

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761037Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # BLA # 761037	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Kevzara Established/Proper Name: sarilumab Dosage Form: injection, prefilled syringes 150 and 200mg		Applicant: sanofi Agent for Applicant (if applicable):
RPM: Christine Ford		Division:
NDA Application Type: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) BLA Application Type: <input type="checkbox"/> 351(k) <input checked="" type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<p><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></p> <ul style="list-style-type: none"> Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <p><input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>notify CDER OND IO</i>) Date of check:</p> <p><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>
❖ Actions		
<ul style="list-style-type: none"> Proposed action User Fee Goal Date is <u>5/22/2017</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> Previous actions (<i>specify type and date for each action taken</i>) 		<input type="checkbox"/> None CR 10/28/16
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		<input type="checkbox"/> Received
❖ Application Characteristics ³		

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority: Standard Priority
 Chemical classification (new NDAs only):
 (*confirm chemical classification at time of approval*)

- | | |
|---|---|
| <input type="checkbox"/> Fast Track | <input type="checkbox"/> Rx-to-OTC full switch |
| <input type="checkbox"/> Rolling Review | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input type="checkbox"/> Orphan drug designation | <input type="checkbox"/> Direct-to-OTC |
| <input type="checkbox"/> Breakthrough Therapy designation | |

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager; Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other required actions: [CST SharePoint](#))

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)
 Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

- Submitted in response to a PMR
 Submitted in response to a PMC
 Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS: MedGuide
 Communication Plan
 ETASU
 MedGuide w/o REMS
 REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
❖ Public communications (<i>approvals only</i>)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
❖ Patent Information (<i>NDAs only</i>)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) CR 10/28/16
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)	<input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input checked="" type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
<ul style="list-style-type: none"> • Most-recent draft labeling 	<input checked="" type="checkbox"/> Included
❖ Proprietary Name	
<ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) 	5/2/17, 6/2/16, 3/31/16, 12/21/15 4/21/17, 6/2/16, 12/18/15
❖ Labeling reviews (<i>indicate dates of reviews</i>)	RPM: <input type="checkbox"/> 10/5/16 DMEPA: <input type="checkbox"/> None 5/15/17, 5/4/17, 9/2/16 DMPP/PLT (DRISK): 5/22/17 (DRISK), 9/29/16 (DMPP) <input type="checkbox"/> None OPDP: <input type="checkbox"/> None 9/28/16 SEALD: <input type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None OBP: <input type="checkbox"/> None 5/8/17, 10/25/16 Other: <input type="checkbox"/> None
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting (<i>indicate date of each review</i>)	Reviewed 9/30/16
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDAs/NDA supplements only: Exclusivity Summary (<i>signed by Division Director</i>)	<input type="checkbox"/> Completed
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	

⁴ Filing reviews for scientific disciplines are NOT required to be included in the action package.

<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director’s Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC 6/15/16 If PeRC review not necessary, explain: _____ 	
❖ Breakthrough Therapy Designation	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> • Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded) 	
<ul style="list-style-type: none"> • CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) 	
<ul style="list-style-type: none"> • CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) <p>(<i>completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site</i>)</p>	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) (<i>do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package</i>)	2017 – 5/19, 5/15, 5/4, 4/21, 4/13 2016 – 12/15, 12/5, 10/20, 10/13, 10/12, 10/7, 9/27, 13, 8 (2), and 7; 8/31, 19, 17, 5, and 2; 7/15, 14, 12, and 1; 6/27, 17, 13, 10, and 1; 5/27, 26, and 23; 4/21, 14, and 7; 3/29, 21, 15, 10, 7, and 3; 2/29, 24, and 17; 1/12 2015 – 12/28 and 12/1; 11/6
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	Safety Outcome Trial subcommittee 7/28/16
❖ Minutes of Meetings	
<ul style="list-style-type: none"> • If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A or no mtg
<ul style="list-style-type: none"> • Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> No mtg 10/22/2014 CMC 12/16/2014
<ul style="list-style-type: none"> • EOP2 meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> No mtg 9/15/2011 CMC 10/26/2011
<ul style="list-style-type: none"> • Mid-cycle Communication (<i>indicate date of mtg</i>) 	<input type="checkbox"/> N/A 4/6/2016
<ul style="list-style-type: none"> • Late-cycle Meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> N/A 9/7/16 follow-up telecon minutes 7/25/2016 LCM 7/13/16 LCM package
<ul style="list-style-type: none"> • Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>) 	End of Review 12/16/16

❖ Advisory Committee Meeting(s) • Date(s) of Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input type="checkbox"/> None 5/22/17, 10/28/2016
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 5/22 and 5/18/17, 10/5/2016
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 5/16/17, 10/3/2016
PMR/PMC Development Templates (<i>indicate total number</i>)	<input type="checkbox"/> None 2 – PREA
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review See CDTL
• Clinical review(s) (<i>indicate date for each review</i>)	5/16/17, 10/4/16, 12/23/15
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	Clinical review 10/4/16 page 442
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>) ⁵	<input type="checkbox"/> None 6/13/16
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> N/A
❖ Risk Management • REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>) • REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) • Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)	10/30/15 <input type="checkbox"/> None 9/29/16
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	<input type="checkbox"/> None requested 9/2, 8/11, and 7/18/16
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review 5/18/17
Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 9/2/16, 12/29/15

⁵ For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see “Section 508 Compliant Documents: Process for Regulatory Project Managers” located in the CST electronic repository).

Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 8/29/16, 12/23/15
❖ OSI Clinical Pharmacology Inspection Review Summary <i>(include copies of OSI letters)</i>	<input checked="" type="checkbox"/> None requested
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> No separate review 10/19/16
• Supervisory Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> No separate review 9/2/16
• Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None 9/22, 9/2, and 8/24/16, 12/16/15
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input type="checkbox"/> None Included in 8/24/16 P/T review, page 49
❖ OSI Nonclinical Inspection Review Summary <i>(include copies of OSI letters)</i>	<input checked="" type="checkbox"/> None requested
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews ⁶	
• Tertiary review <i>(indicate date for each review)</i>	<input type="checkbox"/> None
• Secondary review (e.g., Branch Chief) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 2017- 4/21 2016- 10/24, 10/20, 12/28/15
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team <i>(indicate date of each review)</i>	<input type="checkbox"/> None 2/7/17 and 2016 - 9/14 (2), 8/18, 5/12, 4/14
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	Page 6 of CMC review 10/20/16
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> Facilities inspections (indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation) <i>(only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i>	<input checked="" type="checkbox"/> Acceptable 3/31/2017 Re-evaluation date: <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable

⁶ Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

Day of Approval Activities	
❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) 	<input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>Notify CDER OND IO</i>)
<ul style="list-style-type: none"> • Finalize 505(b)(2) assessment 	<input type="checkbox"/> Done
❖ For Breakthrough Therapy (BT) Designated drugs: <ul style="list-style-type: none"> • Notify the CDER BT Program Manager 	<input type="checkbox"/> Done (<i>Send email to CDER OND IO</i>)
❖ For products that need to be added to the flush list (generally opioids): Flush List <ul style="list-style-type: none"> • Notify the Division of Online Communications, Office of Communications 	<input type="checkbox"/> Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after <i>confirming that applicant received courtesy copy of approval letter</i>	<input checked="" type="checkbox"/> Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input checked="" type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

ELECTRONIC CORRESPONDENCE

Date: May 19, 2017

To: Sarah Feathers, PharmD Global Regulatory Affairs	From: Christine Ford, MS, RPh Regulatory Project Manager
Company: Sanofi-Aventis U.S. LLC	Division of Pulmonary, Allergy, and Rheumatology Products
Phone: 617-768-6099	Fax number: 301-796-9728
Email: sarah.feathers@sanofi.com	Phone number: 301-796-3420

Subject: BLA 761037 sarilumab
FDA labeling comments – Prescribing Information

Total no. of pages including cover: 30

Comments: *Response requested as soon as possible, no later than 9 am May 22, 2017*

Please call or send an email to confirm receipt at christine.ford@fda.hhs.gov

Document to be mailed: YES NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-3420. Thank you.

We refer to BLA 761037 for Kevzara (sarilumab) prefilled syringes and have the following labeling comments. Additional labeling changes may be forthcoming as we continue to review the labeling.

FDA edits were made as tracked changes to your proposed Prescribing Information emailed May 18, 2017. Any additional proposed changes you may have can be made in a similar fashion by using the clean Word version of the attached labeling and edit using tracked changes.

Submit revised draft labeling incorporating the requested changes to me via secure email at christine.ford@fda.hhs.gov as soon as possible, but no later than 9:00 AM Monday, May 22, 2017. Your response will subsequently need to be submitted officially to the BLA.

If you have any questions, please contact Christine Ford at 301-796-3420.

APPEARS THIS WAY ON ORIGINAL

Drafted by: JMaynard, TPermutt, BChowdhury, CRosebraugh/ 5.19.2017
cford/ 5.19.2017

Finalized: thru SBarnes by cford/ 5.19.2017

27 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

CHRISTINE H FORD
05/19/2017



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

ELECTRONIC CORRESPONDENCE

Date: May 15, 2017

To: Sarah Feathers, PharmD Global Regulatory Affairs	From: Christine Ford, MS, RPh Regulatory Project Manager
Company: Sanofi-Aventis U.S. LLC	Division of Pulmonary, Allergy, and Rheumatology Products
Phone: 617-768-6099	Fax number: 301-796-9728
Email: sarah.feathers@sanofi.com	Phone number: 301-796-3420

Subject: BLA 761037 sarilumab
FDA labeling comments – Prescribing Information

Total no. of pages including cover: 31

Comments: *Response requested no later than noon Wednesday, May17, 2017*

Please call or send an email to confirm receipt at christine.ford@fda.hhs.gov

Document to be mailed: YES NO

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If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-3420. Thank you.

We refer to BLA 761037 for Kevzara (sarilumab) prefilled syringes and have the following labeling comments. Additional labeling changes may be forthcoming as we continue to review the labeling.

FDA edits were made as tracked changes to your proposed Prescribing Information submitted March 22, 2017. Any additional proposed changes you may have can be made in a similar fashion by using the clean Word version of the attached labeling and edit using tracked changes.

Submit revised draft labeling incorporating the requested changes to me via secure email at christine.ford@fda.hhs.gov no later than noon May 17, 2017. Your response will subsequently need to be submitted officially to the BLA.

If you have any questions, please contact Christine Ford at 301-796-3420.

APPEARS THIS WAY ON ORIGINAL

Drafted by: SPeng, JMaynard, Yongman Kim, GLevin/ 5.15.2017
cford/ 5.15.2017

Initialed by: SBarnes/ 5.15.2017

Finalized: cford/ 5.15.2017

28 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

CHRISTINE H FORD
05/15/2017



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

ELECTRONIC CORRESPONDENCE

Date: May 4, 2017

To: Sarah Feathers, PharmD Global Regulatory Affairs	From: Christine Ford, MS, RPh Regulatory Project Manager
Company: Sanofi-Aventis U.S. LLC	Division of Pulmonary, Allergy, and Rheumatology Products
Phone: 617-768-6099	Fax number: 301-796-9728
Email: sarah.feathers@sanofi.com	Phone number: 301-796-3420

Subject: BLA 761037 sarilumab
FDA request for information – Statistics

Total no. of pages including cover: 3

Comments: *Information requested no later than Monday, May 8,2017*

Please call or send an email to confirm receipt at christine.ford@fda.hhs.gov

Document to be mailed: YES NO

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BLA 761037 for sarilumab prefilled syringes is currently under review, and we have the following request for information:

We have had additional internal discussions regarding the most appropriate way to evaluate treatment effects on radiographic progression. We believe there is some potential utility in an analysis that attempts to evaluate the following estimand: the mean difference in mTSS change per year between sarilumab and placebo in all randomized patients in a setting where placebo patients do not receive escape therapy. We request that you carry out an additional analysis that targets this estimand with a more appropriate methodology than the previously implemented linear extrapolation approach. The new results might be considered for inclusion in labeling instead of the results based on all observed data (including data collected after escape on all treatment arms).

We recommend that you utilize a linear mixed effects model that includes all radiographic data observed prior to escape (+14 days), including such data collected at any time point during the 52-week double-blind period. Patient data on the placebo arm after escape (+14 days) should be considered missing. Observed patient data on both sarilumab arms after escape should be included in the analysis. The model should include as covariates: time (study day of x-ray / 365.25), treatment, treatment-by-time interaction, region, and prior biologic use. The treatment-by-time interaction coefficients for the two sarilumab dosing regimens represent differences in slopes (differences in mean changes per year) versus placebo and are of primary interest. This analysis still relies on strong and unverifiable assumptions (e.g., that missing values after escape in placebo patients who escape are similar to observed values in placebo patients who do not escape, conditional on a linear model of the baseline covariates and the time of the x-ray, and the observed value prior to escape). However, it more appropriately handles statistical uncertainty (presuming the assumptions hold) than the single-imputation linear extrapolation approach.

Submit results from the analysis and any datasets and programming code used to generate the results.

The requested information should be submitted as official responses to the BLA no later than Monday, May 8, 2017. If you have any questions, please contact Christine Ford at 301-796-3420.

Drafted by: Yongman Kim, GLevin/ 5.4.2017
Thru: JMaynard, BChowdhury/ 5.4.2017

Initialed by: SBarnes/ 5.4.2017

Finalized: cford/ 5.4.2017

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/s/

CHRISTINE H FORD
05/04/2017



BLA 761037

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Sanofi-Aventis U.S. LLC
c/o Genzyme, a Sanofi Company
500 Kendall St.
Cambridge, MA 02142

ATTENTION: Sarah Feathers, PharmD
Global Regulatory Lead

Dear Dr. Feathers:

Please refer to your Biologics License Application (BLA) dated and received March 22, 2017, submitted under section 351(a) of the Public Health Service Act for Sarilumab, 150 mg/1.14 mL and 200 mg/1.14 mL.

We also refer to your correspondence, dated and received March 22, 2017, requesting review of your proposed proprietary name, Kevzara.

We have completed our review of the proposed proprietary name, Kevzara and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your March 22, 2017 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review. Additionally, if your application receives a complete response, a new request for name review for your proposed name should be submitted when you respond to the application deficiencies.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,
(<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Michael Sinks, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-2684. For any other information regarding this application, contact Christine Ford, Regulatory Project Manager in the Office of New Drugs, at (301) 796-3420.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

DANIELLE M HARRIS on behalf of TODD D BRIDGES
05/02/2017



BLA 761037

**ACKNOWLEDGE -
CLASS 1 COMPLETE RESPONSE**

Sanofi US Services Inc.
55 Corporate Drive
Bridgewater, NJ 08807

Attention: Sarah Feathers, PharmD
Global Regulatory Affairs

Dear Dr. Feathers:

We have received your resubmission to your biologics license application submitted under section 351(a) of the Public Health Service Act for sarilumab on March 22, 2017.

We consider this resubmission a complete, class 1 response to our action letter. Therefore, the user fee goal date is May 22, 2017.

If you have any questions, call me at (301) 796-3420.

Sincerely,

{See appended electronic signature page}

Christine Ford, MS, RPh
CAPT, U.S. Public Health Service
Sr. Regulatory Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

CHRISTINE H FORD
04/21/2017

Ford, Christine

From: Ford, Christine
Sent: Thursday, April 13, 2017 5:06 PM
To: Sarah.Feathers@sanofi.com
Cc: Ford, Christine
Subject: Request for information: BLA 761037 sarilumab

Dear Sarah,
BLA 761037 for sarilumab and your submission dated 3/22/2017 is under review, and we have the following request for information.

We note that in study EFC11072 patients randomized to the placebo group could have remained on placebo for up to 52 weeks. We acknowledge that there were provisions for escape during the study, but note that during the study, approximately 49.2% of patients remained on placebo for 52 weeks. Please justify that the patients who remained on placebo for 52 weeks in the study were provided treatment appropriate and consistent with the severity of their disease and acceptable at the time the study was done.

Please confirm receipt of this information request, and provide an official response to the BLA as soon as possible but no later than 2 weeks from receipt of this request.

If you have any questions, please contact me at 301-796-3420. Thank you for your cooperation.

Regards,
Christine

Christine Ford, MS, RPh
CAPT, USPHS
Sr. Regulatory Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products
FDA/CDER/OND/ODE II
Phone 301-796-3420
Fax 301-796-9728
christine.ford@fda.hhs.gov

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/s/

CHRISTINE H FORD
04/13/2017



BLA 761037

MEETING MINUTES

Sanofi US Services Inc.
55 Corporate Drive
Bridgewater, NJ 08807

Attention: Sarah Feathers, PharmD
Global Regulatory Affairs

Dear Dr. Feathers:

Please refer to your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act for Kevzara (sarilumab) injection, 150 mg/1.14 mL and 200 mg/1.14 mL prefilled syringes.

We also refer to the telecon between representatives of your firm and the FDA on December 16, 2016. The purpose of the meeting was to discuss requirements for a complete BLA resubmission.

A copy of the official minutes of the telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-3420.

