk of cardiovascular events on sarilumab during the time frame of the clinical trials. That being said, there were very few events observed overall and we therefore have limited ability to rule out increases in risk based on the currently available clinical data. Additional safety concerns included hypersensitivity reactions and gastrointestinal perforation.

Based on the data in this submission and the seriousness of RA, the benefit/risk profile of sarilumab is adequately favorable to support the 200 mg dose regimen, with dose reduction to 150 mg as needed for laboratory abnormalities. Compared to the 150 mg dose, the 200 mg dose demonstrated numerical trends suggesting additional benefit on both clinical and radiographic outcomes. While there were some dose-related safety signals, the safety profile of both doses is acceptable given the severity of this disease and the demonstrated benefits. The identified safety concerns can be addressed through appropriate product labeling.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<u>Analysis of Condition</u>	<ul style="list-style-type: none"> <li>• Rheumatoid arthritis (RA) is an autoimmune disease that causes chronic symmetric inflammation of joints. It can also cause inflammation outside of the joints in a variety of locations, such as the lungs, heart, and blood vessels.</li> <li>• RA affects 1% of the adult population in the United States (US) and is the most common type of autoimmune inflammatory arthritis.</li> <li>• RA significantly impacts the lives of patients due to pain and decreased physical function. In addition, patients with RA have higher mortality rates than the general population.</li> <li>• The goal of treatment is early and aggressive use of medications to try to prevent functional impairment and irreversible joint damage.</li> </ul>	<p>Rheumatoid arthritis is a serious condition and is the most common type of autoimmune inflammatory arthritis. Most patients have a chronic progressive disease that is associated with morbidity and increased mortality.</p>
<u>Current Treatment Options</u>	<ul style="list-style-type: none"> <li>• All patients with RA are generally treated with disease modifying antirheumatic drugs (DMARDs). There are multiple drugs approved by the FDA for the treatment of RA. Generally, methotrexate (MTX) is the first line of therapy for RA. Treatment with a tumor necrosis factor-alpha (TNF-<math>\alpha</math>) antagonist as add-on or as monotherapy is generally the recommended next line of treatment. However, between 30% and 40% of patients fail to respond or become intolerant to anti-TNF-<math>\alpha</math> therapy. For these patients, additional anti-TNF-<math>\alpha</math> therapies or therapies that target different pathways can be used.</li> <li>• Tocilizumab is approved for the treatment of RA and has the same target as sarilumab (interleukin-6 receptor).</li> </ul>	<p>There are multiple current treatment options for patients with RA.</p>
<u>Benefit</u>	<ul style="list-style-type: none"> <li>• Sarilumab is proposed for treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more DMARDs. The efficacy of sarilumab was established in two phase 3 clinical trials. One trial was placebo controlled for 52 weeks (n=1197) and one trial was placebo controlled for 24 weeks (n=546).</li> <li>• The primary endpoint in both phase 3 trials was the proportion of patients who achieved an ACR20 response at Week 24.</li> <li>• The ACR20 response is calculated as a &gt;20% improvement in:                             <ul style="list-style-type: none"> <li>• tender joint count and</li> <li>• swollen joint count and</li> <li>• 3 of the 5 remaining ACR core set measures</li> </ul> </li> </ul>	<p>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.</p> <p>Although the two pivotal phase 3 studies did not include an active comparator, the degree in</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<ul style="list-style-type: none"> <li>○ Patient Global Assessment of Arthritis on a visual analog scale (VAS)</li> <li>○ Physician Global Assessment of Arthritis on a VAS</li> <li>○ Patient Assessment of Pain on a VAS</li> <li>○ Patient Assessment of Physical Function</li> <li>○ Acute Phase Reactant</li> </ul> <p>Fifty percent and 70 percent improvement (ACR50 and ACR70) are similarly calculated using these higher levels of improvement.</p> <ul style="list-style-type: none"> <li>● In both studies, patients treated with either 200 mg or 150 mg of sarilumab + MTX/DMARD every two weeks had higher ACR20, ACR50, and ACR70 response rates versus placebo-treated patients at Week 24. In study EFC11072 Part B the difference (95% confidence interval) from placebo for ACR20 at 24 weeks was 25% (18%, 31%) and 33% (27%, 40%) for the 150 mg and 200 mg dose groups, respectively. In study EFC10832, the difference (95% confidence interval) from placebo for ACR20 at 24 weeks was 22% (13%, 32%) and 27% (18%, 37%).</li> <li>● Both studies demonstrated that patients receiving sarilumab 200 mg or 150 mg every two weeks had greater improvement from baseline in physical function, as measured by the Health Assessment Questionnaire-Disability Index (HAQ-DI) compared to placebo.</li> <li>● Results from Study EFC11072 Part B showed that both doses of sarilumab were associated with significantly less radiographic progression of structural damage as compared to placebo. Although there was only a single study assessing radiographic progression, the evidence is sufficient due to the highly statistically significant p-values and the consistency of the results across the two doses and with different analysis techniques.</li> <li>● For the vast majority of endpoints, sarilumab 200 mg was associated with numerically higher responses than 150 mg. The data suggest trends towards more radiographic inhibition with the 200 mg dose as compared to the 150 mg dose.</li> </ul>	<p>reduction in signs and symptoms of RA and inhibition of radiographic progression appears to be similar to other DMARDs approved for RA. Without effective treatment, joint damage progresses chronically and irreversibly and results in impaired physical function and disability. Thus, effective therapies are needed for RA.</p>
<b><u>Risk</u></b>	<ul style="list-style-type: none"> <li>● The safety of sarilumab in combination with DMARDs was evaluated in phase 2 and phase 3 studies, consisting of 3,019 patients, which included 132 patients on sarilumab monotherapy. The drug exposure data are considered adequate. The safety profile for sarilumab was consistent with the known safety profile of tocilizumab.</li> </ul>	<p>The size of the safety database for sarilumab is adequate. Its safety profile is well characterized and consistent with the safety profile of tocilizumab, a medication approved for RA.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<ul style="list-style-type: none"> <li>• Major safety concerns:</li> <li>• <u>Serious infections</u>: Serious and sometimes fatal infections due to bacterial, mycobacterial, fungal, viral, or other opportunistic pathogens were reported in patients receiving sarilumab for RA.</li> <li>• <u>Laboratory parameters</u>: Sarilumab is associated with decreases in neutrophils and platelet counts. In addition, sarilumab is associated with increases in liver enzymes and lipid parameters, such as LDL cholesterol, HDL cholesterol, and triglycerides. In general, these laboratory abnormalities appeared to be dose-related. While neutropenia appeared to be dose-related, there did not appear to be an association between neutropenia and the development of infections. Liver enzyme elevations were mostly mild, and no cases were consistent with Hy’s law criteria.</li> <li>• <u>Gastrointestinal perforation</u>: Events of gastrointestinal perforation were reported in clinical studies, primarily as complications of diverticulitis.</li> <li>• <u>Immunosuppression</u>: While no imbalance in malignancy was seen in the clinical trials, treatment with immunosuppressants may increase the risk of malignancies.</li> <li>• <u>Hypersensitivity reactions</u>: Hypersensitivity reactions, such as rash and urticaria, have been reported in association with sarilumab.</li> </ul>	<p>The main safety concerns associated with sarilumab are immunosuppression and laboratory parameter changes, including neutropenia, thrombocytopenia, and elevations in lipid parameters and liver function tests. Overall, the risks observed are deemed acceptable with proper warnings.</p> <p>Each drug approved for RA is associated with toxicities.</p>
<p><b><u>Risk Management</u></b></p>	<ul style="list-style-type: none"> <li>• The safety concerns with sarilumab are well-characterized. Healthcare providers are familiar with treatments for RA associated with immunosuppression and lipid elevations.</li> <li>• Tocilizumab has a boxed warning for serious infections, including active tuberculosis, invasive fungal infections, and bacterial, viral and other infections due to opportunistic pathogens.</li> </ul>	<p>These risks can be communicated to healthcare professionals through labeling (including a Medication Guide). The labeling will include a boxed warning for serious infections. In addition, the labeling will contain Warnings and Precautions for the major safety signals. The safety section of the label will be similar to that of tocilizumab. Routine pharmacovigilance and labeling are adequate to address the safety issues associated with sarilumab.</p>

## 2. Background

Sanofi-aventis U.S. LLC, A SANOFI COMPANY (sanofi) submitted biologics license application (BLA) 761037 on October 30, 2015, 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 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. (b) (4)

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<sup>®</sup>, 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.

Rheumatoid arthritis (RA) is a chronic, symmetric inflammatory polyarthritis that primarily involves synovial joints. In RA, synovial tissues become inflamed and proliferate, forming pannus that invades bone, cartilage, and ligament and leads to joint damage and deformities. Destruction of synovial joints can lead to severe disability and premature mortality.<sup>1,2</sup>

RA affects approximately 1% of the adult population in North America and Northern Europe.<sup>3</sup> The disease is three times more frequent in women than men. Prevalence rises with age and is highest in woman older than 65 years.

<sup>1</sup> Scott DL, et al. Long-term outcome of treating rheumatoid arthritis: results after 20 years. *Lancet* 1987;1:1108-11.

<sup>2</sup> Mitchell DM, et al. Survival, prognosis, and causes of death in rheumatoid arthritis. *Arthritis Rheum* 1986;29:706-14.

<sup>3</sup> Gabriel SE, et al. Epidemiological studies in incidence, prevalence, mortality, and comorbidity of the rheumatic diseases. *Arthritis Res Ther* 2009;11(3):229.

While there is heterogeneity in the natural history of RA, it is generally a chronic, progressive disease. Patients can develop joint destruction, severe physical disability and multiple co-morbidities. In contrast to clinical symptoms, structural damage is irreversible and cumulative.<sup>4</sup>

All patients diagnosed with RA are generally treated with disease-modifying antirheumatic drugs (DMARDs). A variety of non-biologic DMARDs are approved for RA, including corticosteroids, various nonsteroidal anti-inflammatory drugs (NSAIDs), sulfasalazine, auranofin, methotrexate (MTX), azathioprine, penicillamine, cyclosporine, and leflunomide. Non-biologic DMARDs, such as MTX, are the first line of therapy for RA.<sup>5</sup> Treatment with a tumor necrosis factor-alpha (TNF- $\alpha$ ) antagonist is generally the next line of treatment for patients with ongoing disease activity. Currently approved TNF- $\alpha$  antagonists include etanercept (ENBREL), infliximab (REMICADE), adalimumab (HUMIRA), golimumab (SIMPONI), certolizumab pegol (CIMZIA), golimumab IV (SIMPONI ARIA), infliximab-dyyb (INFLECTRA), and etanercept-szsz (ERELZI). Between 30% and 40% of patients fail to respond or become intolerant to anti-TNF- $\alpha$  therapy.<sup>6</sup> For patients with ongoing disease activity, the therapeutic strategy usually involves trying another TNF- $\alpha$  antagonist or switching to a medication with a different mechanism of action. Approved alternative therapies include an orally bioavailable Janus kinase (JAK) inhibitor (tofacitinib/XELJANZ OR XELJANZ XR), and biological DMARDs targeting the B-cell antigen CD-20 (rituximab/RITUXAN), cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4; abatacept/ORENCIA), and the pro-inflammatory cytokines IL-1 (anakinra/KINERET) and IL-6 (tocilizumab/ACTEMRA).

The long-term goal of treatment is prevention of irreversible joint destruction and functional impairment given the significant impact on patients and public health. The short-term goal of treatment is improvement in signs, symptoms, and functional status.

### **Key Regulatory Interactions**

Key regulatory interactions are listed below by date. Points of discussion or Division recommendations are provided as a bulleted list for each meeting or interaction. The development program for sarilumab occurred under IND 100632.

August 2, 2007 – Pre-IND meeting

---

<sup>4</sup> Scott DL. Radiographic progression in established rheumatoid arthritis. *J Rheumatol Suppl* 2004;69:55-65.

<sup>5</sup> Katchamart W, et al. Methotrexate monotherapy versus methotrexate combination therapy with non-biologic disease modifying anti-rheumatic drugs for rheumatoid arthritis. *Cochrane Database Syst Rev* 2010;4:CD008495.

<sup>6</sup> Smolen JS, et al. Rheumatoid arthritis therapy reappraisal: strategies, opportunities and challenges. *Nat Rev Rheumatol* 2015;11(5):276-89.

- Agreement on initial clinical study design and CMC data to support initial development

September 29, 2009 – Type C meeting (Discussion of design of EFC11072 (Phase 2/3) study)

- Expectations for Study EFC11072, which contains an operationally seamless design, were established. Potential adaptive study design proposals were considered and the sponsor elected not to utilize an adaptive design.
- FDA indicated that patients in Part B cohort 1 should not be included in efficacy analyses, but should be included in safety analyses
- Safety database at time of BLA submission is expected to include at least 1,000-1,500 patients treated for 1 year at the proposed dose
- Agreement that it was reasonable to evaluate different patient populations (MTX-inadequate response (IR) and DMARD-IR)
- Agreement for waiver for thorough QT study

February 23, 2011 – Type C meeting (Comparability of Phase 2 ((b)(4)F2) and Phase 3 ((b)(4)F3) drug product)

- Agreement that the planned switch to the (b)(4)F3 drug product in the phase 3 portion of Study EFC11072 could proceed based on data provided. FDA noted that data linking the (b)(4)F2 and (b)(4)F3 formulations should be submitted in the BLA.
- Concerns were raised regarding cases of neutropenia in the development program. FDA emphasized the importance of establishing adequate dose ranging.
- Limited discussion occurred (b)(4)

September 15, 2011 – End of Phase 2 (EOP2) meeting

- Agreed that the two proposed phase 3 trials, in conjunction with an acceptable safety profile, should be adequate to support submission of a BLA for sarilumab for the treatment of RA
- Recommended incorporation of tocilizumab into a phase 3 study for use as a benchmark for safety comparison
- Noted that the adequacy of a single study to support a claim of inhibition of structural damage in patients with RA will be a review issue
- Advised to conduct a 12-week study using the autoinjector to obtain pharmacokinetic and actual use data in patients with RA
- Recommended use of an adjudication committee for major cardiovascular events
- Agreement on the clinical pharmacology and nonclinical programs

October 26, 2011 – CMC EOP2 meeting

- Agreement on expectations for stability data
- Expectations for [REDACTED] <sup>(b) (4)</sup> human factors evaluation described

April 10, 2012 – Advice/Information Request to submission dated March 13, 2012 (regarding study EFC11072)

- Agreed with modification of the terminology for the primary objectives and co-primary endpoints while maintaining the previously proposed hierarchical testing procedure
- Advised on handling of missing data
- Provide analysis of HAQ-DI at Week 24 as a secondary analysis
- Reasonable to evaluate statistical significance of the treatment effect on the ACR20 endpoint even in the absence of a significant effect on the other two co-primary endpoints. However, FDA may not consider this sufficient for regulatory purposes and would need to consider this in the context of the overall risk-benefit assessment.

June 14, 2012 – Advice/Information Request to submission dated April 13, 2012 (regarding study MSC12665)

- Agreed with proposed patient population and endpoints in study MSC12665

November 9, 2012 – Advice/Information Request to submission dated September 25, 2012

- Agreed with proposal to assess relative safety of sarilumab vs. tocilizumab for 24 weeks
- Noted that a trial of 200 patients divided among 3 treatment arms was anticipated to have a relatively large amount of variability and it was not clear whether the number of patients would be adequate to make reliable comparisons between tocilizumab and sarilumab. The sponsor was advised that they could proceed with the proposed trial, but it was noted that additional data could be required.

May 15, 2013 – Advice/Information Request to submission dated November 12, 2012

- Agreed with proposed analyses for the radiographic data and HAQ-DI endpoint
- Agreed with approach to handling missing data for ACR20 and van der Heijde total Sharp score, but did not agree with approach for HAQ-DI. For HAQ-DI, an approach that appropriately estimates the variance of the treatment effect, but does not perpetuate a treatment effect, such as multiple imputation, was requested.

August 21, 2013 – Advice/Information Request to submission dated June 3, 2013 (regarding SAP for Study EFC13752)

- Recommended re-defining primary analysis of HAQ-DI to a time point before many treatment discontinuations have occurred, such as 16 weeks, to minimize the amount of missing data

September 30, 2013 – Advice/Information Request to submission dated May 30, 2013 (regarding study EFC13752)

- Did not agree with proposed design of study EFC13752 (b) (4) It was noted that an evaluation of sarilumab monotherapy is not a requirement, but is of interest from the perspective of safety and immunogenicity.
- Recommended several potential study designs, noting the study should be 6 months or longer to assess immunogenicity

December 4, 2013 – FDA response regarding carcinogenicity assessment (submission dated August 16, 2011)

- Agreed that no additional nonclinical studies were needed to address the carcinogenic potential of sarilumab

January 10, 2014 – Advice/Information Request to submission dated August 12, 2013

- Agreed with iPSP

August 19, 2014 – Type C meeting (written responses only)

- Agreed with the content, structure, and version of the electronic submission datasets to be included in the BLA
- Agreed with the proposed BIMO listings and provisions for narratives

October 22, 2014 – pre-BLA meeting

- Agreement reached regarding the proposed pooling strategies for the safety analyses
- Recommended additional safety analyses to better characterize sarilumab's safety profile and to address the complexity in the study design
- Noted that data from study EFC13752 (monotherapy safety study) was not required at the time of BLA submission

December 16, 2014 – CMC pre-BLA meeting

- All facilities should be registered with FDA at the time of the BLA submission and ready for inspection
- Outlined specific microbiology information that should be included in the BLA
- Agreement on comparability between products made with industrial versus the clinical filing lines

In summary, there were multiple interactions between the Agency and sanofi and there was general agreement with sanofi's proposed development program.

### 3. Product Quality

#### Quality Review Team

<i>Discipline</i>	<i>Reviewer</i>	<i>Branch/Division</i>
<i>Product Quality</i>	<i>Gerald Feldman</i>	<i>Division of Biotechnology Review and Research IV</i>
<i>Microbiology Quality Assessment</i>	<i>Lakshmi Narasimhan Candace Gomez-Broughton</i>	<i>Division of Microbiology Assessment</i>
<i>Manufacturing Facilities</i>	<i>Laura Fontan</i>	<i>Division of Inspectional Assessment</i>
<i>Business Regulatory Process Manager</i>	<i>Melinda Bauerlien</i>	<i>OPRO/OPQ</i>
<i>Quality Application Technical Lead</i>	<i>Michele Dougherty</i>	<i>Division of Biotechnology Review and Research IV</i>

- **General product quality considerations**

#### Overview

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.

#### Drug Substance

Sarilumab is a human monoclonal antibody (mAb) of the IgG kappa isotype that binds the interleukin 6 receptor (IL-6R). Sarilumab has a molecular weight of approximately 150 kDa. The primary mechanism of action is the inhibition of the binding of interleukin 6 (IL-6) to the IL-6R. Sarilumab binds to the IL-6R with a dissociation constant of 60.2 pM. Binding of sarilumab to IL-6R prevents ligand-induced receptor activation and subsequent signaling through downstream signaling pathways. The potency assay used to assess the biological activity of sarilumab for release and stability is a cell-based assay that assesses the ability of sarilumab to block IL-6-induced proliferation of human DS-1 cells in vitro. The potency is reported as % relative potency to that of a qualified reference standard. Sarilumab is produced by expression of recombinant DNA encoding sarilumab nucleotide sequence in a Chinese Hamster Ovary (CHO) cell line using standard cell culture. The Regeneron designation for the DS manufacturing process is (b) (4)

Sanofi

has provided CMC data to support the comparability of the processes.

### Drug Product

Sarilumab solution for injection is a clear, colorless to pale yellow, aqueous (b) (4) sterile solution, pH 6.0. Sarilumab solution for injection is supplied, for subcutaneous (SC) injection, as a single-use prefilled syringe (PFS) drug product (DP) presentation in two strengths, 131.6 mg/mL and 175 mg/mL, providing doses of 150 mg and 200 mg, respectively. Table 1 provides a summary of the PFS components and presentations for the 150 mg and 200 mg dose forms. The bulk PFS container closure system is comprised of a (b) (4) 1-mL-long, clear glass (Type I (b) (4)) syringe, equipped with a staked (b) (4) (27 gauge, ½-inch, (b) (4)) needle, and closed with a (b) (4) elastomer (b) (4) soft needle shield and (b) (4) elastomer (b) (4) plunger stopper. On the PFS, the finger flange and product label are differentially colored for each dose form. The 150 mg dose form contains a light orange finger flange. The 200 mg dose form contains a dark orange finger flange (Table 2).

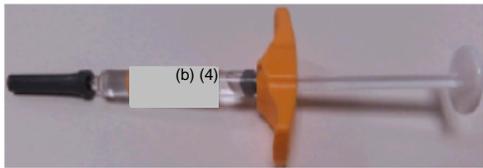
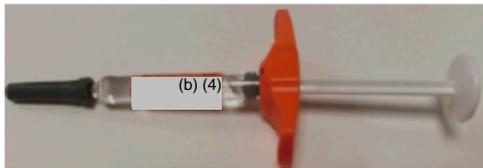
The data provided in the BLA support an expiry of 24 months for the drug product when stored at the recommended storage conditions of 2-8°C. The data provided in the BLA do support storage of the drug product for up to 14 days at (b) (4)°C once removed from the refrigerator.

**Table 1: Summary of the PFS Components and Presentations for the 150 mg and 200 mg Dose Forms**



Source: Module 2.3.P, Table 1, page 8, submitted 10/30/15

**Table 2: Prefilled Syringes (PFS)**

	150 mg	200 mg
		
Plunger rod	white	white
Finger flange	Light orange	Dark orange

The labels affixed to the syringes in the figures are mock ups of the actual labels that will be included on the commercial prefilled syringe

Source: Module 2.3.P, Table 2, page 9, submitted 10/30/15

Quality postmarketing commitments (PMC) have been recommended

(b) (4)

#### *Human factors validation study*

Sanofi performed a Human Factors validation study to evaluate the use of the sarilumab prefilled syringe (PFS), the associated label and packaging, and the Instructions for Use (IFU). The Division of Medication Error Prevention and Analysis (DMEPA) reviewed the Human Factors validation study. There were failures that occurred in critical tasks in the study, however, most of the failures were related to standard practice associated with this type of injectable product, such as hand washing or cleaning the injection site. Of the 139 participants, there was only one failure related to injection of sarilumab. An untrained participant failed to press on the plunger to inject the full dose. The participant removed the needle from the injection pad prior to administration of the full dose and a small amount of liquid remained in the syringe. The participant realized the error and performed a second injection successfully. The design of the PFS is standard for the indicated RA patient population, and DMEPA did not have any recommendations for modifications based on the study data. Sanofi made revisions to the IFU to further clarify the storage and checking the drug information, and DMEPA found these modifications acceptable.

The Center for Devices and Radiological Health, Office of Device Evaluation (CDRH/ODE) was consulted for review of the sarilumab 150 and 200mg pre-filled syringes. Based on the information reviewed, CDRH/ODE found that the sanofi provided sufficient information related to the bench performance testing, biocompatibility, sterility, shelf life, and shipping studies to support the safe and effective use of the device. As a result, CDRH/ODE recommends approval of the BLA for this combination product.

The Office of Compliance at CDRH (CDRH/OC) evaluated sanofi's compliance with applicable Quality System Requirements. From the perspective of the applicable Quality System Requirements, CDRH/OC noted that the application is approvable.

- **Facilities Review/Inspection**

The drug substance manufacturing site is Regeneron Pharmaceuticals (Rensselaer, NY). A pre-approval inspection of the drug substance manufacturing site was conducted from 02/01/16 to 02/05/16. The compliance status of the manufacturing site was found to be acceptable.

The site for manufacture of the drug product is Sanofi Winthrop Industrie (LeTrait, France). The compliance status of the drug product manufacturing site is currently under assessment. A GMP inspection was conducted from 07/07/16 to 07/19/16. Thirteen observations were noted:

1. The firm has repeatedly refused to provide the requested documentation for review [REDACTED] (b) (4)
2. The firm does not have a thorough understanding of the requirements for submission of NDA Field Alerts.
3. The written complaint record did not include the reason an investigation was found not to be necessary when an investigation into unexplained discrepancies was not conducted.
4. Investigations were found to be inadequate for two media fill failures and there have been 4 deviations opened for bioburden excursions.
5. Aseptic process simulations were found inadequate.
6. Procedures designed to prevent microbiological contamination of drugs products purporting to be sterile are not established.
7. Routine calibration and inspection of electronic equipment is not performed according to a written program designed to assure proper performance.
8. The equipment used in the manufacture, processing, and packaging [REDACTED] (b) (4) is not adequate construction and design for its intended use.

9. Equipment and utensils are not sanitized at appropriate intervals to prevent contamination that would alter the safety, identity, strength, quality or purity of the drug product.
10. The firm does not have scientific rationale or justification for the placement of their non-viable particle monitors.
11. The controlled areas within the manufacturing department are not maintained in a state of control.
12. Qualification/requalification studies were found deficient.
13. Reports of analysis from component suppliers are accepted in lieu of testing each component for conformity with all appropriate written specifications, establishing the reliability of the supplier's analyses through appropriate written specifications, establishing the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals.

Additional details of these deficiencies are listed in the Form 483. The inspection resulted in a "provisional official action indicated" recommendation. The status of the facility is currently under review with the CDER Office of Compliance. If OPQ recommends withholding approval based on these facilities issues, this would impact the overall approvability of this application.

Please see the OPQ review for additional details.

- **Other notable issues (resolved or outstanding)**

(b) (4)

At the time of this review, the Office of Pharmaceutical Quality, CDER, recommends withholding approval for KEVZARA (sarilumab) manufactured by Sanofi, Inc. due to the initial official action indicated status of the Sanofi, Inc drug product manufacturing facility, Le Trait, France. When the compliance status of the Sanofi, Inc. Le Trait DP site is determined to be acceptable, OPQ will provide an updated recommendation on approval. If the Office of Pharmaceutical Quality recommends withholding approval based on the facilities issues at the time of action, this will impact the overall approvability of this application.

## 4. Nonclinical Pharmacology/Toxicology

*Pharm-Tox Reviewer: Eleni Salicru, PhD; Supervisor/Team Leader: Timothy Robison, PhD, DABT*

- **General nonclinical pharmacology/toxicology considerations**

The nonclinical safety program for sarilumab was performed in cynomolgus monkeys, which were established as the most pharmacologically relevant nonclinical species. As determined by surface plasmon resonance (SPR), sarilumab binds human IL-6R and cynomolgus monkey IL-6R with equilibrium dissociation constants (Kd) of 54.4 pM and 123 pM, respectively.

Results from a number of GLP-compliant repeat-dose toxicology studies in cynomolgus monkeys with sarilumab by intravenous (IV) administration for durations up to 6 months and by SC administration for 3 months did not identify any significant dose-limiting toxicity or target organs of toxicity at IV doses up to 50mg/kg/week or SC doses up to 100mg/kg/week (two weekly doses of 50mg/kg). There were no deaths that were attributed to treatment with sarilumab. Microscopic findings were limited to effects at the injection site (minimal to moderate perivascular mixed inflammatory cell infiltrates). The most common effects related to treatment with sarilumab were decreased levels of neutrophils, fibrinogen, and/or C-reactive protein (CRP). These decreases were considered pharmacodynamics (PD) effects of inhibiting IL-6 signaling. In most cases, these effects were not dose-dependent and were generally reversible during the recovery period. The 6-month study revealed slight decreases in primary and secondary IgG responses following antigen challenge.

- **Carcinogenicity**

Based on species specificity, a rodent carcinogenicity study with sarilumab was not considered feasible. The Executive Carcinogenicity Assessment Committee (ECAC) concurred that a carcinogenicity study was not feasible. No nonclinical studies were required to evaluate the potential carcinogenicity of sarilumab. A review of the scientific literature related to the role of IL-6/IL-6R pathway in cancer was conducted.

- **Reproductive toxicology**

The reproductive and developmental toxicity of sarilumab was evaluated in an enhanced pre- and postnatal development (ePPND) study in pregnant cynomolgus monkeys. Further, a murine surrogate monoclonal antibody to sarilumab that binds mouse IL-6Ra (i.e., REGN844) was developed and used for a fertility study in mice. In the ePPND study, there was no evidence of embryotoxicity or fetal malformations. There were some concerns about the adequacy of this study based upon the small number of animals per group at the time of necropsy and absence of immune function testing in the offspring during the postnatal period, which may lead to uncharacterized effects beyond the one month of age in monkeys. Fertility and reproduction were unaffected in male and female mice

treated with REGN844 at SC doses up to 100 mg/kg twice per week. In the literature, there are data that inhibition of IL-6 signaling may interfere with cervical ripening and dilation and myometrial contractile activity leading to potential delays of parturition.

- **Other notable issues (resolved or outstanding)**

The Pharmacology/Toxicology team believes the information in this application is adequate to support approval. No outstanding issues have been identified or phase 4 commitments recommended.

## 5. Clinical Pharmacology

*Clinical pharmacology reviewers: Jianmeng Chen, MD, PhD and Sheetal Agarwal, PhD, RAC; Team Leader: Anshu Marathe; Supervisor: Suresh Doddapaneni, PhD  
Pharmacometrics Reviewer: Jianmeng Chen, MD, PhD; Pharmacometrics Team Leader: Jingyu Yu, PhD*

- **General clinical pharmacology considerations, including absorption, food effects, bioavailability, etc**

Sarilumab is a recombinant human immunoglobulin (IgG)1 monoclonal antibody that binds to both soluble and membrane-bound interleukin-6 (IL-6) receptors (sIL-6R $\alpha$  and mIL-6R $\alpha$ ) and inhibits IL-6 mediated signaling. By binding to IL-6 $\alpha$  with high affinity, sarilumab blocks the binding of IL-6 and interrupts the cytokine-mediated inflammatory signaling cascade.

Sarilumab exhibits nonlinear PK with target mediated drug disposition. It is well absorbed after SC administration ( $T_{max}$  of 2 to 4 days and a bioavailability of 80%), exhibits an apparent volume of distribution of 7.3 L, which indicates distribution primarily in the circulatory system.

Sarilumab exposure increases in a greater than dose proportional manner. At steady state,  $AUC_{0-14 \text{ days}}$  is two-fold higher with sarilumab 200 mg q2w compared to sarilumab 150 mg q2w. Steady state appears to be achieved in 14 to 16 weeks following repeated q2w SC administration, with a 2- to 3- fold accumulation for  $AUC_{0-14 \text{ days}}$ . The effective half-life is ~17-19 days based on accumulation (AUC) steady state.

### *Immunogenicity*

Persistent anti-drug antibody (ADA) response was observed in 2%, 5.6%, and 4% of patients in the placebo and sarilumab 150 and 200 mg q2w treatment groups across the placebo controlled immunogenicity population (Pool 1), with 0.2%, 1.6%, and 1% of patients also exhibiting NAb. Positive ADA status has an impact on PK (a 24% to 28% lower exposure when compared to ADA negative patients), with concentrations in patients with persistent response being lower (by 32% to 41%) than in patients with transient response. Sarilumab concentrations in this small number of Nab positive patients appeared to be lower than in Nab negative patients (by 49% to 59%), but this did not impact discontinuations for lack or loss of efficacy.

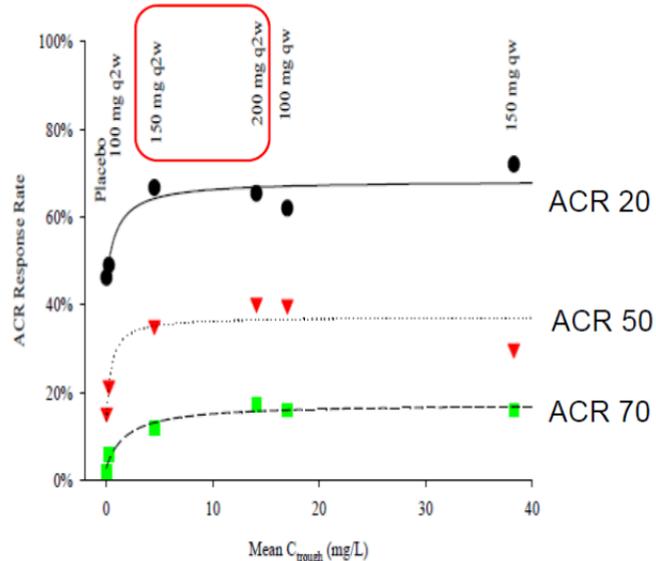
After adjusting for PK, the ADA status does not have additional impact on exposure-response analysis for efficacy endpoints such as DAS28, or safety endpoints such as ANC, ALT, or LDL. While sarilumab exposure in ADA positive patients was lower than in ADA negative patients, this did not lead to discontinuations due to lack or loss of efficacy. See Section 8 (Safety) for additional discussion of immunogenicity.

