# Summary Basis for Regulatory Action

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| From       | Curtis J Rosebraugh, MD, MPH  
Director, Office of Drug Evaluation II |
| Subject    | Summary Review |
| NDA/BLA #  | BLA 761037 |
| Supp #     |              |
| Applicant Name | Sanofi-Aventis U.S. LLC |
| Proprietary / Established (USAN) Names | Kevzara  
Sarilumab |
| Dosage Forms / Strength/Dose | 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 |
| Proposed Indication(s) | 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) |
| Action:    | Approval    |
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 and to the first cycle reviews 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-6Rα) 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.

This resubmission to the original complete response was to address manufacturing issues that were identified during the first review cycle. These issues have been adequately addressed.

The only issue of substance with this cycle of review was how best in labeling to statistically represent the results from study EFC11072 (the radiographic progression study). The issues regarding trial design and how to best represent the results in labeling have been captured adequately in the clinical and statistical reviews. In brief, there was not any disagreement that this study was positive and demonstrated that sarilumab decreased the progression of structural damage as assessed by x-ray and the modified total Sharp Score. Rather, there was a wide range of opinion whether the results should be continued to be represented by linear extrapolation or some other method such as linear mixed effects or all observed data analysis.\(^1\)

All methods have their strengths and weakness and the linear extrapolation method has elements that the statistical group has been evolving beyond which brought this issue to the forefront. Initial consideration between stats and the sponsor around the use of all observed data occurred during the first review cycle, but were never formalized with all the review team as manufacturing deficiencies took precedence. During this cycle however, consideration of the various methods occurred including a discussion of linear mixed effects which occurred rather late in the review cycle. This allowed for only limited internal discussion and limited discussion with the sponsor. After conferring with upper management, it was decided, with agreement from Dr. Permutt, that for this particular application we would continue representing the results with linear extrapolation. This should not be viewed as a validation of this type of method over others but rather a practical acknowledgement that timely consideration and debate of new methods of evaluation is necessary when supplanting one that has been used for years and is typical of an evolutionary process.

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 and the manufacturing issues identified in the

\(^1\) Details of each type of analysis are present in other reviews.
first review cycle have been resolved. Sarilumab will add another option to the armamentarium of health care providers. I recommend an approval action.
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
05/22/2017