Sincerely,

{See appended electronic signature page}

Christine Ford, MS, RPh
CAPT, U.S. Public Health Service
Sr. Regulatory Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type A
Meeting Category: End of Review Conference

Meeting Date and Time: December 16, 2016 2:30 – 3:30 PM
Meeting Location: Teleconference

Application Number: BLA 761037
Product Name: Kevzara (sarilumab)
Indication: Rheumatoid arthritis (RA)
Sponsor/Applicant Name: Sanofi US Services Inc. (Sanofi)

Meeting Chair: Dr. Badrul Chowdhury, Director
Meeting Recorder: Christine Ford, Regulatory Project Manager

FDA ATTENDEES:

Badrul A. Chowdhury, MD, PhD, Director, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Janet Maynard, MD, MHS, Clinical Team Leader, DPARP
Suzette Peng, MD, Clinical Reviewer, DPARP
Nona Colburn, MD, Clinical Reviewer, DPARP
Christine Ford, MS, RPh, Regulatory Project Manager, DPARP
Gregory Levin, PhD, Biometrics Team Leader, Division of Biometrics II (DBII)
Yongman Kim, PhD, Biometrics Reviewer DBII
Michele Dougherty, PhD, Application Team Lead, Division of Biotechnology Review and Research IV (DBRRIV)
Gerald Feldman, PhD, Product Quality Reviewer, DBRRIV
Anshu Marathe, PhD, Team Leader, Division of Clinical Pharmacology II (DCPII)
Jianmeng Chen, PhD, Clinical Pharmacology Reviewer, DCPII
Mishale Mistry, PharmD, MPH, Team Leader, Division of Medication Error & Prevention Analysis (DMEPA)
Teresa Mcmillan, PharmD, Safety Evaluator, DMEPA
Peter Qiu, PhD, Branch Chief, Inspectional Assessment Branch I (IABI), Office of Process and Facilities (OPF)
Laura Fontan, Consumer Safety Officer, IABI/OPF
Kennerly Chapman, PhD, Deputy Director for Management & Operations, Office of Manufacturing Quality (OMQ)/Office of Compliance (OC)
Milind Ganjawala, Acting Director, Division of Drug Quality II/OMQ/OC

SPONSOR ATTENDEES:

Sanofi:

Jonathan Sadeh – Global Project Head
Claudia Pena-Rossi – Clinical Lead
Rachpal Malhotra – Pharmacovigilance
Alex Boddy – Lead Statistician
Nia Tatsis – Regulatory Head, Sanofi-Genzyme
Barry Sickles – Regulatory Head, North America
Clive Brading – Head of Quality Compliance
Sarah Feathers – Global Regulatory Lead

Regeneron:

Neil Graham – Program lead
Janie Parrino - Clinical Lead
Ned Braunstein Regulatory Head
Patricia Riley – Regulatory Lead

Background:

Following a Complete Response action on October 28, 2016, Sanofi requested a Type A meeting to discuss requirements for a complete BLA resubmission.

After review of the briefing package, FDA sent preliminary responses to Sanofi's questions in an emailed letter dated December 15, 2016. Sanofi emailed areas for additional discussion are incorporated into the body of the minutes as well as provided as an Attachment at the end of the minutes.

Below are the applicant's questions from the briefing package in *italics*; FDA's responses (meeting preliminary comments) in normal font; and Sanofi's December 15, 2016, emailed responses also noted in *italics*. A summary of meeting discussions, if any, are found in **bold normal font** following the specific area of discussion.

QUESTIONS AND RESPONSES

Question 1

The sponsor is requesting a full waiver of the safety update requirement pursuant to CFR 314.90, as the CRL for BLA761037 is based on manufacturing issues. No deficiencies pertaining to safety were identified during the review and the planned DSUR will provide sufficient new safety information learned about the drug that may reasonably affect the statement of contraindications, warnings, precautions, and adverse reactions in the draft labeling. Does the Agency Agree?

FDA response:

As noted in the Complete Response letter dated October 28, 2016, include a safety update as part of any future resubmission. If the planned DSUR will provide sufficient new safety information learned about the drug that may reasonably affect the statement of

contraindications, warnings, precautions, and adverse reactions in the draft labeling, it would be reasonable to cross reference the DSUR in the resubmission.

Sanofi's 12/15/16 emailed response:

Attached is a brief summary of the content of the sarilumab DSUR. We would like to confirm that the content of the DSUR is sufficient to facilitate acceptance of the application.

We recognize that information requests for additional safety analyses may occur during review of the resubmission.

Discussion:

FDA stated that Sanofi's DSUR proposal is acceptable.

Question 2

- a) *Does the Agency agree this proposed resubmission constitutes a complete response addressing all deficiencies noted in the CRL and is sufficient to support review and approval of BLA761037?*

FDA response:

Your responses to the deficiencies noted in the Complete Response Letter (CRL) will be assessed during the review of the resubmission. A pre-license inspection at the drug production manufacturing site will be required to confirm that deficiencies have been addressed.

Sanofi's 12/15/16 emailed response:

We seek to understand the most expeditious strategy for submission and timing for sarilumab BLA761037. Specifically in light of the prior approval inspection scheduled (b) (4) (which will inspect (b) (4) for sarilumab)

Discussion:

Sanofi asked if the Agency could specify what would be inspected during the required prior approval inspection (PAI).

FDA stated that, as long as there are no changes to manufacturing, the PAI would focus (b) (4) for sarilumab; one inspection for both sarilumab and (b) (4) would also be considered.

Sanofi confirmed that no manufacturing changes are planned.

In response to Sanofi's inquiry, FDA responded that, although the regulatory decision will be made after receipt, the BLA resubmission submitted after a favorable PAI result and no manufacturing changes may qualify as a Class 1 resubmission. Refer to CDER MAPP 6020 at the following website:

<http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/ucm082002.pdf>

- b) *Does the Agency agree pursuant to SOPP 8405.1 and MAPP 6020.4 the response to BLA 761037 CRL would be classified as a Type 1 resubmission with a 2-month review clock?*

FDA response:

The classification of the resubmission will be made after preliminary review of the resubmission. A favorable prior approval facility(ies) inspection recommendation is needed. Therefore, if you plan to submit your response to the CRL by December 30, 2016, as proposed in your meeting package, it would be classified as a Class 2 resubmission.

Question 3

Provided a Type 1 resubmission is granted, can the Agency accommodate a proprietary name request review within the 60 day Type 1 resubmission timeline?

FDA response:

We will make an effort to accommodate your timeline. However, there is no guarantee that the proprietary name request will be reviewed within 60 days.

Question 4 - Labeling

[REDACTED] (b) (4)
As such, the sponsor requests to maintain the statement as originally submitted 26 Oct 2016. Does the Agency agree?

FDA response:

We are concerned [REDACTED] (b) (4)
While inclusion of specific information in the prescribing information will be a review issue, we have concerns with inclusion of the proposed statement.

Sanofi's 12/15/16 emailed response:

We wish to further discuss the Agency's comments regarding radiographic data in the sarilumab label.

Discussion:

Sanofi noted [REDACTED] (b) (4)

FDA expressed understanding [REDACTED] (b) (4)
Currently, the sarilumab label does show radiographic results (u) (4)

(b) (4)

The Agency's intent is to present information that would be the most clear and helpful for prescribers.

Sanofi responded that they will consider FDA's comments and have additional internal discussions.

Sanofi's 12/15/16 emailed response:

We seek to understand next steps for resubmission (b) (4)

Discussion:

Sanofi stated that (b) (4) was denied (b) (4) and was informed that they do not need to resubmit the request. They requested confirmation that (b) (4) does not have to be resubmitted with the BLA resubmission.

FDA responded that they will provide clarification with the minutes of the telecon.

POST-MEETING CLARIFICATION:

(b) (4)

ISSUES REQUIRING FURTHER DISCUSSION:

There were no issues requiring further discussion.

ATTACHMENTS AND HANDOUTS:

Sanofi's December 15, 2016, emailed responses to FDA's meeting preliminary comments begin on the next page.

Ford, Christine

Subject: FW: Meeting preliminary comments BLA 761037 sarilumab type A meeting
Attachments: DSUR Summary_12_15_2016.docx

From: Sarah.Feathers@genzyme.com [<mailto:Sarah.Feathers@genzyme.com>]
Sent: Thursday, December 15, 2016 8:29 PM
To: Ford, Christine
Subject: RE: Meeting preliminary comments BLA 761037 sarilumab type A meeting

Hi Christine,

In preparation for tomorrow's meeting we would like to further discuss the following topics:

- We seek to understand the most expeditious strategy for submission and timing for sarilumab BLA761037. Specifically in light of the prior approval inspection scheduled (b) (4) (which will inspect (b) (4) for sarilumab)
- Attached is a brief summary of the content of the sarilumab DSUR. We would like to confirm that the content of the DSUR is sufficient to facilitate acceptance of the application.
 - o We recognize that information requests for additional safety analyses may occur during review of the resubmission.
- We wish to further discuss the Agency's comments regarding radiographic data in the sarilumab label
- We seek to understand next steps for resubmission (b) (4)

We appreciate the Agency's time and look forward to the discussion tomorrow. Please feel free to reach out should you or your team have any questions.

Kindly,
Sarah

Sarah Feathers, PharmD

Global Regulatory Affairs

Genzyme center, 500 Kendall Street, Cambridge, MA – 02142 |

Tel: +1 617-768-6099 | cell: (b) (6)

Email: sarah.feathers@genzyme.com



From: Ford, Christine [<mailto:Christine.Ford@fda.hhs.gov>]
Sent: Thursday, December 15, 2016 11:04 AM
To: Feathers, Sarah GZ/US
Cc: Ford, Christine
Subject: Meeting preliminary comments BLA 761037 sarilumab type A meeting
Importance: High

Hi Sarah,
Please see attached courtesy copy of the meeting comments and confirm receipt.
Let me know if you have any questions. thanks! c

Christine Ford, MS, RPh
CAPT, USPHS
Sr. Regulatory Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products
FDA/CDER/OND/ODE II
Phone 301-796-3420
Fax 301-796-9728
christine.ford@fda.hhs.gov

DSUR Content Summary

The 6th annual Development Safety Update Report (DSUR) for sarilumab summarizes safety data received from 15 November 2015 to 14 November 2016 from all nonclinical and clinical studies for all indications (rheumatoid arthritis, (b) (4)). The DSUR is compiled in accordance with the International Council on Harmonization (ICH) E2F guideline.

Cumulative data are provided for 3836 patients with Rheumatoid Arthritis. (b) (4)

Two studies were completed during the reporting period, a Phase 1 study in Japanese patients with RA and the extension phase of study MSC12665 (autoinjector usability). Ongoing studies include open-label extensions of sarilumab in patients with RA, Japanese studies in RA (b) (4)

Based on the clinical development program, important identified risks for sarilumab are serious infections and hypersensitivity reactions. The important potential risks for sarilumab are as follows: increased risk of infection secondary to neutropenia; thrombocytopenia and potential risk of bleeding; clinically evident hepatic injury; impact on CV outcome (major adverse cardiovascular events) secondary to LDL elevation; gastrointestinal perforations; and malignancy. The risk of hypersensitivity reactions was added to the risks during this reporting period. All risks are currently described in the proposed USPI.

Evaluation of the data for the DSUR did not reveal additional safety findings that would warrant modification of the proposed USPI.

A table of contents is provided below to summarize the key data and tables planned for inclusion in the DSUR. All DSUR sections, tables and appendices in accordance with ICH E2F will be included. US specific regional appendices will also be included.

APPEARS THIS WAY ON ORIGINAL

Summary Table of Contents

INVENTORY OF CLINICAL TRIALS ONGOING AND COMPLETED DURING THE REPORTING PERIOD

ESTIMATED CUMULATIVE EXPOSURE

ESTIMATED CUMULATIVE SUBJECT EXPOSURE IN THE DEVELOPMENT PROGRAM

Cumulative exposure in RA patients or healthy subjects in Phase 1 studies

Cumulative exposure in RA patients in Phase 2 and 3 studies

Cumulative exposure in patients (b) (4)

Cumulative exposure in patients (b) (4)

DATA IN LINE LISTINGS AND SUMMARY TABULATIONS

Line Listing of Serious Adverse Reactions in Phase 1 Clinical Studies during the reporting period

Line-Listing of Serious Adverse Reactions in Rheumatoid Arthritis Studies*

Line-Listing of Serious Adverse Reactions in (b) (4) Studies*

Line-Listing of Serious Adverse Reactions in (b) (4) Study

Cumulative Summary Tabulation of Serious Adverse Events in Phase 1 Clinical Studies

Cumulative Summary Tabulation of Serious Adverse Events in Rheumatoid Arthritis Studies*

Cumulative Summary Tabulation of Serious Adverse Events in (b) (4) Studies*

Cumulative Summary Tabulation of Serious Adverse Events in (b) (4) Study

Tabulation of Serious Adverse Reactions in (b) (4) study

Cumulative summary tabulations of demographic data

Cumulative summary tabulation of serious adverse reactions

List of subjects who died during the reporting period

List of subjects who dropped out of study treatment in association with adverse events during the reporting period

NON-CLINICAL DATA

SUMMARY OF IMPORTANT RISKS

CONCLUSIONS

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/s/

CHRISTINE H FORD
01/13/2017



BLA 761037

MEETING PRELIMINARY COMMENTS

Sanofi US Services Inc.
55 Corporate Drive
Bridgewater, NJ 08807

Attention: Sarah Feathers, PharmD
Global Regulatory Affairs

Dear Dr. Feathers:

Please refer to your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act for Kevzara (sarilumab) injection, 150 mg/1.14 mL and 200 mg/1.14 mL prefilled syringes.

We also refer to your November 21, 2016, correspondence requesting a Type A meeting to discuss requirements for a complete BLA resubmission.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

If you have any questions, call me at (301) 796-3420.

Sincerely,

{See appended electronic signature page}

Christine Ford, MS, RPh
CAPT, U.S. Public Health Service
Sr. Regulatory Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type: Type A
Meeting Category: End of Review Conference

Meeting Date and Time: December 16, 2016 2:30 – 3:30 PM
Meeting Location: Teleconference

Application Number: BLA 761037
Product Name: Kevzara (sarilumab)
Indication: Rheumatoid arthritis (RA)
Sponsor/Applicant Name: Sanofi US Services Inc. (Sanofi)

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the teleconference scheduled for December 16, 2016, between Sanofi and the Division of Pulmonary, Allergy, and Rheumatology Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Contact the RPM if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

Background:

Following a Complete Response action on October 28, 2016, Sanofi requested a Type A meeting to discuss requirements for a complete BLA resubmission.

QUESTIONS AND PRELIMINARY RESPONSES

Sanofi 's questions in *italics font* are followed by the Agency's responses in normal font.

Question 1

The sponsor is requesting a full waiver of the safety update requirement pursuant to CFR 314.90, as the CRL for BLA761037 is based on manufacturing issues. No deficiencies pertaining to safety were identified during the review and the planned DSUR will provide sufficient new safety information learned about the drug that may reasonably affect the statement of contraindications, warnings, precautions, and adverse reactions in the draft labeling. Does the Agency Agree?

FDA response:

As noted in the Complete Response letter dated October 28, 2016, include a safety update as part of any future resubmission. If the planned DSUR will provide sufficient new safety information learned about the drug that may reasonably affect the statement of contraindications, warnings, precautions, and adverse reactions in the draft labeling, it would be reasonable to cross reference the DSUR in the resubmission.

Question 2

a) Does the Agency agree this proposed resubmission constitutes a complete response addressing all deficiencies noted in the CRL and is sufficient to support review and approval of BLA761037?

FDA response:

Your responses to the deficiencies noted in the Complete Response Letter (CRL) will be assessed during the review of the resubmission. A pre-license inspection at the drug production manufacturing site will be required to confirm that deficiencies have been addressed.

b) Does the Agency agree pursuant to SOPP 8405.1 and MAPP 6020.4 the response to BLA 761037 CRL would be classified as a Type 1 resubmission with a 2-month review clock?

FDA response:

The classification of the resubmission will be made after preliminary review of the resubmission. A favorable prior approval facility(ies) inspection recommendation is needed. Therefore, if you plan to submit your response to the CRL by December 30, 2016, as proposed in your meeting package, it would be classified as a Class 2 resubmission.

Question 3

Provided a Type 1 resubmission is granted, can the Agency accommodate a proprietary name request review within the 60 day Type 1 resubmission timeline?

FDA response:

We will make an effort to accommodate your timeline. However, there is no guarantee that the proprietary name request will be reviewed within 60 days.

Question 4 - Labeling

(b) (4)

(b) (4)

Does the Agency agree?

FDA response:

We are concerned

(b) (4)

While inclusion of specific information in the prescribing information will be a review issue, we have concerns with inclusion of the proposed statement.

APPEARS THIS WAY ON ORIGINAL

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/s/

CHRISTINE H FORD
12/15/2016



BLA 761037

MEETING REQUEST GRANTED

Sanofi US Services Inc.
55 Corporate Drive
Bridgewater, NJ 08807

Attention: Sarah Feathers, PharmD
Global Regulatory Affairs

Dear Dr. Feathers:

Please refer to your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act for Kevzara (sarilumab) injection, 150 mg/1.14 mL and 200 mg/1.14 mL prefilled syringes.

We also refer to your November 21, 2016, correspondence requesting a Type A meeting to discuss requirements for a complete BLA resubmission. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type A meeting.

The teleconference is scheduled as follows:

Date: Friday, December 16, 2016
Time: 2:30 – 3:30 PM
Phone Arrangements: Please provide a CALL-IN NUMBER and PASSCODE to the FDA

CDER Participants:

Badrul A. Chowdhury, MD, PhD, Director, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Sarah Yim, MD, Supervisory Associate Director, DPARP
Janet Maynard, MD, MHS, Clinical Team Leader, DPARP
Suzette Peng, MD, Clinical Reviewer, DPARP
Christine Ford, MS, RPh, Regulatory Project Manager, DPARP
Gregory Levin, PhD, Biometrics Team Leader, Division of Biometrics II (DBII)
Yongman Kim, PhD, Biometrics Reviewer DBII
Michele Dougherty, PhD, Application Team Lead, Division of Biotechnology Review and Research IV (DBRRIV)
Gerald Feldman, PhD, Product Quality Reviewer, DBRRIV
Anshu Marathe, PhD, Team Leader, Division of Clinical Pharmacology II (DCPII)
Jianmeng Chen, PhD, Clinical Pharmacology Reviewer, DCPII
Teresa Mcmillan, PharmD, Safety Evaluator, Division of Medication Error & Prevention Analysis (DMEPA)
Representative(s) from Division of Inspectional Assessment (DIA), Office of Compliance

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

We acknowledge receipt of the meeting package included with the meeting request. We also acknowledge receipt of the desk copies of the meeting package. If the materials presented in the meeting package are inadequate to prepare for the meeting, we may cancel or reschedule the meeting.