*Dose selection/Exposure response*

The proposed recommended dose (b) (4) is 200 mg once every two weeks. The proposed label suggests not initiating (b) (4) in patients with ANC < 2000/mm<sup>3</sup>, platelets < 150,000/mm<sup>3</sup> or liver transaminases above 1.5 X ULN. Reduction of dose from 200 mg once every 2 weeks to 150 mg once every 2 weeks is recommended for management of neutropenia, thrombocytopenia, and elevated liver enzymes. (b) (4) may be used as monotherapy or in combination with methotrexate (MTX) or other traditional DMARDs as a subcutaneous injection.

See Section 7 (dose selection) regarding the sanofi's rationale to support the proposed dose based on dose-ranging in study EFC11072 Part A. In terms of PK considerations, following every week (100 and 150 mg qw) and every other week (100, 150, and 200 mg q2w) dose regimens in the phase 2 dose-ranging study (EFC11072 Part A), the efficacy (ACR20, ACR50, and ACR70 scores and the DAS28 CRP) was apparent only at concentrations achieved with doses of 150 mg q2w or above (Figure 1, Figure 2). Furthermore, a plateau was reached for all efficacy endpoints at sarilumab concentrations achieved at the 200 mg q2w dose, with further increase in exposure by as much 2.7-fold (150 mg qw) providing only marginal change in the responses. Thus, 150 mg q2w and 200 mg q2w doses were considered appropriate for the Phase 3 program.

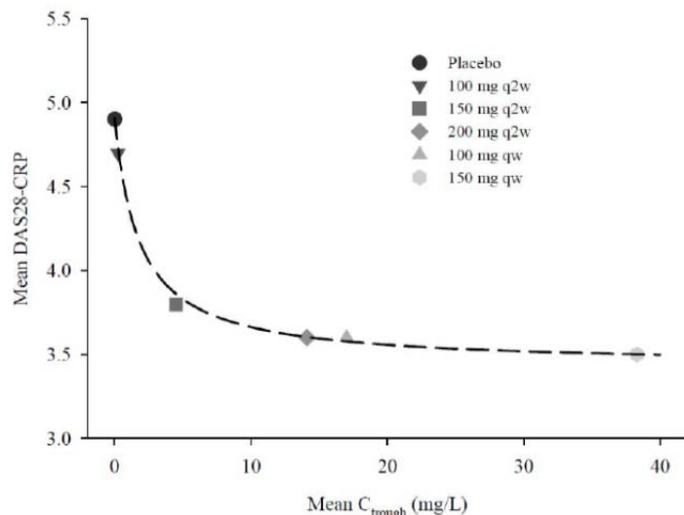
**Figure 1: Response rate of American College of Rheumatology 20, 50, and 70% improvement versus trough concentrations of functional sarilumab at Week 12 in patients with RA (EFC11072 Part A)**



Source: Summary of clinical pharmacology, Figure 16, page 74, submitted 10/30/15

APPEARS THIS WAY ON ORIGINAL

**Figure 2: DAS28-CRP versus trough concentrations of serum functional sarilumab at Week 12 in patients with rheumatoid arthritis (EFC11072 Part A)**



Source: Summary of clinical pharmacology, Figure 20, page 80, submitted 10/30/15

In the phase 3 studies, increased efficacy with respect to ACR20, ACR50, ACR70, CDAI, and DAS28 was observed with increasing exposure ( $C_{trough}$ ) within the concentration range observed at 150 mg q2w and 200 mg q2w doses. Consistent with the dose-response seen for efficacy parameters, there was a dose response for safety parameters. Specifically, the change from baseline in ANC was related to sarilumab concentration within the concentration range observed in the phase 2 and 3 studies at the studied dose regimens (100 and 150 mg qw; 100, 150, and 200 mg q2w). Based on the pharmacodynamics of the changes in ANC, laboratory results should be obtained at the end of the dosing interval when considering dose modification.

### *Pharmacodynamics*

Several potential pharmacodynamics markers were assessed in clinical studies, including IL-6, sIL-6R $\alpha$ , and several inflammatory markers (acute phase proteins CRP, SAA, and fibrinogen, and an indirect index of these proteins, the erythrocyte sedimentation rate [ESR]). Following single or multiple doses of sarilumab, IL-6 levels increased and then declined with further treatment in a dose dependent manner; and sIL-6R $\alpha$  (representing free IL-6R $\alpha$  and sIL-6R $\alpha$  bound to sarilumab) levels increased with time and with increasing sarilumab exposure.

After repeated q2w SC administration of 150 or 200 mg sarilumab, a dose dependent decrease in CRP levels was observed as early as Week 2, reached steady state by Week 24, and was sustained throughout treatment. The 200 mg dose suppressed CRP levels throughout the 2 week interval, while CRP levels had a tendency to rebound towards the end of the dosing interval with the 150 mg dose, suggesting a lower IL-6R $\alpha$  blockade at this dose.

- **Pathway of elimination, including metabolism, half-life, and excretion.**

*Drug metabolism*

No specific in vitro or in vivo metabolism or excretion studies were conducted for sarilumab as it is an IgG1 monoclonal antibody that is catabolized by ubiquitous proteolytic enzymes, not restricted to hepatic tissue.

*Drug elimination and half-life*

Sarilumab exhibits nonlinear PK with target mediated drug disposition. Sarilumab clearance is governed by two parallel pathways: a nonlinear, target mediated pathway predominating at lower concentrations and a nonspecific, linear pathway predominating at higher concentrations. Based on population PK analysis, in the range of serum concentrations achieved over the dosing interval at therapeutic doses of sarilumab, target mediated clearance represents a large portion of total clearance, while linear clearance represents only 7% to 26% of total clearance at 150 mg q2w and 22% to 40% of total clearance at 200 mg q2w.

The effective half-life is ~17-19 days based on accumulation (AUC) at steady state.

Population PK analysis identified that body weight, ADA, drug product (b) (4) F2 and sex had an impact on linear clearance (CL). Non-linear clearance (Vmax) was impacted by body weight, albumin, BSA-normalized creatinine clearance and baseline CRP levels. Absorption (Ka) was impacted by drug product (b) (4) F2. No dose adjustment is recommended for the starting dose with respect to any of the covariates. The post-hoc analysis showed that age, sex, race, albumin, baseline CRP and concomitant methotrexate did not meaningfully influence the pharmacokinetics of sarilumab. Compared to ADA negative patients, ADA positive status decreased the steady state AUC<sub>0-14</sub>, C<sub>max</sub>, and C<sub>trough</sub> by 24%, 18%, and 48% respectively for the 150 mg q2w dose, and 28%, 22%, and 43% respectively for the 200 mg q2w dose. Although body weight influenced the pharmacokinetics of sarilumab, no dose adjustments are recommended for any of these demographics.

- **Drug-drug interactions**

Administration of concomitant MTX, the most commonly prescribed DMARD for patients with RA, did not impact sarilumab clearance, as assessed by population PK analyses. Prior use of biologics (for RA treatment), had no appreciable impact on sarilumab PK based on graphical exploration of the post-hoc predicted exposure data.

A DDI study evaluating effect of sarilumab on simvastatin, a sensitive CYP3A4 substrate, showed that in 17 patients with RA, exposure of simvastatin and simvastatin acid decreased by 45% and 36%, respectively, following a single 40 mg oral dose of simvastatin one week after a single SC dose of sarilumab 200 mg. The labeling will reflect that the modulation of IL-6 effect on CYP enzymes by sarilumab may be clinically relevant for CYP substrates with a narrow therapeutic index, where the dose is individually adjusted. Upon initiation or discontinuation of sarilumab, in patients being treated with CYP substrate medicinal products, therapeutic monitoring of effect (e.g., warfarin) or drug concentration (e.g., theophylline) should be performed and the individual dose of the medicinal product should be adjusted as needed. Caution should be exercised when sarilumab is co-administered with CYP3A4 substrates (e.g. oral contraceptives or statins) as there may be a reduction in exposure which may reduce the effectiveness of the CYP3A4 substrate.

- **Demographic interactions/specific populations**

No formal study was conducted in special populations (such as patients with renal or hepatic impairment) because the disposition of sarilumab, an IgG antibody, is not expected to be impacted by renal or hepatic function. The main source of intrinsic PK variability identified in patients using population PK analysis is body weight, with a decrease in weight resulting in an increase in exposure. However, no dose adjustment for body weight is needed. None of the other demographic characteristics (age, race, or sex) have a relevant effect on the PK of sarilumab.

- **Bridging between the formulation(s) tested in clinical studies and the to-be-marketed formulation**

The planned-to-be-marketed drug product is identical to the drug product used in phase 3 studies. The drug product presentation was a vial in early phase 1 and 2 clinical studies, later changed to a PFS introduced during the pivotal Phase 3 studies. The Phase 2 ((b)(4)F2) and Phase 3 ((b)(4)F3) products are linked through two relative bioavailability studies in healthy subjects and RA patients that indicated that there were no meaningful differences in functional sarilumab exposure or immunogenicity (ADA) when the 2 products were administered.

- **Thorough QT study or other QT assessment**

A formal QT study was not required as biologic products like sarilumab are generally not expected to interact with cardiac ion channels. The QT interval was evaluated in the clinical trials that were part of the RA clinical development program. No clinical safety signals related to the QT interval were identified.

- **Other notable issues (resolved or outstanding)**

The Office of Clinical Pharmacology has determined that the information in BLA 761037 is acceptable from a clinical pharmacology perspective. No outstanding issues have been identified or Phase 4 commitments recommended.

## **6. Clinical Microbiology**

Not applicable

## **7. Clinical/Statistical- Efficacy**

*Clinical Primary Reviewer: Suzette Peng, MD*

*Statistical Reviewer: Yongman Kim, PhD; Statistical Team Leader: Gregory Levin, PhD*

### ***Overview of the clinical program***

Two phase 3 studies (EFC1170 Part B cohort 2 and EFC10832) have been submitted as the primary evidence of efficacy of sarilumab (Table 3). In addition, one phase 2 study (EFC11702 Part A) informed dose selection. Patients completing trials EFC1170 Part A and B and EFC10832 and three other trials (ACT11575, SFY13370, and EFC13752) could enroll in a long term safety study (LTS11210), which is discussed in Section 8.

**Table 3: Summary of Phase 2 and 3 Studies in RA Submitted for the BLA**

Protocol (Dates)	Overview	Patient Population (Background meds)	Treatment Arms (SC)	N per Arm	Primary Endpoints/Notes	Duration (wks)
<b>Phase 3 studies</b>						
EFC11702 Part B <sup>a</sup>  199 centers, EU, North America, South America, Asia, Australia, New Zealand, and South Africa  (3/11-10/13)	Phase 3, R, DB, PC, rescue <sup>b</sup> at 16 weeks	MTX-IR  (MTX)	<b>Cohort 1:</b> SAR 100 mg qw SAR 150 mg qw SAR 100 mg q2w SAR 150 mg q2w SAR 200 mg q2w Placebo  <b>Cohort 2:</b> SAR 150 mg q2w SAR 200 mg q2w Placebo	29 27 28 30 28 30  400 399 398 N=1197	ACR20 at wk 24 HAQ-DI at wk 16 mTSS at wk 52  Key secondary: major clinical response over 52 weeks	52
EFC10832  240 centers, worldwide  (10/12-3/15)	Phase 3, R, DB, PC, rescue <sup>c</sup> at 12 weeks	TNF-IR  (DMARDs <sup>d</sup> )	SAR 150 mg q2w SAR 200 mg q2w Placebo	181 184 181 N=546	ACR20 at wk 24 HAQ-DI at Wk 12	24
<b>Phase 2 studies</b>						
EFC11072 Part A <sup>a</sup>  102 centers  EU, North America, South America, Australia, Korea, and South Africa  (3/10-5/11)	Phase 2, R, DB, PC  No escape	MTX-IR  (MTX)	SAR 100 mg qw SAR 150 mg qw SAR 100 mg q2w SAR 150 mg q2w SAR 200 mg q2w Placebo	50 50 51 51 51 52 N=306	ACR20 at wk 12  Patients in Part A did not participate in Part B	12

Abbreviations: EU=Europe; DB=double blind; DMARD=disease modifying antirheumatic drug; MTX=methotrexate; MTX-IR=inadequate response to methotrexate; PC=placebo controlled; qw=weekly; q2w=every other week; R=randomized; SAR=sarilumab; TNF=tumor necrosis factor; ACR=American College of Rheumatology; HAQ-DI=Health Assessment Questionnaire Disability Index; mTSS=modified Total Sharp Score

a EFC11072 was conducted as a seamless Phase 2/3 Study. Part A was the dose-ranging portion of the study. Part B was the Phase 3 study. Cohort 2 is the primary population for the efficacy evaluation.

b Patients with an inadequate response were rescued with open-label sarilumab 200 mg q2w

c Patients with an inadequate response were allowed to enter LTS11210 to be rescued with open-label sarilumab 200 mg q2w

d Concomitant DMARDs: MTX, leflunomide, hydroxychloroquine, or sulfasalazine

Source: modified from Summary of Clinical Efficacy, Module 2.7.3, Table 1, page 15, submitted 10/30/15

### ***Study Designs***

The primary evidence of efficacy is from trials EFC11072 and EFC10832. Both studies were double-blind, placebo-controlled studies in patients with moderately to severely active RA and provided open-label rescue therapy for patients with inadequate response to double-blind treatment. In nearly all study design features (eligibility criteria, study schedule, primary efficacy outcome variable and analysis, secondary and exploratory outcome measures and analyses), the studies were similar. Sarilumab was administered in a prefilled syringe in both studies. The two studies differed mainly in trial duration (52 weeks for study EFC11072 and 24 weeks for study EFC10832) and treatment prior to studies (MTX for study EFC11072 and TNF $\alpha$  antagonists in study EFC10832). Also, only study EFC11072 included a radiographic assessment of structural damage progression and the time point of escape was earlier in study EFC10832 (12 weeks) than EFC11072 (16 weeks).

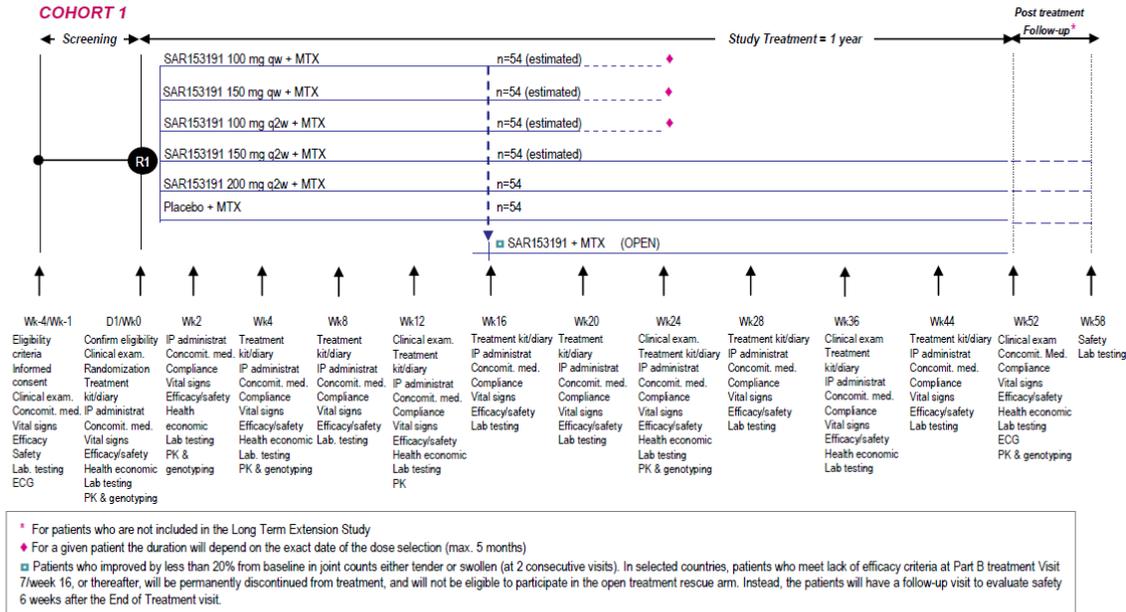
### **EFC11072 Part B**

EFC11072 had an operationally seamless design. Part A (dose-ranging) used a phase 2 design to select the dose regimens and Part B (pivotal) evaluated the selected dose regimens in a phase 3 study. The overall study design allowed ongoing patient recruitment, without interruption, but ensured complete protection of the double-blind.

See the section on Dose Selection for a description of Part A. Patients from Part A did not participate in Part B. Patients who completed Part A and were eligible could enter an open-label, long-term, extension study (LTS11210). The results from Part A were presented in a separate study report.

EFC11072 Part B was a randomized, multicenter, multinational, double-blind, parallel-group, placebo-controlled, 52-week study to assess the efficacy and safety of sarilumab, administered with concomitant MTX, in patients with moderately to severely active RA. Part B consisted of Cohort 1 and Cohort 2. Patients in Cohort 1 were randomly assigned to receive either placebo qw, sarilumab 100 mg qw, sarilumab 150 mg qw, sarilumab 100 mg q2w, sarilumab 150 mg q2w, or sarilumab 200 mg q2w in a ratio of 1:1:1:1:1:1 (Figure 3). Once the results from Part A were known and the doses for further evaluation in Part B were selected, patients in Cohort 1, who were taking the selected doses of sarilumab 150 mg q2w or 200 mg q2w or placebo, continued in this study. After dose selection, blinding of the patients in Cohort 1 who were receiving the selected doses (or placebo) was maintained. Patients in the “non-selected” sarilumab dose groups in Cohort 1 were discontinued from Study EFC11072 and could enter Study LTS11210. Patients for Part B Cohort 2 were recruited after dose selection from Part A and were randomly assigned to receive either placebo q2w, sarilumab 150 mg q2w, or sarilumab 200 mg q2w, in a ratio of 1:1:1 (Figure 4). Randomization was stratified by region and prior biologic use.

Figure 3: Study Schema for Study 11072 Part B Cohort 1

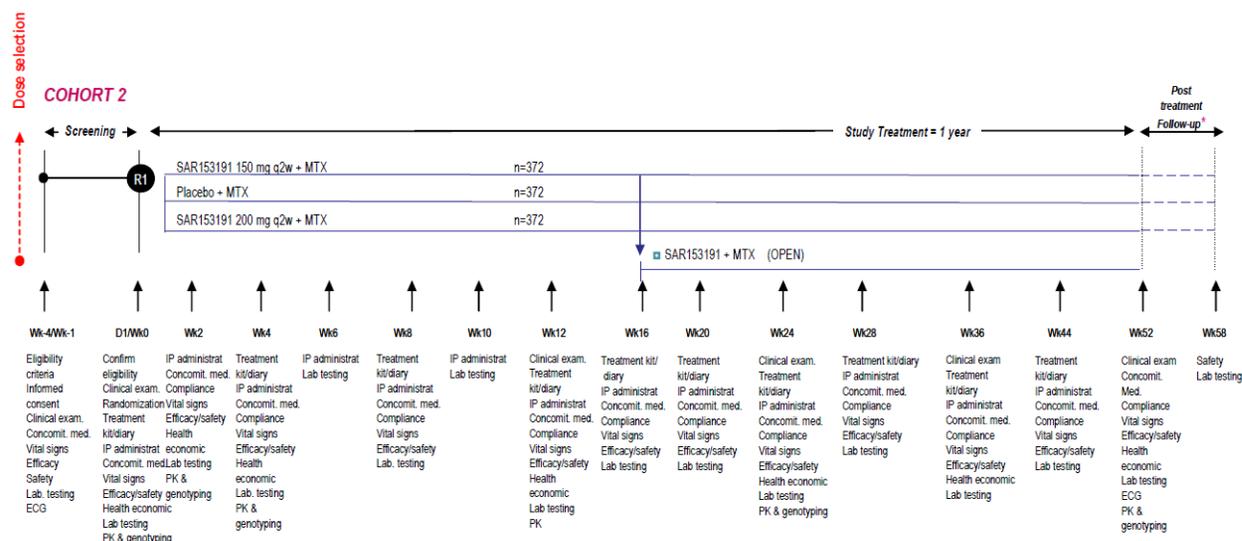


Open-label sarilumab was administered at a dose of 150 mg qw until the site was approved to enroll patients in Cohort 2.  
 Source: Excerpted from the Clinical Study Report for Study 11072, page 24, submitted 10/30/15

APPEARS THIS WAY ON ORIGINAL

**Figure 4: Study Schema for Study 11072 Part B Cohort 2**

Open-label sarilumab was administered at a dose of 200 mg q2w.



Source: Excerpted from the Clinical Study Report for Study 11072, page 25, submitted 10/30/15

As noted in the regulatory history, the design of this study was discussed and agreed upon with FDA. The operationally seamless design of this study required that patient enrollment in Part B start after the last patient was randomized in Part A, without waiting for the dose selection based on the results from Part A. To ensure complete protection of the double-blind, Part B patients belonged to 2 distinct cohorts according to the time of their enrollment. Only patients in Cohort 2 were included in the efficacy analyses.

The enrolled patients with RA had an inadequate response to MTX, defined as having at least 8 of 68 tender joints, 6 of 66 swollen joints, and CRP > 6 mg/L (10 mg/L prior to protocol amendment) at screening and baseline visits after at least 12 weeks of MTX therapy. In addition, patients were to have at least 1 bone erosion documented by X-ray or to be anti-CCP antibody or RF positive. Patients with prior therapy with a TNF-antagonist or other biologic agent within 3 months prior to randomization were excluded.

Patients who did not achieve an adequate response, defined as less than a 20% improvement compared with baseline in swollen or tender joints count for 2 consecutive visits or based on the Investigator’s judgment, were eligible for rescue with sarilumab 200 mg

q2w at any time after Week 16. Patients who received rescue therapy remained in the study and completed all protocol-specified assessments.

There were 3 co-primary efficacy endpoints: American College of Rheumatology 20% (ACR20) response rate at Week 24, change from baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI) at Week 16, and change from baseline in van der Heijde mTSS at Week 52. The percentage of patients achieving a Major Clinical Response was the key secondary endpoint.

### **EFC10832**

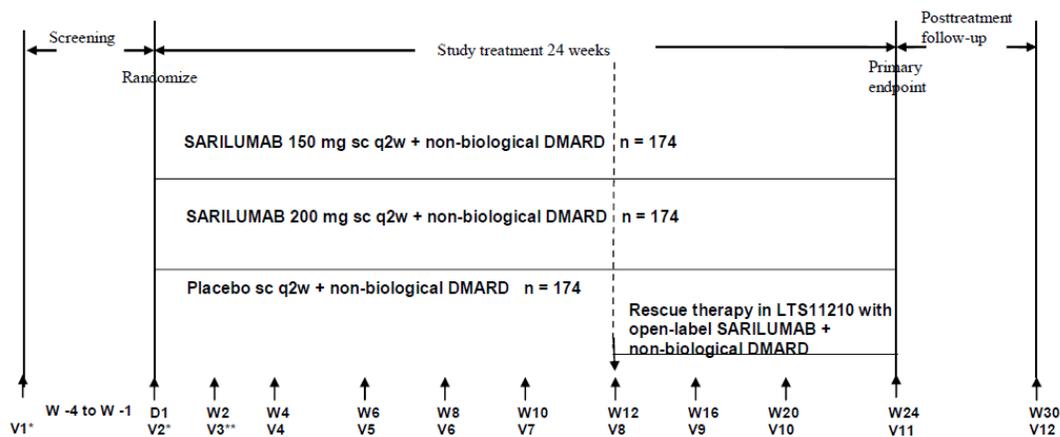
EFC10832 was a randomized, multicenter, multinational, double-blind, parallel-group, placebo-controlled, 24-week study to assess the efficacy and safety of sarilumab, administered with concomitant DMARDs, in patients with moderately to severely active RA with a history of inadequate response to or intolerance of TNF antagonists. Inadequate clinical response was defined by the investigator, after being treated for at least 3 consecutive months, and/or intolerance to at least 1 anti-TNF $\alpha$  agent, resulting in or requiring their discontinuation. Active RA was defined as having at least 8 of 68 tender joints, 6 of 66 swollen joints, and CRP  $\geq$ 8 mg/L after at least 12 weeks of non-biologic DMARD (MTX, sulfasalazine, hydroxychloroquine, or leflunomide) therapy.

Patients who did not achieve an adequate response to double-blind treatment were allowed to be rescued with sarilumab by entering the open-label extension study, LTS11210, at any time after Week 12.

Patients were randomized 1:1:1 to receive placebo, sarilumab 150 mg q2w, or sarilumab 200 mg q2w plus the concomitant DMARD that the patient was receiving at baseline. Randomization was stratified by region and by number of prior TNF antagonists (1, >1). There were 2 co-primary endpoints: ACR20 response rate at Week 24 and change from baseline in HAQ-DI at Week 12.

APPEARS THIS WAY ON ORIGINAL

Figure 5: Study Schema for Study EFC10832



Source: Excerpted from the Clinical Study Report for Study EFC10832, page 20, submitted 10/30/15

### Brief Description of Efficacy Endpoints

- *ACR Response Rates*

In 1995, the American College of Rheumatology (ACR) published a definition of improvement for clinical trials in RA, which have since been used in drug development trials to demonstrate evidence of efficacy for signs and symptoms of RA.<sup>7</sup> The ACR20 response is calculated as a >20% improvement in:

- tender joint count (of 68 joints) and
- swollen joint count (of 66 joints) and
- 3 of the 5 remaining ACR core set measures
  - Patient Global Assessment of Arthritis on a visual analog scale (VAS)
  - Physician Global Assessment of Arthritis on a VAS

<sup>7</sup> DT Felson, et al. Arthritis Rheum 1995. June, 38(6):727-735.

- Patient Assessment of Pain on a VAS
- Patient Assessment of Physical Function (e.g. Health Assessment Questionnaire)
- Acute Phase Reactant (Erythrocyte Sedimentation Rate or C-reactive protein)

Fifty percent and 70 percent improvement (ACR50 and ACR70) are similarly calculated using these higher levels of improvement.

- *Health Assessment Questionnaire-Disability Index (HAQ-DI)*

The Agency has historically recognized a distinct claim in RA for “improvement in physical function” based on outcome measures such as the HAQ-DI.<sup>8</sup> This instrument assesses a patient’s level of functional ability and includes questions pertaining to fine movements of the upper extremity, locomotor activities of the lower extremities, and activities that involve both upper and lower extremities. There are 20 questions in 8 categories of functioning which represent a comprehensive set of functional activities: dressing, rising, eating, walking, hygiene, reach, grip, and usual activities. Patients respond on a four-level difficulty scale ranging from zero (no difficulty) to three (unable to do). The 8 category scores are averaged into an overall HAQ-DI score on a scale from zero (no disability) to 3 (completely disabled). The most widely accepted figure on the minimal clinically important difference in the HAQ-DI score is an improvement (decrease) of at least 0.22 units.

- *Disease Activity Score (DAS)-28*

The DAS28 is a composite index of RA disease activity which incorporates the number of tender and swollen joints (out of 28 possible), a patient global assessment of disease activity (0-100 mm visual analog scale), and erythrocyte sedimentation rate (ESR) results.<sup>9</sup> An alternative equation is available for use with c-reactive protein (CRP) results. These variables are summed and weighted mathematically into a single numerical value ranging from 0 to 10. Comparing the DAS28 and the ACR response criteria, beyond the differences in number of maximum tender or swollen joints counted (e.g. DAS28 does not include the joints of the feet), additional variables of physician global assessment, patient pain, and HAQ score are incorporated into the ACR response criteria. The DAS28 has additional utility in measuring the level of disease activity at a given time point, whereas the ACR response criteria are calculated

---

<sup>8</sup> B Bruce and JF Fries, “The Health Assessment Questionnaire (HAQ).” Clin Exp Rheumatol 2005; 23 (Suppl 39):S14-S18.

<sup>9</sup> J Fransen and PLCM van Riel, “The Disease Activity Score and the EULAR Response Criteria.” Clin Exp Rheumatol 2005; 23 (Suppl 39): S93-S99.

as improvement in the variables over a set period of time. A DAS28 score  $>5.1$  is indicative of high disease activity, and  $<3.2$  of low disease activity. A score of  $<2.6$  has been used to describe an even lower threshold of disease activity.

- *Radiographic Outcome: Van der Heijde modified Sharp Score*

The Van der Heijde-modified Sharp radiographic scoring method grades the presence of erosions in the joints of the hands and feet, and the presence of joint space narrowing (JSN) in the hands, wrists, and feet.<sup>10</sup> The scores for each feature for the individual joints are summed. Erosions are assessed at 16 locations in each hand and wrists and 12 locations in each foot, using a 6-point scale from 0 to 5. Scores are derived based on the number and size of discrete erosions in each location, but are summed to a maximum of 5. Thus, the maximum erosion score for the hands/wrists is 160, and the maximum erosion score for the feet is 120, for a maximum total erosion score of 280. JSN scores are based on 15 locations in each hand and wrist and 6 locations in each foot, scored using a 5-point scale from 0 to 4: 0 = normal; 1 = focal or minimal and generalized narrowing; 2 = generalized narrowing  $<50\%$ ; 3 = generalized narrowing  $>50\%$  or subluxation; and 4 = ankylosis or complete dislocation. The maximum total JSN for the hands/wrists is 120, and the maximum total JSN for the feet is 48, for a maximum total JSN score of 168. Therefore, the theoretical maximum modified total Sharp Score (mTSS) is 448, although the actual clinical range in RA drug development trials is typically much lower because a given individual typically only has a fraction of his or her joints affected by radiographically evident damage.

- *Major clinical response*

A major clinical response is defined as the event of maintaining an improvement as assessed by the ACR70 for at least 24 consecutive weeks during a 52-week period.

- *SF-36*

The medical outcome short form health survey (SF-36) is an instrument used to measure health-related quality of life or general health status. It consists of 8 subscales that are scored individually: physical functioning (10 items), role-physical (4 items), bodily pain (2 items), general health (5 items), vitality (4 items), social functioning (2 items), role-emotional (3 items), and mental health (5 items). Two summary scores, the Physical Component Summary (PCS) and the Mental Component Summary (MCS) also can be computed.

---

<sup>10</sup> S Boini and F Guillemin, "Radiographic scoring methods as outcome measures in rheumatoid arthritis: properties and advantages." *Ann Rheum Dis* 2001; 60:817-827.

### ***Dose selection***

The proposed recommended starting dose is 200 mg every two weeks. For patients with decreased neutrophil count, decreased platelet count or elevated liver transaminases, the recommended dose is 150 mg every two weeks.

Sanofi selected sarilumab doses of 150 and 200 mg every two weeks based on dose-ranging safety and efficacy data from study EFC11072 Part A. EFC11072 Part A was a randomized, multicenter, double-blind, parallel-group, placebo-controlled 12-week study to assess the safety and efficacy of sarilumab, administered with concomitant MTX, in patients with moderately to severely active RA who had an inadequate response to MTX. Randomization was stratified by past biologic treatment (yes/no) and region.

Patients were randomly allocated to placebo or sarilumab 100 mg q2w, 150 mg q2w, 200 mg q2w, 100 mg qw, or 150 mg qw in a ratio of 1:1:1:1:1. The primary endpoint was the proportion of patients who achieved an ACR20 response at Week 12. In the primary approach to analysis of ACR20, patients who discontinued treatment for lack of efficacy were considered non-responders; response status for patients who were rescued or discontinued study due to other reasons were determined using their last observations prior to the rescue or discontinuation. Sensitivity analyses were performed with other approaches to missing data.

A total of 306 patients were randomized to receive placebo (N=52) or sarilumab 100 mg q2w (N=51), 150 mg q2w (N=51), 100 mg qw (N=50), 200 mg q2w (N=52) or 150 mg qw (N=50). The key results for the American College of Rheumatology (ACR) Responses are summarized in Table 4 and Figure 6, which demonstrate a dose-response for efficacy.

Based on the efficacy data, sanofi concluded that 100 mg q2w was not an effective dose and 150 mg q wk was the maximally effective dose. As noted in the regulatory history section above, at EOP2 the Agency review team agreed with the selection of 150 mg and 200 mg every two weeks, however raised concerns with the number of cases of neutropenia. In the safety data, there appears to be a dose response (150 mg qw >200 mg q2w >100 mg qw >150 mg q2w >100 mg q2w > placebo) for changes in some laboratory parameters, such as neutrophil count (Figure 7). Based on consideration of the safety and efficacy data, sanofi's selection of 150 mg and 200 mg every two weeks for evaluation in Phase 3 was reasonable.