If you have any questions, call me at (301) 796-3420.

Sincerely,

{See appended electronic signature page}

Christine Ford, MS, RPh
CAPT, U.S. Public Health Service
Sr. Regulatory Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

CHRISTINE H FORD
12/05/2016



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

ELECTRONIC CORRESPONDENCE

Date: October 20, 2016

To: Sarah Feathers, PharmD Global Regulatory Affairs	From: Christine Ford, MS, RPh Regulatory Project Manager
Company: Sanofi-Aventis U.S. LLC	Division of Pulmonary, Allergy, and Rheumatology Products
Phone: 617-768-6099	Fax number: 301-796-9728
Email: sarah.feathers@genzyme.com	Phone number: 301-796-3420

Subject: BLA 761037 sarilumab
FDA labeling comments – Prescribing Information, Medication Guide, IFU

Total no. of pages including cover: 51

Comments: *Response requested no later than October 26, 2016*

Please call or send an email to confirm receipt at christine.ford@fda.hhs.gov

Document to be mailed: YES NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-3420. Thank you.

We refer to BLA 761037 for Kevzara (sarilumab) prefilled syringes and have the following labeling comments. Additional labeling changes may be forthcoming as we continue to review the labeling.

FDA edits were made as tracked changes to your proposed Prescribing Information submitted September 23, 2016. Any additional proposed changes you may have can be made in a similar fashion by using the clean Word version of the attached labeling and edit using tracked changes.

Submit revised draft labeling incorporating the requested changes to me via secure email at christine.ford@fda.hhs.gov no later than October 26, 2016. Your response will subsequently need to be submitted officially to the BLA.

If you have any questions, please contact Christine Ford at 301-796-3420.

APPEARS THIS WAY ON ORIGINAL



Drafted by: review team via sharepoint/ 10.20.2016
cford/ 10.20.2016

Initialed by: SBarnes/ 10.20.2016

Finalized: cford/ 10.20.2016

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/s/

CHRISTINE H FORD
10/20/2016



BLA 761037

INFORMATION REQUEST

Sanofi-aventis U.S. LLC
Attention: Sarah Feathers, Pharm.D.
Global Regulatory Lead
55 Corporate Drive, Mail Stop 55D-220B
Bridgewater, NJ 08807

Dear Dr. Feathers:

Please refer to your Biologics License Application (sBLA) dated and received October 30, 2015, submitted under section 351(a) of the Public Health Service Act for sarilumab (SAR153191/REGN88).

We are reviewing your submission and have the following request for information. We request a prompt written response in order to continue our evaluation of your application.

We do not accept that [REDACTED] ^{(b) (4)} could be permitted in the event of a process deviation unless a pre-existing protocol was in place for such a case. Said protocol should include data to (including stability data) support any specific [REDACTED] ^{(b) (4)} step demonstrating minimal impact on product quality.

If you have questions, call me, at (301) 796-0906.

Sincerely,

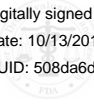
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Melinda Bauerlien, M.S.
Senior Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



Melinda
Bauerlien

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Date: 10/13/2016 01:09:44PM
GUID: 508da6dc0002676de5faf5b4bf3d0f72



Ford, Christine

From: Ford, Christine
Sent: Wednesday, October 12, 2016 4:37 PM
To: 'Sarah.Feathers@genzyme.com'
Cc: Ford, Christine
Subject: Labeling comment: BLA 761037 sarilumab

Dear Sarah,

We refer to BLA 761037 for sarilumab and have the following comment regarding your revised carton labeling submitted on September 21, 2016.

We note you added the strength per mL on the carton labeling so that the strength presentations appear as 150 mg/1.14 mL (131.6 mg/mL) and 200 mg/1.14 mL (^{(b) (4)} mg/mL). However for the 200 mg/1.14 mL prefilled syringe (PFS), 175.4 mg/mL appears more accurate. We recommend revising the strength per mL to 175.4 mg/mL for the 200 mg PFS. Submit revised carton labeling to the BLA no later than October 17, 2016.

Kindly confirm receipt of this information request and contact me at 301-796-3420 if you have any questions. Thank you for your cooperation.

Regards,
Christine

Christine Ford, MS, RPh
CAPT, USPHS
Sr. Regulatory Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products
FDA/CDER/OND/ODE II
Phone 301-796-3420
Fax 301-796-9728
christine.ford@fda.hhs.gov

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/s/

CHRISTINE H FORD
10/12/2016



BLA 761037

INFORMATION REQUEST

Sanofi-aventis U.S. LLC
Attention: Sarah Feathers, Pharm.D.
Global Regulatory Lead
55 Corporate Drive, Mail Stop 55D-220B
Bridgewater, NJ 08807

Dear Dr. Feathers:

Please refer to your Biologics License Application (sBLA) dated and received October 30, 2015, submitted under section 351(a) of the Public Health Service Act for sarilumab (SAR153191/REGN88).

We are reviewing your submission and have the following request for information. We request a prompt written response by COB October 12, 2016 in order to continue our evaluation of your application.

In Section 3.2.S.2.2 you state that (b) (4) is not permitted under this BLA. However, there is nothing to restrict (b) (4). Indicate under what circumstances, if any, (b) (4) may occur, and provide the protocol supporting that activity.

If you have questions, call me, at (301) 796-0906.

Sincerely,

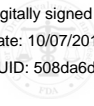
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Melinda Bauerlien, M.S.
Senior Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



Melinda
Bauerlien

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BLA 761037

INFORMATION REQUEST

Sanofi-aventis U.S. LLC
Attention: Sarah Feathers, Pharm.D.
Global Regulatory Lead
55 Corporate Drive, Mail Stop 55D-220B
Bridgewater, NJ 08807

Dear Dr. Feathers:

Please refer to your Biologics License Application (sBLA) dated and received October 30, 2015, submitted under section 351(a) of the Public Health Service Act for sarilumab (SAR153191/REGN88).

We are reviewing your submission and have the following request for information. We request a prompt written response by COB September 30, 2016 in order to continue our evaluation of your application.

With regard to your submission Amendment No. 0031; Sequence No. 0031 dated 07/21/2016, in your response to Item #3 you agreed to revise the (b) (4) limit (b) (4) as this limit is supported by full scale production data.

Furthermore, in your response to Item #11 of this submission you agreed to revise SOP QC3758 to reflect that future primary reference standards will only be qualified according to the qualification protocol in the SOP and that future primary reference standards can only be qualified against the existing primary reference standard.

We appreciate these agreements but note that the BLA has not been amended accordingly. Please revise and update the appropriate sections of the BLA as agreed upon in this submission.

If you have questions, call me, at (301) 796-0906.

Sincerely,

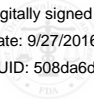
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Melinda Bauerlien, M.S.
Senior Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



Melinda
Bauerlien

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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

ELECTRONIC CORRESPONDENCE

Date: September 13, 2016

To: Sarah Feathers, PharmD Global Regulatory Affairs	From: Christine Ford, MS, RPh Regulatory Project Manager
Company: Sanofi-Aventis U.S. LLC	Division of Pulmonary, Allergy, and Rheumatology Products
Phone: 617-768-6099	Fax number: 301-796-9728
Email: sarah.feathers@genzyme.com	Phone number: 301-796-3420

Subject: BLA 761037 sarilumab
FDA labeling comments – Prescribing Information, Carton and container

Total no. of pages including cover: 35

Comments: *Response requested no later than September 20, 2016*

Please call or send an email to confirm receipt at christine.ford@fda.hhs.gov

Document to be mailed: YES NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-3420. Thank you.

We refer to BLA 761037 for Kevzara (sarilumab) prefilled syringes and have the following labeling comments. Additional labeling changes may be forthcoming as we continue to review the labeling.

FDA edits were made as tracked changes to your proposed Prescribing Information submitted March 16, 2016. Any additional proposed changes you may have can be made in a similar fashion by using the clean Word version of the attached labeling and edit using tracked changes.

The following are comments regarding your proposed labeling submitted March 16 and June 14, 2016.

A. All Labels and Labeling (Container Labels and Carton Labeling)

The NDC number is denoted by a placeholder (XXXXXX -XXXX-XX). Submit the actual NDC number and ensure that the middle 4 digits (XXXX) are different between the strengths.

B. Carton Labeling

1. Remove (b) (4) wherever presented.
2. The strength statement is not presented consistently in accordance with USP General Chapter <1>. Wherever presented, the strength statement should be as follows:

150 mg/1.14 mL or 200 mg/1.14 mL

3. We note the instructions for use (IFU) states to use the syringe within 14 days after taking it out of the refrigerator; however, the carton labeling lacks this information. Additionally, there is no method for end-users to track when they removed the product from refrigerator storage. Therefore, revise the storage instructions to include room temperature storage instructions.

Store in a refrigerator at 36°F to 46°F (2°C to 8°C) in the original carton to protect from light. Do NOT freeze. Do NOT shake.

If needed, patients/caregivers may store KEVZARA at room temperature up to 77°F (25°C) up to 14 days in the outer carton. Do not store above 77°F (25°C). After removal from the refrigerator, use KEVZARA within 14 days or discard.

Date removed from the refrigerator ___/___/___.

4. Revise the list of ingredients to state the volume delivered and the milligram amounts of each ingredient. For example:

Each prefilled syringe delivers 1.14 mL of solution containing 150 mg sarilumab, arginine (8.94 mg), histidine (3.71 mg), polysorbate 20 (2.28 mg), sucrose (57 mg) and Water for Injection, USP.

Submit revised draft labeling incorporating the requested changes to me via secure email at christine.ford@fda.hhs.gov no later than September 20, 2016. Your response will subsequently need to be submitted officially to the BLA.

If you have any questions, please contact Christine Ford at 301-796-3420.

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Drafted by: review team via sharepoint/ 9.9.2016
cford/ 9.9.2016

Initialed by: ARamsey for SBarnes/ 9.12.2016; 9.13.2016
SPeng, JMaynard/ 9.12.2016
ESalicru, TRobison/ 9.12.2016
JMChen, AMarathe/ 9.12.2016
YMKim, GLevin/ 9.12.2016
OBP – GFeldman, FMills, MDougherty/ 9.12.2016
JAbdus-Samad/ 9.13.2016
TMcmillan, MMistry/ 9.13.2016

Finalized: cford/ 9.13.2016

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/s/

CHRISTINE H FORD
09/13/2016



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

ELECTRONIC CORRESPONDENCE

Date: September 8, 2016

To: Sarah Feathers, PharmD Global Regulatory Affairs	From: Christine Ford, MS, RPh Regulatory Project Manager
Company: Sanofi-Aventis U.S. LLC	Division of Pulmonary, Allergy, and Rheumatology Products
Phone: 617-768-6099	Fax number: 301-796-9728
Email: sarah.feathers@genzyme.com	Phone number: 301-796-3420

Subject: BLA 761037 sarilumab
FDA request for information: Postmarketing commitments – Product Quality

Total no. of pages including cover: 3

Comments: *Response requested no later than September 16, 2016*

Please call or send an email to confirm receipt at christine.ford@fda.hhs.gov

Document to be mailed: YES NO

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We refer to BLA 761037 for sarilumab and request your agreement to fulfill the following as postmarketing commitments and completion of the milestone timelines (Final Report Submission dates). In addition, provide a brief rationale for the proposed milestone timelines.

Quality Postmarketing commitments (PMC)



Submit your response to me via secure email at christine.ford@fda.hhs.gov no later than COB September 16, 2016. Your response will subsequently need to be submitted officially to the BLA. If you have any questions, please contact me at 301-796-3420.

APPEARS THIS WAY ON ORIGINAL

Drafted by: FMills, GFeldman, MDougherty/ 9.6.2016
SSeymour/ 9.7.2016
cford/ 9.8.2016

Initialed by: SBarnes/ 9.8.2016
SSeymour/ 9.8.2016

Finalized: cford/ 9.8.2016

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/s/

CHRISTINE H FORD
09/08/2016



BLA 761037

INFORMATION REQUEST

Sanofi-aventis U.S. LLC
Attention: Sarah Feathers, Pharm.D.
Global Regulatory Lead
55 Corporate Drive, Mail Stop 55D-220B
Bridgewater, NJ 08807

Dear Dr. Feathers:

Please refer to your Biologics License Application (sBLA) dated and received October 30, 2015, submitted under section 351(a) of the Public Health Service Act for sarilumab (SAR153191/REGN88).

We are reviewing your submission and have the following request for information. We request a prompt written response by COB September 12, 2016 in order to continue our evaluation of your application.

With regard to your transfer of analytical tests between sites:

- Since the analytical tests for reduced and non-reduced CE-SDS and SE-HPLC have been demonstrated to be stability-indicating, the transfer exercise for these assays should include an assessment of stability samples to confirm that the assay performs comparably at the receiving site to detect changes in product quality. Provide data demonstrating that at the receiving site these assays can detect changes in product quality that are due to conditions that have been demonstrated to induce product degradation.
- For all assays where comparative testing is performed using DS (b) (4) samples, provide all assay results from both the sending and receiving sites.
- In your transfer study for the CEX-HPLC assay, you report (b) (4) results (b) (4) based on the analysis of 3 DS lots. The (b) (4) results (b) (4) are deemed acceptable based in part on your observation (b) (4) however, (b) (4) the rationale for accepting these results is no longer valid and do not appear to support the transfer of the assay.

If you have questions, call me, at (301) 796-0906.

Sincerely,

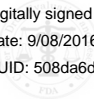
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Melinda Bauerlien, M.S.
Senior Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



Melinda
Bauerlien

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MEMORANDUM OF TELECONFERENCE

Teleconference Date: August 10, 2016

Application Number: BLA 761037

Product Name: Kevzara (sarilumab) prefilled syringes

Sponsor/Applicant Name: Sanofi US Services Inc.

Indication: Rheumatoid arthritis

Subject: Follow-up to Late-cycle meeting regarding lipid effects

FDA Participants:

Badrul Chowdhury, MD, PhD, Director, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

Sally Seymour, MD, Deputy Director of Safety, DPARP

Janet Maynard, MD, MHS, Clinical Team Leader, DPARP

Suzette Peng, MD, Clinical Reviewer, DPARP

Yongman Kim, PhD, Biometrics Reviewer, Division of Biometrics II

Christine Ford, Regulatory Project Manager, DPARP

Applicant representatives:

Sanofi

Jonathan Sadeh, Global Project Lead

Nancy Liu, Statistician

Yong Lin, Clinical Lead

Rachpal Malhotra, Pharmacovigilance

Sarah Feathers, Regulatory Lead

Nia Tatsis, Head Regulatory Sanofi Genzyme

Mike Halpin, Head, NA Region Regulatory Sanofi Genzyme Products

Regeneron

Janet Van Adelsberg, Clinical Lead

Janie Parrino, Clinical

Pat Reilly, Regulatory Lead

Ned Braunstein, Head of Regulatory

BACKGROUND:

BLA 761037 for sarilumab in treatment of rheumatoid arthritis is currently under FDA review. During the late-cycle meeting, FDA indicated that internal discussions were occurring regarding the need for additional postmarketing data given the observed increases in lipid parameters, such as LDL cholesterol, HDL cholesterol, and triglycerides, with sarilumab use. This was the follow-up teleconference to convey the Agency's current thinking regarding the need for additional postmarketing safety data.

DISCUSSION:

FDA stated that, after internal discussions, the Agency did not plan to require a cardiovascular outcomes trial for sarilumab. Although not expected to change, the applicant will be notified if there is any alteration from this plan. However, it was noted that there are ongoing studies evaluating cardiovascular outcomes in the setting of treatment with drugs approved for rheumatoid arthritis. Sanofi should note that the outcomes from these studies may have potential implications for their product. If data generated from these ongoing studies indicate significant safety concerns or other negative outcomes, there may be labeling ramifications for sarilumab or additional studies may be required for sarilumab.

Sanofi indicated that they understood the FDA's position and did not have any questions.

The teleconference was then concluded.

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/s/

CHRISTINE H FORD
09/07/2016



BLA 761037

INFORMATION REQUEST

Sanofi-aventis U.S. LLC
Attention: Sarah Feathers, Pharm.D.
Global Regulatory Lead
55 Corporate Drive, Mail Stop 55D-220B
Bridgewater, NJ 08807

Dear Dr. Feathers:

Please refer to your Biologics License Application (sBLA) dated and received October 30, 2015, submitted under section 351(a) of the Public Health Service Act for sarilumab (SAR153191/REGN88).

We are reviewing your submission and have the following request for information. We request a prompt written response by COB September 8, 2016 in order to continue our evaluation of your application.

Please update section P.3.4 Control of critical steps and intermediates and other relevant sections

(b) (4)

If you have questions, call me, at (301) 796-0906.

Sincerely,

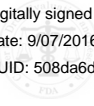
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Melinda Bauerlien, M.S.
Senior Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



Melinda
Bauerlien

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BLA 761037

INFORMATION REQUEST

Sanofi-aventis U.S. LLC
Attention: Sarah Feathers, Pharm.D.
Global Regulatory Lead
55 Corporate Drive, Mail Stop 55D-220B
Bridgewater, NJ 08807

Dear Dr. Feathers:

Please refer to your Biologics License Application (sBLA) dated and received October 30, 2015, submitted under section 351(a) of the Public Health Service Act for sarilumab (SAR153191/REGN88).

We are reviewing your submission and have the following request for information. We request a prompt written response by September 2, 2016 in order to continue our evaluation of your application.

FDA comments on firm's response submitted in Sequence # 0035 to the information request dated 17-Aug-2016:

We acknowledge your clarification

(b) (4)

If you have questions, call me, at (301) 796-0906.

Sincerely,

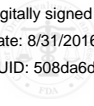
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Melinda Bauerlien, M.S.
Senior Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



Melinda
Bauerlien

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BLA 761037

INFORMATION REQUEST

Sanofi-aventis U.S. LLC
Attention: Sarah Feathers, Pharm.D.
Global Regulatory Lead
55 Corporate Drive, Mail Stop 55D-220B
Bridgewater, NJ 08807

Dear Dr. Feathers:

Please refer to your Biologics License Application (sBLA) dated and received October 30, 2015, submitted under section 351(a) of the Public Health Service Act for sarilumab (SAR153191/REGN88).

We are reviewing your submission and have the following request for information. We request a prompt written response by September 2, 2016 in order to continue our evaluation of your application.

- A review of your (b) (4) records identified (b) (4) were outside the acceptance range for this assay ((b) (4) % of reference standard). Provide an explanation (b) (4)

If you have questions, call me, at (301) 796-0906.

Sincerely,

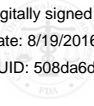
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Senior Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
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Melinda
Bauerlien

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BLA 761037

INFORMATION REQUEST


Sanofi-aventis U.S. LLC
Attention: Sarah Feathers, Pharm.D.
Global Regulatory Lead
55 Corporate Drive, Mail Stop 55D-220B
Bridgewater, NJ 08807

Dear Dr. Feathers:

Please refer to your Biologics License Application (sBLA) dated and received October 30, 2015, submitted under section 351(a) of the Public Health Service Act for sarilumab (SAR153191/REGN88).



We are reviewing your submission and have the following request for information. We request a prompt written response by August 23, 2016 in order to continue our evaluation of your application.

1.

 (b) (4)
The data may be provided as a PMC

study report.

2.

 (b) (4)
Please re-define  (b) (4)

If you have questions, call me, at (301) 796-0906.

Sincerely,

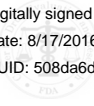
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Senior Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



Melinda
Bauerlien

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BLA 761037

INFORMATION REQUEST

Sanofi-aventis U.S. LLC
Attention: Sarah Feathers, Pharm.D.
Global Regulatory Lead
55 Corporate Drive, Mail Stop 55D-220B
Bridgewater, NJ 08807

Dear Dr. Feathers:

Please refer to your Biologics License Application (sBLA) dated and received October 30, 2015, submitted under section 351(a) of the Public Health Service Act for sarilumab (SAR153191/REGN88).

We are reviewing your submission and have the following request for information. We request a prompt written response by August 10, 2016 in order to continue our evaluation of your application.

1. The proposed in-process limit [REDACTED] ^{(b) (4)} is high ^{(b) (4)}
[REDACTED] Please tighten the in-process limit [REDACTED] ^{(b) (4)} and revise sections 3.2.P.3 and 3.2.P.4 with the revised in-process limit [REDACTED] ^{(b) (4)}
2. As per Table 1 in Section 3.2.P.3.1, PFS sarilumab release testing for sterility is performed at Sanofi Winthrop Industrie [REDACTED] ^{(b) (4)} Please submit method qualification information and data to support sarilumab sterility testing [REDACTED] ^{(b) (4)}
3. In Sanofi's endotoxin method qualification report, the MVD calculations are based on a ^{(b) (4)} EU/mg specification instead of the ^{(b) (4)} EU/mg release specification. In addition, Table 1 ("MVD Calculations") incorrectly lists the MVD for the 131.6mg/mL product as ^{(b) (4)} and for the 175.0 mg/mL product as ^{(b) (4)} Please provide updated MVD calculations and correct the table accordingly.
4. Please provide the following information regarding the simulated shipping validation performed as per ASTM D4169-9.
 - a. Indicate the number of product-filled syringes which were tested for endotoxin, container closure integrity, and plunger position.
 - b. Indicate the number of media-filled syringes which were tested for sterility.
5. Please provide the simulated shipping conditions that were used for the plunger movement study which was performed to demonstrate that the sterility of sarilumab drug product will not be compromised during air transportation.

6. Section P.3.4, 4.4.1 [REDACTED] ^{(b) (4)} states that bioburden sampling for routine manufacturing will be performed [REDACTED] ^{(b) (4)} Please indicate the exact sampling point [REDACTED] ^{(b) (4)}

If you have questions, call me, at (301) 796-0906.

Sincerely,

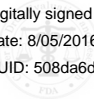
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Senior Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



Melinda
Bauerlien

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Date: 8/05/2016 06:08:45AM
GUID: 508da6dc0002676de5faf5b4bf3d0f72





BLA 761037

INFORMATION REQUEST

Sanofi-aventis U.S. LLC
Attention: Sarah Feathers, Pharm.D.
Global Regulatory Lead
55 Corporate Drive, Mail Stop 55D-220B
Bridgewater, NJ 08807

Dear Dr. Feathers:

Please refer to your Biologics License Application (sBLA) dated and received October 30, 2015, submitted under section 351(a) of the Public Health Service Act for sarilumab (SAR153191/REGN88).

We are reviewing your submission and have the following request for information. We request a prompt written response by August 18, 2016 in order to continue our evaluation of your application.

1. The BLA includes in Section 3.2.S.2.3 Control of Material, in the Working Cell Bank document in section 3, a description of the protocol (b) (4).
Confirm that the protocol described utilizes (b) (4).
Update the protocol to include an assessment of the quality attributes, with appropriate acceptance criteria, (b) (4).
2. We note that the sarilumab (b) (4) is assayed (b) (4).
Provide a risk assessment to evaluate the risk of using a (b) (4) assay (b) (4).
The assessment should consider risks including, but not limited to, (b) (4) raw materials used in your manufacturing process, raw material testing requirements, the sensitivity of your assay to detect specific viruses that may have been introduced (b) (4).

If you have questions, call me, at (301) 796-0906.

Sincerely,

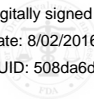
{See appended electronic signature page}

Melinda Bauerlien, M.S.
Senior Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



Melinda
Bauerlien

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CDER Medical Policy Council Safety Outcome Trial Subcommittee
July 28, 2016

Subcommittee Members:

Robert Temple, Chair
John Jenkins, OND
Curtis Rosebraugh, OND
Donna Griebel, OND
Ellis Unger, OND
Norman Stockbridge, OND
Jean-Marc Guettier, OND

Leonard Sacks, OMP
Karim Calis, OMP
Mwango Kashoki, OND
David Moeny, OSE
Mat Soukup, OB
Sally Seymour, OND
Melina Griffis, Executive Secretary

Attendees:

Badrul Chowdhury, OND
Mary Parks, OND
Sarah Yim, OND
Janet Maynard, OND
Suzette Peng, OND
Mary Robert, OND

Raj Nair, OND
Yongman Kim, OB
Gregory Levin, OB
Lisa LaVange, OB

Application: BLA 761037; sarilumab

Background

Members of the Division of Pulmonary, Allergy, and Rheumatology Products presented a summary of the primary safety data in the sarilumab application. In addition, information was presented related to previous regulatory actions taken by the Division for drug products of similar action and safety profile (please refer to the attached memorandum for specific detail). Below is the specific question presented to the committee for discussion.

Question for SOT Committee:

Would the committee recommend a cardiovascular outcomes trial based on small imbalances in cardiovascular events observed in the clinical trial data and recognizing that similar post-marketing trials have been requested for other rheumatoid arthritis products that cause elevations in lipid parameters?

Discussion: Based on the current safety profile of sarilumab, a majority of committee members were not in favor of recommending a cardiovascular outcomes trial. 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. Additionally, the committee discussed the current PMR for tocilizumab, another IL-6 inhibitor that has a similar effect on lipids and questioned why the Division would not apply the same principles when requiring a PMR for sarilumab. A few committee members were in favor of consistent policy and recommended a CVOT for sarilumab unless the Division was prepared to release the PMR for tocilizumab. The

Division was not in favor of recommending a CVOT for several reasons as outlined in the background document. Below is the specific vote of each committee member and any corresponding comments:

Robert Temple- No, study feasibility is a concern.

John Jenkins- recusal due to supervisor role

Curtis Rosebraugh- recusal due to supervisor role

Donna Griebel- Yes, unless the Division was prepared to release the current PMR for tocilizumab.

Ellis Unger- No; would consider releasing PMR for tocilizumab (though it might not be ethical to stop the trial)

Norman Stockbridge- No, current safety data base does not show a signal.

Jean-Marc Guettier-Yes

Leonard Sacks- No

Karim Calis- No, primarily because of feasibility concerns.

Mwango Kashoki-No, if Division was prepared to release the current PMR for tocilizumab.

David Money- No, study feasibility and conduct is a concern.

Mat Soukup- No

Sally Seymour- No

Action Items: None

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BRIEFING MEMORANDUM

Date: July 13, 2016

From: Division of Pulmonary, Allergy, and Rheumatology Products
Office of New Drugs

To: Members of the Safety Outcomes Trials Subcommittee

Re: Potential Cardiovascular Outcomes Trial for sarilumab (BLA 761037)

Objectives of the Meeting

To obtain input from the Safety Outcomes Trials (SOT) Subcommittee on whether a cardiovascular outcome trial (CVOT) should be a postmarketing requirement (PMR) for sarilumab based on small imbalances in cardiovascular events observed in the clinical trial data and recognizing that similar trials have been requested for other rheumatoid arthritis products that cause elevations in lipid parameters

A. Executive Summary

The primary question for this meeting is whether you would recommend a cardiovascular outcomes trial based on small imbalances in cardiovascular events observed in the clinical trial data and recognizing that similar post-marketing trials have been requested for other rheumatoid arthritis products that cause elevations in lipid parameters. Sarilumab is a monoclonal antibody to the interleukin-6 (IL-6) receptor. As background, a previous biologic approved on January 8, 2010, with the same mechanism of action (tocilizumab, Actemra®) was required to perform a cardiovascular outcomes trial to assess whether the lipid abnormalities seen premarketing are associated with an increased risk of cardiovascular thromboembolic events. In the pre-marketing tocilizumab studies, there was not an imbalance in myocardial infarctions or strokes compared to controls. Similar to tocilizumab, sarilumab is associated with elevations in lipid parameters.

As additional background, tofacitinib (a small molecule oral JAK-inhibitor) was approved on November 6, 2012 and was required to perform a controlled clinical trial to evaluate the long-term safety of tofacitinib in patients with rheumatoid arthritis. The trial was powered based on a targeted number of MACE events and a targeted number of malignancies. While the

mechanism of action of tofacitinib is different than sarilumab, tofacitinib was associated with elevations in lipid parameters. The exposure-adjusted incidence of MACE in the RA phase 3 studies was similar in the tofacitinib treatment arms compared to placebo.

The primary safety data in the sarilumab application are derived from two randomized, double-blind placebo controlled studies: EFC11072 and EFC10832 in 1,740 patients. Study EFC11072 Part A was a phase 2 study that included 242 patients. There were 5 additional studies that also inform safety. Similar to other programs in rheumatoid arthritis, the placebo controlled period of the pivotal studies was limited to 12-16 weeks, after which patients could receive sarilumab as rescue therapy for ongoing disease activity. In addition, patients could receive sarilumab in an uncontrolled, long-term extension and dose modifications could occur for laboratory abnormalities. Given these complexities, including cross-over between treatment arms, modifications in dose, and lack of a comparator in the long-term study, there are limitations in the interpretation of the safety data after the placebo-controlled period.

For the safety analyses, Pool 1 is comprised of patients from the placebo-controlled studies, EFC11072 and EFC10832, who received sarilumab (doses of 150 mg q2w or 200 mg q2w) or placebo. Pool 1a is a subset of Pool 1. It only includes patients from the phase 3 placebo-controlled population (EFC11072 Part B Cohort 2 and EFC10832). The safety analyses for Pool 1a focus on the pre-rescue period for both studies (0-16 weeks for EFC11072 and 0-12 weeks for EFC10832).

In the clinical program, sarilumab exposure was associated with increases in lipid parameters. At Week 4, the mean increase in LDL was 12 mg/dL and 16 mg/dL, the mean increase in HDL was 3 mg/dL and 3 mg/dL, and the mean increase in triglycerides was 19 mg/dL and 27 mg/dL for the 150 mg and 200 mg dose groups, respectively. Thus, there appeared to be a dose response for elevations in LDL and triglycerides. The increases in lipid parameters are similar to what was observed in the tocilizumab and tofacitinib programs.

In Pool 1a, for the pre-rescue period, there were 582 patients in the 200 mg sarilumab group, 579 patients in the 150 mg sarilumab group, and 579 patients in the placebo group. There was 1 MACE (primary: CV death, myocardial infarction, stroke, or hospitalization for unstable angina or transient ischemic attack) in each of the sarilumab treatment groups (150 mg and 200 mg) and 0 events in the placebo group in the (Pool 1a) analysis. This yields cumulative incidence proportions of 0.2%, 0.2%, and 0% for the sarilumab 200 mg, 150 mg, and placebo arms. The estimated risk difference between sarilumab 200 mg and placebo was 0.2% (95% CI: -0.2%, 0.5%). The estimated difference between sarilumab 150 mg and placebo was also 0.2% (95% CI: -0.2%, 0.5%). Of note, these results were similar for Pool 1.

The applicant also carried out additional analyses in Pool 2, which includes the long-term safety population. There are limitations in interpretation of these analyses because of the lack of a comparator group and the greater exposure to 200 mg compared to 150 mg. Nevertheless, the analyses also include more follow-up time and, therefore, more events. There were 12, 2, and 28 events on sarilumab 200 mg, 150 mg, and any sarilumab dose for incidence rates per 100 person-years of 0.7, 0.3, and 0.6, respectively.

The primary question for this meeting is whether you would recommend a cardiovascular outcomes trial based on these data. Recognizing that similar post-marketing trials have been requested for other rheumatoid arthritis products that cause elevations in lipid parameters, the Division does not recommend requiring a cardiovascular outcomes trial.

Division's Rationale for Not Recommending a Cardiovascular Outcomes Trial

The Division's rationale for not recommending a cardiovascular outcomes trial is based on three primary factors. First, the clinical implication of mild elevations in lipid parameters is unclear. Further, while sarilumab is associated with increases in lipid parameters, it is also associated with decreased systemic inflammation. Rheumatoid arthritis is associated with increased risk of cardiovascular disease, related not only to traditional cardiovascular risk factors, but also a chronic inflammatory state. It is hypothesized that decreased systemic inflammation leads to decreased cardiovascular risk and clinical trials are exploring this hypothesis. Sarilumab is associated with marked reductions in systemic inflammation, as measured by c-reactive protein (CRP) levels. While there is clearly a link between lipid elevations and cardiovascular disease, there are other factors that impact cardiovascular risk and sarilumab's reduction in systemic inflammation is notable. Second, there was only a small numerical imbalance in cardiovascular events in the placebo-controlled portion of the phase 3 trials and the incidence of cardiovascular events was low overall. In the placebo-controlled population, no events were observed in the placebo group and 2 events of MACE were observed in each treatment group (incidence rate [95% CI] in each treatment group: 0.5 [0.05, 1.63]). This incidence rate is lower than published background rates in the RA population. Third, there was no indication that the risk of MACE events increased with longer duration of exposure as the exposure-adjusted incidence rates for adjudicated MACE for any dose of sarilumab were stable in the long-term safety population. Of note, the data with sarilumab are very similar to tocilizumab, which was required to perform a cardiovascular outcomes trial. Clinical trials with tocilizumab did not show an imbalance in cardiovascular events, but did demonstrate elevations in lipid parameters. Tocilizumab was the first IL-6 inhibitor approved and it was approved when there were significant concerns about cardiovascular disease. Based on post-marketing safety data and multiple years of experience with tocilizumab and other IL-6 inhibitors, there is less cardiovascular concern. There is an ongoing cardiovascular outcomes study, which will help us confirm that there is not a cardiovascular risk with tocilizumab. If the tocilizumab cardiovascular outcomes trial shows positive findings of concern, we can consider this a new safety concern and ask sarilumab to perform a cardiovascular outcomes trial at a later date. Given these factors and considerations, the Division does not recommend a cardiovascular outcomes trial for sarilumab.

B. Background

Sarilumab is a fully human IgG1 monoclonal antibody to the IL-6 receptor (IL-6R). Sanofi submitted a biologic license application (BLA) for sarilumab in October 2015, and the PDUFA goal date is October 30, 2016. Sanofi's proposed indication is 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 drug (DMARD). Of note, patients RA have an increased prevalence of atherosclerotic coronary artery disease compared to the general population. It is postulated that the presence of chronic inflammation in RA may enhance the development of atherosclerosis. It is hypothesized that treatment of underlying inflammation and disease activity may decrease the risk of atherosclerosis.

Tocilizumab

Tocilizumab (Actemra) has the same mechanism of action as sarilumab, as it is a humanized monoclonal antibody to IL-6R. It was first approved by the FDA in January 2010 for the treatment of moderately to severely active RA. It is currently also approved for polyarticular juvenile idiopathic arthritis (pJIA) and systemic JIA (sJIA). During the review of tocilizumab's original BLA, it was noted that treatment with tocilizumab resulted in mild-to-moderate increases in all lipid parameters. The division's analysis of the sponsor's data, however, did not appear to reveal an increased risk of myocardial infarction during the time frame of the clinical trials (24 weeks) or the long-term extension. Both DMEP and DCRP were consulted at the time to provide an opinion on a potential cardiovascular risk associated with the lipid parameter changes. Both divisions had similar conclusions. First, it would be difficult to "predict net cardiovascular risk on the basis of drug-associated lipid increases due to multiple and complex effects of drugs." "An appropriately designed, adequately powered cardiovascular outcome study would provide the most definitive answer to the question of cardiovascular risk." DMEP suggested that the required sample sizes for a non-inferiority outcome trial comparing the incidence of MACE in patients on DMARDs and patients on tocilizumab + DMARDs would need to be very large. However, given concerns regarding the risks of serious cardiovascular events, a post-marketing cardiovascular outcome trial was required. Specifically, the division required a randomized, controlled trial to rule out a moderate increase in the risk of serious cardiovascular events with tocilizumab, e.g., stroke, non-fatal MI, cardiovascular death. Hoffmann-LaRoche's study WA25204 (a clinical outcomes study to evaluate the effects of IL-6 receptor blockade with TCZ in comparison with etanercept on the rate of cardiovascular events in patients with moderate to severe RA) has completed enrollment with 3,080 patients. The study will be completed on 2/28/18 and final study report is anticipated on 2/28/19.