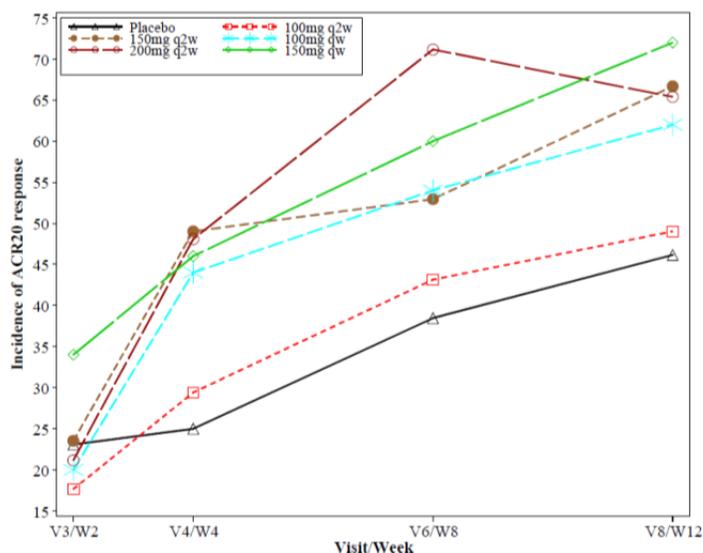
**Table 4: Percentage of patients with ACR20, ACR50, and ACR70 responses at Week 12 in EFC11072 Part A**

	Placebo (N=52)	SAR 100 Q2W (N=51)	SAR 150 Q2W (N=51)	SAR 100 QW (N=50)	SAR 200 Q2W (N=52)	SAR 150 QW (N=50)
ACR20	46	49	67	62	65	72
OR, CI vs. placebo	--	1.17 (0.52, 2.61)	2.38 (1.06, 5.35)	1.99 (0.85, 4.64)	2.34 (1.03, 5.29)	3.84 (1.53, 9.63)
ACR50	15	22	35	40	40	30
ACR70	2	6	12	16	17	16

SAR=sarilumab; ACR=American College of Rheumatology

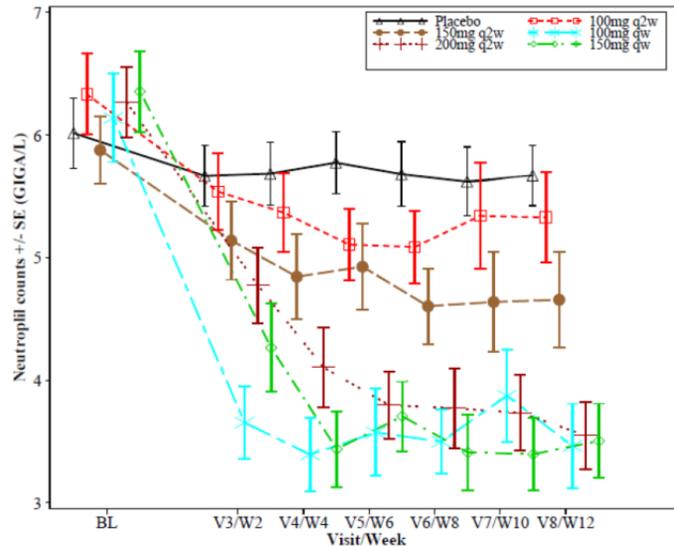
Source: Summary of Clinical Efficacy, Table 4, page 25, Clinical Study Report, EFC11072, Part A, Table 16, page 94, Table 21, page 104, submitted 10/30/15

**Figure 6: Incidence of ACR20 response at each visit in study EFC11072 Part A**



Source: Clinical Study Report, EFC11072, Part A, Figure 2, page 97, submitted 10/30/15

Figure 7: Absolute Neutrophil Count (ANC) at each visit in Study EFC11072 Part A



Source: Clinical Study Report, EFC11072, Part A, Figure 14, page 182, submitted 10/30/15

### Statistical considerations

#### EFC11072 Part B

For EFC11072 Part B, the primary analysis population was the ITT population for Part B Cohort 2. The data collected after treatment discontinuation or rescue were set to missing. Based on the analysis plan, all patients automatically became non-responders for all time points beyond the time point they started rescue medication or discontinued study treatment. Therefore, the binary endpoint is a composite response endpoint defined by: (1) achieving at least 20% improvement in both the swollen and tender joint counts at Week 16; (2) remaining in the study through the time point of interest (e.g., Week 24); and (3) achieving a response in the outcome of interest at the time point of interest (e.g., ACR20 at Week 24).

The primary and key secondary efficacy endpoints were tested for each sarilumab dose versus placebo in a testing strategy designed to protect the family-wise type 1 error rate at  $\alpha=5\%$  (two-sided). Sanofi proposed a hierarchical testing procedure with a Bonferroni

correction to adjust for the multiple doses and endpoints. Thus, a hierarchical testing procedure was used for the multiple endpoints at  $\alpha = 0.025$  for each dose regimen separately. The hierarchy was:

1. Incidence of ACR20 response at Week 24,
2. Change from baseline in HAQ-DI at Week 16,
3. Change from baseline in the modified total Sharp score at Week 52,
4. Incidence of achieving major clinical response during the 52-week period.

Sanofi and the statistical reviewer performed multiple sensitivity analyses to assess the impact of missing data, including tipping point analyses were performed.

### **EFC10832**

That statistical methods including analysis set, models, handling of subjects who escaped to rescue from Week 12, and handling missing data due to dropout were the same as in Study EFC11072. In order to protect the family-wise type 1 error rate at  $\alpha=5\%$  (two-sided), sanofi proposed a similar hierarchical testing procedure with a Bonferroni correction to adjust for the multiple doses and endpoints as in Study EFC11072. A hierarchical testing procedure was used for the multiple endpoints at  $\alpha = 0.025$  for each dose regimen separately. The hierarchy was:

1. Incidence of ACR20 response at Week 24,
2. Change from baseline in HAQ-DI at Week 12,
3. Change from baseline in DAS28-CRP at Week 24,
4. Incidence of ACR50 response at Week 24,
5. Incidence of ACR70 response at Week 24,
6. Incidence of DAS28-CRP < 2.6 response at Week 24,
7. Change from baseline in Clinical disease activity index (CDAI) at Week 24,
8. Change from baseline in HAQ-DI at Week 24,
9. Change from baseline in SF36-PCS at Week 24,
10. Change from baseline in SF36-MCS at Week 24,
11. Change from baseline in Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue at Week 24,
12. Change from baseline in Morning Stiffness VAS at Week 24,
13. Change from baseline in Work Productivity Survey (WPS)-RA at Week 24,
14. Change from baseline in RA impact disease score (RAID) at Week 24,
15. Change from baseline in EQ-5D-3L at Week 24

### ***Patient disposition, demographic, and baseline characteristics***

#### **EFC11072 Part B Cohort 2**

A total of 1,197 patients were randomized in EFC11072 Part B Cohort 2 (400 in the sarilumab 150 mg q2w group, 399 in the sarilumab 200 mg q2w group, and 398 in the placebo group), and of those, 1,194 were treated (398 in each group). Of the 398 patients in the placebo group, 95 (24%), 117 (29%), and 135 (34%) were rescued to sarilumab 200 mg by Week 16, 24, and 52, respectively. More patients were rescued on the placebo arm than the sarilumab arms.

The demographic and baseline disease characteristics were generally balanced and comparable between the treatment groups. The majority of patients were female (82%) and Caucasian (86%), with mean age of 51 years, and a mean weight of 74 kg. The mean duration of RA was 9 years, 28% of the patients had previously been treated with biologic DMARDs, 85% were positive for rheumatoid factor, and 87% were positive for anti-CCP antibody. The mean baseline DAS28-CRP was 5.96.

#### **EFC10832**

A total of 546 patients were randomized (181 in the sarilumab 150 mg q2w group, 184 in sarilumab 200 mg q2w group, and 181 in the placebo group). Approximately two-thirds (66%) of patients completed 24 weeks and 91% completed 12 weeks. The number of patients who discontinued study treatment prior to Week 12 was comparable among treatment groups. However, more patients in the placebo group (44%) discontinued study treatment prior to Week 24 compared to the sarilumab groups (29%), largely due to a difference in the proportion of patients who met escape criteria and were rescued with open-label sarilumab.

Baseline demographics and disease characteristics were well balanced among the treatment groups. The majority of patients were female (82%) and Caucasian (71%), with mean age of 53 years and a mean weight of 78 kg. The mean duration of RA was 12 years. All patients had previously been treated with TNF antagonists. Of the patients, 76% were positive for rheumatoid factor, and 78% were positive for anti-CCP antibody. The mean baseline DAS28-CRP was 6.20.

### ***Efficacy findings***

- *ACR Response Rates*

The primary endpoint in both trials was the ACR20 response at Week 24. As shown in Table 5, sarilumab treatment was associated with a higher proportion of ACR responders in both trials at both 150 mg and 200 mg once every two week doses, and the difference was statistically significant compared to the placebo control groups. The primary analysis utilizing nonresponder imputation (NRI) was supported by additional sensitivity, including tipping point analyses, as these analyses were generally consistent. See the statistical review by Dr. Kim for additional details. The 200 mg dose was associated with a slightly higher proportion of responders in both trials.

Analyses of all the components of ACR were statistically significant in favor of both sarilumab doses and there was no single component driving the efficacy in terms of ACR20 response.

**Table 5: Summary of ACR20 Response Rates at Week 24 in phase 3 RA studies**

Treatment group	n/N (%)	Comparison	Odds Ratio	95% CI	p-value
<b>EFC11072 Part B</b>					
SAR 150mg (N=400)	232/400 (58)	vs. placebo	2.8	(2.1, 3.7)	<0.0001
SAR 200mg (N=399)	265/399 (66)	vs. placebo	4.0	(3.0, 5.3)	<0.0001
Placebo (N=398)	133/398 (33)	--	--	--	--
<b>EFC10832</b>					
SAR 150mg (N=181)	101/181 (56)	vs. placebo	2.7	(1.7, 4.2)	<0.0001
SAR 200mg (N=184)	112/184 (61)	vs. placebo	3.3	(2.1, 5.1)	<0.0001
Placebo (N=181)	61/181 (34)	--	--	--	--

SAR=sarilumab; ACR=American College of Rheumatology; NRI=nonresponder imputation; CI=confidence interval

Primary analysis with NRI

Study EFC11072: p-value based on CMH test stratified by prior biologic use and region

Study EFC110832: CMH test stratified by number of previous anti-TNFs and region.

Source: Clinical Study Report for Study EFC11072 (page 103) and 15.2 (page 4) and Clinical Study Report for Study EFC10832 (page 81) & 15.2 (page 83), submitted 10/30/15

Consistent with the primary endpoint results, the proportion of patients experiencing ACR50 and ACR70 levels of improvement was higher in the sarilumab groups compared to the placebo control groups. In studies EFC11072 and EFC10832, the proportion of patients experiencing ACR50 levels of improvement was slightly higher in the 200 mg dose group than the 150 mg dose group. For study EFC11072, the proportion of patients experiencing ACR70 levels of improvement was slightly higher in the 200 mg dose group than the 150 mg dose group, while the opposite was observed in study EFC10832.

- *Health Assessment Questionnaire-Disability Index (HAQ-DI)*

Both phase 3 trials assessed the treatment effect of sarilumab on HAQ-DI. The change in HAQ-DI score was assessed from baseline to Week 16 in Study EFC11072 and to Week 12 in Study EFC10832. It was assessed just prior to escape in both studies. Sarilumab was associated with statistically significant improvement (decrease) in HAQ-DI (mean change from baseline), with sarilumab treatment groups experiencing approximately a 0.2 unit improvement over placebo in the studies. In both trials, the 200 mg dose group appeared to be associated with slightly greater improvement in HAQ-DI.

For this continuous endpoint, all assessments are set to missing from the time a patient receives rescue medication or discontinues study medication early. No imputation is performed. FDA reanalyzed the data utilizing cumulative responder curves with worst score imputation for missing data, which showed separation of the curves between the sarilumab dosing regimens and placebo, supporting the Applicant’s analysis. See the statistical review for additional details.

**Table 6: Applicant’s analysis of change from baseline in HAQ-DI at Week 16 (EFC11072) or Week 12 (EFC10832)**

Treatment group	n	LS Mean Change (SE)	Comparison	Mean difference	95% Confidence Interval	p-value
<b>EFC11072 Part B</b>						
SAR 150mg (N=400)	362	-0.53 (0.03)	vs. placebo	-0.24	(-0.31, -0.16)	<0.0001
SAR 200mg (N=399)	365	-0.55 (0.03)	vs. placebo	-0.26	(-0.34, -0.18)	<0.0001
Placebo (N=398)	378	-0.29 (0.03)	--	--	--	--
<b>EFC10832</b>						
SAR 150mg (N=181)	165	-0.46 (0.04)	vs. placebo	-0.20	(-0.32, -0.09)	0.0007
SAR 200mg (N=184)	171	-0.47 (0.04)	vs. placebo	-0.21	(-0.33, -0.10)	0.0004
Placebo (N=181)	170	-0.26 (0.04)	--	--	--	--

Note: All assessments are set to missing from the time a patient receives rescue medication or discontinues study medication early. No imputation is performed.  
 Study EFC11072: MMRM with PROC MIXED assuming an unstructured covariance structure: model = baseline, treatment, prior biological use, region, visit, and treatment-by-visit interaction.  
 Study EFC10832: MMRM with PROC MIXED assuming an unstructured covariance structure: model = baseline, treatment, number of previous anti-TNFs, region, visit, and treatment-by-visit interaction.  
 Source: Excerpted from the Clinical Study Report for Study EFC11072 (page 104) and Clinical Study Report for Study EFC10832 (page 82), submitted 10/30/15

In study EFC11072, patients treated with sarilumab + MTX (57% in the 200 mg treatment group and 54% in the 150 mg treatment group) achieved a clinically relevant improvement in HAQ-DI (change from baseline of  $\geq 0.3$  units) at Week 16 compared to 43% in the placebo + MTX treatment group (nominal p-value <0.0001).

- *Major clinical response at Week 52*

Major clinical response (MCR) was defined as the event of achieving and maintaining ACR70 for at least 24 consecutive weeks during the 52 week period. This endpoint was only assessed in study EFC11072 as study EFC10832 was only 24 weeks in duration. A statistically significantly larger proportion of patients in the sarilumab dose groups achieved major clinical response compared to the placebo group (Table 7). There were a slightly higher proportion of responders in the 200 mg group compared to the 150 mg group.

**Table 7: Applicant’s analysis of major clinical response at Week 52**

Treatment group	Response n (%)	Comparison	Odds ratio (95% CI)	p-value
<b>EFC11072 Part B</b>				
SAR 150mg (N=400)	51 (13)	vs. placebo	4.7 (2.5, 8.9)	<0.0001
SAR 200mg (N=399)	59 (15)	vs. placebo	5.6 (2.9, 10.5)	<0.0001
Placebo (N=398)	12 (3)	--	--	--

Note: Major clinical response = Achieving ACR70 for at least 24 consecutive weeks during the 52-week period. Patients are considered ACR70 non-responders from the time they started rescue medication or discontinued study medication. P-value based on CMH test stratified by prior biologic use and region.  
 Source: Excerpted from the Clinical Study Report for Study EFC11072, page 113, submitted 10/30/15

- *Change from baseline in DAS28-CRP at Week 24*

The mean reduction in DAS28-CRP at Week 24 in patients treated with sarilumab was statistically significantly greater compared to patients treated with placebo (Table 8) in both studies. The change from baseline was numerically greater for the 200 mg dose compared to the 150 mg dose.

APPEARS THIS WAY ON ORIGINAL

**Table 8: Applicant’s analysis of change from baseline in DAS28-CRP at Week 24 in phase 3 RA studies**

Treatment group	n	LS Mean Change (SE)	Comparison	Mean difference	95% Confidence Interval	p-value
<b>EFC11072 Part B</b>						
SAR 150mg (N=400)	308	-2.45 (0.08)	vs. placebo	-1.29	(-1.50, -1.07)	<0.0001
SAR 200mg (N=399)	314	-2.82 (0.08)	vs. placebo	-1.65	(-1.87, -1.44)	<0.0001
Placebo (N=398)	249	-1.17 (0.08)	--	--	--	--
<b>EFC10832</b>						
SAR 150mg (N=181)	126	-2.35 (0.11)	vs. placebo	-0.97	(-1.28, -0.66)	<0.0001
SAR 200mg (N=184)	136	-2.82 (0.11)	vs. placebo	-1.44	(-1.75, -1.13)	<0.0001
Placebo (N=181)	99	-1.38 (0.12)	--	--	--	--

Note: DAS28-CRP = 0.56 x sqrt(28TJC) + 0.28 x sqrt(28SJC) + 0.36 x Log(CRP+1) + 0.014 x Patient global VAS + 0.96.  
 All assessments are set to missing from the time a patient receives rescue medication or discontinues study medication early. No imputation is performed.  
 EFC11072: MMRM with PROC MIXED assuming an unstructured covariance structure: model = baseline, treatment, prior biological use, region, visit, and treatment-by-visit interaction.  
 EFC10832: MMRM with PROC MIXED assuming an unstructured covariance structure: model = baseline, treatment, number of previous anti-TNFs, region, visit, and treatment-by-visit interaction.  
 Source: Excerpted from the Clinical Study Report for Study EFC11072-16.2.6-EN (page 327) and Clinical Study Report for Study EFC10832-16.2.6-EN (page 193), submitted 10/30/15

In the proposed label, the applicant included results related to a low level of disease activity as measured by DAS28-CRP<2.6. In study EFC11072 Part B, the proportion of patients of patients with DAS28-CRP<2.6 was 8.5%, 31%, and 34% for placebo, sarilumab 150 mg, and sarilumab 200 mg once every two weeks, respectively. These results were similar to the results at 24 weeks for Study EFC10832. While the results of the DAS28-CRP<2.6 support the efficacy of sarilumab for RA, it is important to note that patients achieving a DAS28-CRP, approximately half had at least one active joints. Of the patients treated with sarilumab 200 mg who achieved a DAS28-CRP<2.6, 22% had 3 or more active joints.

- *Change from baseline in SF-36 at Week 24*

The mean change in SF36-PCS at Week 24 in patients treated with sarilumab was statistically significantly greater compared to patients treated with placebo (Table 9) in both studies. For SF-36 MCS, the results were statistically significantly greater for sarilumab 200 mg versus placebo and trended towards statistical significance for sarilumab 150 mg versus placebo. For study EFC11072, physical function, role-physical, bodily pain, general health, vitality, role-emotional, and mental health favored sarilumab 200 mg compared to placebo (p<0.025 for each). Similar findings were seen in study EFC10832, but the role-emotional domain was not significantly improved for sarilumab 200 mg compared to placebo (p>0.025).

**Table 9: Applicant’s analysis of change from baseline in SF-36 in phase 3 RA studies**

Treatment group	n	LS Mean Change (SE)	Comparison	Mean difference	95% Confidence Interval	p-value
<b>EFC11072 Part B</b>						
<b>SF-36 PCS</b>						
SAR 150mg (N=400)	299	8.0 (0.4)	vs. placebo	2.8	(1.6, 4.1)	<0.0001
SAR 200mg (N=399)	309	8.4 (0.4)	vs. placebo	3.2	(2.0, 4.4)	<0.0001
Placebo (N=398)	246	5.2 (0.5)	--	--	--	--
<b>SF-36 MCS</b>						
SAR 150mg (N=400)	352	5.5 (0.5)	vs. placebo	1.3	(0.1, 2.7)	0.06
SAR 200mg (N=399)	345	7.5 (0.5)	vs. placebo	4.3	(2.8, 5.8)	<0.0001
Placebo (N=398)	361	4.2 (0.5)	--	--	--	--
<b>EFC10832</b>						
<b>SF-36 PCS</b>						
SAR 150mg (N=181)	123	7.7 (0.7)	vs. placebo	3.3	(1.5, 5.0)	0.0004
SAR 200mg (N=184)	134	8.5 (0.6)	vs. placebo	4.1	(2.3, 5.8)	<0.0001
Placebo (N=181)	99	4.4 (0.7)	--	--	--	--
<b>SF-36 MCS</b>						
SAR 150mg (N=181)	160	5.1 (0.8)	vs. placebo	1.6	(-0.3, 3.6)	0.1
SAR 200mg (N=184)	165	6.5 (0.7)	vs. placebo	3.0	(1, 4.9)	0.003
Placebo (N=181)	169	3.5 (0.7)	--	--	--	--

Note: All assessments are set to missing from the time a patient receives rescue medication or discontinues study medication early. No imputation is performed.  
 EFC11072: MMRM with PROC MIXED assuming an unstructured covariance structure: model = baseline, treatment, prior biological use, region, visit, and treatment-by-visit interaction.  
 EFC10832: MMRM with PROC MIXED assuming an unstructured covariance structure: model = baseline, treatment, number of previous anti-TNFs, region, visit, and treatment-by-visit interaction.  
 Source: Excerpted from the Clinical Study Report for Study EFC11072-16.2.6-EN (page 413) and Clinical Study Report for Study EFC10832-16.2.6-EN (page 253), submitted 10/30/15

- *Change from baseline in mTSS at Week 52*

The primary radiographic endpoint in Study EFC11072 was assessed at Week 52. Approximately 44% of placebo patients were left on placebo at Week 52. There was also an assessment of radiographs at Week 24. Approximately 64% of placebo patients were left on placebo at Week 24. Also, there was less missing data at Week 24.

Patients with missing data due to dropout or rescue had their data imputed using linear extrapolation from baseline to their last radiographs prior to exiting their assigned treatment group or escaping to rescue. This imputation method has been used historically in

other RA development programs assessing structural damage, but has inherent limitations, particularly as the length of the extrapolation period increases and the amount of missing data increases. Scoring of all radiographs was done by two separate central blinded assessors.

As shown in Table 10, in the primary analysis, the mean change in mTSS at Week 52 in patients treated with the sarilumab dosing regimens was statistically significantly less compared to patients treated with placebo. A sensitivity analysis, using the post rescue data for patients who crossed over to sarilumab from Week 16, was consistent with results from the pre-specified analysis with linear extrapolation. Similar analyses at Week 24, when there was less missing data, also provided evidence of a treatment effect (Table 10). As anticipated, the treatment effect was smaller at Week 24 than Week 52. Other sensitivity analyses and tipping point analyses supported the robustness of the results at Week 52. For example, a sensitivity analysis used the same model, using the post rescue data for patients who crossed over to sarilumab from Week 16 and it was consistent with the pre-specified primary analysis (Table 11).

**Table 10: Applicant’s analysis of change from baseline in mTSS at Week 52 and Week 24 (EFC11072 Part B)**

Treatment group	n	LS Mean Change (SE)	Comparison	Mean difference	p-value
<b>Week 52</b>					
SAR 150mg (N=400)	352	0.90 (4.66)	vs. placebo	-1.88	<0.0001
SAR 200mg (N=399)	359	0.25 (4.61)	vs. placebo	-2.53	<0.0001
Placebo (N=398)	352	2.78 (7.73)	--	--	--
<b>Week 24</b>					
SAR 150mg (N=400)	340	0.43 (2.71)	vs. placebo	-0.72	<0.0018
SAR 200mg (N=399)	343	0.14 (2.25)	vs. placebo	-1.01	<0.0001
Placebo (N=398)	348	1.15 (3.44)	--	--	--

Note: For Week 52 analysis, rank ANCOVA model stratified by prior biologic use and region was used with linear extrapolation for missing data due to dropout or escape to rescue.

For Week 24 analysis, the same model was used with post rescue data.

Source: Excerpted from the Clinical Study Report for Study EFC11072 (page 105), submitted 10/30/15 and Table 12 of the statistical review by Dr. Kim

**Table 11: Applicant’s sensitivity analysis of change from baseline in mTSS at Week 52 (EFC11072 Part B)**

Treatment group	n	LS Mean Change (SE)	Comparison	Mean difference	p-value
<b>Week 52</b>					
SAR 150mg (N=400)	318	0.60 (3.56)	vs. placebo	-1.44	<0.0001
SAR 200mg (N=399)	316	0.17 (2.97)	vs. placebo	-1.87	<0.0001
Placebo (N=398)	325	2.04 (4.52)	--	--	--

Note: Rank ANCOVA model stratified by prior biologic use and region with post rescue data  
 Source: Excerpted from the Clinical Study Report for Study EFC11072-15.2 (page 16), submitted 10/30/15

Results in Table 12 show that more patients had no radiographic progression in the sarilumab 150 mg and 200 mg dose groups compared to placebo. In addition, there were numerically more patients with no radiographic progression in the 200 mg versus the 150 mg dose group.

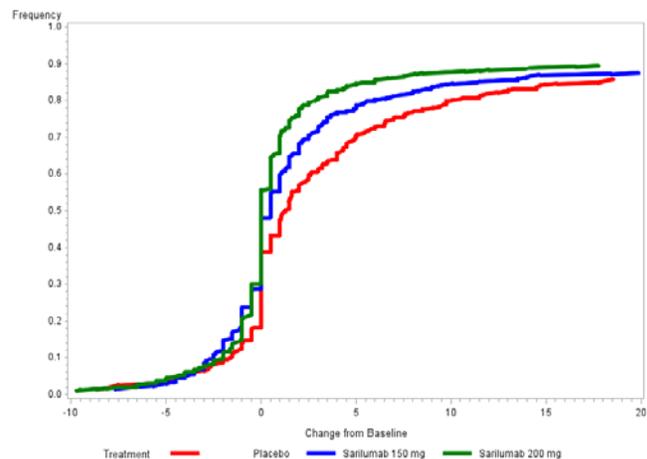
**Table 12: Applicant’s analysis of rates of no radiographic progression from baseline to Week 52 in mTSS**

Treatment group	No progression n (%)	Comparison	Odds Ratio (95% CI)	p-value
<b>Week 52</b>				
SAR 150mg (N=400)	191 (48)	vs. placebo	1.5 (1.1, 1.9)	<0.0094
SAR 200mg (N=399)	222 (56)	vs. placebo	2.0 (1.5, 2.7)	<0.0001
Placebo (N=398)	154 (39)	--	--	--

Note: Radiographic progression of the mTSS is defined as a change from baseline in the mTSS >0. The linear extrapolation method is used to impute missing or post rescue Week 52 modified total Sharp scores.  
 p-value based on CMH test stratified by prior biologic use and region.  
 Source: Excerpted from the Clinical Study Report for Study EFC11072 (page 110), submitted 10/30/15

As illustrated in Figure 8, cumulative distribution curves with worst scores imputation for missing data showed some separation of the curves between sarilumab dosing regimens and placebo.

**Figure 8: Cumulative distribution of change from baseline in mTSS at Week 52**



Source: Figure 4 of the statistical review by Dr. Kim

Therefore, the data are supportive of the treatment effect of sarilumab on structural damage progression. Further, the data suggest trends towards more radiographic inhibition with the 200 mg dose as compared to the 150 mg dose. Although there was only a single study assessing radiographic progression, the evidence is sufficient due to the highly statistically significant p-values and the consistency of results across the two doses and when including post-rescue data.

- **Discussion of statistical and clinical efficacy reviews with explanation for CDTL’s conclusions and ways that any disagreements were addressed**

The clinical and statistical review teams are in agreement that sarilumab at both 150 mg and 200 mg doses is efficacious for signs and symptoms (ACR responses, DAS28) as well as for physical function (HAQ-DI) and inhibition of radiographic progression. In general, the 200 mg dose appeared to be associated with a small amount of additional benefit over the 150 mg dose, and this was consistent across the vast majority of endpoints and studies.

- **Includes discussion of notable efficacy issues both resolved and outstanding**

There are no unresolved issues.

## 8. Safety

### *Studies contributing to integrated safety analyses and the Applicant's pooling and attribution strategies*

A summary of the studies contributing to the primary integrated safety analyses may be found in Table 13. These included 2 phase 3 studies (EFC11072 Part B and EFC10832), 1 phase 2 study (EFC11072 Part A), and studies to support safety, including a tocilizumab active comparator study (SFY13370), an etanercept active comparator study (EFC11574), an autoinjector usability study (MSC12665), a long-term extension study (LTS11210), and a monotherapy study (EFC13752). Two studies, ACT11575 and EFC11574, were terminated early due to delays in the studies, not due to any identified safety or efficacy concerns.

As noted in Table 13, placebo controlled periods were limited to 12 to 24 weeks for all of the studies, except for EFC11702 Part B, which was 52 weeks with the option for rescue starting at Week 16. For study EFC10832, the placebo-controlled period was 24 weeks, with the option for rescue starting at Week 12. The remainder of the studies were placebo or active controlled for the entire study, without the option for rescue given the fairly limited study duration (12 to 24 weeks). In study EFC11702 Part B, starting at Week 16, patients with a lack of efficacy, which was defined as less than 20% improvement compared to baseline in swollen joint counts (SJC) or tender joint count (TJC) for 2 consecutive visits or any other clear lack of efficacy (based on investigator judgment) could initiate open label sarilumab at the highest available dose at the time of transfer into the rescue treatment arm. Unlike many other study designs in RA, patients could continue on placebo until 52 weeks if they did not meet rescue criteria. In study EFC10832, the same rescue criteria were used, but starting at Week 12. Patients in study EFC10832 entered the ongoing long-term safety study LTS11210 at the time of rescue, while patients in study EFC11702 Part B remained in the study until Week 52 when they were eligible to enter study LTS11210.

APPEARS THIS WAY ON ORIGINAL

**Table 13: Summary of Phase 2 and 3 Studies in RA Submitted for the BLA**

Protocol (Dates)	Overview	Patient Population (Background medications)	Treatment Arms (SC)	N per Arm	Primary Endpoints/Notes	Duration (wks)
<b>Phase 3 studies</b>						
EFC11702 Part B <sup>a</sup>  199 centers, EU, North America, South America, Asia, Australia, New Zealand, and South Africa  (3/11-10/13)	Phase 3, R, DB, PC, rescue <sup>b</sup> at 16 weeks	MTX-IR (MTX)	<b>Cohort 1:</b> SAR 100 mg qw SAR 150 mg qw SAR 100 mg q2w SAR 150 mg q2w SAR 200 mg q2w Placebo  <b>Cohort 2:</b> SAR 150 mg q2w SAR 200 mg q2w Placebo	29 27 28 30 28 30  400 399 398 N=1197	ACR20 at wk 24 HAQ-DI at wk 16 mTSS at wk 52  Key secondary: major clinical response over 52 weeks	52
EFC10832  240 centers, worldwide  (10/12-3/15)	Phase 3, R, DB, PC, rescue <sup>c</sup> at 12 weeks	TNF-IR (DMARDs <sup>d</sup> )	SAR 150 mg q2w SAR 200 mg q2w Placebo	181 184 181 N=546	ACR20 at wk 24 HAQ-DI at Wk 12	24
<b>Studies to support safety</b>						
LTS11210  334 centers  (6/10-data cutoff 3/15)	OL, uncontrolled extension study	From 5 other sarilumab trials (EFC11072 Parts A and B, ACT11575, EFC10832, SFY13370, and EFC13752)  (DMARDs or none)	SAR 150 mg q2w SAR 200 mg q2w SAR 150 mg qw	57 1607 312	Safety	Up to 5 years
MSC12665  57 centers  (4/14-2/15)	Autoinjector usability study	DMARD-IR (DMARDs)	SAR 150 mg q2w AI SAR 200 mg q2w AI SAR 150 mg q2w PFS SAR 200 mg q2w PFS	56 52 53 56	Device usability and PK	12
SFY13370  68 centers in North America, South	Tocilizumab safety comparator study	TNF-IR (DMARDs)	SAR 150 mg q2w SAR 200 mg q2w Tocilizumab 4mg/kg IV	49 51 102	Safety	24

America, and EU (3/13-10/14)						
EFC13752 28 centers (6/14-5/15)	Monotherapy safety study	DMARD-IR  (None)	SAR 150 mg q2w SAR 200 mg q2w	65 67	Safety, immunogenicity	24
EFC11574 228 centers (5/13-1/15)	Comparison to etanercept and MTX	Adalimumab and MTX-IR	SAR 150 mg q2w SAR 200 mg q2w Etanercept 50 mg qw Sub study SAR 150 mg q2w	13 13 17 322	DAS28-CRP at wk 24  Terminated early due to study delays	24
<b>Phase 2 studies</b>						
EFC11072 Part A <sup>a</sup> 102 centers EU, North America, South America, Australia, Korea, and South Africa (3/10-5/11)	Phase 2, R, DB, PC  No escape	MTX-IR (MTX)	SAR 100 mg qw SAR 150 mg qw SAR 100 mg q2w SAR 150 mg q2w SAR 200 mg q2w Placebo	50 50 51 51 51 52 N=306	ACR20 at wk 12  Patients in Part A did not participate in Part B	12
ACT11575 10 centers, US (11/10-9/11)	Phase 2, R, DB, PC, AC	≤ 2 TNF-IR	SAR 150 mg qw GOL 50 mg q4w Placebo	7 5 4 N=16	Terminated early due to study delays	12

Abbreviations: EU=Europe; DB=double blind; DMARD=disease modifying antirheumatic drug; MTX=methotrexate; MTX-IR=inadequate response to methotrexate; PC=placebo controlled; qw=weekly; q2w=every other week; R=randomized; SAR=sarilumab; TNF=tumor necrosis factor; AC=active controlled; GOL=golimumab; ACR=American College of Rheumatology; HAQ-DI=Health Assessment Questionnaire-Disability Index; mTSS=modified Total Sharp Score; AI=autoinjector; PFS=prefilled syringe  
 a EFC11072 was conducted as a seamless Phase 2/3 Study. Part A was the dose-ranging portion of the study. Part B was the Phase 3 study. Cohort 2 is the primary population for the efficacy evaluation.

b Patients with an inadequate response were rescued with open-label sarilumab 200 mg q2w

c Patients with an inadequate response were allowed to enter LTS11210 to be rescued with open-label sarilumab 200 mg q2w

d Concomitant DMARDs: MTX, leflunomide, hydroxychloroquine, or sulfasalazine

Source: modified from Tabular Listing of all Clinical Studies, submitted 10/30/15

Patients in EFC11072, EFC10832, EFC13752, SFY13370, and ACT11575 were able to enroll into an open-label uncontrolled extension study (LTS11210). Prior to phase 3 dose selection, 316 patients received sarilumab 150 mg qw in LTS11210. After phase 3 dose selection, 1682 patients received sarilumab 200 mg q2w in LTS11210. Dose reduction to 150 mg q2w was permitted for safety reasons defined in the protocol. An important consideration in the safety analyses was that the vast majority of patients received

sarilumab 200 mg in the long-term extension study. Since patients only received 150 mg for safety reasons defined in the protocol, comparisons between the 150 mg and 200 mg doses have significant limitations.