Tofacitinib

Tofacitinib, a JAK-inhibitor, is a small molecule medication that was approved for RA in November 2012. Although it has a different mechanism of action compared to sarilumab, it also causes an elevation in lipid parameters. At the time of approval, the FDA required Pfizer to perform a controlled clinical trial to evaluate the long-term safety of tofacitinib in patients with RA. (b) (4)

Sarilumab

Thus far, in the review of BLA 761,037, it is noted that sarilumab is also associated with an elevation in all lipid parameters. In the double-blind period, there is a small imbalance in cardiovascular events with sarilumab compared to placebo. The pertinent data from the sarilumab development program are provided below.

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C. Sarilumab Pivotal Trials

The development program for sarilumab is extensive. Table 1 displays all the trials that are relevant to BLA 761,037. EFC11072 Part B and EFC10832 are the pivotal studies and provide the primary support for efficacy. All the studies in Table 1 are included by the applicant to support sarilumab's safety. For the purpose of our question to the SOT subcommittee, trials EFC11072 Parts A and B, EFC10832, and LTS11210 are most relevant, are highlighted in yellow in Table 1, and are further discussed below.

Table 1. 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
Phase 2 Study							
EFC11072 Part A (MOBILITY)	Randomized, double-blind, placebo-controlled, dose-ranging study	Sarilumab SC 100mg qw 150mg qw 100mg q2w 150mg q2w 200mg q2w Placebo SC qw	% of patients who achieved ACR20 at Week 12	12 weeks	306 randomized 305 treated 270 completed	Patients with RA receiving MTX	Completed
101 centers initiated Worldwide							
ACT11575	Multicenter, multinational, randomized, double-blind, parallel-group, placebo- and active-controlled study	Sarilumab SC 150mg qw 150mg q2w Golimumab SC 50 mg q4w PBO SC qw		12 weeks	16 randomized 16 treated 13 completed	Patients with RA who do not respond to ≤ 2 TNF α blockers	Terminated early due to study delays
10 centers USA							
Phase 3 Studies							
EFC11072 Part B (SARIL-RA-MOBILITY)	Multicenter, randomized, double-blind, parallel-group,	Cohort 1: Sarilumab SC 100mg qw	ACR20 response at Week 24 Change from	52 weeks Rescue	1369 randomized 1366 treated	Patients with RA receiving MTX	Completed

199 centers Worldwide	placebo-controlled study	150mg q2w 100mg q2w 150mg q2w 200mg q2w PBO SC qw Cohort 2: Sarilumab SC 150mg q2w 200mg q2w PBO SC q2w	baseline in HAQ-DI at Week 16 Change in mTSS at Week 52	assessment at Week 16	1020 completed		
EFC10832 (SARIL-RA-TARGET) 240 centers Worldwide	3-arm, multicenter, randomized, double-blind, parallel group, placebo-controlled 24-week study	Sarilumab SC 150mg q2w 200mg q2w PBO SC	ACR20 response rate at Week 24 Change from baseline in HAQ-DI at Week 12	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- α and who receiving a non-biologic DMARD	Completed
LTS11210 (SARIL-RA-EXTEND) 334 centers Worldwide	Multicenter, multinational, open-label, uncontrolled long-term study	Sarilumab SC 150mg q2w 200mg q2w 150mg qw All doses adjusted to 200mg q2w after pivotal dose selection	Primary objective: to evaluate long-term safety of sarilumab in patients with RA Secondary objective: to evaluate long-term efficacy	\leq 5 years from first treatment in initial study	1998 randomized 1998 treated 1558 completed	Patients with RA who completed or transferred from 5 other sarilumab trials	Ongoing

SFY13370 (SARIL-RA-ASCERTAIN) 68 centers Worldwide	Randomized, double-blind, double-dummy, parallel group, 3-arm, 24-week, active comparator controlled study	Sarilumab SC 150mg q2w 200mg q2w PBO SC q2w Tocilizumab IV 20mg/ml q4w PBO IV q4w	Primary objective: to assess safety of sarilumab and tocilizumab in patients with RA	24 weeks	202 randomized 202 treated 184 completed	Patients with RA who are inadequate responders to or intolerant of TNF α antagonists	Completed
EFC13752 (SARIL-RA-ONE) 28 centers Worldwide	Multicenter, worldwide, randomized, open-label, parallel-group, 2-arm, study	Sarilumab SC 150mg q2w 200mg q2w	Primary objective: immunogenicity Secondary objective: safety through Week 24	24 weeks	132 randomized 132 treated 116 completed	Patients with RA who are inadequate responders to or are intolerant of ≥ 1 nonbiologic DMARD	Completed
EFC11574 (SARIL-RA-COMPARE) 228 centers Worldwide	Three-arm, multicenter, multinational, double-blind, double-dummy, parallel-group, active comparator controlled study	Sarilumab SC 150mg q2w 200mg q2w PBO SC q2w Etanercept SC 50mg qw PBO SC qw	Change from baseline in DAS28-CRP at Week 24 <i>(Not analyzed because of study termination)</i> Safety	Randomized phase: 24 weeks Substudy phase: 52 weeks	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
MSC12665 (SARIL-RA-EASY)	Multicenter, worldwide, randomized, open-	Sarilumab (autoinjector) SC 150mg q2w	Number of validated AI-associated	12 weeks Extension	217 randomized 217 treated	Patients with RA who are candidates	Ongoing

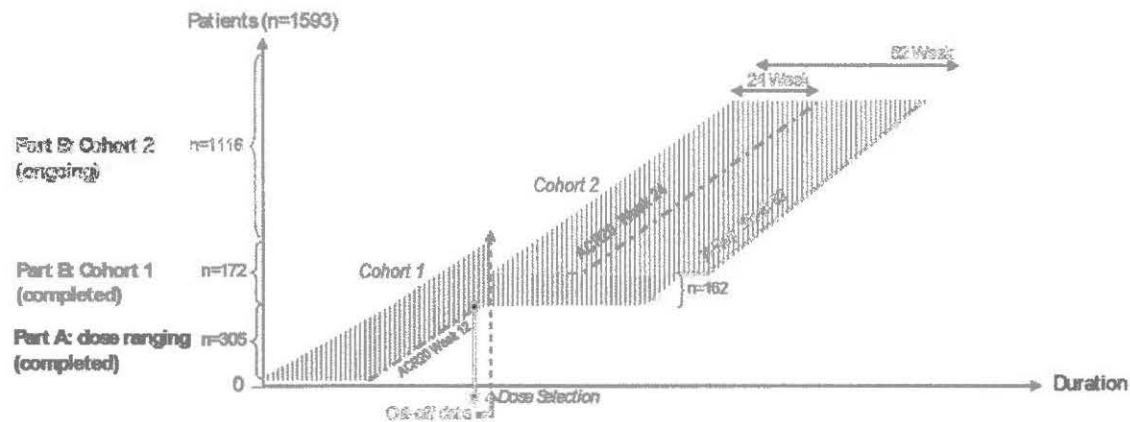
57 centers Worldwide	label, parallel-group, 4-arm, 12-week study followed by a 1-year open-label extension phase	200mg q2w Sarilumab (pre-filled syringe) SC 150mg q2w 200mg q2w	product technical failures	phase: 52 weeks	201 completed	for anti-IL6R therapy receiving ≥1 nonbiologic DMARD	
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EFC11072 was a randomized, double-blind, placebo-controlled, multicenter, two-part, dose-ranging, and confirmatory study. Part A was the phase 2 dose-ranging study. It was a 12-week study, evaluating 6 treatment arms of sarilumab + methotrexate (MTX) (5 active dose regimens and placebo). The doses studied were 100mg qw, 150mg qw, 100mg q2w, 150mg q2w, and 200mg q2w. The primary endpoint was proportion of subjects who achieved ACR20 at Week 12. Patients from Part A did not participate in Part B of the study. Patients, who completed Part A and were eligible, then entered the open-label, long-term extension study LTS11210. Based on the data from Part A, 2 doses of sarilumab were selected to be further studied in Part B.

Part B was a 52-week study intended to confirm the efficacy and safety of the 2 dose regimens (150mg q2w and 200mg q2w) selected from Part A. The study started as a 6-arm study (Cohort 1), during which subjects were randomly assigned to receive placebo q2w, sarilumab 100mg qw, sarilumab 150mg qw, sarilumab 100mg q2w, sarilumab 150mg q2w, or sarilumab 200mg q2w. Once the results of 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. Patients receiving the non-selected doses in Cohort 1 could enter the open-label study LTS11210. Patients on the selected doses in Cohort 1 remained blinded. In addition, patients were recruited for Cohort 2 and were randomly assigned to receive placebo q2w, sarilumab 150mg q2w, or sarilumab 200mg q2w. Figure 1 ~~Figure 1~~ is a schematic that shows the transition from Part A to Part B Cohorts 1 and then Cohort 2.

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Figure 1. Graphic of EFC11072 Parts A and B



Study EFC11072 Part B, Cohort 2 is one of the pivotal studies to support efficacy. Starting at Week 16, patients with a lack of efficacy, defined as less than 20% improvement compared to baseline in swollen joint count or tender joint counts for 2 consecutive visits, or any other clear lack of efficacy based on Investigator judgment, could be “rescued” by permitting the patient to take open-label sarilumab at the highest available dose at the time of transfer to the rescue treatment arm. Rescued patients continued in the study according to their planned visit schedule. Patients, who met lack of efficacy criteria but were not rescued, were discontinued from the study. The maximum duration of study per patient was 62 weeks (4 weeks for screening, 52 weeks for treatment, and 6 weeks for follow-up). The applicant had 3 “co-primary” endpoints: (1) incidence of ACR 20 response at Week 24, (2) change from baseline in HAQ-DI at Week 16, and (3) change from baseline in mTSS at Week 52. All patients who completed Part B and were eligible could enter open-label study LTS11210.

EFC10832 is the second pivotal study for sarilumab. Overall, the study design is similar to EFC11072 Part B, Cohort 2. Important differences include some baseline patient characteristics, the timing of rescue therapy, the duration of study, and the efficacy endpoints. Subjects in study EFC11072 were inadequate responders to MTX therapy, whereas subjects in study EFC10832 were inadequate responders or intolerant of TNF- α antagonists. The assessment for lack of efficacy in

EFC10832 began at Week 12 onwards. Subjects who were rescued could receive open-label sarilumab in long-term safety study LTS11210. The total maximum duration of participation for a patient was 34 weeks (4 weeks screening, 24 weeks double-blind treatment, and 6 weeks post-treatment follow-up). The co-primary endpoints were (1) incidence of ACR20 response at Week 24 and (2) change from baseline in the HAQ-DI at Week 12.

The last study for the subcommittee to consider is LTS11210, an ongoing, multicenter open-label, long-term study. Subjects could be enrolled from the following studies: ACT11575, EFC11072, EFC10832, SFY13370, and EFC13752. Upon enrollment in the open-label study, subjects initially received 150mg qw, which was the highest dose studied prior to the phase 3 dose selection. Once the dose regimens were selected, the highest dose was 200mg q2w. Therefore, new enrolled subjects received 200mg q2w. Patients who were already enrolled were switched to 200mg q2w. All enrolled subjects could reduce the dose to 150mg q2w if he/she developed neutropenia, thrombocytopenia, or an increase in liver enzymes (ALT).

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D. Safety Data Pooling Strategy

For the analysis of safety, the applicant pooled the data from the studies in Table 1 into 3 major groups. The applicant's pooling strategy is summarized below in Table 2.

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Table 2. Summary of safety population

Pool and Population	Treatment Group (n)	Studies (Treatment Duration)
Pool 1 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) ^a EFC10832 (24 weeks)
Pool 1a 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) ^a EFC10832 (24 weeks)
Pool 2 Sarilumab + DMARD long-term safety population	150mg q2w initial dose + DMARD ^b (n=1155) 200mg q2w initial dose + DMARD ^b (n=1351) Any sarilumab dose + DMARD ^c (n=2887)	EFC11072 Part A (12 weeks) EFC11072 Part B (52 weeks) EFC10832 (24 weeks) SFY13370 (24 weeks) EFC11574 main study ^d (24 weeks) EFC11574 substudy ^d (52 weeks) MSC12665 (52 weeks) LTS11210 ^e (5 years)
Pool 3 Sarilumab monotherapy population	150mg q2w initial dose ^b (n=65) 200mg q2w initial dose ^b (n=67) Any sarilumab dose (n=132)	EFC13752 (24 weeks) LTS11210 ^f (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

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 are 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 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).

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.

Analysis of safety is particularly complicated for sarilumab because of the design of the studies 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.

To address the complicated study design, the applicant provides a few additional analyses in addition to standard analyses. These include the following:

- 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). The “pre-rescue period” is defined as 0-16 weeks for EFC11072 Part B and 0-12 weeks for EFC10832. 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 0-12, 0-24, and 0-52 weeks. For example, for the 0-12 week sensitivity analyses, the analyses were performed on the randomized patients and the rescued patients who were within the first 12 weeks of treatment with the given regimen.
- 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 analysis conducted separately 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.

For this briefing document, most of the safety analysis will be presented for Pool 1a with a focus on the pre-rescue period and, thus, represents the data least affected by the variable dosing regimens. In addition, we will review the long-term safety population, exposure-adjusted analyses, sensitivity analyses, and model-based analyses for cardiovascular events. Pool 3 (sarilumab monotherapy) will not be presented.

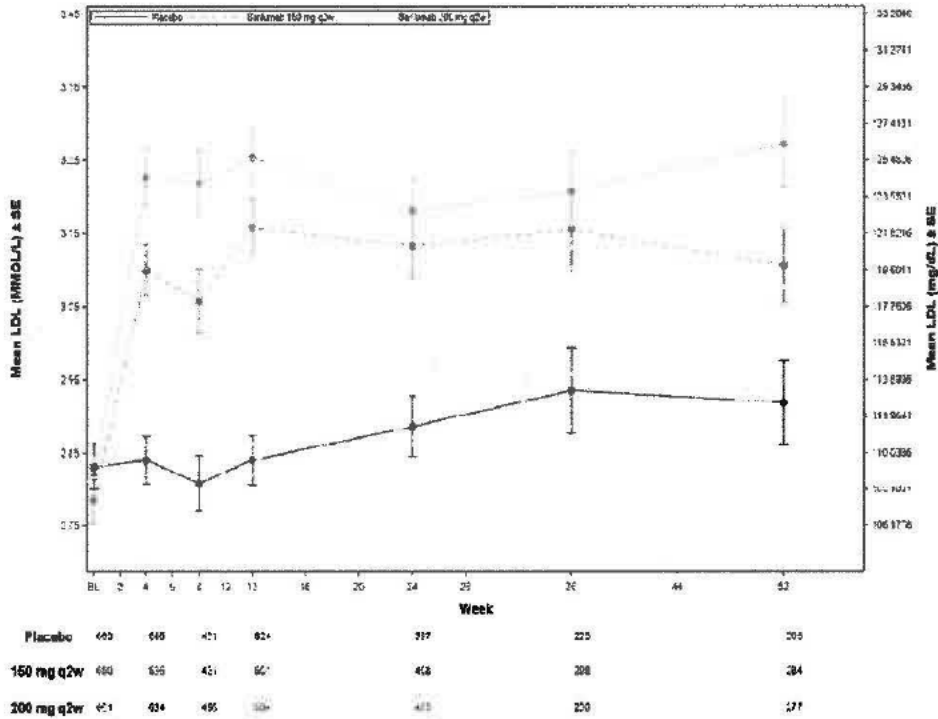
E. Elevation in Lipids

Because of the known association of elevations in lipid parameters with tocilizumab, patients were excluded from the sarilumab 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). The following 3 figures (Figures 2-4) 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%).

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Figure 2. Mean LDL across Visits during the Entire TEAE Period (Pool 1)

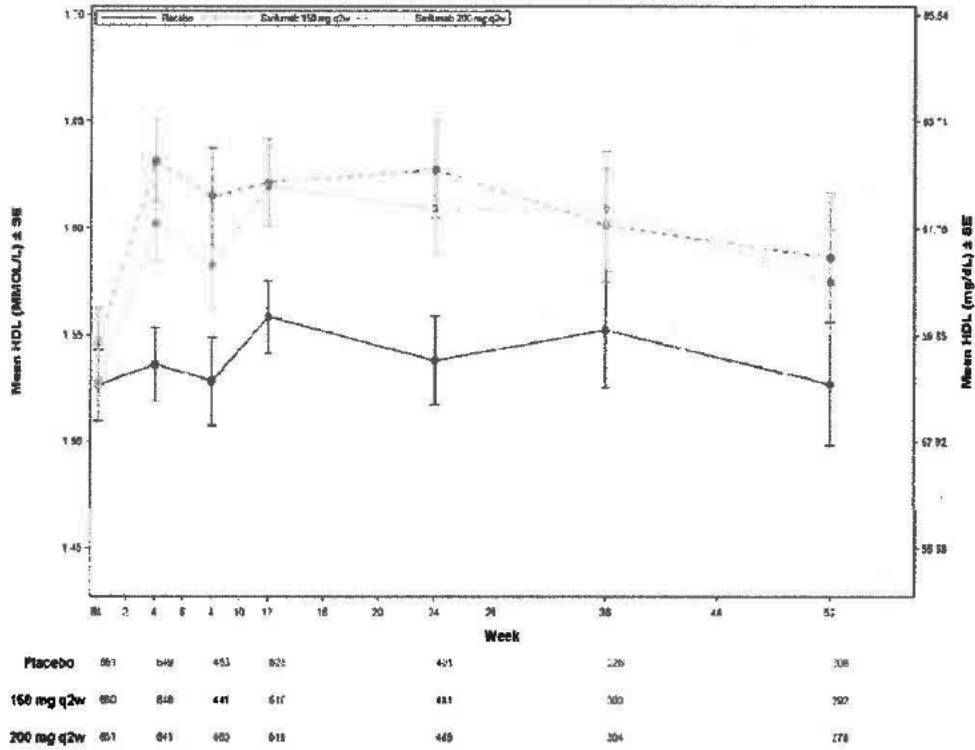


Normal range: 2.28-5.21 mmol/L (88-201 mg/dL)
 Source: Integrated Summary of Safety, Figure 24, page 221.