Table 14 provides sanofi's pooling strategy. The initial focus of the integrated safety analyses was the phase 3 and phase 2 study data for patients who received sarilumab (150 mg q2w or 200 mg q2w) or who received placebo in the double-blind treatment period (Pool 1). Given the design of study EFC11072, patients enrolled in Part A and Part B cohort 1 were included in safety, but not efficacy analyses. This pool only includes safety data from the double-blind treatment period. Therefore, once a patient enters the rescue period and receives open-label sarilumab, the patient's data are no longer included. Additional safety analyses were performed in the subset of patients that was also used for the primary efficacy analyses (EFC11072 Part B Cohort 2 and EFC10832, Pool 1a).

APPEARS THIS WAY ON ORIGINAL

**Table 14: Summary of Safety Populations**

<b>Pool and Population</b>	<b>Treatment Group (n)</b>	<b>Studies (Treatment Duration)</b>
<b>Pool 1</b> Placebo-controlled population	150mg q2w + DMARD (n=660) 200mg q2w + DMARD (n=661) Placebo + DMARD (n=661)	EFC11072 Part A (12 weeks) EFC11072 Part B (52 weeks) <sup>a</sup> EFC10832 (24 weeks)
<b>Pool 1a</b> Phase 3 placebo-controlled population	150mg q2w + DMARD (n=579) 200mg q2w + DMARD (n=582) Placebo + DMARD (n=579)	EFC11072 Part B Cohort 2 (52 weeks) <sup>a</sup> EFC10832 (24 weeks)
<b>Pool 2</b> Sarilumab + DMARD long-term safety population	150mg q2w initial dose + DMARD <sup>b</sup> (n=1155) 200mg q2w initial dose + DMARD <sup>b</sup> (n=1351) Any sarilumab dose + DMARD <sup>c</sup> (n=2887)	EFC11072 Part A (12 weeks) EFC11072 Part B (52 weeks) EFC10832 (24 weeks) SFY13370 (24 weeks) EFC11574 main study <sup>d</sup> (24 weeks) EFC11574 substudy <sup>d</sup> (52 weeks) MSC12665 (52 weeks) LTS11210 <sup>e</sup> (5 years)
<b>Pool 3</b> Sarilumab monotherapy population	150mg q2w initial dose <sup>b</sup> (n=65) 200mg q2w initial dose <sup>b</sup> (n=67) Any sarilumab dose (n=132)	EFC13752 (24 weeks) LTS11210 <sup>f</sup> (5 years)

a Only data from the double-blind period are included in Pool 1 or Pool 1a.

b Only includes patients whose first sarilumab dose was either 150 or 200 mg q2w and includes data up to dose modification or discontinuation.

c Including the non-selected doses/regimens: 100 mg q2w, 100 mg qw, and 150 mg qw

d Main study: adalimumab non-responders; substudy: adalimumab responders

e Includes only patients receiving concomitant DMARDs, therefore, specifically patients from EFC11072, EFC10832, SFY13370, ACT11575

f Includes only patients receiving sarilumab as monotherapy who entered from EFC13752

Source: Dr. Peng's clinical review

Pool 2 provides information on the long-term safety of sarilumab. Pool 2 includes all patients who received sarilumab in the RA clinical development program, specifically, EFC11072 Parts A and B, EFC10832, SFY13370, EFC11574, MSC12665, and LTS11210. Attribution to treatment for the long-term safety population is categorized into 3 groups:

- Sarilumab 150 mg q2w initial dose + DMARD: includes patients whose initial dose of sarilumab was 150 mg q2w and only for the period that they received that dose. Therefore, no data are included after any dose medication (due to rescue or enrollment

in LTS11210). After a patient was rescued or enrolled in the open-label LTS11219, all adverse events that occurred in this particular patient are also counted in the “any sarilumab dose” group.

- Sarilumab 200 mg q2w initial dose + DMARD: includes patients whose initial dose of sarilumab was 200 mg q2w and only for the period that they received that dose. If a patient initiated on 200 mg was enrolled in the open-label LTS11219 and continued 200 mg q2w, this patient continues to be counted in this group. Additionally, if a patient, who initially received placebo, was rescued or enrolled in LTS11219, this patient is included in this group from the time point that he/she is started on 200 mg q2w.
- Any sarilumab dose + DMARD: includes patients on any dose of sarilumab. Therefore, this group includes subjects who received the initial dose of sarilumab 150 mg or 200 mg q2w, including data from both prior to and after any dose modification. Both of the previously described groups, “sarilumab 150 mg q2w initial dose” and “sarilumab 200 mg q2w initial dose,” are subsets of this group. Additionally, this group includes subjects who received non-selected dosing regimens (e.g., 100 mg q2w, 100 mg qw, and 150 mg qw).

Pool 3 consists only of patients who received sarilumab as monotherapy in study EFC13752 and certain patients who continued monotherapy in LTS11210. Subjects in Pool 3 are grouped similarly to the subjects in the long-term safety population.

The analysis of safety data from the clinical studies in patients with RA is complicated by differences in study duration, duration of placebo-controlled periods, time of rescue, and comparator and background therapy. An important consideration is that patients who enrolled in the long-term extension study (LTS11210) received the highest dose of sarilumab under study. This led to much higher exposure to 200 mg q2w and limits interpretation of dose comparisons in the long-term extension study.

Given the complexities of the study design, sanofi performed a variety of sensitivity analyses, including by various time periods (Table 15) and model based analyses for selected endpoints. All of the safety data on either placebo or sarilumab from the integrated studies were included in the model (ie, placebo exposure from Pool 1 and sarilumab+DMARD exposure from Pool 2). A generalized estimating equation (GEE) model was used for the analyses of the incidence or the number of the events. Given the non-randomized nature of comparisons based on such analyses, the treatment exposure (ie, time to first event), within-subject correlation, differences between studies and important baseline factors were adjusted in the GEE model. Baseline factors were considered and a forward selection procedure used to decide which baseline factors were included in the final model. Only the following endpoints were evaluated with this model-based analysis: serious infections, grade 3-4 neutropenia, ALT >3x ULN, malignancy, and MACE.

**Table 15: Additional safety analyses on placebo-controlled studies**

Endpoints	EFC11072 (Part B, Cohort 2)	EFC10832	Pool 1 and 1a
Common AEs ( $\geq 2\%$ in at least one treatment group)	0-12 weeks	0-12 weeks	0-12 weeks
	0-16 weeks		0-24 weeks
			0-52 weeks (ie, entire TEAE period)
			pre-rescue period
Targeted events (SAEs, AESIs, discontinuations due to AEs, and deaths)	0-12 weeks	0-12 weeks;	0-12 weeks
	0-16 weeks	0-24 weeks (ie, entire TEAE period)	0-24 weeks
	0-24 weeks		0-52 weeks (ie, entire TEAE period)
	0-52 weeks (ie, entire TEAE period)		pre-rescue period

Pool 1 (ie, EFC11072 (Part A [selected doses] and Part B Cohort 1 [selected doses] and Cohort 2) and EFC10832)

Pool 1a (EFC11072, Part B, Cohort 2 and EFC10832)

Pre-rescue period for Pool 1 contains 0-12 weeks from EFC10832 and EFC11072 Part A and 0-16 weeks from EFC11072 Part B and for Pool 1a contains 0-12 weeks from EFC10832 and 0-16 weeks from EFC11072 Part B

Source: Integrated Summary of Safety, Table 6, page 42, submitted 10/30/15

For this review, the safety analysis will focus on Pool 1a and the pre-rescue period (0-16 weeks for study EFC10832 and 0-12 weeks for study EFC11072 Part B). The pre-rescue period represents the data least affected by the variable dosing regimens and cross-over between study arms. For certain adverse events where it was beneficial to evaluate 52 weeks of exposure data, Pool 1 was evaluated. For deaths, serious adverse events (SAEs), and certain adverse events of special interest (AESI), the review also focused on the long-term safety population, any exposure-adjusted analyses, sensitivity analyses (based on exposure), and the sanofi’s model-based analyses.

In addition, analyses were performed from study SFY13370 which compared the safety of sarilumab to tocilizumab, which has the same mechanism of action.

Sanofi provided an assessment for Adverse Events of Special Interest (AESI), including leukopenia, thrombocytopenia, infections (common, serious, opportunistic infections, tuberculosis), hepatic disorders, diverticulitis/potential GI perforations, GI ulcerations, elevation in lipids, anaphylaxis, hypersensitivity, injection site reactions, malignancy, lupus-like syndrome, demyelinating disorders,

major adverse cardiovascular events (MACE), and immunogenicity. The evaluated AESI were reasonable given the safety profile of tocilizumab, which has the same mechanism of action, and other immunosuppressive drugs approved for RA.

- **Adequacy of the drug exposure experience (i.e., the safety database)**

As of the BLA submission, a total of 3,019 patients received at least 1 dose of sarilumab ± DMARD in the phase 2 and 3 RA clinical development program, providing 4405.7 patient-years of cumulative exposure (Table 16). This includes 132 patients treated with sarilumab as monotherapy (66.8 patient-years). At the higher dose of 200 mg q2w, approximately 1,200 patients have >48 weeks of exposure. At both doses of 200 mg q2w and 150 mg q2w, over 1,650 patients have >48 weeks of exposure.

Notably, the majority of patients with longer durations of exposure (i.e. greater than 48 weeks) received sarilumab 200 mg once every two weeks. Long-term exposure is limited in the 150 mg q2w initial dose group because, by protocol design, patients were required to receive the highest dose under study in the ongoing open-label extension study LTS11210. In the LTS11210 study, patients were allowed to reduce their dose to 150 mg q2w for protocol-defined laboratory abnormalities, providing additional exposure in the 150 mg q2w dose group.

The size and scope of the safety database were reasonable and consistent with the safety database of other biologic products approved for RA.

APPEARS THIS WAY ON ORIGINAL

**Table 16: Exposure to Sarilumab from the phase 2 and 3 studies in RA**

	Sarilumab <sup>a</sup> + DMARD 150 mg q2w Any exposure <sup>c</sup> (N=1617)	Sarilumab <sup>b</sup> ± DMARD 200 mg q2w Any exposure <sup>c</sup> (N=2267)	Any Sarilumab Dose <sup>d</sup> (N=3019)
<b>Overall</b>			
Number of patients	1617	2267	3019
Total exposure (patient years)	1177	2951	4406
<b>Number of patients with duration of study treatment by category [n]</b>			
≥ 12 weeks	1406	1977	2741
≥ 24 weeks	984	1679	2353
≥ 48 weeks	477	1220	1564
≥ 96 weeks	121	716	1028
≥ 144 weeks	45	334	628
≥ 192 weeks	15	8	194
≥ 240 weeks	0	0	22

Includes data from studies EFC11072, EFC10832, SFY13370, EFC11574, EFC13752, MSC12665, LTS11210

a includes both 150 mg q2w + DMARD and 150 mg q2w monotherapy

b includes both 200 mg q2w + DMARD and 150 mg q2w monotherapy

c exposure at any time

d includes all sarilumab doses, including 100mg qw, 100mg q2w, 150mg qw, 150mg q2w, 200mg q2w

Source: Integrated Summary of Safety Appendix 1.3, Table 1.3.1, page 898, submitted 10/30/15

- **Key safety results, including deaths, serious adverse events (SAEs), discontinuations due to AEs, other AEs, results of laboratory tests, and immunogenicity**

### *Death*

As of April 29, 2015, there were a total of 26 deaths reported in the RA clinical development program. Of these, 22 occurred in sarilumab-treated patients, 3 occurred in placebo-treated patients, and 1 occurred in a tocilizumab-treated patient. For deaths that occurred during the treatment-emergent period, the exposure adjusted incidence rate of death was lower in the sarilumab+DMARD group [0.4/100 patient-years (95% CI 0.26, 0.66)] than the placebo group [0.8/100 patient-years (95% CI 0.16, 2.28)]. An additional two deaths were reported after April 29, 2015.

Notably, of the 24 deaths that occurred on sarilumab, the vast majority occurred in patients on sarilumab 200 mg (17/24 deaths, 71%). However, 13 of the 17 subjects who died while taking sarilumab 200 mg q2w were in the long-term safety study, during which the 200 mg dose was the only dose offered. When evaluating the exposure-adjusted incidence rate of death over time, there was no increase. Further, the exposure-adjusted incidence rate of death during the placebo controlled portion of the study was balanced between the doses (Table 17). Specifically, for Pool 1a, the exposure adjusted incidence rate per 100 patient years, was lower for sarilumab 200 mg (0.2) and sarilumab 150 mg (0.5) than placebo (0.9). Thus, the higher number of deaths in 200 mg compared to the 150 mg dose group in the long-term safety population likely reflects the study design and the increased exposure to 200 mg.

**Table 17: TEAE leading to death in Phase 3 placebo-controlled safety population (Pool 1a)**

<b>TEAE leading to death</b>	<b>Raw incidence rate n/N (%)</b>	<b>Exposure adjusted incidence rate n/PY (rate per 100 PYs)</b>
Sarilumab 200 mg	1/582	1/408.1 (0.2)
Sarilumab 150 mg	2/579	2/403.9 (0.5)
Placebo	3/579	3/348.7 (0.9)

All patients received background DMARDs

Source: ISS appendix 1.12.1.25, page 8412, submitted 10/30/15

The medical officer reviewed all of the narratives for patient deaths and categorized them into four main categories: infection, cardiovascular events (CV), malignancy, and other. The causes of death in sarilumab-treated patients were consistent with the profile of an immunosuppressant and also with the underlying patient population.

### ***Serious Adverse Events (SAE)***

The proportion of patients experiencing an SAE and the exposure-adjusted incidence of SAE during the pre-rescue period of the two phase 3 studies (Pool 1a) is summarized in Table 18. The proportion of patients experiencing an SAE was higher in the sarilumab dose groups compared to placebo. Also, the proportion of patients experiencing an SAE was higher in the 200 mg than the 150 mg dose group. The same observations were noted for the exposure-adjusted incidence rates. The increased proportion of SAEs with the 200 mg versus the 150 mg dose group was primarily secondary to an increased frequency of blood and lymphatic systemic disorders, such as neutropenia and leukopenia.

The most common SAE (by system organ class (SOC)) for all treatment arms was Infections and Infestations. In this SOC, both sarilumab treatment arms were numerically higher than that of placebo (0.7% placebo and 1% in sarilumab 150 mg and 200 mg).

Notably, there was not a difference between the doses. Thus, while there was an increased frequency of neutropenia and leukopenia with the 200 mg dose group, there was not an increased frequency of serious infections with the 200 mg dose group compared to the 150 mg dose group.

These adverse events of special interest will be discussed in more detail in sections to follow.

**Table 18: Patients with SAEs by SOC during the pre-rescue period of the phase 3 RA trials (Pool 1a)**

	Placebo + DMARD	Sarilumab 150mg q2w + DMARD	Sarilumab 200mg q2w + DMARD
<b>Any SAEs</b>			
Raw incidence rate n/N (%)	12/579 (2.1%)	19/579 (3.3%)	34/582 (5.8%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	12/155.6 (7.7)	19/151.4 (12.5)	34/151.0 (22.5)
<b>Infections and infestations</b>			
Raw incidence rate n/N (%)	4/579 (0.7%)	6/579 (1.0%)	6/582 (1.0%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	4/158.8 (2.5)	6/157.5 (3.8)	6/156.9 (3.8)
<b>Neoplasms benign, malignant, and unspecified (incl cysts and polyps)</b>			
Raw incidence rate n/N (%)	2/579 (0.3%)	1/579 (0.2%)	0/582
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	2/160.7 (1.2)	1/159.1 (0.6)	0/160.6 (0)
<b>Blood and lymphatic systemic disorders</b>			
Raw incidence rate n/N (%)	0/579	1/579 (0.2%)	7/582 (1.2%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	0/161.4 (0.0)	1/158.9 (0.6)	7/160.3 (4.4)
<b>Psychiatric disorders</b>			
Raw incidence rate n/N (%)	0/579	1/579 (0.2%)	1/582 (0.2%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	0/161.3 (0)	1/160.0 (0.6)	1/160.9 (0.6)
<b>Nervous system disorders</b>			
Raw incidence rate n/N (%)	2/579 (0.3%)	1/579 (0.2%)	1/582 (0.2%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	2/160.9 (1.2)	1/159.6 (0.6)	1/161.0 (0.6)
<b>Cardiac disorders</b>			
Raw incidence rate n/N (%)	1/579 (0.2%)	2/579 (0.3%)	2/582 (0.3%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	1/160.6 (0.6)	2/159.8 (1.3)	2/160.6 (1.2)
<b>Vascular disorders</b>			
Raw incidence rate n/N (%)	0/579	0/579	2/582 (0.3%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	0/161.3 (0)	0/159.1 (0)	2/160.8 (1.2)
<b>Respiratory, thoracic, and mediastinal disorders</b>			
Raw incidence rate n/N (%)	0/579	3/579 (0.5%)	3/582 (0.5%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	0/161.3 (0)	3/158.9 (1.9)	3/161.0 (1.9)
<b>Gastrointestinal disorders</b>			
Raw incidence rate n/N (%)	2/579 (0.3%)	0/579	2/582 (0.3%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	2/161.5 (1.2)	0/158.9	2/160.8 (1.2)
<b>Hepatobiliary disorders</b>			
Raw incidence rate n/N (%)	1/579 (0.2%)	2/579 (0.3%)	1/582 (0.2%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	1/161.2 (0.6)	2/159.5 (1.3)	1/160.9 (0.6)

<b>Musculoskeletal and connective tissue disorders</b>			
Raw incidence rate n/N (%)	1/579 (0.2%)	1/579 (0.2%)	4/582 (0.7%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	1/160.1 (0.6)	1/159.3 (0.6)	4/160.5 (2.5)
<b>Renal and urinary disorders</b>			
Raw incidence rate n/N (%)	0/579	0/579	1/582 (0.2%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	0/161.3	0/159.7	1/582 (0.2%)
<b>General disorders and administration site conditions</b>			
Raw incidence rate n/N (%)	1/579 (0.2%)	0/579	0/582
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	1/161.5 (0.6)	0/160.0 (0)	0/160.3 (0)
<b>Investigations</b>			
Raw incidence rate n/N (%)	0/579	2/579 (0.3%)	3/582 (0.5%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	0/161.6 (0)	2/159.5 (1.3)	3/160.7 (1.9)
<b>Injury, poisoning, and procedural complications</b>			
Raw incidence rate n/N (%)	2/579 (0.2%)	2/579 (0.3%)	3/582 (0.5%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	2/161.5 (1.2)	2/159.6 (1.3)	3/160.3 (1.9)

Note: SOC's shaded in orange; Table sorted by SOC internationally agreed order and decreasing frequency of PT in the sarilumab 200mg q2w treatment group.

n (%) = number and percentage of patients with at least one TEAE

a Number of patients with at least 1 event per 100 patient-years, where the exposure time for patients who have experienced the specific adverse event experience was defined as the time to first adverse experience of interest whereas the exposure time for those who have not had this adverse experience was total TEAE period duration

Source: Sanofi Response to MCC Agency Request (April 19, 2016), Appendix Table 5, dated May 2, 2016; page 13-28; adapted from Dr. Peng's clinical review

In the long-term safety population (Pool 2) the exposure-adjusted event rates were slightly higher for the 200 mg than the 150 mg dose group. Specifically, the exposure-adjusted event rate was 13.7 events per 100 patient-years for 150 mg q2w initial dose, 15.6 events per 100 patient-years for 200 mg q2w initial dose, and 15.2 events per 100 patient-years for any sarilumab dose (Table 19). The event rate was similar to that in Pool 1a for 150mg and was lower for 200 mg. As seen in the pre-rescue period, Infections and Infestations remained the most common SOC for all treatment arms. The most frequent preferred terms (PTs) in any SOC were pneumonia (27 [0.9% patients]), rheumatoid arthritis (21 [0.7%] patients), osteoarthritis (20 [0.7%] patients), and neutropenia (16 [0.6%] patients).

APPEARS THIS WAY ON ORIGINAL

**Table 19: Overview of SAEs in ≥ 3 patients in the Entire TEAE Period (Pool 2)**

Primary SOC	Sarilumab + DMARD					
	150mg q2w Initial Dose		200mg q2w Initial Dose		Any Dose	
	Raw incidence rate (N=1155) n (%)	Exposure adjusted event rate (PY= 701.9) n <sub>E</sub> (n <sub>E</sub> /100 PYs)	Raw incidence rate (N=1351) n (%)	Exposure adjusted event rate (PY=1758.6) n <sub>E</sub> (n <sub>E</sub> /100 PYs)	Raw incidence rate (N=2887) n (%)	Exposure adjusted event rate (PY=4481.8) n <sub>E</sub> (n <sub>E</sub> /100 PYs)
<b>Any class</b>	62 (5.4%)	96 (13.7)	187 (13.8%)	275 (15.6)	439 (15.2%)	681 (15.2)

Source: adapted from Dr. Peng’s clinical review

Sanofi evaluated the SAE rate by 6-month intervals for the long-term safety population. In general, the exposure adjusted event rates are similar over time, but the confidence interval widens with time.

***Discontinuations due to Adverse Events***

In the placebo controlled safety population, the proportion of patients discontinuing due to an adverse event was higher in the sarilumab treatment arms compared to placebo and was slightly higher in the 200 mg dose group than the 150 mg dose group (Table 20). The most common AEs (by PT) in the sarilumab arms leading to discontinuation were neutropenia, increased ALT, and herpes zoster, in descending order. Of note, there were certain laboratory parameters and adverse events (including opportunistic infections, such as herpes zoster) that were pre-specified to trigger discontinuations. Adverse events related to infections and laboratory abnormalities are discussed in further detail in separate sections.

In the long-term safety population, the exposure-adjusted rates of AEs were 20.5 events per 100 patient-years in the sarilumab 150 mg q2w arm and 13.6 events per 100 patient-years in the 200 mg q2w initial dose arm. The three most common PTs leading to discontinuation were the same as the ones from the double-blind period, that is, neutropenia, alanine aminotransferase increased, and herpes zoster.

APPEARS THIS WAY ON ORIGINAL

**Table 20: Summary of Adverse Events Leading to Discontinuation in the Pre-Rescue Period (Pool 1a)**

	Placebo + DMARD	Sarilumab 150mg q2w + DMARD	Sarilumab 200mg q2w + DMARD
<b>AEs leading to permanent treatment discontinuation</b>			
Raw incidence rate n/N (%)	18/579 (3.1%)	37/579 (6.4%)	44/582 (7.6%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	18/156.3 (11.5)	37/147.0 (25.2)	44/146.8 (30.0)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		3.6% (1.0, 6.1)	4.8% (2.1, 7.5)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			1.2% (-1.8, 4.3)

PY: patient-years; pre-rescue period contains 0-12 weeks from EFC10832 and 0-16 weeks from EFC11072

n (%) = number and percentage of patients with at least one TEAE

a Number of patients with at least 1 event per 100 patient-years, where the exposure time for patients who have experienced the specific adverse event experience was defined as the time to first adverse experience of interest whereas the exposure time for those who have not had this adverse experience was total TEAE period duration

b The rate difference and its 95% confidence interval were estimated using the M&N method stratified by the study, using the CMH weight

Source: ISS Appendix 1.12.1.50, page 8279, submitted 10/30/15

### ***Common adverse events***

Table 21 presents the common TEAEs by SOC for the first 12 weeks from Pool 1a. In the first 12 weeks of the phase 3 RA studies, more patients in the sarilumab arms experienced any TEAE as compared to subjects in the placebo arm (42% placebo arm, 50% sarilumab 150 mg, and 53% sarilumab 200 mg). Adverse events in the Infections and Infestations SOC were the most common adverse event. The most common infections were upper respiratory tract infection, urinary tract infection, and nasopharyngitis. Blood and lymphatic system disorders were next most common, with neutropenia being the most common preferred term. The most common TEAEs (by PT) were neutropenia, increased ALT, and injection site erythema. All of these TEAEs occurred more frequently in patients on sarilumab. All of the SOCs, except metabolism and nutrition disorders and nervous system disorders, were more common with the 200 mg dose compared to the 150 mg dose.

APPEARS THIS WAY ON ORIGINAL

**Table 21: Number (%) of patients with TEAE(s) by primary SOC (0-12 weeks) – Phase 3 placebo-controlled safety population (Pool 1a)**

	Placebo + DMARD (N=579) n (%)	Sarilumab 150mg q2w + DMARD (N=579) n (%)	Sarilumab 200mg q2w + DMARD (N=582) n (%)
<b>Treatment-emergent adverse events (SOC)</b>			
Any class	242 (42)	287 (50)	306 (53)
Infections and infestations	92 (16)	106 (18)	120 (21)
Blood and lymphatic system disorders	12 (2)	38 (7)	67 (12)
Metabolism and nutrition disorders	8 (1)	26 (5)	20 (3)
Nervous system disorders	27 (5)	24 (4)	23 (4)
Gastrointestinal disorders	39 (7)	31 (5)	49 (8)
Musculoskeletal and connective tissue disorders	44 (8)	22 (4)	30 (5)
General disorders and administration site conditions	16 (3)	43 (7)	50 (9)
Investigations	23 (4)	46 (8)	47 (8)
Injury, poisoning, and procedural complications	37 (6)	24 (4)	32 (6)

Source: Summary of Clinical Safety, Table 20, page 65, submitted 10/30/15

### ***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)

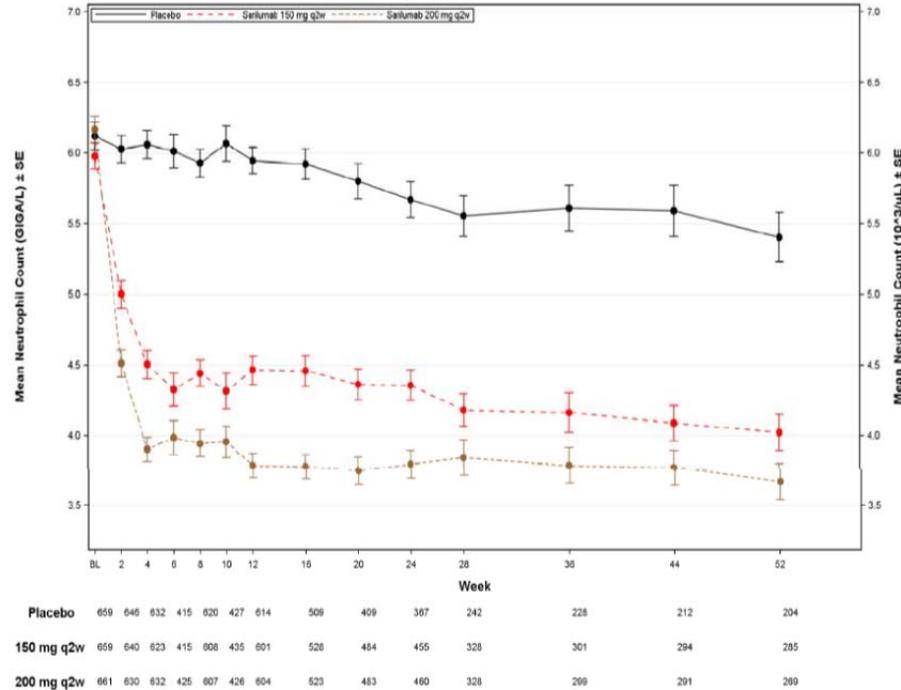
In addition, there were protocol-specified criteria for discontinuation or withholding of drug dependent on grade of neutrophil count and whether infection was present. Additionally, in the long-term safety study, the dose of sarilumab could be reduced based on specific criteria related to ANC grade. Protocols also required reporting of ANC <1.0 Giga/L as an adverse event.

### ***White blood cells/Neutrophils***

Transient decreases in ANC have been associated with IL-6 inhibition. Patients with WBC count <3.0 Giga/L or neutrophil count <2.0 Giga/L were excluded from sarilumab clinical trials. In addition, there were protocol-specified criteria for discontinuation or withholding of drug dependent on grade of neutrophil count and whether infection was present.

Figure 9 displays the mean change in ANC across visits during the double-blind treatment period. The decrease in ANC was evident 2 weeks after initiation of therapy, which was the first time point measured, and stabilized after Week 4. In the sarilumab+DMARD groups, at Week 4, the mean decrease was 2.3 10<sup>9</sup>/L in 200 mg q2w and 1.5 10<sup>9</sup>/L in 150 mg q2w. Although a decrease was observed, mean values remained in the normal range.

**Figure 9: Mean ANC across Visits during the Double-Blind Treatment Period (Pool 1)**



Normal range: 1.96 – 7.23 Giga/L

Source: Integrated Summary of Safety, Figure 11, dated October 6, 2015; page 157.

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 q2w group (41%) compared to the 150 mg q2w group (32%), although in the majority of patients the lowest ANC value remained above  $\geq 1.0$  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%).

For Pool 2, Sanofi also analyzed whether there was an association between neutropenia and actual infection. Table 22 presents the incidence of infection in patients based on whether they had an ANC measured lower than the lower limit of normal. Overall, it appears that the proportion of patients with infections and serious infections were generally the same whether subjects had measured neutropenia.

**Table 22: Incidence of Infection in Subjects with and without ANC  $<$  LLN in the Long-Term Safety Population (Pool 2)**

Criteria, n(%)	Sarilumab + DMARD		
	150 mg q2w Initial Dose (PY=701.9)	200 mg q2w Initial Dose (PY=1758.6)	Any Dose (PY=4481.8)
Patients with infection and ANC $\geq$ LLN	240/743 (32%)	295/687 (43%)	642/1487 (43%)
Patients with infection and ANC $<$ LLN	125/410 (31%)	277/659 (42%)	671/1392 (48%)
Patients with serious infection and ANC $\geq$ LLN	11/743 (2%)	29/687 (4%)	76/1487 (5%)
Patients with serious infection and ANC $<$ LLN	6/410 (2%)	35/659 (5%)	82/1392 (6%)

ANC = absolute neutrophil count; LLN = lower limit of normal

Maximum grade of neutropenia defined based on the lowest ANC during the entire TEAE period was selected for each patient

Infection may have occurred before or after the laboratory assessment

Source: Adapted from Dr. Peng's clinical reviewer, ISS, Table 64, dated October 6, 2015; page 165

The rate of ANC  $< 1.0$  Giga/L did not increase over time with long-term administration (Pool 2). The majority of patients with ANC  $< 1.0$  Giga/L continued with sarilumab therapy. The decrease in ANC  $< 1.0$  Giga/L was generally transient.

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.

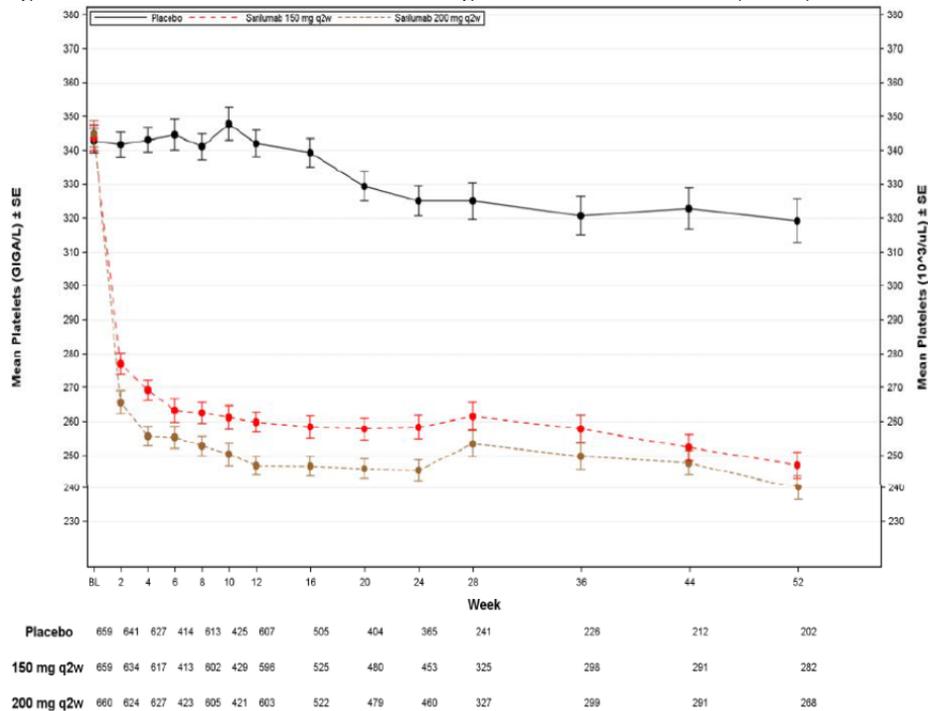
WBC counts decrease with sarilumab treatment in a similar pattern to that observed for ANC. The WBC count decrease is primarily due to a decrease in neutrophils. No clinically meaningful differences between sarilumab and placebo were observed in the other WBC types.

*Platelet count*

Over the double-blind treatment period (Pool 1), there was a clear trend toward a decline in platelets in patients on sarilumab. Figure 10 displays the mean platelet counts over time through the end of the double-blind period. At Week 4, a mean decrease of 91 Giga/L for sarilumab 200 mg q2w and 75 Giga/L for sarilumab 150 mg q2w was observed, and then mean platelet counts stabilized throughout the remainder of treatment. During the 0-12 week period in the phase 3 placebo-controlled population (Pool 1a), platelet count <100 Giga/L was observed in 7 (1.2%) patients in the 200 mg q2w sarilumab group, in 4 patients (0.7%) in 150 mg q2w sarilumab group, and in no patients in the placebo group. Thus, there appears to be a small difference between doses with the higher dose having a slightly greater decline in platelet counts. Of the 57 patients on any dose of sarilumab who had a platelet count <100 Giga/L, the majority (58%) normalized on-treatment. Sanofi did not find any correlation between decreased platelets and clinical adverse events.

APPEARS THIS WAY ON ORIGINAL

**Figure 10: Mean Platelets Across Visits during the Double-Blind Period (Pool 1)**



Normal range: 140-400 Giga/L

Source: Integrated Summary of Safety, Figure 14, dated October 6, 2015; page 173.

*Hepatic enzyme abnormalities*

Liver function test abnormalities were relatively common in the RA clinical development program. The incidence of elevations in ALT was 58% in the 200 mg q2w sarilumab group, 51% in the 150 mg q2w sarilumab group, and 33% in the placebo group. In all treatment groups, the majority of elevations in ALT were between 1-3xULN. A numerically higher incidence was observed in 200 mg q2w compared to 150 mg q2w for elevations between 1-3xULN, but the incidence was similar in both treatment groups for elevations >3xULN.

A mean increase in ALT and AST was observed in the sarilumab groups compared to placebo. This increase was observed at 2 weeks after initiation of therapy (i.e., first time point measured). At Week 4, a mean increase in ALT of 7.14-8.61 IU/L and AST of 3.58-4.22 IU/L was observed, and then ALT stabilized throughout the remainder of treatment whereas a small increase in AST was observed (5.57-5.60 IU/L at Week 52). The mean values remained within the normal range. At Week 52, the mean increase in unconjugated bilirubin was 3.62 IU/L (0.21 mg/dL) in the 200 mg q2w treatment group, 2.77 IU/L (0.16 mg/dL) in the 150 mg q2w treatment group, and 0.45 IU/L (0.03 mg/dL) in the placebo group. A mean decrease in alkaline phosphatase was observed in the sarilumab+DMARD groups compared to placebo. All mean values remained within normal ranges.

Four patients (1 from 200 mg q2w, 2 from 150 mg q2w and 1 from placebo) had ALT >3xULN and TB >2xULN, all of which had alternative plausible explanations and, therefore, did not fulfil the criteria for Hy's law. Six patients (all from sarilumab groups), had an ALT >10xULN, of which 2 patients also had an increase in total bilirubin >2xULN. There were potential confounders in these cases, including other medications and medical events. Thus, none of the cases were clearly suggestive of drug induced hepatic injury.

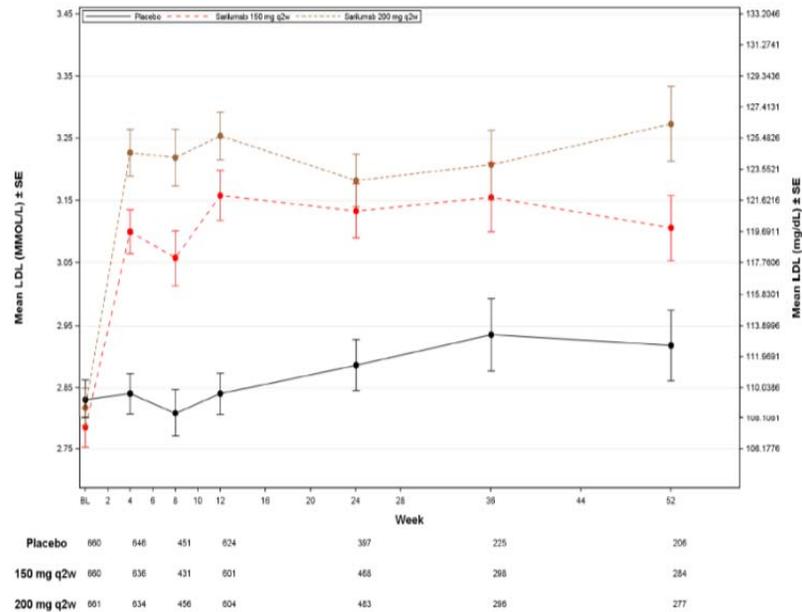
#### *Elevation in lipids*

The mean LDL, HDL, and triglycerides during the TEAE period in the placebo-controlled population are displayed in Figure 11, Figure 12, and Figure 13, respectively. Compared to placebo+DMARD, a mean increase from baseline in LDL, HDL, and triglycerides was observed in the sarilumab+DMARD treatment groups. Sanofi concluded that the increase was similar between the 2 sarilumab doses, however the increase in LDL appears slightly larger for the 200 mg group compared to the 150 mg group. At Week 4, the mean increase in LDL was ~14 mg/dL (16%), the mean increase in triglycerides was ~23 mg/dL (23%), and the mean increase in HDL was ~3 mg/dL (6%). After the initial elevation, the values remained relatively stable. There were no reports of pancreatitis secondary to increases in triglycerides. The event rate of MACE, is discussed separately.

At baseline, the majority of patients had a NCEP ATPIII classification of optimal (LDL <100 mg/dL) or near or above optimal (LDL 100 to <130 mg/dL). Based on average post-baseline LDL values, the majority of patients did not have a shift in LDL classification. Of those who shifted up a NCEP ATPIII LDL classification, the majority shifted up one classification with a numerically higher incidence observed in the sarilumab treatment groups compared to placebo. A numerically higher incidence of patients on sarilumab initiated statins compared to placebo with no difference observed between the 2 doses of sarilumab (16 patients [2.4%] in 200 mg q2w), 16 patients [2.4%] in 150 mg q2w and 3 [0.5%] in placebo).

Internal consultation from the Division of Metabolic and Endocrine Products (DMEP) was obtained regarding the implications of these lipid parameter changes. DMEP consultants were of the opinion that it is difficult to predict the net effect of sarilumab on cardiovascular risk in patients with RA. It was noted that there is a complex interplay of inflammation with lipid levels and CV risk in patients with RA. Additional discussion of cardiovascular outcomes is provided below.

**Figure 11: Mean low density lipoprotein (LDL) across visits during the entire TEAE period-Placebo-controlled safety population (Pool 1)**

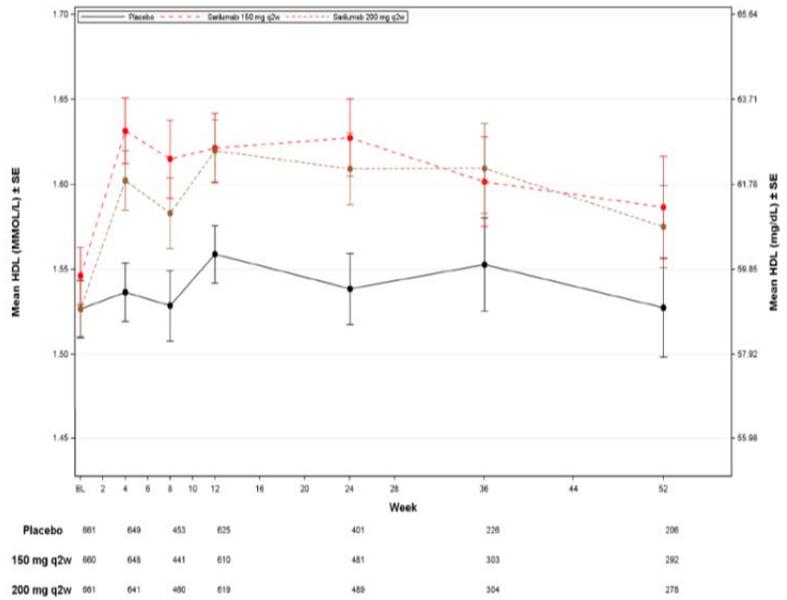


Normal range: 2.28 - 5.21 mmol/L (88-201 mg/dL)  
 PGM=PRODOPS/SAR153191/OVERALL/CSS/REPORT/PGM/lab\_meanplot\_s\_g.sas OUT=REPORT/OUTPUT/lab\_meanplot\_ldl\_s\_g\_p1.rtf  
 (29JUN2015 - 10:04)

Source: Summary of Clinical Safety, Module 2.7.4, Figure 21, page 159, submitted 10/30/15

APPEARS THIS WAY ON ORIGINAL

Figure 12: Mean high density lipoprotein (HDL) across visits during the entire TEAE period-Placebo-controlled safety population (Pool 1)

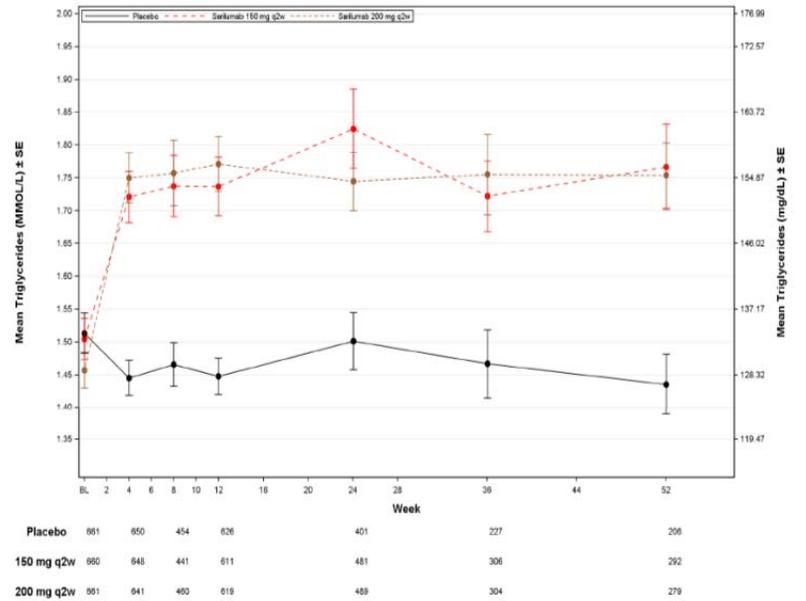


Normal range: 0.96 – 2.38 mmol/L (37 – 92 mg/dL)  
 PGM=PRODOPS/SAR153191/OVERALL/CSS/REPORT/PGM/lab\_meanplot\_s\_g.sas OUT=REPORT/OUTPUT/lab\_meanplot\_hdl\_s\_g\_p1\_j.rtf  
 (29JUN2015 - 10:01)

Source: Summary of Clinical Safety, Module 2.7.4, Figure 22, page 160, submitted 10/30/15

APPEARS THIS WAY ON ORIGINAL

Figure 13: Mean triglycerides across visits during the entire TEAE period-Placebo-controlled safety population (Pool 1)



Normal range: 0.59 – 2.96 mmol/L (52-262 mg/dL)  
 PGM=PRODOPS/SAR153191/OVERALL/CSS/REPORT/PGM/lab\_meanplot\_s\_g.sas OUT=REPORT/OUTPUT/lab\_meanplot\_trig\_s\_g\_p1\_i.rtf  
 (29JUN2015 - 10:10)

Source: Summary of Clinical Safety, Module 2.7.4, Figure 23, page 161, submitted 10/30/15

- **Submission-specific safety issues**

### Infections

During the pre-rescue period in the phase 3 studies, the proportion of patients with infections, serious infections, and opportunistic infections was increased with sarilumab treatment compared to placebo (Table 23). However, the proportion of patients with infections, serious infections, and opportunistic infections was fairly balanced between the 150 mg and 200 mg dose groups. Similar observations were noted during the entire 52-week, double-blind treatment period. The most common infections in all treatment arms (by preferred term) were upper respiratory tract infection, urinary tract infection, and nasopharyngitis.

*Serious infections*

During the 52-week pooled safety period, rate of serious infection (per 100 patient years) was 3.2, 2.7, and 4.3 in the placebo, 150 mg, and 200 mg treatment arms, respectively. Thus, the rate of serious infections was higher in the sarilumab 200 mg group than the placebo and 150 mg groups. The rate of serious infections was lower in the sarilumab 150 mg group than placebo. In the long-term safety population (Pool 2), similar trends were observed with the number of serious infections (per 100 patient years) of 2.4, 3.7, and 3.6 for the 150 mg, 200 mg, and any dose groups. Utilizing model based analyses, similar trends were observed. While there is variability in the published data, the rates and types of serious infections observed with sarilumab treatment are consistent with other immunosuppressive products approved for the treatment of RA.<sup>11</sup>

APPEARS THIS WAY ON ORIGINAL

---

<sup>11</sup> DE Furst. The risk of infections with biologic therapies for rheumatoid arthritis. *Semin Arthritis Rheum* 2010;39:327-346.

**Table 23: Summary of overall infections during the pre-rescue period (Pool 1a) and serious infections during 52-week double-blind treatment period (Pool 1) and entire TEAE period (model-based analysis)**

	Placebo + DMARD	Sarilumab 150mg q2w + DMARD	Sarilumab 200mg q2w + DMARD
<b>Pre-Rescue Period (Pool 1a)</b>			
<b>Infections</b>			
Raw incidence rate n/N (%)	100/579 (17.3%)	122/579 (21.1%)	130/582 (22.3%)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		5.0% (-0.1, 10.2)	6.1% (0.9, 11.3)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			1.1% (-4.3, 6.5)
<b>Serious Infections</b>			
Raw incidence rate n/N (%)	4/579 (0.7%)	6/579 (1.0%)	6/582 (1.0%)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		0.3% (-0.7, 1.4)	0.4% (-0.7, 1.4)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			0.0% (-1.2, 1.2)
<b>Opportunistic Infections</b>			
Raw incidence rate n/N (%)	2/579 (0.3%)	2/579 (0.3%)	4/582 (0.7%)
Rate difference vs. PBO + DMARD (95% CI) <sup>b</sup>		-0.0% (-0.7, 0.7)	0.3% (-0.5, 1.2)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) <sup>b</sup>			0.3% (-0.5, 1.2)
<b>52 week double-blind treatment (Pool 1)</b>			
Total patients with ≥ 1 serious infection (%)	12 (1.8%)	12 (1.8%)	19 (2.9%)
Number of patients with ≥ 1 serious infection per 100 pt-yrs	3.2	2.7	4.4
Total number of serious infections (per 100 pt-yrs)	15 (3.9)	16 (3.6)	23 (5.2)
<b>Model based analysis of patients with ≥1 serious infection during TEAE period</b>			
Raw incidence rate n/N (%)	12/661 (1.8)	17/1155 (1.5)	64/1351 (4.7)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>c</sup>	12/378.9 (3.2)	17/698.3 (2.4)	64/1720.5 (3.7)
Rate ratio vs. PBO + DMARD (95% CI)		0.77 (0.37, 1.60) <sup>d</sup>	1.19 (0.64, 2.20) <sup>d</sup>
Rate ratio vs. sarilumab 150mg + DMARD (95% CI)			1.55 (0.91, 2.65) <sup>d</sup>

n (%) = number and percentage of patients with at least one TEAE

a Number of patients with at least 1 event per 100 patient-years, where the exposure time for patients who have experienced the specific adverse event experience was defined as the time to first adverse experience of interest whereas the exposure time for those who have not had this adverse experience was total TEAE period duration

b The rate difference and its 95% confidence interval were estimated using the M&N method stratified by the study, using the CMH weight

c Number of patients with at least one event per 100 patient-years (PYs), where the exposure time for patients who have experienced the specific adverse experience was defined as the time to first adverse experience of interest whereas the exposure time for those who have not had this adverse experience was total TEAE period duration

d The rate ratio and its 95% confidence interval (CI) were estimated using the GEE (Poisson distribution with exposure calculated based on the time to first event as an offset), adjusted for treatment and the important baseline factors (age, weight, RA duration of disease, diabetes), assuming an exchangeable covariance structure for the within-subject correlations

Source: Modified from Dr. Peng's clinical review, ISS Appendix 1.12.1.52, dated September 29, 2015, page 8287-8 and ISS, Table 51, dated October 6, 2015; page 139-40; Sanofi response to IR (June 10 and 13, 2016), Appendix B 1.12.3.1, dated June 15, 2016, page 8

### *Infections leading to death*

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 immunosuppression. The proposed prescribing information includes a boxed warning regarding the risk of serious infections leading to hospitalization or death.

### *Opportunistic infections*

During the double blind period (Pool 1), there were 3 patients (0.5%) on placebo, 4 patients (0.6%) on 150 mg, and 6 patients (0.9%) on 200 mg sarilumab with at least one opportunistic infection. Herpes zoster was the most common opportunistic infection with 3 patients on placebo, 4 patients on 150 mg, and 5 patients on 200 mg developing herpes zoster or ophthalmic herpes zoster. There were no cases of tuberculosis during the double-blind treatment period.

In the long-term safety population, the rates of opportunistic infections remained fairly stable for sarilumab (0.6 per 100 PY for 150 mg, 1.1 per 100 PY for 200 mg, and 1.0 per 100 PY for any dose) with 44 patients having opportunistic infections in the any dose group. Of the 44 patients, 36 patients had herpes zoster (0.8 events per 100 patient years). Six patients had Candida infections (0.2 events per 100 patient-years). Also, 2 subjects in the any dose arm had tuberculosis (TB) (0.04 events per 100 patient-years). Of the two patients who had tuberculosis, one had cutaneous tuberculosis and one had pulmonary tuberculosis. In the ongoing studies not included in the integrated safety database, there were two additional opportunistic infections (Pneumocystis pneumonia and non-disseminated herpes zoster) that occurred in patients treated with sarilumab after the cutoff of April 30, 2015 and prior to July 31, 2015.

The number and pattern of opportunistic infections observed with sarilumab treatment suggests significant immunosuppression that is apparent with both doses, although somewhat higher with the 200 mg dose compared to the 150 mg dose.

### *Herpes zoster*

Herpes was the most common opportunistic infection. Of the 36 patients with herpes zoster, 7 events were SAEs. No case of disseminated herpes zoster was reported.

### *Diverticulitis/potential GI perforations*

Events of GI perforation have been reported in clinical trials of tocilizumab in RA patients, primarily as complications of diverticulitis. Patients with a history of inflammatory bowel disease or severe diverticulitis or previous GI perforation were excluded from the sarilumab clinical development program.

A total of 7 patients on sarilumab + DMARD had either complicated diverticulitis or GI perforation not secondary to surgical complication. No events occurred in a patient on placebo. In summary, in the placebo-controlled population, there was 1 patient on sarilumab (0.11 events/100 patient-years [95% CI: 0.00, 0.63]) who experienced a GI perforation; no event occurred in a patient on placebo. In the sarilumab+DMARD long-term safety population, 6 additional events were reported for an overall event rate of GI perforations of 0.16 events/100 patient-years (95% CI: 0.06, 0.32), which was consistent with rate in the placebo-controlled population. The events of GI perforation were primarily due to complications of diverticulitis including lower GI perforation and abscess.

### ***Major Adverse Cardiovascular Events***

An external cardiovascular events adjudication committee (CAC) comprised of 2 cardiologists and 1 neurologist was utilized in the phase 3 studies. The CAC reviewed and adjudicated all deaths and serious CV AEs in a blinded fashion. Serious CV adverse events sent for adjudication were identified by a list of SMQs as specified in the CAC Charter. In addition, any non-SAE requiring a CV procedure was sent for adjudication.

MACE (primary) is defined as CV death (including undetermined cause of death), MI, stroke, hospitalization for UA, or hospitalization for TIA, and MACE (narrow) is defined as CV death (including undetermined cause of death), MI, and stroke.

Overall, approximately 38% of patients had baseline cardiovascular disease, such as hypertension, diabetes, dyslipidemia, coronary artery disease (CAD), ischemic cerebrovascular disease, or family history of CAD. In the placebo-controlled population (Pool 1), no events were observed in placebo, and 2 events of MACE were observed in each of the sarilumab treatment groups (incidence rate [95% CI] in each group: 0.5 [0.05, 1.63]. Of the four patients, each had CV risk factors including hypertension, active tobacco use, diabetes, and obesity. One patient with sudden death did not have known cardiovascular risk factors, but was found to have chronic ischemic heart disease with left ventricular hypertrophy at autopsy.

For the long-term safety population (Pool 2), the exposure-adjusted incidence rate for MACE (narrow) was 0.3 per 100 pt-yrs for sarilumab 150 mg q2w and 0.6 per 100 pt-yrs for sarilumab 200 mg q2w. In model-based analyses (Table 24), sanofi compared the rates of MACE in the treatment arms. While there were more events in the sarilumab 200 mg dose group than the 150 mg dose group,

a granular analysis of the timing of these events suggested that this was related to the study design, in which the vast majority of patients received 200 mg in the long-term safety study. Importantly, the exposure adjusted rates remained relatively consistent with the rates observed during the controlled periods of the phase 3 studies. Thus, there were elevations in LDL, HDL, and triglycerides on sarilumab, but there was no clear increase in the risk of cardiovascular events on sarilumab during the time frame of the clinical trials. That being said, there were very few events observed overall and we therefore have limited ability to rule out increases in risk based on the currently available clinical data.

**Table 24: Model-based Analyses on Patients with at least one MACE during the TEAE period**

	Placebo + DMARD	Sarilumab 150mg q2w + DMARD	Sarilumab 200mg q2w + DMARD	Any Sarilumab + DMARD
<b>MACE (narrow)</b>				
Raw incidence rate n/N (%)	0/661 (0)	2/1155 (0.2)	11/1351 (0.8)	23/2887 (0.8)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	0/382.3 (0)	2/701.7 (0.3)	11/1757.1 (0.6)	23/4475.3 (0.5)
Rate ratio vs. PBO + DMARD (95% CI)		--	--	--
Rate ratio vs. sarilumab 150mg + DMARD (95% CI)			2.31 (0.50, 10.72) <sup>b</sup>	

a Number of patients with at least one event per 100 patient-years (PYs), where the exposure time for patients who have experienced the specific adverse experience was defined as the time to first adverse experience of interest whereas the exposure time for those who have not had this adverse experience was total TEAE period duration

b The rate ratio and its 95% confidence interval (CI) were estimated using the GEE (Poisson distribution with exposure calculated based on the time to first event as an offset), adjusted for treatment and the important baseline factors (age, gender, RA duration of disease), assuming an exchangeable covariance structure for the within-subject correlations

Source: Modified from Dr. Peng's clinical review, Sanofi response to IR (July 12, 2016), Tables 1 and 2, dated July 14, 2016, pages 7-8

The cardiovascular and lipid considerations were discussed at an SOT meeting on July 28, 2016. The committee was asked whether they would recommend a cardiovascular outcomes trial based on small imbalances in cardiovascular events observed in clinical trial data and recognizing that similar post-marketing trials have been requested for other rheumatoid arthritis products that cause elevations in lipid parameters. Tocilizumab, which has the same mechanism of action and also causes elevation in lipid parameters, is performing a post-marketing cardiovascular outcomes trial. Based on the current safety profile of sarilumab, a majority of committee members were not in favor of recommending a cardiovascular outcomes trial (9: No, 2: Yes, 2: recusal due to supervisor role). Study feasibility was raised as a concern because a trial to answer the question of whether the increase in cholesterol associated with sarilumab was associated with an effect on MACE would be very large in size, similar to the IMPROVE-IT trial. Members also voiced concerns about interpretation of a CVOT given that patients may receive treatment for elevated lipids during the course of the study. Based on the extensive internal discussions, it was decided not to request a post-marketing CVOT. However, sanofi was informed that ongoing studies evaluating cardiovascular outcomes in the setting of treatment with drugs approved for RA, might have future implications for sarilumab, such as labeling changes or additional required studies.

### ***Anaphylaxis/Hypersensitivity***

Hypersensitivity and anaphylaxis are adverse events that have been identified with all biologic DMARDs in the treatment of rheumatoid arthritis, and, thus, these were AESIs in the sarilumab clinical development program. As described in the protocols, investigators utilized the criteria described by Sampson<sup>12</sup> to capture all possible cases of anaphylaxis. During the pre-rescue period (Pool 1a), the percentage of patients with hypersensitivity was 2%, 4%, and 4% for the placebo, sarilumab 150 mg, and sarilumab 200 mg groups. Thus, the percentage of patients with hypersensitivity reactions was higher in sarilumab compared to placebo, but the same for the 150 mg and 200 mg dose groups. The most common hypersensitivity reactions were injection site rash, rash, urticaria, eczema, and rash generalized. There were no cases of anaphylaxis during the development program.

### ***Injection site reactions***

During the double-blind period (Pool 1), the percentage of patients with injection site reactions was higher in sarilumab treatment arms (5.5% and 5.3% for 150 mg and 200 mg, respectively) compared to placebo (0.9%). There were no serious injection site reactions. Injection site reactions are an anticipated adverse event for this biologic product.

### ***Malignancy***

During the pre-rescue period, the proportion of patients with malignancy was low in each treatment arm and was fairly similar between groups (Table 25). When excluding NMSC, the exposure adjusted incidence rate (per 100 PYs) was slightly higher for sarilumab 150 mg (1.2) than placebo (0.6) or sarilumab 200 mg (0). Similar results were seen in the entire double-blind treatment period. The incidence rate (per 100 PYs) for the entire double-blind treatment period was 0.3, 1.1, and 0.5 for the placebo, sarilumab 150 mg, and sarilumab 200 mg groups, respectively. There were no hematologic malignancies. The solid tumors that were observed included breast cancer (2 patients on 150 mg and 1 patient on 200 mg), malignant melanoma (1 patient on 150 mg and 1 patient on 200 mg), appendiceal cancer (1 patient on 150 mg), and renal cancer (1 patient on placebo and 1 patient on 150 mg). In general, the types of cancers are typical given the patient population (based on age, gender, and underlying RA). Appendiceal cancer is a less common type of cancer, but review of the narrative did not establish a clear relationship with sarilumab.

---

<sup>12</sup> Sampson HA, et al. Second symposium on the definition and management of anaphylaxis: summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium 2006;117(2):391-7.

**Table 25: Summary of Malignancies in the Pre-Rescue Period (Pool 1a)**

	Placebo + DMARD	Sarilumab 150mg q2w + DMARD	Sarilumab 200mg q2w + DMARD
<b>Pre-Rescue (Pool 1a)</b>			
<b>Malignancy</b>			
Raw incidence rate n/N (%)	2/579 (0.3%)	3/579 (0.5%)	2/582 (0.3%)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	2/161.2 (1.2)	3/159.2 (1.9)	2/160.4 (1.2)
<b>Malignancy excluding NMSC</b>			
Raw incidence rate n/N (%)	1/579 (0.2%)	3/579 (0.5%)	0/582
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	1/161.4 (0.6)	3/159.2 (1.2)	0/160.6 (0.0)

n (%) = number and percentage of patients with at least one TEAE

a Number of patients with at least 1 event per 100 patient-years, where the exposure time for patients who have experienced the specific adverse event experience was defined as the time to first adverse experience of interest whereas the exposure time for those who have not had this adverse experience was total TEAE period duration

b The rate difference and its 95% confidence interval were estimated using the M&N method stratified by the study, using the CMH weight

Source: ISS Appendix 1.12.1.52, page 8291-8292, submitted 10/30/15

In the long-term safety population, the exposure-adjusted incidence rate in the 150 mg group was higher than the 200 mg group, but was similar to the pre-rescue period (Table 26). Overall, the types of malignancies observed followed the pattern of malignancies that would generally be expected in the underlying patient population. In addition to the appendiceal cancer discussed above, the more uncommon cancers included one case of small intestinal cancer and one case of plasmacytoma. Solid tumors (such as breast cancer, malignant melanoma, and renal and pelvic cancer) were the most commonly occurring cancers excluding nonmelanoma skin cancer. The rate of malignancies was stable over time (Figure 14).

APPEARS THIS WAY ON ORIGINAL

**Table 26. Overview of Malignancy TEAEs in the Long-Term Safety Population (Pool 2)**

	Sarilumab		
	150mg Q2W Initial Dose	200mg Q2W Initial Dose	Any Dose
Total number of patients	1155	1351	2887
Total treatment duration in pt-yrs <sup>a</sup>	701.9	1758.6	4481.8
<b>Total patients with ≥ 1 malignancy (%)</b>	<b>9 (0.8%)</b>	<b>14 (1.0%)</b>	<b>33 (1.1%)</b>
<b>Number of patients with ≥ 1 malignancy per 100 pt-yrs</b>	<b>1.3</b>	<b>0.8</b>	<b>0.7</b>
Total patients with ≥ 1 malignancy excluding NMSC (%)	8 (0.7%)	8 (0.6%)	23 (0.8%)
Number of patients with ≥ 1 malignancy excluding NMSC per 100 pt-yrs	1.1	0.5	0.5

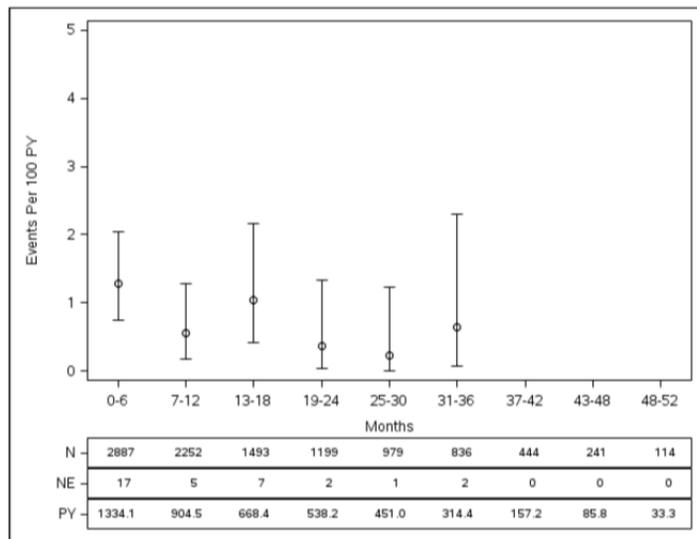
Search criteria: SMQ Malignant or unspecified tumors

a For patients with no such event, the duration is up to the end of the treatment duration

Source: ISS, Table 119, page 273, submitted 10/30/15

APPEARS THIS WAY ON ORIGINAL

**Figure 14: Exposure adjusted rate of malignancy (95% CI) by 6 month intervals during the entire TEAE period – Any sarilumab dose group in the sarilumab+DMARD long-term safety population (Pool 2)**



N: sample size. NE: number of events in a 6-month period. PY: patient-years.  
 The 95% confidence interval was calculated using the exact method.  
 PGM=PRODOPS/SAR153191/OVERALL/CSS/REPORT/PGM/ae\_expo\_adju\_s\_g.sas OUT=REPORT/OUTPUT/ae\_expo\_adju\_malg\_s\_g\_i.rtf  
 (29JUN2015 - 18:34)

Source: ISS, Figure 30, page 274, submitted 10/30/15

Sanofi performed a model-based analysis on malignancies (Table 27). Combining the data from Pools 1 and 2, the overall incidence of malignancies in any arm remained low with only small differences between sarilumab and placebo as well as between sarilumab doses.