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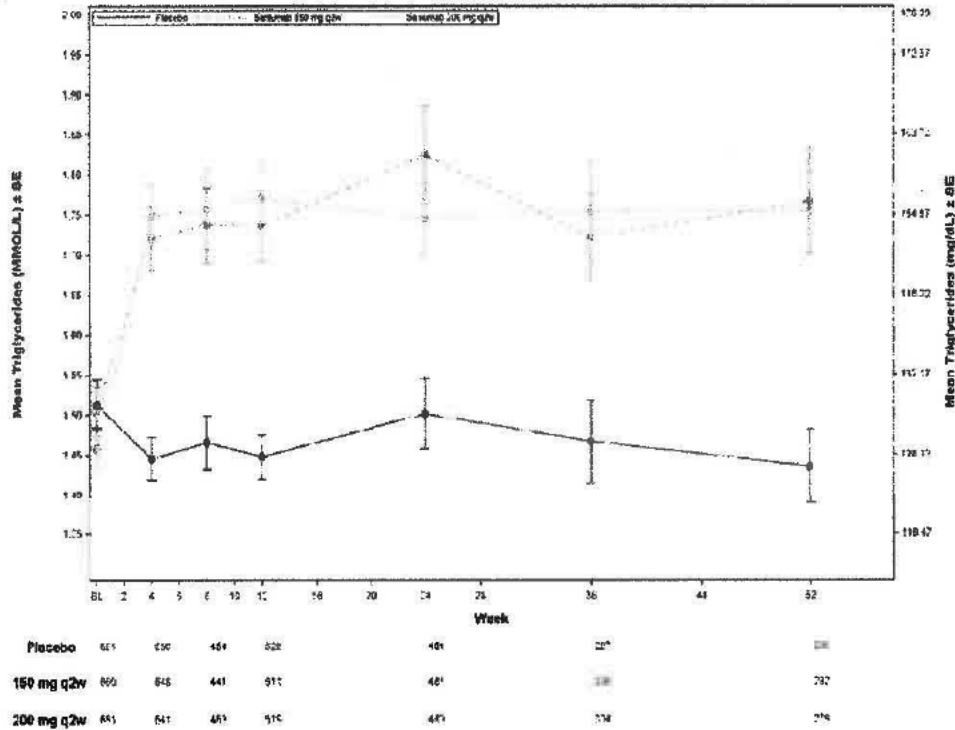
Figure 3. Mean HDL across Visits during the Entire TEAE Period (Pool 1)



Normal range: 0.96-2.38 mmol/L (37-92 mg/dL)
 Source: Integrated Summary of Safety, Figure 25, page 222.

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Figure 4. Mean Triglycerides across Visits during the Entire TEAE 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, except 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 3 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.

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Table 3. Elevation in Lipids during Pre-Rescue Period (Pool 1a)

	Placebo + DMARD	Sarilumab 150mg q2w + DMARD	Sarilumab 200mg q2w + DMARD
Elevation in Lipids			
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) ^a	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

Pre-rescue period = 0-12 weeks from EFC10832 and 0-16 from EFC11072

^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

Table 4 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.

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Table 4. Elevation in Lipids during the Double-Blind Treatment Period (Pool

	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
Total patients with ≥ 1 Elevation in lipids (%)	13 (2.0%)	39 (5.9%)	33 (5.0%)
Number of patients with ≥ 1 Elevation in lipids per 100 pt-yrs	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 5](#) below presents the patients by their baseline and post-baseline LDL values.

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Table 5. Number of Patients by NCEP ATP III LDL Classification According to Baseline Status and Post-Baseline Values during Entire TEAE Period (Pool 1).

Laboratory Parameter Baseline Post-baseline n/N1(%)	Placebo + DMARD	Sarilumab 150mg q2w + DMARD	Sarilumab 200mg q2w + DMARD
LDL			
Total^a			
< 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

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 entire TEAE period, but no difference was observed between the 2 doses of sarilumab (16 patients [2.4%] in 200mg q2w; 16 patients [2.4%] in 150mg q2w; 3 patients [0.5%] in placebo).

F. 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). The applicant utilized FDA-accepted definition of 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.

Table 6 presents the incidence rates of MACE (primary and narrow) for placebo, sarilumab 150mg q2w, and sarilumab 200mg q2w for the pre-rescue

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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% (-0.2, 0.5). The same risk difference was calculated for sarilumab 200mg q2w.

Table 6. Summary of CV events during Pre-Rescue Period (Pool 1a)

	Placebo + DMARD	Sarilumab 150mg q2w + DMARD	Sarilumab 200mg q2w + DMARD
MACE (primary)			
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) ^a	0/161.6 (0)	1/159.7 (0.6)	1/161.0 (0.6)
Rate difference vs. PBO + DMARD (95% CI) ^b		0.2% (-0.2, 0.5)	0.2% (-0.2, 0.5)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) ^b			0.0% (-0.5, 0.5)
MACE (narrow)			
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) ^a	0/161.6 (0)	1/159.7 (0.6)	1/161.0 (0.6)
Rate difference vs. PBO + DMARD (95% CI) ^b		0.2% (-0.2, 0.5)	0.2% (-0.2, 0.5)
Rate difference vs. sarilumab 150mg + DMARD (95% CI) ^b			0.0% (-0.5, 0.5)

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

Pre-rescue period = 0-12 weeks from EFC10832 and 0-16 from EFC11072

a Number of patients with at least one 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

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% (-0.1, 0.7).

The 4 events adjudicated as MACE in the sarilumab groups were 2 CV deaths and 2 strokes. In regards to the 2 CV deaths, one was a subject on 150mg q2w who suffered a sudden death, and one was a subject on 200mg q2w who suffered cardiac arrest after a stroke. Both events deemed as strokes were embolic: one with an aortic thrombus (sarilumab 150mg q2w) and one with non-infectious endocarditis (sarilumab 200mg q2w). Of note, there was one subject in the placebo group who developed an acute myocardial infarction and ischemic stroke in the setting of infectious endocarditis; however, these events occurred when the patient was off placebo. Therefore, the placebo event was not included in these analyses.

Sensitivity analyses done on Pool 1a also revealed similar findings for subjects based on exposure through Week 52 (Error! Reference source not found.Table 7). This analysis included patients who were initially 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 is 0.8 for sarilumab 150mg per 100 pt-yrs and 0.6 for sarilumab 200mg per 100 pt-yrs.

Table 7. Sensitivity Analyses of CV Events during TEAE Period (Weeks 0-52, Pool 1a)

n(%)	Sarilumab 150mg q2w + DMARD		Sarilumab 200mg q2w + DMARD ^a	
	Raw incidence rate n/N (%)	Exposure adjusted incidence rate ^b n/PY (rate per 100 PYs)	Raw incidence rate n/N (%)	Exposure adjusted incidence rate ^b n/PY (rate per 100 PYs)
MACE primary	2/579 (0.3%)	2/403.7 (0.5)	2/881 (0.2%)	2/581.3 (0.3)
MACE narrow	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 24 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 8 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 the complexities in the study design, the higher incidence rate for the 200 mg dose group compared to the 150 mg dose group is difficult to interpret.

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Table 8. 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)
MACE (primary)	2 (0.3)	12 (0.7)	28 (0.6)
MACE (narrow)	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.

We asked Sanofi to further break down the data presented in Table 8. Specifically, we asked Sanofi to present the adjudicated CV events (namely, MACE primary and narrow) for all treatment groups as randomized, all treatment groups once they were rescued or received open-label treatment (PBO → sarilumab 200mg q2w; sarilumab 150mg q2w → sarilumab 200mg q2w; sarilumab 200mg q2w → sarilumab 200mg q2w [OL]), and all the treatment groups who had to decrease down to 150mg q2w during the open-label period because of laboratory abnormalities (PBO → sarilumab 200mg q2w → sarilumab 150mg q2w; sarilumab 150 mg q2w → sarilumab 200mg q2w → sarilumab 150mg q2w; sarilumab 200mg q2w → sarilumab 200mg q2w [OL] → sarilumab 150mg q2w). The applicant provided the data as presented in [Table 9](#). With this more granular analysis of the CV events, it is

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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, that is, those who started on 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 (Table 8Table 8) may not represent a true dose response, especially given that a dose response was not seen in the placebo-controlled period.

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Table 9. Summary of CV Events in Pivotal Studies and OLE (EFC11072, EFC10832, LTS11210)

Treatment	Raw incidence rate n/N (%)	Exposure adjusted incidence rate^a n/PY (n/100 PY)	Exposure adjusted event rate^b n_E/PY (n_E/100 PY)
MACE (primary)			
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
MACE (narrow)			
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	0/71	0/88.4	0/88.4

(OL) →

150mg q2w (dose decrease)

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, Sanofi provided a model-based analysis of MACE. All the safety data on placebo and sarilumab were included in these analyses.

Table 10 ~~Table 10~~ shows the model-based analysis on MACE primary and narrow. The exposure-adjusted incidence rate of sarilumab (0.6 per 100 PYs for any sarilumab dose) exceeds that of placebo (0 per 100 PYs). Additionally, in this analysis, the exposure adjusted incidence rate for sarilumab 200mg (0.7 per 100 PYs) was higher than that for sarilumab 150mg (0.3 per 100 PYs); however, there are limitations to these analyses given the study design.

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Table 10. Model-based Analysis on Patients with at least one MACE during the TEAE period

	Placebo + DMARD	Sarilumab 150mg q2w + DMARD	Sarilumab 200mg q2w + DMARD	Any Sarilumab + DMARD
MACE (primary)				
Raw incidence rate n/N (%)	0/661 (0)	2/1155 (0.2)	12/1351 (0.9)	27/2887 (0.9)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) ^a	0/382.3 (0)	2/701.7 (0.3)	12/1756.3 (0.7)	27/4469.7 (0.6)
Rate ratio vs. PBO + DMARD (95% CI)		Not estimable	Not estimable	Not estimable
Rate ratio vs. sarilumab 150mg + DMARD (95% CI)			2.49 (0.54, 11.40) ^b	
MACE (narrow)				
Raw incidence rate n/N (%)	0/661 (0)	2/1155 (0.2)	11/1351 (0.8)	24/2887 (0.8)
Exposure adjusted incidence rate n/PY (rate per 100 PYs) ^a	0/382.3 (0)	2/701.7 (0.3)	11/1757.1 (0.6)	24/4475.6 (0.5)
Rate ratio vs. PBO + DMARD (95% CI)		Not estimable	Not estimable	Not estimable
Rate ratio vs. sarilumab 150mg + DMARD (95% CI)			2.31 (0.50, 10.72) ^b	

^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 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. Please note, only patients on sarilumab 150mg q2w or 200mg q2w initial dose+DMARD groups were included in the analysis.

Source: Sanofi response to IR (June 10 and 13, 2016), Appendix B 1.12.3.6 and 1.12.3.7, dated June 15, 2016, page 13-14 and IR response dated July 12, 2016.

APPEARS THIS WAY ON ORIGINAL

Ford, Christine

From: Ford, Christine
Sent: Friday, July 15, 2016 1:57 PM
To: Pat Reilly (Patricia.Reilly@regeneron.com)
Cc: 'Sarah.Feathers@genzyme.com'; Ford, Christine
Subject: Information request: BLA 761037 sarilumab - CDRH

Dr. Reilly,
BLA 761037 for sarilumab is currently under review, and we have the following request for information.

In your submission dated June 22, 2016 (response to Question #1 in the 6/17/16 information request), related to the complaints noted during the clinical trial conducted 2011-2015, you state "that the defects of the PFS found during clinical studies were not encountered during the Human Factor Studies. The sarilumab prefilled syringe has been found to be reasonably safe and effective for the intended users, uses and use environments. Since the submission of the BLA 761037 for sarilumab to the agency, the internal SOP on incoming controls for the syringe with the staked needle component was upgraded. The critical incoming controls performed on syringe component of the sarilumab prefilled syringe are found in the below table and the visual control of the broken needle and the functional control of the hooked or blunt point defect were already part of the submitted section 3.2.P.7."

However, your response does not answer why the needle breakage problems were occurring in the first place during the clinical study, and whether or not a root cause analysis was conducted on the clinical study adverse event reports. Please provide additional information on why the needle breakage was occurring and whether a root cause analysis was conducted to determine why this was occurring.

Kindly confirm receipt of this information request, and provide an official response to the BLA no later than July 19, 2016, if possible. If you have any questions, please contact me at 301-796-3420. Thank you for your cooperation.

Regards,
Christine

Christine Ford, MS, RPh
CAPT, USPHS
Sr. Regulatory Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products
FDA/CDER/OND/ODE II
Phone 301-796-3420
Fax 301-796-9728
christine.ford@fda.hhs.gov

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/s/

CHRISTINE H CHUNG

07/15/2016

Christine Ford (formerly Chung)



BLA 761037

INFORMATION REQUEST

Sanofi-aventis U.S. LLC
Attention: Jennifer Cairns, Ph.D.
Director, Global Regulatory Affairs
55 Corporate Drive, Mail Stop 55D-220B
Bridgewater, NJ 08807

Dear Dr. Cairns:

Please refer to your Biologics License Application (sBLA) dated and received October 30, 2015, submitted under section 351(a) of the Public Health Service Act for sarilumab (SAR153191/REGN88).

We are reviewing your submission and have the following request for information. We request a prompt written response by July 21, 2016 in order to continue our evaluation of your application.

1. We note that section 3.2.S.2.2 identifies process details and operating parameters in addition to critical and general process parameters and general and critical quality attributes. Both process details (b) (4) [redacted] have associated limits, ranges, and/or set points. Section 3.2.S.2.4 defines the minimum response associated with excursions related to acceptance criteria or actions limits for C/GQAs and C/GPPs. Clarify the actions taken if excursions in parameters identified as a process detail or excursions in an operating parameter take place.
2. In Section 3.2.S.2.2, Table 1 (b) (4) [redacted] Provide a rationale for the different limits.
3. We note in Table 5 of Section 3.2.S.2.2 in "Description of manufacturing and process controls – DS" (b) (4) [redacted] In section 3.2.S.2.5 "Process validation and or evaluation" Table 14 (b) (4) [redacted] indicates the limit (b) (4) [redacted] These values are (b) (4) [redacted] provided in S.2.2. Revise the limit (b) (4) [redacted]

- (b) (4)
4. No data for process qualification runs (b) (4) are provided (b) (4) defined (b) (4) in Table 5 of Section 3.2.S.2.2 in “Description of manufacturing and process controls – DS.” Provide data (b) (4) or indicate where the information can be found in the submission.
 5. Provide the total days (b) (4) for all process qualification lots run (b) (4) to demonstrate that the process can be run to consistently to remain (b) (4) as defined in S.2.5
 6. Section 3.2.S.2.2 in “Description of manufacturing and process controls – DS” in table 1 indicates a limit (b) (4). The validation report (b) (4) in table 18 defines the (b) (4) time (b) (4) as (b) (4) days. Provide the (b) (4) time (b) (4) to demonstrate that the process (b) (4) is within the claimed validated parameters. Provide the same information (b) (4) or indicate the table in report (b) (4) or associated report where the information can be found.
 7. FDA notes that (b) (4) additional information is included (b) (4). For example, Table 18 (b) (4) includes parameters (b) (4). For all (b) (4) runs performed for process qualification (b) (4) provide these additional data to support that the process qualification (b) (4) met the intended targets (b) (4).
 8. Section 3.2.S.2.2 in “Description of manufacturing and process controls – DS” in table 1 defines parameters (b) (4) including total batch time and production time, with associated limits. The data for these parameters for (b) (4) qualification lots are not provided in the report (b) (4). Provide these data to the BLA. Additionally, provide the amount in kilograms (b) (4) for the validation runs. Provide traces for the (b) (4) parameters (b) (4). Provide the same information for process qualification runs (b) (4) or identify the tables in associated reports related to process qualification (b) (4) where the information can be found.
 9. Section 3.2.S.2.2 in “Description of manufacturing and process controls – DS” in Table 5 identifies a production time limit for the following unit operations: (b) (4). Provide these data (b) (4) or provide the location in the BLA where the information can be found.
 10. We note that (b) (4) is not identified as a parameter (b) (4) in section 3.2.S.2.2 in “Description of manufacturing and process controls – DS”). Per ASTM guidance (b) (4) and published literature (b) (4) is an important parameter that should be controlled as it has

the potential to impact the efficiency (b) (4) Define a limit (b) (4) performed for the sarilumab manufacturing process and (b) (4) from the process qualification runs (u) (4) The parameter should be classified appropriately according to the risk to safety and efficacy of sarilumab. Update section 3.2.S.2.2 accordingly.

Regarding the Reference Standard Program:

11. SOP (b) (4) indicates (b) (4)
(b) (4)
(b) (4)
(b) (4)
In both cases, instructions include (b) (4) The FDA does not agree that it is appropriate (b) (4) without prior Agency approval. Additionally, (b) (4) we do not agree (b) (4)
(b) (4)
The Agency requests that these (b) (4) are removed from SOP (b) (4) The Agency recommends (b) (4)

If this is not possible then the Agency recommends that detailed protocols for the situations describe above are submitted as supplements to the BLA.