APPEARS THIS WAY ON ORIGINAL

**Table 27: Model-based Analyses on Patients with at least one Malignancy during the TEAE Period**

	Placebo + DMARD	Sarilumab 150mg q2w + DMARD	Sarilumab 200mg q2w + DMARD	Any Sarilumab + DMARD
<b>Malignancy</b>				
Raw incidence rate n/N (%)	3/661 (0.5)	9/1155 (0.8)	14/1351 (1.0)	33/2887 (1.1)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) <sup>a</sup>	3/380.8 (0.8)	9/700.5 (1.3)	14/1749.0 (0.8)	33/4466.6 (0.7)
Rate ratio vs. PBO + DMARD (95% CI)		1.51 (0.35, 6.49) <sup>b</sup>	1.14 (0.31, 4.28) <sup>b</sup>	0.76 (0.32, 1.81) <sup>c</sup>
Rate ratio vs. sarilumab 150mg + DMARD (95% CI)			0.96 (0.29, 3.26) <sup>b</sup>	

a Number of patients with at least one event per 100 patient-years (PYs), where the exposure time for patients who have experienced the specific adverse experience was defined as the time to first adverse experience of interest whereas the exposure time for those who have not had this adverse experience was total TEAE period duration

b The rate ratio and its 95% confidence interval (CI) were estimated using the GEE (Poisson distribution with exposure calculated based on the time to first event as an offset), adjusted for treatment and the important baseline factors (age, gender, geographic region, prior biologic use, medical history of malignancy), assuming an exchangeable covariance structure for the within-subject correlations

c The rate ratio and its 95% confidence interval (CI) were estimated using the GEE (Poisson distribution with exposure calculated based on the time to first event as an offset), adjusted for treatment and the important baseline factors (age, gender, geographic region, prior biologic use, medical history of malignancy), assuming an exchangeable covariance structure for the within-subject correlations

Source: Sanofi response to IR (July 12, 2016), Table 3, dated July 14, 2016, page 9.

### ***Immunogenicity***

As shown in Table 28, the incidence of positive ADA response in the placebo and sarilumab 150 and 200 mg q2w treatment groups across placebo-controlled studies (Pool 1) were 3.5% (21/608), 19.3% (117/607), and 14% (85/607), respectively. Most of these responses were transient, with 2.0%, 5.6%, and 4.0% having a persistent treatment-emergent positive ADA response in the placebo and sarilumab 150 and 200 mg q2w treatment groups, respectively. The majority of the ADA positive patients exhibited low titers ( $\leq 60$ ). Among the persistent treatment-emergent positive ADA responses, only 0.2%, 1.6%, and 1.0% in the placebo, and 150 and 200 mg q2w treatment groups, respectively, exhibited anti-sarilumab NABs. The ADA incidence did not increase over time in the sarilumab treated patients.

Patients who received sarilumab and concomitant MTX had a lower incidence of antibodies to sarilumab than patients who received sarilumab without MTX. In the sarilumab monotherapy population (Pool 3), incidences of positive ADA status for the treatment groups of 150 and 200 mg q2w were 25% and 18%, respectively. Incidences of persistent positive ADA status were 12% and 6% for the 150 mg and 200 mg doses, respectively. Among patients with persistent treatment-emergent positive ADA responses, 11% and 3% exhibited Nabs on the 150 mg and 200 mg doses, respectively.

**Table 28: Overview of ADA during the Double-Blind Period (Pool 1)**

	<b>Placebo + DMARD N=608</b>	<b>Sarilumab 150mg q2w + DMARD N=607</b>	<b>Sarilumab 200mg q2w + DMARD N=609</b>
Number of patients with ADA assay results available	608/608 (100%)	607/607 (100%)	607/609 (99.7%)
Patients with an ADA positive sample at baseline	9/606 (1.5%)	14/599 (2.3%)	10/599 (1.7%)
<b>ADA positive<sup>a</sup> patients during the TEAE period</b>	<b>21/608 (3.5%)</b>	<b>117/607 (19.3%)</b>	<b>85/607 (14.0%)</b>
Neutralizing <sup>b</sup>	1/608 (0.2%)	20/607 (3.3%)	11/607 (1.8%)
Non-neutralizing	20/608 (3.3%)	97/607 (16.0%)	74/607 (12.2%)
Patients with a persistent <sup>c</sup> positive response	12/608 (2.0%)	34/607 (5.6%)	24/607 (4.0%)
Neutralizing <sup>b</sup>	1/608 (0.2%)	10/607 (1.6%)	6/607 (1.0%)

ADA = anti-sarilumab antibody; Negative = below the assay cut point or not drug specific; Positive = drug specific signal above the assay cut point

a ADA positive patients include “treatment-emergent positive” and “treatment-booster positive”

Treatment-emergent positive: patients with no positive assay response at baseline but with a positive assay response during the TEAE period

Treatment-booster positive: patients with a positive ADA assay response at baseline and also have at least 4-fold increase in titer during the TEAE period

b At least one post-baseline measurement classified as neutralizing positive

c Persistent positive response: treatment-emergent positive ADA detected at 2 or more consecutive sampling time points during the TEAE period, where the first and last ADA positive samples are separated by a period of at least 16 weeks. Also, persistent in case last sample analyzed is positive.

Source: Adapted from Dr. Peng’s clinical review, from ISS, Table 107, dated October 6, 2015; page 261.

There was no clear relationship between the development of ADA and efficacy or safety.

### ***Demyelinating disorders***

Demyelinating disorders have been reported with other immunomodulatory biologic agents and the Actemra prescribing information includes a warning for demyelinating disorders, noting that multiple sclerosis and chronic inflammatory demyelinating polyneuropathy were reported rarely in RA clinical studies. In the sarilumab clinical program, there was one case of transverse myelitis and one case of multifocal motor neuropathy which appeared likely to be an axonal rather than demyelinating neuropathy. Therefore, there was not a clear association between sarilumab and demyelinating disorders.

### ***Comparison to Actemra***

In Study SFY13370, sanofi compared sarilumab (150 mg q2w or 200 mg q2w) and tocilizumab (initiated at 4 mg/kg per week followed by an increase to 8 mg/kg, if needed, based on clinical response (as assessed by the investigator)). The study enrolled a total of 202 patients (102 tocilizumab, 49 sarilumab 150 mg, and 51 sarilumab 200 mg). The changes in ANC, platelet counts, ALT, and LDL for sarilumab 150 mg and 200 mg were within the range observed with tocilizumab. When evaluating the proportion of patients with decreases in ANC by maximum grade (Table 29), the proportions of patients with grade 1 or grade 2 decreases in ANC was similar for sarilumab and tocilizumab. However, the proportion of patients with grade 3 or grade 4 decreases in ANC was higher for both doses of sarilumab compared to tocilizumab q4w.

Consistent with the changes in ANC noted, a greater proportion of patients on sarilumab 150 mg and 200 mg had discontinuations secondary to adverse events. There were 6 discontinuations due to reported adverse events of laboratory abnormalities (i.e., neutropenia, decreased neutrophil count, transaminases increased, ALT increased) that occurred in 5 patients (1 patient discontinued due to both leukopenia and neutropenia). However, similar trends were not noted for other adverse events, such as serious adverse events, common adverse events, total infections, and serious infections. For these adverse events, the proportion of patients was fairly balanced between sarilumab and tocilizumab. Importantly, given the small size of the study limited conclusions are possible.

**Table 29: Number (%) of patients with decreases in absolute neutrophil count by maximum grade during TEAE period and other AEs of interest in study SFY13370**

	<b>Tocilizumab q4w + DMARD</b>	<b>Sarilumab 150mg q2w + DMARD</b>	<b>Sarilumab 200mg q2w + DMARD</b>
<b>Absolute neutrophil count (ANC)</b>	N=102 n (%)	N=48 n (%)	N=51 n (%)
Grade 1: $\geq 1.5$ Giga/L – LLN	14 (14)	6 (13)	10 (20)
Grade 2: $\geq 1 - 1.5$ Giga/L	14 (14)	7 (15)	6 (12)
Grade 3: $\geq 0.5 - 1$ Giga/L	1 (1)	2 (4)	5 (10)
Grade 4: $< 0.5$ Giga/L	0	1 (2)	0
<b>Other AEs of interest</b>			
Discontinuations secondary to TEAE	4 (4)	6 (12)	8 (16)
Serious adverse events	7 (7)	1 (2)	3 (6)
Common adverse events	68 (67)	33 (67)	36 (71)
Total patients with $\geq 1$ infection	32 (31)	20 (41)	11 (22)
Total patients with $\geq 1$ serious infection	2 (2)	0	1 (2)

TEAEs=treatment emergent adverse events

Source: ISS, Table 140, page 323, Study report SFY13370, Table 17 (page 75), Table 19 (page 77), Table 20 (page 80), Table 22 (page 83), submitted 10/6/15

- **Concerns identified through U.S. or foreign postmarket experience**

Not applicable—There is not any US or foreign postmarket experience because sarilumab has not received marketing authorization in any country to date.

- **Safety conclusions**

Dr. Peng and I are in agreement that the currently submitted safety data and analyses are adequate to inform the decision regarding the benefit-risk profile of the product. The safety data submitted for sarilumab suggest it is associated with significant 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. There were also events of GI perforation and hypersensitivity.

The safety concerns identified are consistent with other immunosuppressive agents utilized to treat rheumatoid arthritis. In general, the safety signals occurred at higher frequency with the 200 mg than 150 mg dose regimen. However, the potential increase in risk needs to be considered in the context of data suggesting an increase in efficacy with the 200 mg dose. While both the 150 mg and 200 mg doses appeared effective, the 200 mg dose group was associated with numerically higher response rates, including for inhibition of radiographic progression. Thus, benefit/risk considerations are favorable for both doses, and it is reasonable for patients to initiate 200 mg, with the option to reduce the dose for laboratory abnormalities.

- **Discussion of notable safety issues (resolved or outstanding)**

There are no unresolved issues. No post-marketing studies are recommended based on the submitted data.

## **9. Advisory Committee Meeting**

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

## **10. Pediatrics**

- **Extrapolation from one population to another**

Not applicable



(b) (4)

- **Pediatric Review Committee (PeRC) Review Outcome-Post Marketing Commitments (PMCs), deferrals, waivers, pediatric plan, pediatric assessment**

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: An (b) (4) dose-finding study of sarilumab (b) (4) in children and adolescents, aged 2 to 17 (b) (4)
- EFC11783: A (b) (4) study to assess the efficacy and safety of sarilumab in children and adolescents, aged 2 to 1 (b) (4)

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.

## 11. Other Relevant Regulatory Issues

- **Application Integrity Policy (AIP)**—Not warranted, no issues
- **Exclusivity or patent issues of concern**—No issues
- **Financial disclosures**

Sanofi provided a list of one clinical investigator with disclosable financial interests, including equity interests in the sponsor as defined by 21 CFR 54.2(b) and significant payments of other sorts as defined by 21 CFR 54.2(f). Sanofi certified that it did not enter into any financial arrangement with the clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). It is unlikely the one clinical investigator with disclosable financial interests would impact the study results given that the study was large, international, and multicenter.

- **Other Good Clinical Practice (GCP) issues**

The clinical studies were conducted in accordance with Good Clinical Practices and a statement of compliance with Good Clinical Practices is located in each complete study report.

- **Office of Scientific Investigations (OSI) audits**

Three clinical sites covering study protocols EFC11072 and EFC10832 were selected for inspection. These sites principally enrolled relatively large numbers of patients. In addition, Sanofi-Aventis was inspected. In each case, inspection findings supported the acceptability of the clinical data submitted.

- **Any other outstanding regulatory issues**—Not applicable

## 12. 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**

Major issues with the currently proposed labeling (version submitted March 9, 2016 or earlier):

- Indications and usage:
  - Proposed indication: “KEVZARA is indicated for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDs)”
    - The proposed indication is consistent with that of other biologic immunosuppressant drugs for RA and is reasonable.
- Dosage and administration:
  - “KEVZARA may be used as monotherapy or in combination with methotrexate or other traditional DMARDs”
    - The word “traditional” will be replaced with “conventional”
  - “The recommended dose of KEVZARA is 200 mg once every two weeks”
    - Based on considerations of the overall risk/benefit of the 200 mg and 150 mg doses, we agree with sanofi’s proposal to recommend 200 mg once every two weeks
- Boxed warning, contraindications, and warnings and precautions:
  - The originally submitted prescribing information included a BOXED WARNING related to the risk of serious infections, including bacterial, viral, fungal, and other opportunistic infections. The BOXED WARNING will be modified slightly to describe the reported infections.
  - The originally submitted prescribing information included Section 5.1 Serious Infections, Section 5.2 Laboratory (b) (4) (with subsections related to neutrophils, platelet count, liver enzymes, and laboratory abnormalities), Section 5.3 Gastrointestinal Perforations, Section 5.4 Immunosuppression, Section (b) (4) Active Hepatic Disease and Hepatic Impairment (recommendation against use in active hepatic disease or hepatic impairment), and Section (b) (4) (recommendation against use of live vaccines).
    - An additional Warning and Precaution related to Hypersensitivity will be added
- Clinical studies:

- A description of the escape options will be added since this is an important aspect of the study design and interpretation of the results.
- Since the response curves for ACR20 over time are similar for the two phase 3 studies, only one response curve will be included.
- Modifications will be made to the text and table regarding DAS28-CRP<2.6. The goal of these modifications is to indicate that while both doses of sarilumab significantly reduced DAS28-CRP<2.6 compared to placebo, the majority of patients with DAS28-CRP<2.6 still had at least one active joint.
- For the radiographic data, it is recommended that the results be displayed for analyses including data collected after escape and treatment discontinuation, rather than based on linear extrapolation.
- Information [REDACTED] (b) (4) will be removed since the labeling will reflect efficacy information at earlier time points and it is reasonable to assume that efficacy would be maintained.
- Data related to SF-36 will be shown for each of the domains.

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

Review by the patient labeling teams is ongoing at this time.

- **Carton and container labeling**

DMEPA and OBP reviewed the proposed prescribing information and container and carton labeling and recommended changes. These changes will be conveyed to sanofi.

### 13. Postmarketing Recommendations

#### Risk Evaluation and Management Strategies (REMS)

Sanofi proposed Risk Evaluation and Management Strategies (REMS). The REMS consists of [REDACTED] (b) (4). Based on review of the safety and efficacy data submitted, a REMS is not recommended. Product labeling will be adequate to ensure that the product's benefits outweigh its risks in the postmarket setting. Review by the Division of Risk Management (DRISK) has not been finalized, yet the team agrees that a REMS is not required.

Postmarketing Requirements (PMRs) and Commitments (PMCs)

The following quality postmarketing commitments (PMC) have been recommended:



There are ongoing discussions with sanofi regarding this potential postmarketing commitment.

## 14. 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

10/03/2016

This document incorporates minor changes from the CDTL review dated 9/16/16.



Food and Drug Administration  
Center for Drug Evaluation and Research  
ODE II / DPARP / HFD-570  
10903 New Hampshire Ave.  
Silver Spring, MD 20993

MEMO TO FILE

Filing/Planning Review

**BLA:** 761,037  
**Supplement:** 1 (SEQ 0)  
**Reviewer:** Suzette Peng, MD, CDER/OND/DPARP  
**Submitted:** October 30, 2015  
**Reviewed:** December 22, 2015  
**Product:** sarilumab ( (b) (4) anti-IL-6R)  
**Indication:** Rheumatoid Arthritis (RA)  
**Sponsor:** Sanofi-aventis U.S. LLC, A SANOFI COMPANY  
**Submission:** Original BLA  
**Synopsis:** The Sponsor has submitted an original BLA for sarilumab (development name SAR153191, proposed brand name (b) (4)). Sarilumab is a human IgG1 monoclonal antibody that binds to both soluble and membrane-bound IL-6 receptors. The proposed indication is treatment of adult patients with moderately to severely active RA who have had an inadequate response or intolerance to one or more DMARDs. The proposed dose is 200mg every 2 weeks. Patients may reduce the dose to 150mg every 2 weeks for management of neutropenia, thrombocytopenia, and elevated liver enzymes. The proposed available form is the pre-filled syringe (150 mg/1.14 mL and 200 mg/1.14 mL). (b) (4)

The attached Filing/Planning meeting presentation (December 17, 2015) summarizes the sponsor's extensive clinical development program for the RA indication. The following 2 studies are considered to be the pivotal studies to support this indication.

- EFC11702 Part B (SARIL-RA-MOBILITY): randomized, double-blind, placebo-controlled, 2-part, dose-ranging, confirmatory study evaluating efficacy and safety of sarilumab on top of MTX in patients with active RA who are inadequate responders to MTX
- EFC10832 (SARIL-RA TARGET): randomized, double-blind, placebo-controlled, parallel-group study assessing the efficacy and safety of sarilumab added to DMARD therapy in patients with active RA who are inadequate responders or intolerant to TNF- $\alpha$  antagonists

A brief overview of the efficacy data show that sarilumab showed benefit over placebo with statistical significance in all the co-primary endpoints for both pivotal studies.

- EFC11702 Part B

1. ACR20 responders at Week 24
  2. Change from baseline in HAQ-DI at Week 16
  3. Change from baseline in van der Heijde mTSS at Week 52
- EFC10832
    1. ACR20 responders at Week 24
    2. Change from baseline in HAQ-DI at Week 12

Additionally, an overview of the safety data seems consistent with the expected safety with IL-6 antagonists.

**Action Taken:** The submitted efficacy supplement is fileable. There are no clinical comments to be sent to sponsor in the 74-day letter.

APPEARS THIS WAY ON ORIGINAL

## CLINICAL FILING CHECKLIST FOR BLA 761,037

**NDA/BLA Number: 761037**

**Applicant: Sanofi**

**Stamp Date: October 30, 2015**

**Drug Name: Sarilumab**

**NDA/BLA Type: Original**

(b) (4)

**BLA/NME**

On initial overview of the NDA/BLA application for filing:

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comment</b>
<b>FORMAT/ORGANIZATION/LEGIBILITY</b>					
1.	Identify the general format that has been used for this application, e.g. electronic common technical document (eCTD).	X			
2.	Is the clinical section legible and organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
<b>LABELING</b>					
6.	Has the applicant submitted a draft prescribing information that appears to be consistent with the Physician Labeling Rule (PLR) regulations and guidances (see <a href="http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm">http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm</a> )	X			
<b>SUMMARIES</b>					
7.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			
8.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
9.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
10.	Has the applicant submitted a benefit-risk analysis for the product?	X			
11.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).	X			505(b)1
<b>505(b)(2) Applications</b>					
12.	If appropriate, what is the relied upon listed drug(s)?			X	
13.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the listed drug(s)/published literature?			X	
14.	Describe the scientific bridge (e.g., BA/BE studies)			X	
<b>DOSAGE</b>					
15.	If needed, has the applicant made an appropriate attempt to determine the correct dosage regimen for this product (e.g., appropriately designed dose-ranging studies)? Study Number: EFC11072, Part A Study Title: MOBILITY	X			The applicant has performed a dose-ranging study:  Study Number: EFC11072, Part A  Study Title: MOBILITY

File name: Clinical Filing Checklist for BLA 761037

## CLINICAL FILING CHECKLIST FOR BLA 761,037

	Content Parameter	Yes	No	NA	Comment
					Sample Size: 306 (52 PBO, 254 sarilumab)  Treatment Arms: <ul style="list-style-type: none"> <li>• Sarilumab 100mg qw</li> <li>• Sarilumab 150mg q2w</li> <li>• Sarilumab 100mg q2w</li> <li>• Sarilumab 150mg q2w</li> <li>• Sarilumab 200mg q2w</li> <li>• Placebo</li> </ul> Location in submission: Module 5.3.5.1
<b>EFFICACY</b>					
16.	Do there appear to be the requisite number of adequate and well-controlled studies in the application?	X			Pivotal Study #1: EFC11072, Part B, Cohort 2 (SARIL-RA-MOBILITY)  Indication: RA  Pivotal Study #2: EFC10832 (SARIL-RA TARGET)  Indication: RA
17.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
18.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			The evaluated endpoints were consistent with previous Agency agreements and are similar to other development programs in RA.
19.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	X			All studies were globally conducted and, thus, included US sites.
<b>SAFETY</b>					
20.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner	X			Requested safety analyses from the pre-

File name: Clinical Filing Checklist for BLA 761037

## CLINICAL FILING CHECKLIST FOR BLA 761,037

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comment</b>
	previously requested by the Division?				BLA meeting are located in the ISS.
21.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?			X	
22.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
23.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure <sup>1</sup> ) been exposed at the dosage (or dosage range) believed to be efficacious?	X			Dose 200mg: 1200 patients with >48 wks exposure Doses 150 and 200mg: >1650 patients with >48 wk exposure
24.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
25.	Has the applicant submitted the coding dictionary <sup>2</sup> used for mapping investigator verbatim terms to preferred terms?		X		
26.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
27.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
<b>OTHER STUDIES</b>					
28.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
29.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			X	
<b>PEDIATRIC USE</b>					
30.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
<b>PREGNANCY, LACTATION, AND FEMALES AND MALES OF REPRODUCTIVE POTENTIAL USE</b>					
31.	For applications with labeling required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, has the applicant submitted a review of the available information regarding use in pregnant, lactating women, and females and males of reproductive potential (e.g., published literature, pharmacovigilance database, pregnancy registry) in Module 1 (see <a href="http://www.fda.gov/Drugs/DevelopmentApprovalProcess/D">http://www.fda.gov/Drugs/DevelopmentApprovalProcess/D</a>	X			

<sup>1</sup> For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

<sup>2</sup> The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

File name: Clinical Filing Checklist for BLA 761037

## CLINICAL FILING CHECKLIST FOR BLA 761,037

	Content Parameter	Yes	No	NA	Comment
	<a href="http://www.fda.gov/developmentresources/labeling/ucm093307.htm">developmentResources/Labeling/ucm093307.htm</a> )?				
<b>ABUSE LIABILITY</b>					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
<b>FOREIGN STUDIES</b>					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	X			All studies were globally conducted and, thus, included US sites.
<b>DATASETS</b>					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
37.	Are all datasets to support the critical safety analyses available and complete?	X			
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
<b>CASE REPORT FORMS</b>					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
<b>FINANCIAL DISCLOSURE</b>					
41.	Has the applicant submitted the required Financial Disclosure information?	X			
<b>GOOD CLINICAL PRACTICE</b>					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

**IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? \_\_Yes\_\_**

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

No clinical comments will be forwarded to the Applicant for the 74-day letter.

File name: Clinical Filing Checklist for BLA 761037

## CLINICAL FILING CHECKLIST FOR BLA 761,037

Suzette W. Peng, MD	December 23, 2015
Reviewing Medical Officer	Date
Janet Maynard, MD, MHS	December 23, 2015
Clinical Team Leader	Date

FDA U.S. Food and Drug Administration  
Protecting and Promoting Public Health  
www.fda.gov

# BLA 761,037

## sarilumab for Rheumatoid Arthritis (SAR153191 (b) (4))

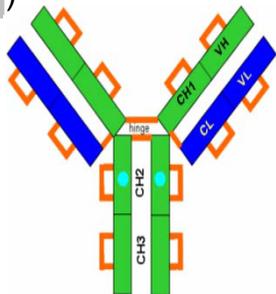
**Filing Meeting: Clinical Presentation**  
**December 17, 2015**

1

FDA U.S. Food and Drug Administration  
Protecting and Promoting Public Health  
www.fda.gov

## Introduction: sarilumab

- Product: SAR153191 (sarilumab (b) (4))
- Sponsor: Sanofi US Services, Inc.
- Mechanism of action
  - Fully human IgG1 mAb to IL-6R
  - Same as tocilizumab
- Proposed indication: treatment of adult patients with moderately to severely active RA who have had an inadequate response or intolerance to one or more DMARDs



2

FDA U.S. Food and Drug Administration  
Protecting and Promoting Public Health  
www.fda.gov

## Introduction: sarilumab

- Proposed dosing
  - 200 mg every 2 weeks
  - Reduction of dose to 150 mg every 2 weeks for management of neutropenia, thrombocytopenia, and elevated liver enzymes
- Proposed available forms
  - Prefilled syringe (PFS, 150 mg and 200 mg)  
(b) (4)

3

FDA U.S. Food and Drug Administration  
Protecting and Promoting Public Health  
www.fda.gov

## Additional Label Claims

- Clinical response at Weeks 12, 24, and 52
  - ACR 20, ACR 50, ACR 70
  - Major clinical response
  - ACR 20 response by visit
  - DAS28 < 2.6 at Week 52
  - Change from baseline in ACR components at Week 24
- Radiographic response at Weeks 24 and 52
  - mTSS, erosion score, and joint space narrowing score
- Physical function response
  - HAQ-DI
- Health related outcomes
  - SF-36 (PCS and MCS)
- Efficacy of sarilumab as monotherapy

4


 U.S. Food and Drug Administration  
 Protecting and Promoting Public Health  
[www.fda.gov](http://www.fda.gov)

## Sarilumab: Regulatory History

- PIND meeting with Sponsor – August 2007
- IND opened in November 2007
- Type C meeting (Sep 29, 2009): clinical development
  - Agency agreed to study EFC 11072 (phase 2/3 study)
  - Need 2 trials for signs/symptoms; 1 might be enough for x-ray
- Type C meeting (Feb 23, 2011)
  - Need to ensure adequate dose-ranging
  - Comparability of Phase 2 and 3 drug product
  - Concern with neutropenia
- EOP2 meeting – September 2011
  - Agreed that efficacy dose-ranging was adequate
  - Safety concerns → recommend active comparator
  - Recommend adjudication committee for MACE

5


 U.S. Food and Drug Administration  
 Protecting and Promoting Public Health  
[www.fda.gov](http://www.fda.gov)

## Sarilumab: Regulatory History

- CMC EOP2 meeting – Oct 2011
- Multiple written correspondences (2012-2013)
  - Efficacy endpoints
  - Advice on studies MSC12665 (AI study) and SFY13370 (tocilizumab comparator) and EFC13752 (monotherapy)
  - Statistical advice on SAP and various endpoints
- iPSP submitted (Aug 2013)
  - Agency letter of agreement (Jan 2014)
- Multiple Type C written responses (2014-present)
  - SAP for EFC10832
  - Electronic data submission plan
  - (b) (4)
  - Pediatric plan

6


 U.S. Food and Drug Administration  
 Protecting and Promoting Public Health  
[www.fda.gov](http://www.fda.gov)

## Sarilumab: Regulatory History

- Pre-BLA meeting – Oct 2014
  - General agreement with proposed content, analyses, and presentation for Summary of Clinical Efficacy
  - Did not agree with pooling strategy for safety analysis
    - Agree with pooling patients from PBO-controlled pivotal studies
    - Analysis of common AEs and AEs of interest by different time intervals
    - Recommend exposure adjusted incidence rates
    - Analysis of safety data after escape
    - For targeted AEs of interest, also recommend integrating safety data from all integrated studies
  - Submit data from EFC13752 (sarilumab monotherapy) with initial BLA submission (rather than 120 day safety update)
  - (b) (4)
- CMC pre-BLA meeting – Dec 2014

7

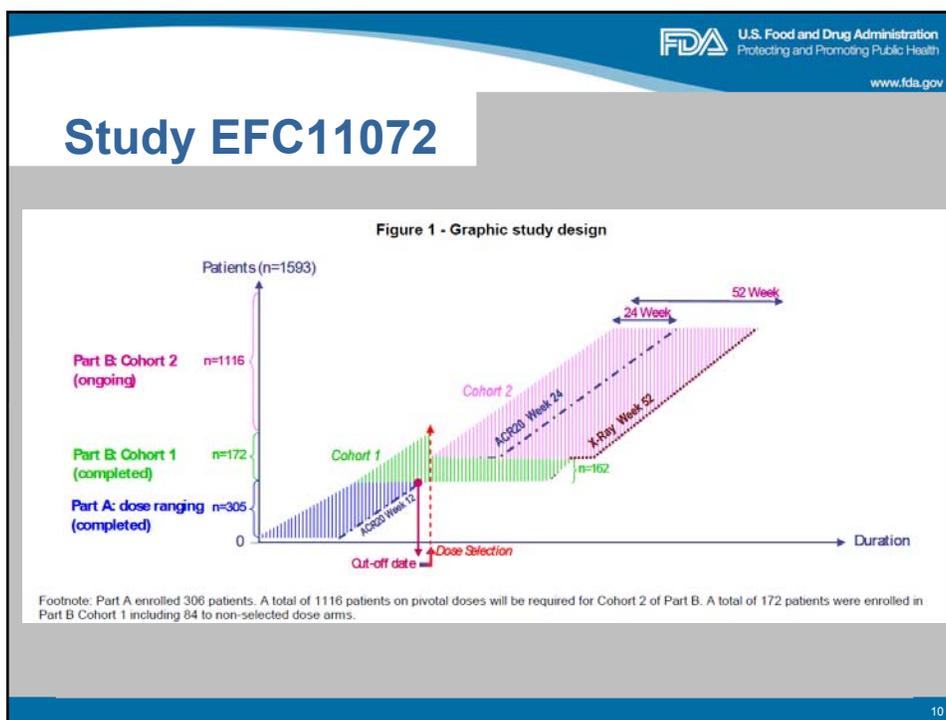

 U.S. Food and Drug Administration  
 Protecting and Promoting Public Health  
[www.fda.gov](http://www.fda.gov)

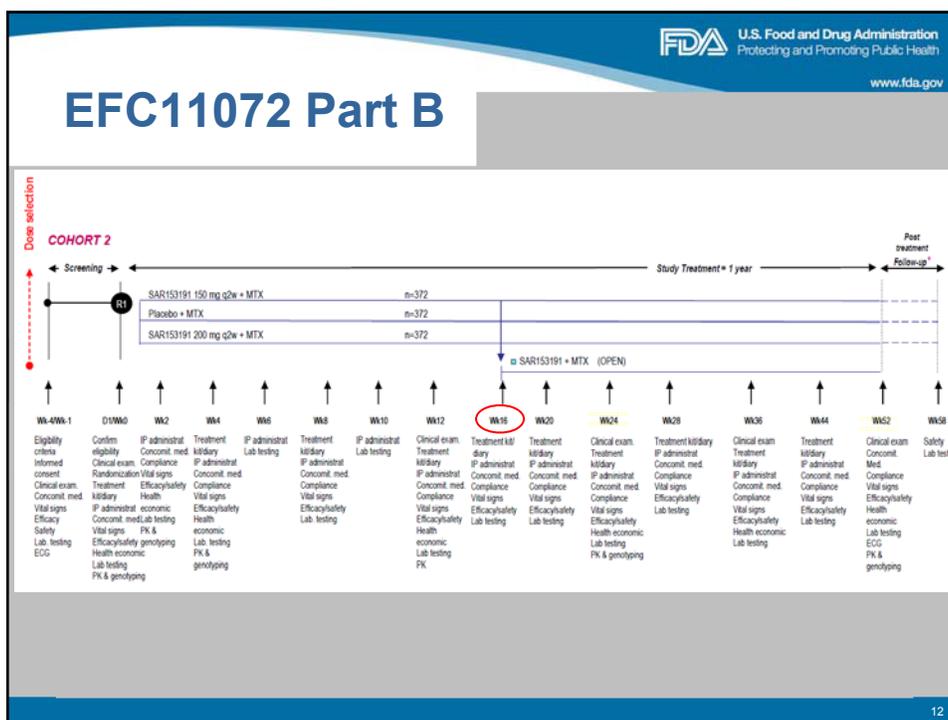
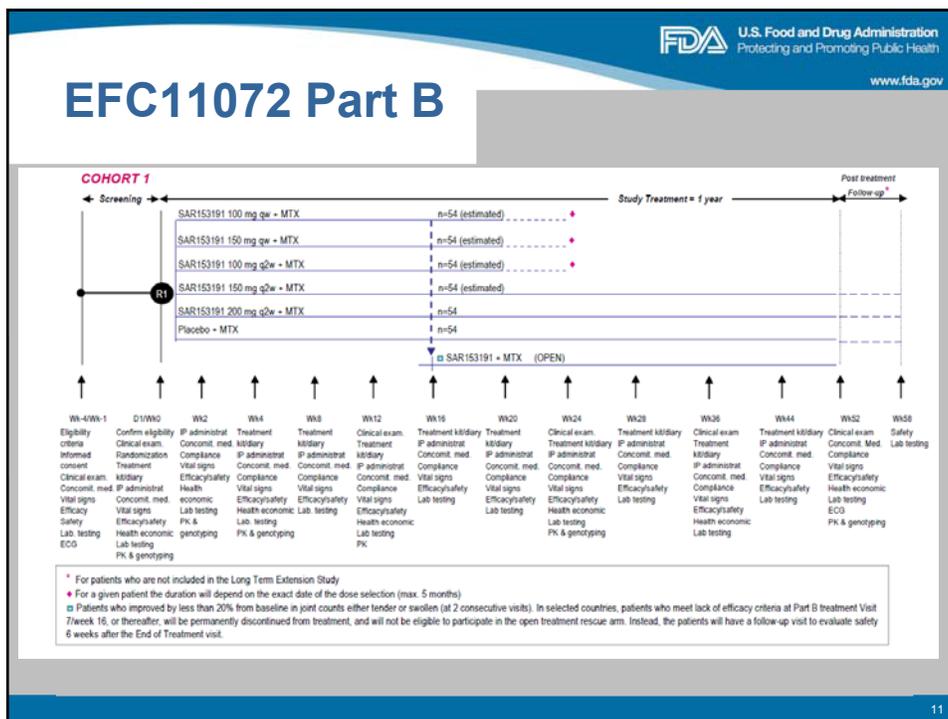
## Sarilumab Clinical Development: Phase 2