12. SOP (b) (4) indicates that (b) (4) should be calculated. It is not clear from information provided in the SOP or the qualification report (b) (4) how the (b) (4) is calculated. Clarify this calculation and update the SOP accordingly.

13. SOP (b) (4) also indicates that (b) (4) the candidate RS is (b) (4) % or (b) (4) %, (u) (4) is calculated as stipulated in Appendix 3 of the SOP. It appears from the SOP that the approach (b) (4)

The Agency does not agree (b) (4)

With respect to the primary reference standard, the Agency recommends that the acceptable relative potency for the primary RS is limited to the proposed (b) (4) %. With respect to the working reference standard, (b) (4) an adequate control strategy should be in place (b) (4)

14. Regarding the stability criteria for the primary and working reference standard found in section 8.1 (Attachment 1) and 8.2 (Attachment 2), respectively of SOP (b) (4), the Agency does not agree that it is appropriate to assess stability of the primary reference standard for attributes such as potency (b) (4)

(b) (4) The Agency suggests that for the primary reference standard, the stability assessment for potency is based on (b) (4)

(b) (4) Alternatively, it may be possible to assess potency and other quality attributes of the primary reference standard (b) (4)

(b) (4) Update the RS SOP (b) (4) accordingly.

If you have questions, call me, at (301) 796-0906.

Sincerely,

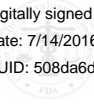
{See appended electronic signature page}

Melinda Bauerlien, M.S.
Senior Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



Melinda
Bauerlien

Digitally signed by Melinda Bauerlien
Date: 7/14/2016 12:06:25PM
GUID: 508da6dc0002676de5faf5b4bf3d0f72



Ford, Christine

From: Ford, Christine
Sent: Tuesday, July 12, 2016 3:42 PM
To: 'Sarah.Feathers@genzyme.com'
Cc: Ford, Christine
Subject: Request for information BLA 761037 sarilumab - MACE

Dear Sarah,
BLA 761037 for sarilumab is currently under review, and we have the following request for information.

We request clarification on the data provided in the model based analyses on patients with at least one MACE during the entire TEAE period (ISS Appendices 1.12.3.6 and 1.12.3.7). Specifically, there is a single event in the placebo + DMARD treatment arm. In the ISS, there are no events in the placebo + DMARD treatment arm in Table 96 (page 236) Pool 1. We do note, however, that there is annotation of 1 MACE in the placebo group in the CSR for EFC11072 Part B. The patient narrative in the CSR describes a 58 year-old male on placebo who developed a transient ischemic attack and then an acute myocardial infarct and ischemic stroke in the setting of infectious endocarditis.

Clarify how you determined the number of MACE events in the placebo treatment arm and the differences between the EFC11072 Part B CSR, MACE analyses in the ISS and ISS Appendices, and the model-based analyses in the ISS Appendices.

Kindly confirm receipt of this information request, and provide an official response to the BLA no later than July 14, 2016. If you have any questions, please contact me at 301-796-3420. Thank you for your cooperation.

Regards,
Christine

Christine Ford, MS, RPh
CAPT, USPHS
Sr. Regulatory Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products
FDA/CDER/OND/ODE II
Phone 301-796-3420
Fax 301-796-9728
christine.ford@fda.hhs.gov

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/s/

CHRISTINE H CHUNG

07/12/2016

Christine Ford (formerly Chung)

Ford, Christine

From: Ford, Christine
Sent: Friday, July 01, 2016 2:28 PM
To: 'Sarah.Feathers@genzyme.com'
Cc: Ford, Christine
Subject: Additional information request BLA 761037 sarilumab - CDRH

Dear Sarah,

We refer to BLA 761037 for sarilumab and to your submission dated June 22, 2016 (response to question 3 of FDA information request dated June 17, 2016). We have the following request for additional information.

You state that the device is in the category of external communicating device with limited (≤ 24 h) contact to tissue, bone or dentin. The device will be administering the drug to the subcutaneous tissue where it is intended to be delivered systemically, and therefore, extractables and leachables can have contact with the blood. We recommend that hemolysis testing is performed on the fluid path components of the final finished device. Accordingly, provide results of hemolysis testing on the needle. Alternatively, provide a justification for why hemolysis testing is not necessary, including information that demonstrates the device materials and any impurities or residuals introduced in the manufacturing process will not result in hemolysis.

Please confirm receipt of this information request, and provide an official response to the BLA no later than July 7, 2016, or provide a timeline for when response will be submitted. If you have any questions, please contact me at 301-796-3420. Thank you for your cooperation.

Regards,
Christine

Christine Ford, MS, RPh
CAPT, USPHS
Sr. Regulatory Management Officer
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/s/

CHRISTINE H CHUNG

07/01/2016

Christine Ford (formerly Chung)



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

ELECTRONIC CORRESPONDENCE

Date: June 27, 2016

To: Sarah Feathers, PharmD Global Regulatory Affairs	From: Christine Ford, MS, RPh Regulatory Project Manager
Company: Sanofi-Aventis U.S. LLC	Division of Pulmonary, Allergy, and Rheumatology Products
Phone: 617-768-6099	Fax number: 301-796-9728
Email: sarah.feathers@genzyme.com	Phone number: 301-796-3420

Subject: BLA 761037 sarilumab
PREA postmarketing requirements/commitments

Total no. of pages including cover: 3

Comments: *Response requested no later than Wednesday July 6, 2016*

Please call or send an email to confirm receipt at christine.ford@fda.hhs.gov

Document to be mailed: YES NO

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We refer to BLA 761037 for sarilumab and request confirmation of your agreement to conduct the following studies and completion of milestone timelines.

PREA Postmarketing requirements (PMR)

1. To conduct a study to assess the pharmacokinetic and pharmacodynamics (PK/PD) parameters and dosing of sarilumab in children ages ≥ 2 years to < 17 years with polyarticular juvenile idiopathic arthritis (pJIA) (study DRI3925).

Final Protocol Submission:	02/2016 (completed)
Trial Completion:	MM/YYYY
Final Report Submission:	03/2018

2. To conduct a study to assess the efficacy and safety of sarilumab in children ages ≥ 2 years to < 17 years with polyarticular JIA (study EFC11783).

Final Protocol Submission:	04/2018
Trial Completion:	MM/YYYY
Final Report Submission:	01/2023

Submit your response to the BLA no later than COB July 6, 2016. If you have any questions, please contact me at 301-796-3420.

APPEARS THIS WAY ON ORIGINAL

Drafted by: cford/ 6.23.2016

Initialed by: SBarnes/ 6.23.2016
SPeng, JMaynard/ 6.23.2016
SSeymour/ 6.24.2016
CHill/ 6.27.2016

Finalized: cford/ 6.27.2016

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/s/

CHRISTINE H CHUNG

06/27/2016

Christine Ford (formerly Chung)

Ford, Christine

From: Ford, Christine
Sent: Friday, June 17, 2016 12:34 PM
To: 'Sarah.Feathers@genzyme.com'
Cc: Ford, Christine
Subject: Request for information: BLA 761037 sarilumab - device

Dear Sarah,
BLA 761037 for sarilumab is currently under review, and we have the following request for information.

1. You have noted on page 20 of P.2.4 Container Closure System that complaints were noted during the clinical trial conducted 2011-2015. However, we do not see any mention of how these complaints were addressed in the device section 3.2.P.7 or within the human factors report. If additional information on these complaints and how they were addressed have already been submitted in the BLA, please provide the location; if not, submit the information. Additionally, provide the location in the BLA where the following has been addressed: the device performance of the staked needle component of the pre-filled syringe.
2. You have provided a declaration of compliance with ISO 10993-1; submit the complete test protocols and test reports for the all device components including the syringe glass barrel and the needle. You have also provided a Biocompatibility Summary (b) (4); submit the complete test protocols and test reports for the (b) (4) components.
3. You have addressed the following biocompatibility endpoints for the Glass Barrel and Needle: cytotoxicity, irritation, sensitization, and systemic toxicity. The needle is within the fluid path of the drug, which when delivered will have indirect contact with the blood. We recommend that hemolysis and material-mediated pyrogenicity endpoints are also addressed for this type and duration of contact. Please provide hemolysis and material-mediated pyrogenicity testing for the needle. Alternatively, a scientific rationale for why this testing is not necessary may be provided.

Kindly confirm receipt of this information request, and provide an official response to the BLA no later than June 22, 2016, or provide a timeline for when the responses will be submitted. If you have any questions, please contact me at 301-796-3420. Thank you for your cooperation.

Regards,
Christine

Christine Ford, MS, RPh
CDR, USPHS
Sr. Regulatory Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products
FDA/CDER/OND/ODE II
Phone 301-796-3420
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christine.ford@fda.hhs.gov

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/s/

CHRISTINE H CHUNG

06/17/2016

Christine Ford (formerly Chung)

Ford, Christine

From: Ford, Christine
Sent: Monday, June 13, 2016 11:10 AM
To: 'Sarah.Feathers@genzyme.com'
Cc: Ford, Christine
Subject: Request for information: BLA 761037 sarilumab - CV events

Dear Sarah,

We appreciate your June 3, 2016, prompt response to our information request dated May 27, 2016. We have the following clarifying questions:

- (1) Please confirm the exposure adjusted event rates for the cardiovascular (CV) events from Table 1. For the randomized population (prior to rescue), they appear to differ from ISS Appendix 1.9.1.12 (page 8032).
- (2) For the 3 AEs (CV events, serious infections, and malignancy), please provide the raw incidence, exposure adjusted incidence rate, and exposure adjusted event rate for the placebo initial dose group.
- (3) We note that the sensitivity analysis of CV events for Pool 1a (0-52 weeks) reflect no additional events as compared to 0-12 weeks or 0-24 weeks. (ISS Appendix 1.12.2.12, page 8444) Therefore, we want to confirm that the additional CV events after rescue, noted in Table 1 of your response, occurred after 52 weeks.

Please confirm receipt of this information request, and provide an official response to the BLA no later than June 15, 2016. If you have any questions, please contact me at 301-796-3420. Thank you for your cooperation.

Regards,
Christine

Christine Ford, MS, RPh
CDR, USPHS
Sr. Regulatory Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products
FDA/CDER/OND/ODE II
Phone 301-796-3420
Fax 301-796-9728
christine.ford@fda.hhs.gov

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/s/

CHRISTINE H CHUNG

06/14/2016

Christine Ford (formerly Chung)

Ford, Christine

From: Ford, Christine
Sent: Friday, June 10, 2016 2:09 PM
To: 'Sarah.Feathers@genzyme.com'
Cc: Ford, Christine
Subject: Request for information: BLA 761037 sarilumab - ISS tables

Dear Sarah,
BLA 761037 for sarilumab is currently under review, and we have the following request for information.

In our review of the adjudicated CV events, we noted a possible error in the exposure adjusted incidence rates for MACE (primary and narrow) in the pre-rescue period for Pools 1 and 1a. Provide clarifications of the patient-years and exposure adjusted incidence rates in the following tables:

- ISS Appendix 1.12.1.20 Summary of adjudicated treatment-emergent CV events during the TEAE period (pre-rescue, Pool 1), page 8209
- ISS Appendix 1.12.1.53 Summary of adjudicated treatment-emergent CV events during the TEAE period (pre-rescue, Pool 1a), page 8294

Please confirm receipt of this information request, and provide an official response to the BLA no later than June 15, 2016. If you have any questions, please contact me at 301-796-3420. Thank you for your cooperation.

Regards,
Christine

Christine Ford, MS, RPh
CDR, USPHS
Sr. Regulatory Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products
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/s/

CHRISTINE H CHUNG

06/10/2016

Christine Ford (formerly Chung)



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

BLA 761037

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Sanofi-Aventis U.S. LLC
500 Kendall Street
Cambridge, MA 02142

ATTENTION: Sarah Feathers, Pharm.D.
Global Regulatory Lead, Sarilumab, Global Regulatory Affairs

Dear Dr. Feathers:

Please refer to your Biologics License Application (BLA) dated and received October 30, 2015, submitted under section 351(a) of the Public Health Service Act for Sarilumab, 150 mg/1.14 mL and 200 mg/1.14 mL.

We also refer to your correspondence, dated and received March 16, 2016, requesting review of your proposed proprietary name, Kevzara.

We have completed our review of the proposed proprietary name, Kevzara and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your March 16, 2016, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,
(<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Neil Vora, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-4845. For any other information regarding this application, contact Christine Ford, Regulatory Project Manager in the Office of New Drugs, at (301) 796-3420.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES
06/02/2016

Ford, Christine

From: Ford, Christine
Sent: Wednesday, June 01, 2016 12:29 PM
To: 'Sarah.Feathers@genzyme.com'
Cc: Ford, Christine
Subject: clarificatn: BLA 761037 sarilumab - safety analysis

Hi Sarah,
As requested, please see the clarifications for the May 27, 2016, information request below, and let me know if there are any additional questions. Thanks. c

- (1) The requested data should include patients from the following studies: EFC11072, EFC10832, and LTS11210.
- (2) We request that the adverse events be counted for the dose the subject was taking at the time of event. Therefore, please add the following groups to those already requested.
 - a. Placebo → sarilumab 200mg q2w (rescue/open-label) → sarilumab 150mg q2w (dose decrease)
 - b. Sarilumab 150mg q2w → sarilumab 200mg q2w (rescue/open-label) → sarilumab 150mg q2w (dose decrease)
 - c. Sarilumab 200mg q2w → sarilumab 200mg q2w (open-label) → sarilumab 150mg q2w (dose decrease)

From: Sarah.Feathers@genzyme.com [<mailto:Sarah.Feathers@genzyme.com>]
Sent: Tuesday, May 31, 2016 9:26 AM
To: Ford, Christine
Subject: RE: request for information: BLA 761037 sarilumab - safety analysis

Hi Christine,
We have a couple clarifying questions regarding the below information request. Based on the reference to rescue and the placebo controlled period, we understand that the requested data is specifically for patients randomized in the placebo controlled studies (EFC11072, EFC10832), including subsequent treatment of these patients in the extension study LTS11210. Is this correct?

Additionally, patients in LTS11210 were permitted to dose decrease from 200mg to 150mg based on laboratory abnormalities. This step was not mentioned in the definition of groups 3,4, and 5 in your request. Could you please clarify if events after dose decrease should be included in these groups? (Example: in group 3 a patient is randomized to placebo, then following rescue receives 200mg. The patient is later dose decreased to 150mg. Events occurring under the 200mg dose will be included in group 3; should the events under 150mg also be included?)

Kindly,
Sarah

Sarah Feathers, PharmD

Global Regulatory Affairs
Genzyme center, 500 Kendall Street, Cambridge, MA – 02142 |
Tel: +1 617-768-6099 | cell: (b) (6)
Email: sarah.feathers@genzyme.com



From: Ford, Christine [<mailto:Christine.Chung@fda.hhs.gov>]
Sent: Friday, May 27, 2016 5:12 PM
To: Feathers, Sarah GZ/US
Cc: Ford, Christine
Subject: request for information: BLA 761037 sarilumab - safety analysis
Importance: High

Hi Sarah,
Please see attached request for additional information and confirm receipt. thanks! c

Christine Ford, MS, RPh
CDR, USPHS
Sr. Regulatory Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products
FDA/CDER/OND/ODE II
Phone 301-796-3420
Fax 301-796-9728
christine.ford@fda.hhs.gov

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/s/

CHRISTINE H CHUNG

06/01/2016

Christine Ford (formerly Chung)



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

ELECTRONIC CORRESPONDENCE

Date: May 27, 2016

To: Sarah Feathers, PharmD Global Regulatory Affairs	From: Christine Ford, MS, RPh Regulatory Project Manager
Company: Sanofi-Aventis U.S. LLC	Division of Pulmonary, Allergy, and Rheumatology Products
Phone: 617-768-6099	Fax number: 301-796-9728
Email: sarah.feathers@genzyme.com	Phone number: 301-796-3420

Subject: BLA 761037 sarilumab
FDA request for information – Clinical

Total no. of pages including cover: 4

Comments: *Information requested no later than Friday, June 3, 2016*

Please call or send an email to confirm receipt at christine.ford@fda.hhs.gov

Document to be mailed: YES NO

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BLA 761037 for (b) (4) (sarilumab) prefilled syringes is currently under review, and we have the following request for information:

We appreciate your response to our information request dated May 26, 2016. Based on your clarification, we request the following additional information for the purpose of evaluating the long-term safety population for three adverse events of special interest (cardiovascular events, serious infections, and malignancy). Please utilize the following 5 treatment groups:

1. Sarilumab 150 mg q2w initial dose
 - a. This group would be similar to your current “sarilumab 150 mg q2w initial dose + DMARD” group. It would include patients whose initial dose of sarilumab was 150 mg q2w. It should only include data up to the dose modification for patients who were rescued or enrolled in LTS 11210, end of study, or data cut-off date.
 - b. As in your current definition, AEs that occur while the patient is on 150 mg should be included in this group, even if he/she receives OL sarilumab at a different dose later.
2. Sarilumab 200 mg q2w initial dose
 - a. This group would only include patients whose initial dose of sarilumab was 200mg q2w at the time of initial randomization. This should only include subjects who are on 200mg q2w during the double-blind placebo period.
 - b. Adverse events that occur when the subject enters the open-label period (200mg) will not be counted in this group.
 - c. Additionally, placebo subjects who are rescued to 200mg q2w are not included in this group.
3. PBO → 200 mg q2w (rescue/OL study)
 - a. This group would include subjects who were initiated on placebo but then received sarilumab 200mg q2w (either rescue or study LTS11210).
 - b. Only AEs that occurred while the subject was administered sarilumab 200mg q2w would be included in this group.
4. Sarilumab 150mg → 200 mg q2w (rescue/OL study)
 - a. This group would include all subjects who were initiated on 150 mg q2w but were then transitioned to OL 200mg q2w (either rescue or study LTS11210).
 - b. Only adverse events that occurred during the open-label administration of sarilumab would be counted.
5. Sarilumab 200mg → 200mg q2w (OL study)
 - a. This group would include all subjects who were initiated on 200 mg q2w but were then transitioned to OL 200mg q2w after entering LTS11210.