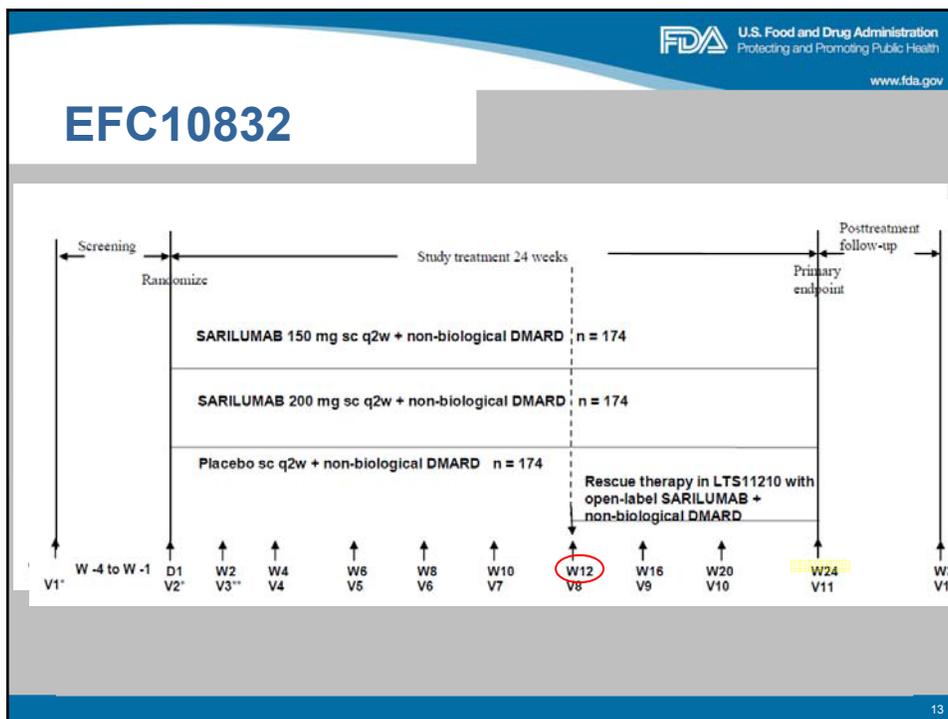
Protocol	Study Population (Background Therapy)	Design	Dose	Total # of Patients
<b>EFC11072 Part A (MOBILITY)</b>  completed	MTX-IR (MTX)	12-week, R, DB, PC, MC, dose-ranging study	<ul style="list-style-type: none"> <li>• Sarilumab 100mg QW, 150mg QW, 100mg Q2W, 150mg Q2W, 200mg Q2W</li> <li>• PBO</li> </ul>	306 (52 PBO, 254 SAR)
<b>ACT11575</b>  Terminated early due to study delays	TNF-IR (MTX)	R, DB, PC/AC	Sarilumab 150mg QW	16 (4 PBO, 7 SAR, 5 golimumab)

8

Protocol	Study	Dose	Study Duration	Total # of Patients
<b>EFC11072 Part B (SARIL-RA-MOBILITY)</b>	R, DB, PC, MC, 2-part, dose-ranging, confirmatory study evaluating efficacy and safety of sarilumab on top of MTX in pts with active RA who are <b>inadequate responders to MTX</b>	Part B: 150mg q2w, 200mg q2w	52 wks  Rescue: Wk 16	1369
<b>LTS11210 (SARIL-RA EXTEND)</b> <i>Ongoing</i>	MC, uncontrolled extension study evaluating the long-term safety and efficacy of sarilumab in pts with RA	200mg q2w	5 years	1998
<b>EFC10832 (SARIL-RA TARGET)</b>	R, DB, PC, PG, PC study assessing the efficacy and safety of sarilumab added to DMARD therapy in pts with active RA who are <b>inadequate responders or intolerant to TNF<math>\alpha</math> antagonists</b>	150mg q2w and 200mg q2w	24 wks  Rescue: Wk 12	546
<b>EFC11574 (SARIL-RA COMPARE)</b> <i>Terminated early</i>	Study assessing the clinical benefits of <b>sarilumab vs. etanercept</b> in pts with active RA who are inadequate responders or intolerant to adalimumab	150mg q2w and 200mg q2w	24 wks	365
<b>SFY13370 (SARIL-RA-ASCERTAIN)</b>	R, DB, DD study assessing the safety and tolerability of <b>sarilumab and tocilizumab</b> in pts with RA who are inadequate responders to or intolerant of TNF $\alpha$ antagonists	150mg sc q2w and 200mg sc q2w	24 wks	202
<b>MSC12665 (SARIL-RA-EASY)</b> <i>Ongoing</i>	MC, R, OL, PG usability study of sarilumab <b>auto-injector</b> device and PFS in pts with moderate to severe active RA who are candidates for anti- L6R therapy	150mg q2w and 200mg q2w (PFS or AI)	12 wks  52-wk LTE	217
<b>EFC13752 (SARIL-RA-ONE)</b>	R, PG study assessing the immunogenicity and safety of <b>sarilumab monotherapy</b> in pts with active RA	150mg sc q2w and 200mg sc q2w	24	132







## Efficacy: Primary Endpoints

	EFC11072 Part B, Cohort 2 (MTX-IR patients)			EFC10832 (TNF-IR patients)		
	Placebo + MTX (N=398)	Sarilumab 150 mg q2w + MTX (N=400)	Sarilumab 200 mg q2w + MTX (N=399)	Placebo + DMARD (N=181)	Sarilumab 150 mg q2w + DMARD (N=181)	Sarilumab 200 mg q2w + DMARD (N=184)
<b>ACR20 responders at Week 24</b>						
Number (%)	133 (33.4%)	232 (58.0%)	265 (66.4%)	61 (33.7%)	101 (55.8%)	112 (60.9%)
Odds ratio		2.773	3.975		2.711	3.284
95% CI versus placebo <sup>a</sup>		(2.077, 3.703)	(2.957, 5.344)		(1.730, 4.247)	(2.108, 5.115)
p-value vs placebo <sup>b</sup>		<0.0001	<0.0001		<0.0001	<0.0001
<b>Change from baseline in HAQ-DI<sup>c</sup></b>						
Mean change (SD)	-0.30 (0.58)	-0.54 (0.55)	-0.58 (0.63)	-0.29 (0.54)	-0.50 (0.64)	-0.49 (0.56)
p-value versus placebo <sup>d</sup>		<0.0001	<0.0001		0.0007	0.0004
<b>Change from baseline to Week 52 in van de Heijde mTSS</b>						
Mean change (SD)	2.78 (7.73)	0.90 (4.66)	0.25 (4.81)	NA	NA	NA
LS mean difference, 95% CI		-1.878 (-2.743, -1.013)	-2.522 (-3.382, -1.662)			
p-value versus placebo <sup>e</sup>		<0.0001	<0.0001			
<b>Key secondary endpoint: Major clinical response<sup>f</sup></b>						
Responders, n (%)	12 (3.0%)	51 (12.8%)	59 (14.8%)	NA	NA	NA
p-value versus placebo <sup>b</sup>		<0.0001	<0.0001			


**U.S. Food and Drug Administration**  
 Protecting and Promoting Public Health  
[www.fda.gov](http://www.fda.gov)

## Tocilizumab (Actemra®)

- **Boxed Warnings**
  - Serious infections
  - TB
- **Warnings and Precautions**
  - Serious infections
  - GI perforation
  - Lab monitoring (neutrophils, plts, lipids, liver function tests)
  - Hypersensitivity reactions (anaphylaxis and death)
  - Avoid live vaccines
- **Common AEs**
  - URI, nasopharyngitis, HA, HTN, ↑ ALT, injection site reactions
- **REMS**
  - Medication guide and communication plan (released Aug 2015)

15


**U.S. Food and Drug Administration**  
 Protecting and Promoting Public Health  
[www.fda.gov](http://www.fda.gov)

## Safety Populations

Population (Pool)	Treatment Group (n) <sup>a</sup>	Studies (Treatment duration)
Placebo-controlled population (Pool 1)	150 mg q2w+DMARD (n=660) 200 mg q2w+DMARD (n=661) Placebo+DMARD (n=661)	EFC11072 Part A (12 weeks) EFC11072 Part B (52 weeks) <sup>b</sup> EFC10832 (24 weeks)
Phase 3 placebo-controlled population (Pool 1a)	150 mg q2w+DMARD (n=579) 200 mg q2w+DMARD (n=582) Placebo+DMARD (n=579)	EFC11072 Part B Cohort 2 (52 weeks) <sup>b</sup> EFC10832 (24 weeks)
Sarilumab+DMARD long-term safety population (Pool 2)	150 mg q2w initial dose+DMARD <sup>c</sup> (n=1155) 200 mg q2w initial dose+DMARD <sup>c</sup> (n=1351) Any sarilumab dose+DMARD <sup>d</sup> (n=2887)	EFC11072 Part A (12 weeks) EFC11072 Part B (52 weeks) EFC10832 (24 weeks) SFY13370 (24 weeks) EFC11574 main study <sup>e</sup> (24 weeks) EFC11574 substudy <sup>e</sup> (52 weeks) MSC12665 (52 weeks) <sup>f</sup> LTS11210 <sup>g</sup> (5 years) <sup>f</sup>
Sarilumab monotherapy population (Pool 3)	150 mg q2w initial dose <sup>c</sup> (n=65) 200 mg q2w initial dose <sup>c</sup> (n=67) Any sarilumab dose (n=132)	EFC13752 <sup>h</sup> (24 weeks) LTS11210 <sup>i</sup> (5 years)

16



U.S. Food and Drug Administration  
Protecting and Promoting Public Health

www.fda.gov

## Sarilumab Exposure

- 3019 patients received at least 1 dose of sarilumab → 4405.7 patient-years
  - 132 patients with sarilumab monotherapy → 66.8 pt-years
  - Dose 200mg q2w: 1200 pts with >48 wks of exposure
  - Both doses: >1650 pts with >48 wks of exposure

**Exposure in Safety Population (Pool 1a)**

	Placebo + DMARD (N=579)	Sarilumab	
		150 mg q2w + DMARD (N=579)	200 mg q2w + DMARD (N=582)
Cumulative exposure to treatment (patient-years)	339.1	389.7	393.3
Duration of study treatment (days)			
Number	579	579	582
Mean (SD)	213.9 (116.8)	245.8 (121.7)	246.8 (120.1)
Median	168.0	210.0	225.5
Min : Max	14 : 408	14 : 385	14 : 408
Number of patients with duration of study treatment by category [n(%)]			
≥ 1 day	579 (100%)	579 (100%)	582 (100%)
>12 weeks	527 (91.0%)	518 (89.5%)	525 (90.2%)
>24 weeks	279 (48.2%)	355 (61.3%)	356 (61.2%)
>36 weeks	205 (35.4%)	285 (49.2%)	285 (49.0%)
>48 weeks	197 (34.0%)	273 (47.2%)	270 (46.4%)



U.S. Food and Drug Administration  
Protecting and Promoting Public Health

www.fda.gov

## Overview of Adverse Events

Treatment	Raw incidence n/N (%)	Exposure adjusted incidence rate <sup>a</sup>	
		n/PY	Rate per 100 PYs
<b>TEAE</b>			
Sarilumab 200 mg q2w +DMARD	488/661 (73.8%)	488/ 193.6	252.0
Sarilumab 150 mg q2w +DMARD	465/660 (70.5%)	465/ 215.5	215.7
Placebo +DMARD	378/661 (57.2%)	378/ 218.2	173.3
<b>Serious TEAE</b>			
Sarilumab 200 mg q2w +DMARD	59/661 (8.9%)	59/ 426.5	13.8
Sarilumab 150 mg q2w +DMARD	42/660 (6.4%)	42/ 433.8	9.7
Placebo +DMARD	31/661 (4.7%)	31/ 375.4	8.3
<b>TEAE leading to death</b>			
Sarilumab 200 mg q2w +DMARD	1/661 (0.2%)	1/ 442.8	0.2
Sarilumab 150 mg q2w +DMARD	2/660 (0.3%)	2/ 442.1	0.5
Placebo +DMARD	3/661 (0.5%)	3/ 383.9	0.8
<b>TEAE leading to permanent treatment discontinuation</b>			
Sarilumab 200 mg q2w +DMARD	83/661 (12.6%)	83/ 428.4	19.4
Sarilumab 150 mg q2w +DMARD	72/660 (10.9%)	72/ 429.8	16.8
Placebo +DMARD	31/661 (4.7%)	31/ 379.8	8.2


**U.S. Food and Drug Administration**  
 Protecting and Promoting Public Health  
[www.fda.gov](http://www.fda.gov)

## Common AEs (Weeks 0-12)

Primary SOC/PT	Sarilumab		
	PBO + DMARD N 579	150mg q2w + DMARD N 579	200mg q2w + DMARD N 582
<b>Infections and infestations</b>	242 (41.8%)	287 (49.6%)	306 (52.6%)
Upper respiratory tract infection	92 (15.9%)	106 (18.3%)	120 (20.6%)
Urinary tract infection	13 (2.2%)	17 (2.9%)	18 (3.1%)
Nasopharyngitis	11 (1.9%)	15 (2.6%)	15 (2.6%)
<b>Blood and lymphatic system disorders</b>	12 (2.1%)	38 (6.6%)	67 (11.5%)
Neutropenia	1 (0.2%)	36 (6.2%)	55 (9.5%)
<b>Metabolism and nutrition disorders</b>	8 (1.4%)	26 (4.5%)	20 (3.4%)
Hypertriglyceridemia	3 (0.5%)	15 (2.6%)	5 (0.9%)
<b>Nervous system disorders</b>	27 (4.7%)	24 (4.1%)	23 (4.0%)
Headache	13 (2.2%)	13 (2.2%)	10 (1.7%)
<b>Gastrointestinal disorders</b>	39 (6.7%)	31 (5.4%)	49 (8.4%)
Diarrhea	13 (2.2%)	7 (1.2%)	13 (2.2%)
<b>Musculoskeletal and connective tissue disorders</b>	44 (7.6%)	22 (3.8%)	30 (5.2%)
Rheumatoid arthritis	14 (2.4%)	2 (0.3%)	9 (1.5%)
<b>General disorders and administrative site conditions</b>	16 (2.8%)	43 (7.4%)	50 (8.6%)
Injection site erythema	4 (0.7%)	20 (3.5%)	19 (3.3%)
<b>Investigations</b>	23 (4.0%)	46 (7.9%)	47 (8.1%)
ALT increased	9 (1.6%)	22 (3.8%)	26 (4.5%)
<b>Injury, poisoning, and procedural complications</b>	37 (6.4%)	24 (4.1%)	32 (5.5%)
Accidental overdose	14 (2.4%)	13 (2.2%)	17 (2.9%)

19


**U.S. Food and Drug Administration**  
 Protecting and Promoting Public Health  
[www.fda.gov](http://www.fda.gov)

## Deaths

Treatment	# of patients	# of patients/100 patient-years (95% CI)	Cause of death (as adjudicated)
Placebo	3	0.8 (0.16, 2.28)	CV death: 0 Non-CV death: 3
Tocilizumab	1	2.1 (0.05, 11.80)	CV death: 1 Non-CV death: 0
Sarilumab	22	NA <sup>a</sup>	
Sarilumab+DMARD: Onset of fatal AE during treatment- emergent period	19	0.4 (0.26, 0.66)	Not adjudicated <sup>b</sup> : 1 CV death: 7
Sarilumab+DMARD: Onset of fatal AE during post-study period <sup>c</sup>	2	NA <sup>a</sup>	Non-CV death: 12 Undetermined cause of death: 2
Sarilumab monotherapy <sup>d</sup>	1	1.4 (0.04, 7.99)	

- Sarilumab 150 mg q2w: 3
- Sarilumab 200 mg q2w: 15

20


 U.S. Food and Drug Administration  
 Protecting and Promoting Public Health  
[www.fda.gov](http://www.fda.gov)

## Serious Adverse Events

Primary System Organ Class Preferred Term	Sarilumab		
	Placebo + DMARD (N=661) n (%)	150 mg q2w + DMARD (N=660) n (%)	200 mg q2w + DMARD (N=661) n (%)
Any class	31 (4.7%)	42 (6.4%)	59 (8.9%)
<b>Infections and infestations</b>	12 (1.8%)	12 (1.8%)	19 (2.9%)
Erysipelas	0	0	3 (0.5%)
Pneumonia	1 (0.2%)	1 (0.2%)	3 (0.5%)
Bronchitis	3 (0.5%)	0	2 (0.3%)
Cellulitis	4 (0.6%)	1 (0.2%)	2 (0.3%)
<b>Blood and lymphatic system disorders</b>	1 (0.2%)	5 (0.8%)	8 (1.2%)
Neutropenia	0	4 (0.6%)	5 (0.8%)
<b>Musculoskeletal and connective tissue disorders</b>	7 (1.1%)	3 (0.5%)	6 (0.9%)
Osteoarthritis	3 (0.5%)	1 (0.2%)	2 (0.3%)
Rheumatoid arthritis	3 (0.5%)	0	2 (0.3%)

21


 U.S. Food and Drug Administration  
 Protecting and Promoting Public Health  
[www.fda.gov](http://www.fda.gov)

## AEs Leading to Discontinuation

Primary System Organ Class Preferred Term	Sarilumab		
	Placebo + DMARD (N=661) n (%)	150 mg q2w + DMARD (N=660) n (%)	200 mg q2w + DMARD (N=661) n (%)
Any class	31 (4.7%)	72 (10.9%)	83 (12.6%)
<b>Infections and infestations</b>	7 (1.1%)	20 (3.0%)	20 (3.0%)
Herpes zoster	3 (0.5%)	3 (0.5%)	5 (0.8%)
<b>Blood and lymphatic system disorders</b>	3 (0.5%)	17 (2.6%)	19 (2.9%)
Neutropenia	2 (0.3%)	15 (2.3%)	13 (2.0%)
Thrombocytopenia	0	1 (0.2%)	3 (0.5%)
<b>Musculoskeletal and connective tissue disorders</b>	6 (0.9%)	1 (0.2%)	3 (0.5%)
Rheumatoid arthritis	5 (0.8%)	0	2 (0.3%)
<b>Investigations</b>	3 (0.5%)	13 (2.0%)	15 (2.3%)
Alanine aminotransferase increased	0	11 (1.7%)	9 (1.4%)
Transaminases increased	1 (0.2%)	2 (0.3%)	4 (0.6%)

22


**U.S. Food and Drug Administration**  
 Protecting and Promoting Public Health  
[www.fda.gov](http://www.fda.gov)

## Proposed REMS

(b) (4)

23


**U.S. Food and Drug Administration**  
 Protecting and Promoting Public Health  
[www.fda.gov](http://www.fda.gov)

## Pediatric Plan

- iPSP letter of agreement – January 2014
  - Partial waiver for children <24 months with pJIA
  - Deferral for children ages 2-17 years with pJIA

### Planned Pediatric Studies

Study	Description
<b>PK studies</b>	
DRI13925	(b) (4) dose-finding study in children (b) (4)
<b>Safety and Efficacy studies</b>	
EFC11783	(b) (4) study to assess efficacy and safety in children (b) (4)

24


**U.S. Food and Drug Administration**  
 Protecting and Promoting Public Health  
[www.fda.gov](http://www.fda.gov)

## Preliminary Conclusions

- Application is fileable from a clinical perspective
- Standard review priority
- Recommend not having Advisory Committee Meeting
  - Significant efficacy
  - No unexpected safety signals (similar to tocilizumab)
- As summarized by the sponsor, sarilumab preliminarily appears to have an adequately favorable risk-benefit profile
  - Robust and durable benefit in treatment of RA
  - Sustained inhibition of joint damage
  - Safety profile consistent with inhibition of IL-6 signaling

25


**U.S. Food and Drug Administration**  
 Protecting and Promoting Public Health  
[www.fda.gov](http://www.fda.gov)

**Efficacy Claims in Currently Approved Labels of Recent (>1998) Disease Modifying Anti-Rheumatic Drugs (DMARDs) for RA**

	Arava	Remicade	Enbrel	Kineret	Humira	Orencia	Rituxan	Cimzia	Simponi	Actemra	Xeljanz	(b) (4)
ACR 20/50/70 Response	x	x	x	x	x	x	x	x	x	x	x	x
ACR components	x	x	x	x	x	x	x	x	x	x	x	x
Time course of response	x	x	x		x	x	x	x	x	x	x	x
Open-label maintenance	x	x	x		x	x						
Major Clinical Response		x	x		x	x		x		x		x
Radiographic response	x	x	x	x	x	x	x	x		x	x	x
Proportion of non-progressors		x	x		x	x	x			x	x	x
Open-label maintenance			x		x							
Physical Function												
HAQ-DI	x	x	x	x	x	x	x	x	x	x	x	x
SF-36	x	x	x	x	x	x					x	x
Open-label maintenance	x	x	x		x	x	x					
DAS28 <2.6												
Proportion of responders						x				x	x	x
Residual active joints						x				x	x	x
Morning stiffness	x		x			x						

26

FDA U.S. Food and Drug Administration  
Protecting and Promoting Public Health  
www.fda.gov

## Midcycle Deliverables

- Efficacy Results
  - Conformation of all results proposed for labeling
- Safety Results
  - Deaths, SAEs, Discontinuations due to AE, common AEs
  - AEs of interest
  - More detailed look at requested analyses

### Consults

- Recommend routine DSI inspection
  - NME

27

FDA U.S. Food and Drug Administration  
Protecting and Promoting Public Health  
www.fda.gov

## Back-up

28

APPEARS THIS  
WAY ON  
ORIGINAL


 U.S. Food and Drug Administration  
 Protecting and Promoting Public Health  
[www.fda.gov](http://www.fda.gov)

## Sarilumab: Clinical Development

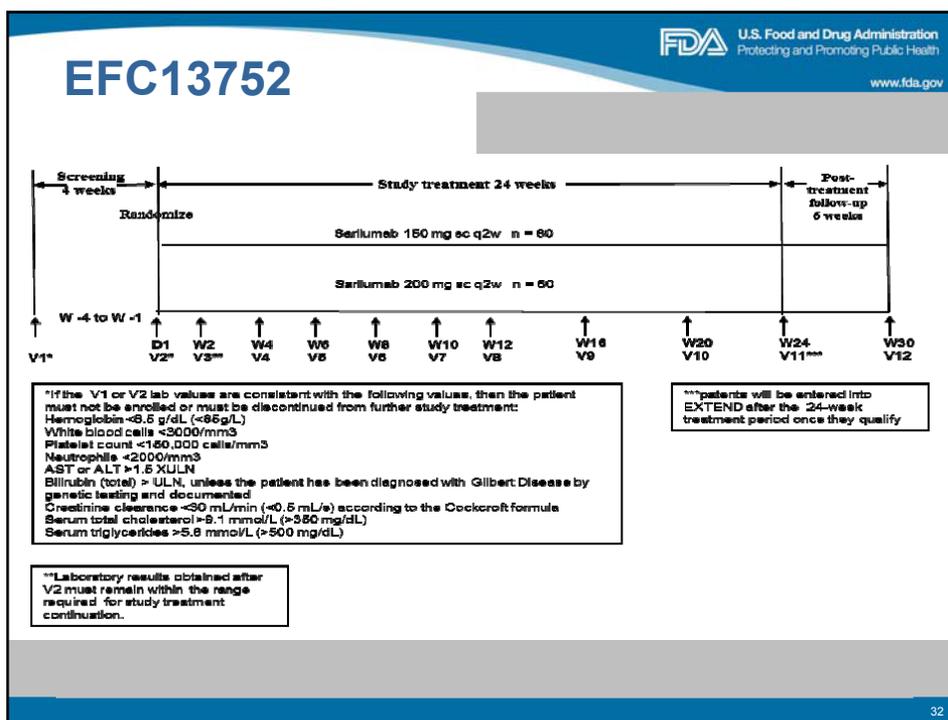
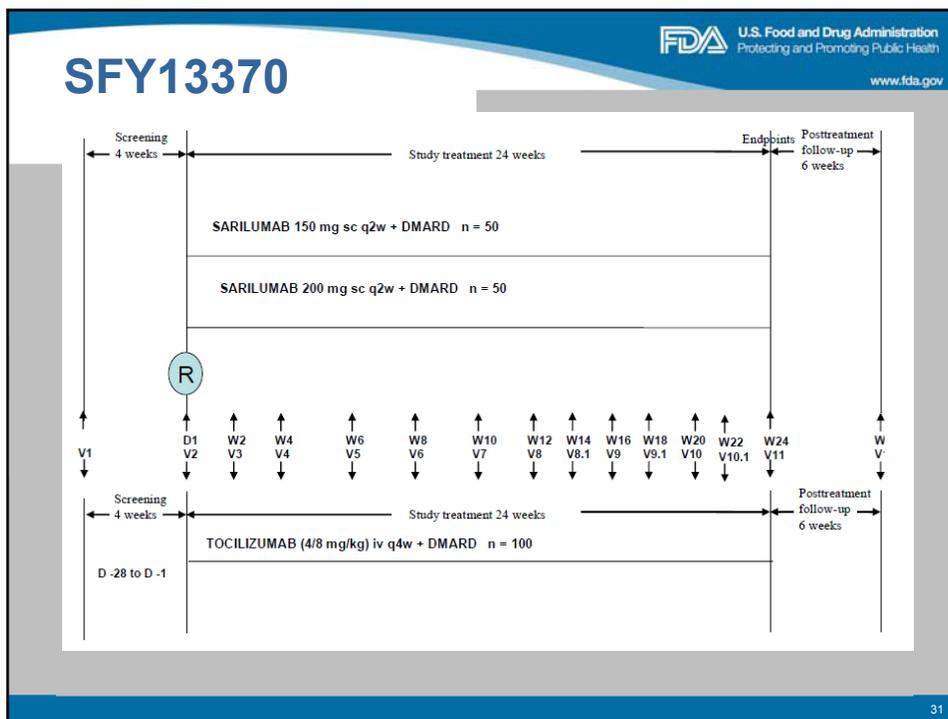
- Phase 1 clinical trials
  - 5 studies – total 146 subjects with RA
  - 1 study – total 53 healthy subjects
- Phase 2 clinical trials
  - MOBILITY (RA) → 5 dose regimens
  - ALIGN (AS) → d/c'ed b/c of lack of efficacy
- Phase 3 clinical trials
  - 150mg q2w and 200mg q2w
  - 4 ongoing studies
  - 1 long-term extension study

29


 U.S. Food and Drug Administration  
 Protecting and Promoting Public Health  
[www.fda.gov](http://www.fda.gov)

## EFC11072 Part A

30




**U.S. Food and Drug Administration**  
 Protecting and Promoting Public Health  
[www.fda.gov](http://www.fda.gov)

## LTS11210

- Ongoing MC, OL, long-term study
- Patients could be enrolled from the following studies
  - ACT11575
  - EFC11072
  - EFC10832
  - SFY13370
  - EFC13752
- Dose: sarilumab 150mg once weekly → 200mg every 2 wks
- Maximum duration of study: 260 weeks

33


**U.S. Food and Drug Administration**  
 Protecting and Promoting Public Health  
[www.fda.gov](http://www.fda.gov)

## EFC11574

The diagram illustrates the study timeline for EFC11574, divided into an OL Phase and a Randomized Phase.

- OL Phase (Open Label):**
  - OL Screen Period:** 16 weeks, starting at OL1 (W -4 to W -1).
  - OL Treatment Period:** 16 weeks, starting at D1 (OL2).
  - Screen Period:** 2-4 weeks, starting at W16 (OL6).
- Randomized Phase:**
  - Screen Period:** 2-4 weeks, starting at W18/20 (D1 R1).
  - R Treatment Period:** 24 weeks, starting at W2 (R2 to 7).
  - Post-treatment Follow-up Period no. 1:** 6 weeks, starting at W22 (F1).
  - Post-treatment Follow-up Period no. 2:** 6 weeks, starting at W24 (R16).

**Enrollment and Treatment:**

- Enroll at OL1.
- Adalimumab 40 mg sc q2w + MTX (n = ~1900-2600) is administered during the OL Treatment Period.
- Randomization occurs at W18/20 (D1 R1).
- Randomized treatment groups (n=233 each):
  - Sarilumab 200 mg sc q2w + MTX
  - Sarilumab 150 mg sc q2w + MTX
  - Etanercept 50 mg sc qw + MTX

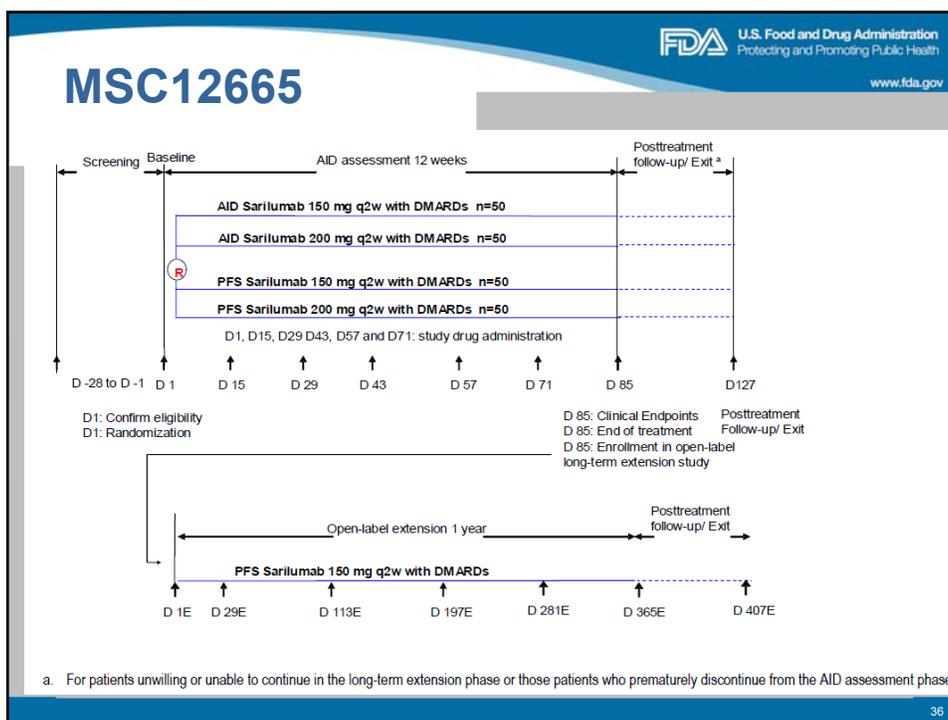
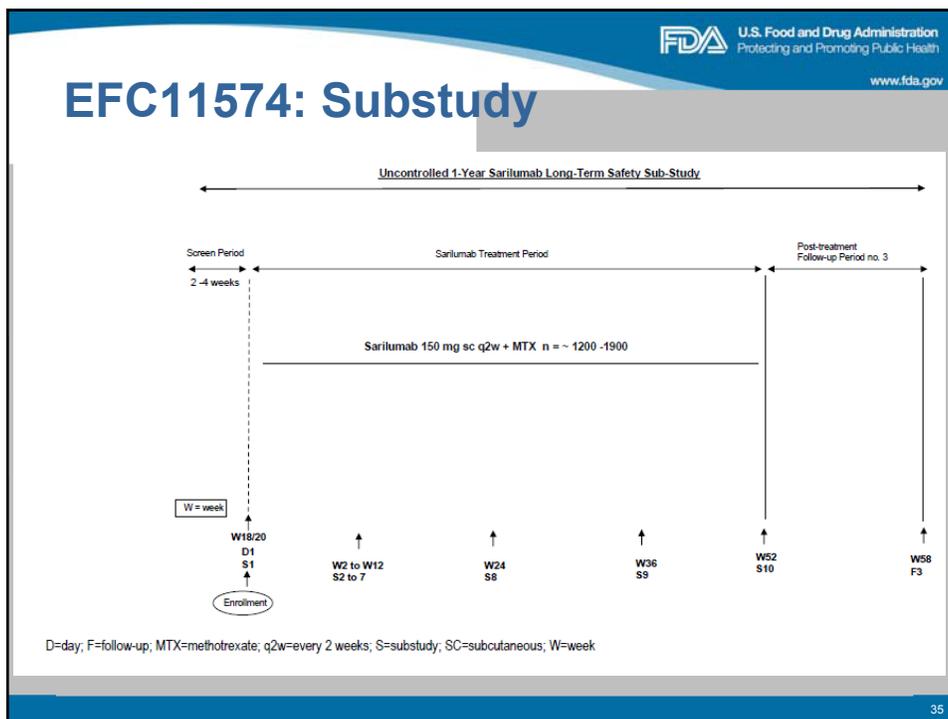
**Key Events and Endpoints:**

- Primary endpoint is assessed at W24 (R16).
- W22 (F1) is a follow-up point for patients not entering the randomized phase.
- W30 (F2) is a follow-up point for all patients entered into the randomized treatment period.

**Legend:**

- OL = Open Label; R = Randomized
- W = Week; ACR = American College of Rheumatology criteria 20% improvement
- ACR20 responders screen for 1-yr sub-study
- ACR20 non-responders screen for randomized study
- D=day, F1= follow-up period 1; F2: follow-up period 2; MTX= methotrexate; q2w= every 2 weeks; SC= subcutaneous;

34




 U.S. Food and Drug Administration  
 Protecting and Promoting Public Health  
[www.fda.gov](http://www.fda.gov)

## Sarilumab Clinical Development: AS

Protocol	Study Population (Background Therapy)	Design	Dose	Total # of Patients
<b>DRI11073</b>	Active AS NSAID-IR	Phase 2 R, DB, PC dose-ranging study  <b>Lack of efficacy</b>	<ul style="list-style-type: none"> <li>Sarilumab 100mg QW, 150mg QW, 100mg Q2W, 150mg Q2W, 200mg Q2W</li> <li>PBO</li> </ul>	301
<b>LTS11298</b>  Terminated early (1.5 yrs) due to lack of efficacy in DRI11073	Active AS NSAID-IR	MC, uncontrolled, long-term extension	Sarilumab 150mg QW	223

37

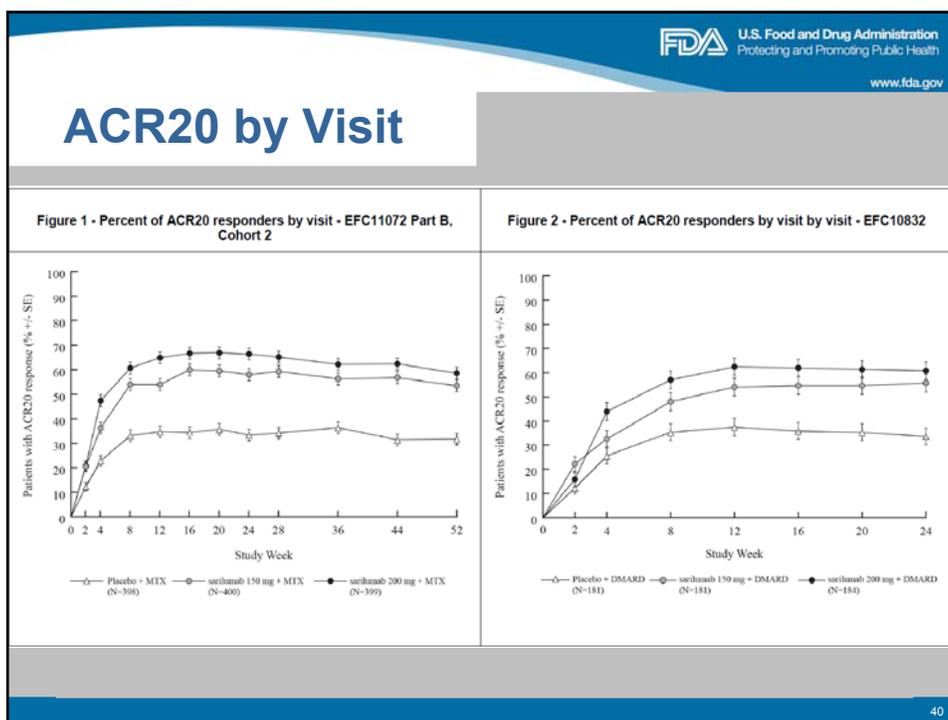

 U.S. Food and Drug Administration  
 Protecting and Promoting Public Health  
[www.fda.gov](http://www.fda.gov)

## Patient Disposition

	EFC11072 Part B, Cohort 2			EFC10832		
	Placebo + MTX (N=398)	Sarilumab 150 mg q2w + MTX (N=400)	Sarilumab 200 mg q2w + MTX (N=399)	Placebo + DMARD (N=181)	Sarilumab 150 mg q2w + DMARD (N=181)	Sarilumab 200 mg q2w + DMARD (N=184)
Randomized	398 (100%)	400 (100%)	399 (100%)	181 (100%)	181 (100%)	184 (100%)
Randomized and not treated	0	2 (0.5%)	1 (0.3%)	0	0	0
Randomized and treated	398 (100%)	398 (99.5%)	398 (99.7%)	181 (100%)	181 (100%)	184 (100%)
Completed	196 (49.2%)	270 (67.5%)	270 (67.7%)	101 (55.8%)	125 (69.1%)	133 (72.3%)
Rescued <sup>a</sup>	156 (39.2%)	55 (13.8%)	46 (11.5%)	63 (34.8%)	25 (13.8%)	26 (14.1%)
Discontinued	46 (11.6%)	73 (18.3%)	82 (20.6%)	17 (9.4%)	31 (17.1%)	25 (13.6%)
Adverse event	21 (5.3%)	50 (12.5%)	57 (14.3%)	9 (5.0%)	18 (9.9%)	17 (9.2%)
Lack of efficacy	3 (0.8%)	5 (1.3%)	6 (1.5%)	5 (2.8%)	4 (2.2%)	2 (1.1%)
Poor compliance to protocol	6 (1.5%)	2 (0.5%)	5 (1.3%)	1 (0.6%)	2 (1.1%)	1 (0.5%)
Other reasons <sup>b</sup>	16 (4.0%)	16 (4.0%)	14 (3.5%)	2 (1.1%)	7 (3.9%)	5 (2.7%)

38

		EFC11072 Part B, Cohort 2			EFC10832		
		Placebo + MTX (N=398)	Sarilumab 150 mg q2w + MTX (N=400)	Sarilumab 200 mg q2w + MTX (N=399)	Placebo + DMARD (N=181)	Sarilumab 150 mg q2w + DMARD (N=181)	Sarilumab 200 mg q2w + DMARD (N=184)
<b>ACR20</b>	<b>Week 12</b>						
	Proportion of patients	34.7%	54.0%	64.9%	37.6%	54.1%	62.5%
	RD, 95% CI vs placebo <sup>a</sup> , p-value vs placebo <sup>b</sup>		19.4% (12.6%, 26.1%), <0.0001	30.2% (23.6%, 36.8%), <0.0001		16.6% (8.7%, 26.5%), 0.0010	25.3% (15.7%, 34.8%), <0.0001
<b>Week 24<sup>c</sup></b>	Proportion of patients	33.4%	58.0%	66.4%	33.7%	55.8%	60.9%
	RD, 95% CI vs placebo <sup>a</sup> , p-value vs placebo <sup>b</sup>		24.6% (18.0%, 31.3%), <0.0001	33.0% (26.5%, 39.5%), <0.0001		22.1% (12.6%, 31.6%), <0.0001	27.4% (17.7%, 37.0%), <0.0001
	RD, 95% CI vs placebo <sup>a</sup> , p-value vs placebo <sup>b</sup>		21.9% (15.2%, 28.5%), <0.0001	27.0% (20.5%, 33.6%), <0.0001	NA	NA	NA
<b>Week 52</b>	Proportion of patients	31.7%	53.5%	58.6%	NA	NA	NA
	RD, 95% CI vs placebo <sup>a</sup> , p-value vs placebo <sup>b</sup>		21.9% (15.2%, 28.5%), <0.0001	27.0% (20.5%, 33.6%), <0.0001	NA	NA	NA
	RD, 95% CI vs placebo <sup>a</sup> , p-value vs placebo <sup>b</sup>		21.9% (15.2%, 28.5%), <0.0001	27.0% (20.5%, 33.6%), <0.0001	NA	NA	NA
<b>ACR50</b>	<b>Week 12</b>						
	Proportion of patients	12.3%	26.5%	36.3%	13.3%	30.4%	33.2%
	RD, 95% CI vs placebo <sup>a</sup> , p-value vs placebo <sup>b</sup>		14.2% (8.9%, 19.6%), <0.0001	24.1% (18.4%, 29.8%), <0.0001		17.1% (9.2%, 25.1%), <0.0001	20.1% (12.0%, 28.3%), <0.0001
<b>Week 24</b>	Proportion of patients	16.6%	37.0%	45.6%	18.2%	37.0%	40.8%
	RD, 95% CI vs placebo <sup>a</sup> , p-value vs placebo <sup>b</sup>		20.4% (14.5%, 26.3%), <0.0001	29.1% (23.0%, 35.1%), <0.0001		18.8% (10.2%, 27.4%), <0.0001	22.8% (14.0%, 31.6%), <0.0001
	RD, 95% CI vs placebo <sup>a</sup> , p-value vs placebo <sup>b</sup>		21.9% (15.8%, 28.0%), <0.0001	24.8% (18.7%, 30.9%), <0.0001	NA	NA	NA
<b>Week 52</b>	Proportion of patients	18.1%	40.0%	42.9%	NA	NA	NA
	RD, 95% CI vs placebo <sup>a</sup> , p-value vs placebo <sup>b</sup>		21.9% (15.8%, 28.0%), <0.0001	24.8% (18.7%, 30.9%), <0.0001	NA	NA	NA
	RD, 95% CI vs placebo <sup>a</sup> , p-value vs placebo <sup>b</sup>		21.9% (15.8%, 28.0%), <0.0001	24.8% (18.7%, 30.9%), <0.0001	NA	NA	NA
<b>ACR70</b>	<b>Week 12</b>						
	Proportion of patients	4.0%	11.0%	17.5%	2.2%	13.8%	14.7%
	RD, 95% CI vs placebo <sup>a</sup> , p-value vs placebo <sup>b</sup>		7.0% (3.4%, 10.6%), 0.0002	13.5% (9.4%, 17.7%), <0.0001		11.6% (6.2%, 17.0%), <0.0001	12.5% (7.1%, 17.9%), <0.0001
<b>Week 24</b>	Proportion of patients	7.3%	19.8%	24.8%	7.2%	19.9%	16.3%
	RD, 95% CI vs placebo <sup>a</sup> , p-value vs placebo <sup>b</sup>		12.5% (7.8%, 17.1%), <0.0001	17.5% (12.6%, 22.5%), <0.0001		12.7% (6.1%, 19.3%), 0.0002	9.2% (2.8%, 15.7%), 0.0050
	RD, 95% CI vs placebo <sup>a</sup> , p-value vs placebo <sup>b</sup>		15.7% (10.6%, 20.8%), <0.0001	17.8% (12.6%, 23.0%), <0.0001	NA	NA	NA
<b>Week 52</b>	Proportion of patients	9.0%	24.8%	26.8%	NA	NA	NA
	RD, 95% CI vs placebo <sup>a</sup> , p-value vs placebo <sup>b</sup>		15.7% (10.6%, 20.8%), <0.0001	17.8% (12.6%, 23.0%), <0.0001	NA	NA	NA
	RD, 95% CI vs placebo <sup>a</sup> , p-value vs placebo <sup>b</sup>		15.7% (10.6%, 20.8%), <0.0001	17.8% (12.6%, 23.0%), <0.0001	NA	NA	NA




**U.S. Food and Drug Administration**  
 Protecting and Promoting Public Health  
[www.fda.gov](http://www.fda.gov)

## ACR Components

Component (mean)	EFC11072 Part B, Cohort 2						EFC10832					
	Placebo + MTX (N=398)		Sarılumab 150 mg q2w + MTX (N=400)		Sarılumab 200 mg q2w + MTX (N=399)		Placebo + DMARD (N=181)		Sarılumab 150 mg q2w + DMARD (N=181)		Sarılumab 200 mg q2w + DMARD (N=184)	
	Baseline	Week 24	Baseline	Week 24	Baseline	Week 24	Baseline	Week 24	Baseline	Week 24	Baseline	Week 24
<b>Tender Joints (0-66)</b>												
Mean	26.80	12.42	27.18	7.07	26.52	7.21	29.42	10.90	27.66	8.49	29.55 (15.54)	8.09
LS mean difference vs placebo (95% CI) <sup>a</sup>				-8.814 (-8.637, -8.991)		-7.301 (-9.120, -5.482)				-3.893 (-6.891, -1.094)		-4.404 (-6.691, -1.094)
p-value vs placebo <sup>b</sup>				<0.0001		<0.0001				0.0065		<0.0001
<b>Swollen Joints (0-66)</b>												
Mean	16.70	7.26	16.59	4.57	16.75	4.53	20.21	6.89	19.60	5.48	19.97	4.83
LS mean difference vs placebo (95% CI) <sup>a</sup>				-3.954 (-5.136, -2.770)		-4.942 (-5.822, -3.461)				-3.370 (-5.256, -1.484)		-3.763 (-5.618, -1.887)
p-value vs placebo <sup>b</sup>				<0.0001		<0.0001				0.0005		<0.0001
<b>Pain VAS (0-100 mm)</b>												
Mean	63.78	42.69	65.36	33.48	66.82	31.36	71.57	41.31	71.02	33.04	74.86	35.16
LS mean difference vs placebo (95% CI) <sup>a</sup>				-13.080 (-16.846, -9.314)		-16.435 (-20.190, -12.680)				-10.632 (-16.492, -4.772)		-12.379 (-18.186, -6.573)
p-value vs placebo <sup>b</sup>				<0.0001		<0.0001				0.0004		<0.0001
<b>Physician global VAS (0-100 mm)</b>												
Mean	62.92	30.54	63.40	22.03	63.51	20.22	68.39	28.93	68.10	21.83	67.76	20.03
LS mean difference vs placebo (95% CI) <sup>a</sup>				-12.963 (-16.226, -9.699)		-15.698 (-18.950, -12.447)				-12.099 (-16.789, -7.408)		-14.673 (-19.306, -10.039)
p-value vs placebo <sup>b</sup>				<0.0001		<0.0001				<0.0001		<0.0001

41


**U.S. Food and Drug Administration**  
 Protecting and Promoting Public Health  
[www.fda.gov](http://www.fda.gov)

## ACR Components

Component (mean)	EFC11072 Part B, Cohort 2						EFC10832					
	Placebo + MTX (N=398)		Sarılumab 150 mg q2w + MTX (N=400)		Sarılumab 200 mg q2w + MTX (N=399)		Placebo + DMARD (N=181)		Sarılumab 150 mg q2w + DMARD (N=181)		Sarılumab 200 mg q2w + DMARD (N=184)	
	Baseline	Week 24	Baseline	Week 24	Baseline	Week 24	Baseline	Week 24	Baseline	Week 24	Baseline	Week 24
<b>Patient global VAS (0-100 mm)</b>												
Mean	63.68	42.29	64.36	32.91	66.32	30.38	68.77	40.26	67.71	32.09	70.89	34.26
LS mean difference vs placebo (95% CI) <sup>a</sup>				-12.525 (-16.136, -8.914)		-17.174 (-20.777, -13.571)				-9.825 (-15.530, -4.121)		-11.516 (-17.159, -5.872)
p-value vs placebo <sup>b</sup>				<0.0001		<0.0001				0.0008		<0.0001
<b>HAQ-DI (0-3)</b>												
Mean	1.61	1.17	1.63	0.99	1.69	1.05	1.80	1.25	1.72	1.05	1.82	1.14
LS mean difference vs placebo (95% CI) <sup>a</sup>				-0.241 (-0.326, -0.156)		-0.252 (-0.336, -0.167)				-0.183 (-0.318, -0.048)		-0.242 (-0.376, -0.109)
p-value vs placebo <sup>b</sup>				<0.0001		<0.0001				0.0078		0.0004
<b>CRP</b>												
Mean	20.46	17.26	22.53	8.85	22.19	3.82	26.02	19.83	23.60	8.76	30.77	3.74
LS mean difference vs placebo (95% CI) <sup>a</sup>				-12.538 (-15.963, -9.212)		-16.963 (-20.218, -13.588)				-11.942 (-15.651, -7.634)		-19.673 (-23.636, -15.709)
p-value vs placebo <sup>b</sup>				<0.0001		<0.0001				<0.0001		<0.0001

42


**U.S. Food and Drug Administration**  
 Protecting and Promoting Public Health  
[www.fda.gov](http://www.fda.gov)

## DAS29-CRP < 2.6

	EFC11072 Part B, Cohort 2			EFC10832		
	Placebo + MTX (N=398)	Sarilumab 150 mg q2w + MTX (N=400)	Sarilumab 200 mg q2w + MTX (N=399)	Placebo + DMARD (N=181)	Sarilumab 150 mg q2w + DMARD (N=181)	Sarilumab 200 mg q2w + DMARD (N=184)
<b>Week 24</b>						
Number of patients (proportion) with DAS28-CRP < 2.6	40 (10.1%)	111 (27.8%)	136 (34.1%)	13 (7.2%)	45 (24.9%)	53 (28.8%)
OR, 95% CI versus placebo <sup>a</sup>		3.551 (2.382, 5.252)	4.690 (3.176, 6.926)		4.622 (2.339, 9.132)	5.801 (2.948, 11.413)
p-value <sup>b</sup>		<0.0001	<0.0001		<0.0001	<0.0001
Number of responders (proportion) with:						
0 active joints	19 (47.5%)	30 (27.0%)	39 (28.7%)	10 (76.9%)	12 (26.7%)	13 (24.5%)
1 active joint	10 (25.0%)	24 (21.6%)	33 (24.3%)	0	13 (28.9%)	7 (13.2%)
2 active joints	3 (7.5%)	15 (13.5%)	19 (14.0%)	0	6 (13.3%)	9 (17.0%)
≥3 active joints	8 (20.0%)	42 (37.8%)	45 (33.1%)	3 (23.1%)	14 (31.1%)	24 (45.3%)
<b>Week 52</b>						
Number of patients (proportion)	34 (8.5%)	124 (31.0%)	136 (34.1%)	NA	NA	NA
OR, 95% CI versus placebo <sup>a</sup>		4.866 (3.218, 7.357)	5.525 (3.673, 8.310)			
p-value <sup>b</sup>		<0.0001	<0.0001			
Number of responders (proportion) with:						
0 active joints	21 (61.8%)	43 (34.7%)	69 (50.7%)			
1 active joint	8 (23.5%)	27 (21.8%)	17 (12.5%)			
2 active joints	2 (5.9%)	19 (15.3%)	20 (14.7%)			
≥3 active joints	3 (8.8%)	35 (28.2%)	30 (22.1%)			

43


**U.S. Food and Drug Administration**  
 Protecting and Promoting Public Health  
[www.fda.gov](http://www.fda.gov)

## HAQ-DI Responders (HAQ-DI ≥ 0.3 unit improvement)

	EFC11072 Part B, Cohort 2			EFC10832		
	Placebo + MTX (N=398)	Sarilumab 150 mg q2w + MTX (N=400)	Sarilumab 200 mg q2w + MTX (N=399)	Placebo + DMARD (N=181)	Sarilumab 150 mg q2w + DMARD (N=181)	Sarilumab 200 mg q2w + DMARD (N=184)
<b>Week 12</b>						
Responders (number [%])	167 (42.0%)	200 (50.0%)	235 (58.9%)	65 (35.9%)	85 (47.0%)	94 (51.1%)
OR, 95% CI versus placebo <sup>a</sup>		1.397 (1.062, 1.854)	2.001 (1.506, 2.658)		1.614 (1.048, 2.485)	1.926 (1.254, 2.957)
p-value versus placebo <sup>b</sup>		0.0204	<0.0001		0.0297	0.0025
<b>Week 24</b>						
Responders (number [%])	133 (33.4%)	204 (51.0%)	205 (51.4%)	57 (31.5%)	78 (43.1%)	87 (47.3%)
OR, 95% CI versus placebo <sup>a</sup>		2.106 (1.577, 2.813)	2.132 (1.597, 2.845)		1.743 (1.106, 2.746)	2.018 (1.305, 3.119)
p-value versus placebo <sup>b</sup>		<0.0001	<0.0001		0.0165	<0.0014
<b>Week 52</b>						
Responders (number [%])	104 (26.1%)	188 (47.0%)	190 (47.6%)			
OR, 95% CI versus placebo <sup>a</sup>		2.530 (1.875, 3.413)	2.613 (1.935, 3.528)			
p-value versus placebo <sup>b</sup>		<0.0001	<0.0001			

44


**U.S. Food and Drug Administration**  
 Protecting and Promoting Public Health  
[www.fda.gov](http://www.fda.gov)

## Radiographic Response

	EFC11072		
	Placebo + MTX (N=398)	Sarilumab 150 mg q2w + MTX (N=400)	Sarilumab 200 mg q2w + MTX (N=399)
<b>van de Heijde mTSS</b>			
<b>Week 24</b>			
Mean change (SD)	1.22 (3.97)	0.54 (2.99)	0.13 (2.60)
LS mean difference, 95% CI <sup>a</sup>		-0.689 (-1.175, -0.203)	-1.085 (-1.570, -0.600)
p-value versus placebo <sup>b</sup>		0.0030	<0.0001
<b>Week 52</b>			
Mean change (SD)	2.78 (7.73)	0.90 (4.66)	0.25 (4.61)
LS mean difference, 95% CI <sup>a</sup>		-1.878 (-2.743, -1.013)	-2.522 (-3.382, -1.662)
p-value versus placebo <sup>b</sup>		<0.0001	<0.0001
<b>Erosion score (0-280)</b>			
<b>Week 24</b>			
Mean change (SD)	0.68 (2.41)	0.26 (1.46)	0.02 (1.23)
LS mean difference, 95% CI <sup>a</sup>		-0.422 (-0.687, -0.156)	-0.660 (-0.926, -0.395)
p-value versus placebo <sup>b</sup>		0.0074	<0.0001
<b>Week 52</b>			
Mean change (SD)	1.46 (4.83)	0.42 (2.50)	0.05 (2.17)
LS mean difference, 95% CI <sup>a</sup>		-1.028 (-1.527, -0.529)	-1.400 (-1.897, -0.904)
p-value versus placebo <sup>b</sup>		<0.0001	<0.0001
<b>Joint space narrowing score</b>			
<b>Week 24</b>			
Mean (SD)	0.54 (2.22)	0.28 (2.07)	0.12 (1.82)
LS mean difference, 95% CI <sup>a</sup>		-0.263 (-0.570, 0.045)	-0.423 (-0.729, -0.116)
p-value versus placebo <sup>b</sup>		0.1514	0.0003
<b>Week 52</b>			
Mean (SD)	1.32 (3.85)	0.47 (2.88)	0.20 (3.21)
LS mean difference, 95% CI <sup>a</sup>		-0.847 (-1.342, -0.352)	-1.120 (-1.612, -0.628)
p-value versus placebo <sup>b</sup>		0.0005	<0.0001

45


**U.S. Food and Drug Administration**  
 Protecting and Promoting Public Health  
[www.fda.gov](http://www.fda.gov)

## No Radiographic Progression

	EFC11072 Part B, Cohort 2		
	Placebo + MTX (N=398)	Sarilumab 150 mg q2w + MTX (N=400)	Sarilumab 200 mg q2w + MTX (N=399)
<b>N (%) of patients with change in mTSS ≤0</b>	154 (38.7%)	191 (47.8%)	222 (55.6%)
OR, 95% CI versus placebo <sup>a</sup>		1.453 (1.095, 1.926)	2.001 (1.506, 2.660)
p-value versus placebo <sup>b</sup>		0.0094	<0.0001
<b>N (%) of patients with change in erosion score ≤0</b>	173 (43.5%)	219 (54.8%)	248 (62.2%)
OR, 95% CI versus placebo <sup>a</sup>		1.570 (1.189, 2.074)	2.155 (1.619, 2.867)
p-value versus placebo <sup>b</sup>		0.0014	<0.0001
<b>N (%) of patients with joint space narrowing score ≤0</b>	220 (55.3%)	247 (61.8%)	281 (70.4%)
OR, 95% CI versus placebo <sup>a</sup>		1.308 (0.986, 1.735)	1.939 (1.445, 2.602)
p-value versus placebo <sup>b</sup>		0.0619	<0.0001

46


**U.S. Food and Drug Administration**  
 Protecting and Promoting Public Health  
[www.fda.gov](http://www.fda.gov)

## Safety Profile in phase 3 studies

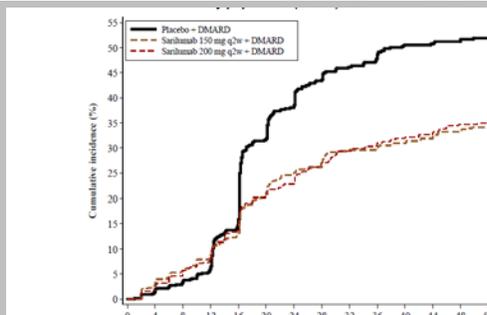
- Higher incidence of TEAEs, SAEs, and TEAEs leading to withdrawal in sarilumab treatment groups
- Most frequent TEAEs and TEAEs leading to discontinuation
  - Neutropenia, infections, and increases in transaminases
- Infections most frequently reported SAEs
- Laboratory abnormalities more common in sarilumab groups
  - Decreases in neutrophil count, elevation in ALT, and elevation in serum LDL

47


**U.S. Food and Drug Administration**  
 Protecting and Promoting Public Health  
[www.fda.gov](http://www.fda.gov)

## Patient Disposition (Pool 1)

	Placebo + DMARD (N=661)	Sarilumab	
		150 mg q2w + DMARD (N=660)	200 mg q2w + DMARD (N=661)
Randomized and treated	661 (100%)	660 (100%)	661 (100%)
Completed the double-blind period	359 (54.3%)	462 (70.0%)	461 (69.7%)
Rescued to sarilumab therapy	231 (34.9%)	86 (13.0%)	81 (12.3%)
Discontinued treatment during the double-blind period	71 (10.7%)	112 (17.0%)	119 (18.0%)
Reason for treatment discontinuation <sup>a</sup>			
Adverse event	31 (4.7%)	73 (11.1%)	83 (12.6%)
Lack of efficacy	13 (2.0%)	11 (1.7%)	10 (1.5%)
Poor compliance to protocol	8 (1.2%)	4 (0.6%)	6 (0.9%)
Other reasons <sup>b</sup>	19 (2.9%)	24 (3.6%)	20 (3.0%)

	0	4	8	12	16	20	24	28	32	36	40	44	48	52
Placebo	661	652	640	622	518	414	354	246	234	227	215	214	213	196
Sari 150mg q2w	660	642	623	606	529	483	447	324	310	308	303	299	293	269
Sari 200mg q2w	661	650	631	610	528	486	457	318	307	302	296	293	283	263

48


**U.S. Food and Drug Administration**  
 Protecting and Promoting Public Health  
[www.fda.gov](http://www.fda.gov)

## Overview of Adverse Events

Treatment	Raw incidence rate n/N (%)	Exposure adjusted incidence rate <sup>a</sup> n/PY (rate per 100 PYs)	Difference in raw incidence rate vs. Placebo+DMARD (95% CI) <sup>b</sup>	Rate difference vs Sariilumab 150 mg q2w+DMARD (95% CI) <sup>b</sup>
<b>TEAE</b>				
Sariilumab 200 mg q2w+DMARD	488/661 (73.8%)	488/193.6 (252.0)	16.7% ( 11.7, 21.7)	3.4% (-1.4, 8.2)
Sariilumab 150 mg q2w+DMARD	465/660 (70.5%)	465/215.5 (215.7)	13.3% ( 8.2, 18.4)	
Placebo +DMARD	378/661 (57.2%)	378/218.2 (173.3)		
<b>Serious TEAE</b>				
Sariilumab 200 mg q2w+DMARD	58/661 (8.9%)	58/426.5 (13.8)	4.3% ( 1.5, 7.0)	2.8% (-0.3, 5.4)
Sariilumab 150 mg q2w+DMARD	42/660 (6.4%)	42/433.8 (9.7)	1.7% (-0.8, 4.1)	
Placebo +DMARD	31/661 (4.7%)	31/375.4 (8.3)		
<b>TEAE leading to death</b>				
Sariilumab 200 mg q2w+DMARD	1/661 (0.2%)	1/442.8 (0.2)	-0.3% (-0.9, 0.3)	-0.2% (-0.7, 0.4)
Sariilumab 150 mg q2w+DMARD	2/660 (0.3%)	2/442.1 (0.5)	-0.2% (-0.8, 0.5)	
Placebo +DMARD	3/661 (0.5%)	3/383.9 (0.8)		
<b>TEAE leading to permanent treatment discontinuation</b>				
Sariilumab 200 mg q2w+DMARD	83/661 (12.6%)	83/428.4 (19.4)	7.9% ( 4.9, 10.9)	1.7% (-1.8, 5.1)
Sariilumab 150 mg q2w+DMARD	72/660 (10.9%)	72/429.8 (16.8)	6.2% ( 3.3, 9.1)	
Placebo +DMARD	31/661 (4.7%)	31/379.8 (8.2)		

49


**U.S. Food and Drug Administration**  
 Protecting and Promoting Public Health  
[www.fda.gov](http://www.fda.gov)

## AESI: ANC

Laboratory parameter Criteria n/N1 (%)	Sariilumab		
	Placebo + DMARD (N=579)	150 mg q2w + DMARD (N=579)	200 mg q2w + DMARD (N=582)
<b>Absolute neutrophil count</b>			
Grade 1: $\geq 1.5$ Giga/L - LLN	13/579 (2.2%)	58/579 (10.0%)	82/580 (14.1%)
Grade 2: $\geq 1 - 1.5$ Giga/L	5/579 (0.9%)	51/579 (8.8%)	68/580 (11.7%)
Grade 3: $\geq 0.5 - 1$ Giga/L	0/579	19/579 (3.3%)	30/580 (5.2%)
Grade 4: $< 0.5$ Giga/L	0/579	4/579 (0.7%)	4/580 (0.7%)

50


 U.S. Food and Drug Administration  
 Protecting and Promoting Public Health  
[www.fda.gov](http://www.fda.gov)

## AESI: Elevated AST or ALT

	Placebo + DMARD N=579	Sarilumab 150 mg + DMARD N=579	Sarilumab 200 mg + DMARD N=582
<b>AST (U/L)</b>			
>ULN – 3x ULN	13.3%	25.1%	28%
>3x ULN – 5x ULN	0%	1.4%	1.0%
>5x ULN	0%	0.7%	0.2%
<b>ALT (U/L)</b>			
>ULN – 3x ULN	23.1%	36.2%	41.6%
>3x ULN – 5x ULN	0.7%	2.9%	2.8%
>5x ULN	0%	1.2%	0.7%

51


 U.S. Food and Drug Administration  
 Protecting and Promoting Public Health  
[www.fda.gov](http://www.fda.gov)

## Pediatric Study Plan

<b>Pediatric PK studies</b>			
Age Group	Type of Study		Request for Deferral
2 to ≤ (b) (4) years	(b) (4) PK/PD study in pJIA	To determine appropriate dose based on safety, PK, and pediatric ACR30 in pts with pJIA (b) (4)	Y
(b) (4)			
<b>Pediatric Efficacy and Safety studies</b>			
(b) (4)			
2 to ≤ (b) (4) years	Efficacy study in pJIA (b) (4)	Efficacy (b) (4)	Y
(b) (4)			

52


**U.S. Food and Drug Administration**  
 Protecting and Promoting Public Health  
[www.fda.gov](http://www.fda.gov)

## Pediatric Plan

- iPSP written responses – November 2013
  - **Partial waiver for children <24 months with pJIA**
  - **Deferral for children ages 2-17 years with pJIA**
  - sJIA studies not triggered by PREA
  - Approval of sarilumab for adult RA will trigger PREA requirement for pJIA
  
- iPSP letter of agreement – January 2014

(b) (4)

53


**U.S. Food and Drug Administration**  
 Protecting and Promoting Public Health  
[www.fda.gov](http://www.fda.gov)

## Planned Pediatric Studies

Study	Description
<b>PK studies</b>	
DRI13925	(b) (4) dose-finding study in children (b) (4)
<b>Safety and Efficacy studies</b>	
EFC11783	(b) (4) study to assess efficacy and safety in children (b) (4)

(b) (4)

54

FDA U.S. Food and Drug Administration  
Protecting and Promoting Public Health  
www.fda.gov

**PFS with flange and plunger rod**



(b) (4)

55

The image shows two pieces of medical equipment, specifically Plunger Filter Systems (PFS), against a grey background. Each device consists of a clear plastic plunger rod with a black handle at the top and a white base at the bottom. A colored flange is attached to the middle of the rod. The device on the left has an orange flange, and the device on the right has a red flange. To the right of the image is a large grey rectangular area, likely representing redacted information. The slide includes the FDA logo and name at the top, the title 'PFS with flange and plunger rod', the website 'www.fda.gov', a redaction code '(b) (4)', and the slide number '55' at the bottom.

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

SUZETTE W PENG  
12/23/2015

JANET W MAYNARD  
12/23/2015