- b. Only adverse events that occurred during the open-label administration of sarilumab would be counted.

We realize that this method of analysis would exclude subjects who may have received non-selected doses of sarilumab. As noted, we request this analysis for the following adverse events of special interest: **cardiovascular events, serious infections, and malignancy**. For cardiovascular events, we request the analyses only for MACE (primary) and MACE (narrow). For serious infections and malignancy, please provide the overall number of events. At this time, we do not request the data by preferred term. We would appreciate if you could start with your evaluation of cardiovascular events and submit that as soon as it is complete.

We would expect that the AEs would be counted under the dose group at which time the AE occurred. For example, in the theoretical situation we presented in the last IR, the subject experienced an AE while he was on 150mg q2w and then another AE during the open-label study. In this alternative grouping, this subject would be counted once in the “sarilumab 150mg q2w initial dose” group (for the first AE) and then once in the “sarilumab 150mg q2w → 200mg q2w” group (for the second AE).

The requested information should be submitted as official responses to the BLA no later than Friday, June 3, 2016, or provide a timeline for when the information will be submitted.

If you have any questions, please contact Christine Ford at 301-796-3420.

APPEARS THIS WAY ON ORIGINAL

Drafted by: SPeng, JMaynard/ 5.27.2016
cford/ 5.27.2016

Initialed by: SBarnes/ 5.27.2016

Finalized: cford/ 5.27.2016

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/s/

CHRISTINE H CHUNG

05/27/2016

Christine Ford (formerly Chung)



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

ELECTRONIC CORRESPONDENCE

Date: May 26, 2016

To: Sarah Feathers, PharmD Global Regulatory Affairs	From: Christine Ford, MS, RPh Regulatory Project Manager
Company: Sanofi-Aventis U.S. LLC	Division of Pulmonary, Allergy, and Rheumatology Products
Phone: 617-768-6099	Fax number: 301-796-9728
Email: sarah.feathers@genzyme.com	Phone number: 301-796-3420

Subject: BLA 761037 (b)(4) (sarilumab)
FDA request for information – Clinical – safety pooling strategy

Total no. of pages including cover: 3

Comments: *Information requested no later than Friday, May 27, 2016*

Please call or send an email to confirm receipt at christine.ford@fda.hhs.gov

Document to be mailed: YES NO

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BLA 761037 for (b) (4) (sarilumab) prefilled syringes is currently under review, and we have the following request for information:

We ask that you clarify whether our understanding of the 3 treatment groups displayed in your pooling strategy for Pool 2, the long term safety population, is correct. Based on information provided (such as on page 32 of the ISS), the following is our understanding of your pooling strategy:

a) Sarilumab 150mg q2w initial dose + DMARD

- This group includes patients whose initial dose was sarilumab 150mg q2w and only includes these patients while they were receiving the 150mg dose. If a subject was rescued or enrolled in LTS11219, he/she is counted in the “any sarilumab dose” group from the time point they were started on 200mg.
- Confirm the following theoretical situation in a subject who started on 150mg q2w and then enrolled in LTS11219. If this subject experienced an AE while he was on 150mg q2w and then another AE during the open-label study, then this subject would be counted once in the “sarilumab 150mg q2w” group **and** twice in the “any sarilumab dose” group.

b) Sarilumab 200mg q2w initial dose + DMARD

- This group includes patients whose initial dose was sarilumab 200mg q2w. Similar to the previous 150mg treatment group, these patients are only counted in this treatment group while they were receiving 200 mg.
- If a subject on 200mg entered LTS11219 and continued to receive 200mg q2w, they remain in this group.
- Also, if a patient, who initially received placebo, was rescued or enrolled in LTS11219, they are included in this group from the time point that they started 200mg q2w.

c) Any sarilumab dose + DMARD

- This group includes patients on any dose of sarilumab. These include the non-selected and selected doses of sarilumab.
- Additionally, as above, this will include the subjects who initiated on 150mg but were switched to 200mg q2w in the open-label study.

The requested information should be submitted as official responses to the BLA no later than Friday, May 27, 2016, or provide a timeline for when the information will be submitted.

If you have any questions, please contact Christine Ford at 301-796-3420.

Drafted by: SPeng, JMaynard/ 5.26.2016
cford/ 5.26.2016

Initialed by: SBarnes/ 5.26.2016

Finalized: cford/ 5.26.2016

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/s/

CHRISTINE H CHUNG

05/26/2016

Christine Ford (formerly Chung)

Ford, Christine

From: Ford, Christine
Sent: Monday, May 23, 2016 10:18 AM
To: 'Sarah.Feathers@genzyme.com'
Cc: Ford, Christine
Subject: Request for information: BLA 761037 sarilumab - CDRH

Dear Sarah,
BLA 761037 for sarilumab is currently under review, and we have the following request for information.

1. You have stated in P.2.P.4 page 19 under the delivery volume batch testing that some finger flanges were broken during the changes, and as a result the design of the flanges were changed. It is not clear how the flanges were changed and whether it was just changed for the testing or changed for the planned combination product. Furthermore, it is not clear how the integrity of the flanges were validated after this change outside of the delivery volume testing. Submit a clarification.
2. Provide the location of testing performed that validate the dimensional compatibility of the plunger rod with the plunger.
3. You have stated that the biocompatibility declaration of compliance according to ISO 10993-1 is provided in document referenced QUA-(b)(4)-2015-01748 for syringe (glass barrel and needle) and soft needle shield, and that the biocompatibility compliance statement from supplier for the plunger rod and finger flange is provided in document referenced QUA-(b)(4)-2015-16693. However, these documents cannot be located. Provide the exact location on where the biocompatibility testing can be found.
4. In table 3 of the stability summary you stated that you have performed stability testing by testing the function of the syringe, specifically break loose/glide force, sterility, container closure integrity, expellable volume, and needle shield removal force. However, the only thing we can locate is the summary table, not the testing to support that the device functions at the end of your stated shelf life. Submit the testing performed to support that your device will function at the end of its stated shelf life.

Please confirm receipt of this information request, and provide an official response to the BLA no later than May 27, 2016. If you have any questions, please contact me at 301-796-3420. Thank you for your cooperation.

Regards,
Christine

Christine Ford, MS, RPh
CDR, USPHS
Sr. Regulatory Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products
FDA/CDER/OND/ODE II
Phone 301-796-3420
Fax 301-796-9728
christine.ford@fda.hhs.gov

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/s/

CHRISTINE H CHUNG

05/23/2016

Christine Ford (formerly Chung)

Ford, Christine

From: Ford, Christine
Sent: Thursday, April 21, 2016 10:35 AM
To: 'Sarah.Feathers@genzyme.com'
Cc: Ford, Christine
Subject: Request for information: BLA 761037 sarilumab - CDRH OC

Dear Sarah,
BLA 761037 for sarilumab is currently under review, and we have the following request for information.

The following deficiency have been identified while doing the documentation review of BLA 761037 for sarilumab 150 and 200 mg prefilled syringes in reference to applicable 21 CFR 820 regulations and manufacturing of the finished combination product:

Summary of information related to Corrective and Preventive Actions (CAPA) as per the requirement of 21 CFR 820.100. CAPA procedures are used to determine the cause of problems and non-conformances, as well as appropriate measures used to correct and prevent such problems and non-conformances from recurring. The CAPA system must account for investigations into failures in the device constituent. CAPA activities for the analysis of sources of quality data to identify existing and potential cause of non-conformances, related investigations, and actions considered to correct and prevent recurrences of problems and non-conformances, including the verification or validation of the actions should be documented under the firm's CAPA System as described in 21 CFR 820.100.

You may find useful information regarding the types of documents to provide in the document called 'Quality System Information for Certain Premarket Application Reviews; Guidance for Industry and FDA Staff,' (2003). This document may be found at <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070897.htm>

Please confirm receipt of this information request, and provide an official response to the BLA no later than May 3, 2016, or provide a timeframe for when responses will be submitted. If you have any questions, please contact me at 301-796-3420. Thank you for your cooperation.

Regards,
Christine

Christine Ford, MS, RPh
CDR, USPHS
Sr. Regulatory Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products
FDA/CDER/OND/ODE II
Phone 301-796-3420
Fax 301-796-9728
christine.ford@fda.hhs.gov

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/s/

CHRISTINE H CHUNG

04/21/2016

Christine Ford (formerly Chung)

Ford, Christine

From: Ford, Christine
Sent: Thursday, April 14, 2016 12:10 PM
To: 'Sarah.Feathers@genzyme.com'
Cc: Ford, Christine
Subject: BLA 761037 sarilumab: IFU for PFS and PFS-S

Dear Sarah,

We acknowledge your March 31, 2016, submission to BLA 761037 for sarilumab and have the following comment:

We recommend that Sanofi (b) (4) match the prefilled syringe (PFS) IFU submitted on October 30, 2015, and currently under review for BLA 761037. Our preliminary analysis has found the PFS-IFU sufficient, and no deficiencies have been identified at this time. Please note however that the PFS-IFU is still under review and additional comments may be forthcoming.

Please confirm receipt of this communication, and contact me at 301-796-3420 if you have any questions.

Regards,
Christine

Christine Ford, MS, RPh
CDR, USPHS
Sr. Regulatory Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products
FDA/CDER/OND/ODE II
Phone 301-796-3420
Fax 301-796-9728
christine.ford@fda.hhs.gov

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/s/

CHRISTINE H CHUNG

04/14/2016

Christine Ford (formerly Chung)

Ford, Christine

From: Ford, Christine
Sent: Thursday, April 07, 2016 2:54 PM
To: 'Sarah.Feathers@genzyme.com'
Cc: Ford, Christine
Subject: Request for information BLA 761037 sarilumab device

Dear Sarah,
BLA 761037 for sarilumab is currently under review, and we have the following request for information.

You have identified DMF [REDACTED] ^{(b) (4)} for the device constituent of your combination product. However, additional information within your BLA could not be located and is needed for the device constituent. Please provide the following:

- We are unable to locate the design specifications for your device constituent. A complete description of the design input controls in the form of device requirements and specifications, which fully describe the attributes of the system and their acceptability in the context of the intended use of the system and the medication being delivered is needed. Provide the detailed location where this information can be found.
- We are unable to locate the risk analysis which characterizes and evaluates the risks to the user or patient both during normal use, reasonable foreseeable mis-use, and potential system failure states. Such an analysis should clearly describe system hazards, mitigations implemented to reduce the risk of those hazards, effectiveness of the mitigation, as well as conclusions of the acceptability of system risks within the final finished system. If the requested analysis has been already submitted, please provide location where these files may be found.
- Provide the location of the dose accuracy testing for your device.

Please confirm receipt of this information request, and provide an official response to the BLA no later than April 20, 2016, if possible. If you have any questions, please contact me at 301-796-3420. Thank you for your cooperation.

Regards,
Christine

Christine Ford, MS, RPh
CDR, USPHS
Sr. Regulatory Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products
FDA/CDER/OND/ODE II
Phone 301-796-3420
Fax 301-796-9728
christine.ford@fda.hhs.gov

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/s/

CHRISTINE H CHUNG

04/07/2016

Christine Ford (formerly Chung)



BLA 761037

MID-CYCLE COMMUNICATION

Sanofi US Services Inc.
55 Corporate Drive
Bridgewater, NJ 08807

Attention: Sarah Feathers, PharmD
Global Regulatory Affairs

Dear Dr. Feathers:

Please refer to your Biologics License Application (BLA) dated and received October 30, 2015, submitted under section 351(a) of the Public Health Service Act for (b) (4) (sarilumab) injection, 150 mg and 200 mg pre-filled syringes (PFS).

We also refer to the teleconference between representatives of your firm and the FDA on April 6, 2016. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call me at (301) 796-3420.

Sincerely,

{See appended electronic signature page}

Christine Ford, MS, RPh
CDR, U.S. Public Health Service
Sr. Regulatory Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Mid-Cycle Communication



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MID-CYCLE COMMUNICATION

Meeting Date and Time: April 6, 2016 11:00 A.M. – 12:00 P.M.

Application Number: BLA 761037
Product Name: sarilumab injection, 150 mg and 200 mg pre-filled syringes (PFS)
Indication: Rheumatoid arthritis
Applicant Name: Sanofi

Meeting Chair: Dr. Janet Maynard, Cross Discipline Team Leader
Meeting Recorder: Christine Ford, Regulatory Project Manager

FDA ATTENDEES:

Janet Maynard, MHS, MD, Cross-Discipline Team Leader
Suzette Peng, MD, Medical Officer
Tim Robison, PhD, Nonclinical Team Leader
Eleni Salicru, PhD, Nonclinical Reviewer
Christine Ford, MS, RPh, Regulatory Project Manager
Gregory Levin, PhD, Biometrics Team Leader
Yongman Kim, PhD, Biometrics Reviewer
Gerald Feldman, PhD, Product Quality Reviewer
Frederick Mills, PhD, Product Quality Reviewer
Lakshmi Narasimhan, PhD, Microbiologist
Anshu Marathe, PhD, Clinical Pharmacology Team Leader
Jianmeng Chen, PhD, Clinical Pharmacology Reviewer
Marc Goldstein, Eastern Research Group

APPLICANT ATTENDEES:

Sanofi:
Simon Cooper, MBBS, Vice President, Global Project Head, Immunology and Inflammation
Owen Hagino, MD, Associate Vice President, Clinical, IL6 Sarilumab
Alex Boddy, MS, Senior Director, Biostatistics
Peter Glascott, PhD, Senior Director, Preclinical Safety; Disposition, Safety and Animal Research
Christine Xu, PhD, Lead Research Investigator II
Deborah Thomas, Senior Director, Reg CMC, Devices
Doris Beyer, MD, MS, Director Global Safety Officer
Pierre Wils, PhD, CMC project leader
Sarah Feathers, PharmD, Global Regulatory Lead, Sarilumab

Regeneron:

Neil Graham, MD, VP, Program Direction
Janet Van Adelsberg, MD, Sr. Director, Clinical Sciences
Janie Parrino, MD, Director, Clinical Sciences
Gene Zhu, PhD, Director, CMC Regulatory Affairs
Albert Torri, PhD, Exec Director, Bioanalytical Sciences
Pat Reilly, PhD, Sr. Director, Regulatory Affairs
Michele Lastro, PhD, Associate Director, CMC Regulatory Sciences

1.0 INTRODUCTION

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

2.0 SIGNIFICANT ISSUES

Clinical

- a. You propose use of 200 mg of sarilumab once every 2 weeks by subcutaneous (SC) injection for the treatment of moderately to severely active rheumatoid arthritis. Reduction of dose from 200 mg every 2 weeks to 150 mg SC once every 2 weeks is recommended for management of neutropenia, thrombocytopenia, and elevated liver enzymes. The overall safety and efficacy of each dose will be reviewed to determine whether the data are adequate to support one or two doses or a weight-tiered starting dose. No additional information or analyses were requested from the Applicant at this time.
- b. Treatment with sarilumab is associated with increases in lipid parameters, such as LDL cholesterol, HDL cholesterol, and triglycerides. Whether additional data are needed to assess potential risks associated with increases in lipid parameters, such as serious cardiovascular events, is under review. While no additional analyses are requested at this time, it is possible that post marketing data would be requested to address this issue.
- c. For your pediatric plan, we note that you have proposed a dose-finding study in children with polyarticular juvenile idiopathic arthritis (pJIA) (DRI13925) and a (b) (4) study to assess efficacy and safety in children with pJIA (EFC11783). It is possible that your pJIA program could be streamlined to include fewer pediatric studies. Specifically, it is possible that you could potentially combine your pediatric studies in pJIA so that your development

program consists of a larger PK study evaluating the safety and efficacy of several doses of sarilumab.

Sanofi clarified that study DRI13925 will start very soon and, thus, it may not be feasible to modify the pediatric plan at this time.

- d. The proposed prescribing information for sarilumab includes safety information from the 12-week placebo controlled population from the two phase 3 efficacy studies from weeks 0 to 12. Given the complexities in the study design of the phase 3 studies and the differences in the study, the optimal presentation of the safety data is under review. It may be preferable to display the safety data for the pre-rescue period, containing data from 0-12 weeks from EFC10832 and 0-16 weeks from EFC11072.

3.0 INFORMATION REQUESTS

- a. Provide the serious adverse events by system organ class and preferred term for the treatment groups for the pre-rescue period, containing data from 0-12 weeks from EFC10832 and 0-16 weeks from EFC11072 for the placebo-controlled safety population (Pool 1).
- b. The bacterial retention study (b) (4) does not appear to be adequate. The applicant's submission dated March 15, 2016 (response to information request), stated that an additional study was performed (b) (4). Submit the protocol and report for this (b) (4) validation study to the BLA file.
- c. We note that real-time stability studies under the proposed or expected storage conditions are available for most, but not all, of the various batches of DS, (b) (4) or DP listed. Provide a complete stability update for all lots described in the BLA for which stability was being assessed.

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

We note that you have proposed a medication guide and communication plan as part of a REMS. While it is reasonable to have a medication guide and communication plan, at this point, we do not anticipate that they would be part of a REMS.

5.0 ADVISORY COMMITTEE MEETING

There are no plans at this time for an AC meeting.

6.0 LATE-CYCLE MEETING /OTHER PROJECTED MILESTONES

LCM is scheduled for July 25, 2016, and the PDUFA goal date is October 30, 2016.

Additional discussion

Sanofi asked the Division if any additional data or information were needed to support the use of sarilumab with or without methotrexate. They noted that data from a study comparing sarilumab monotherapy to adalimumab was submitted to the EMA and could also be submitted to the FDA.

FDA stated that no additional data are requested at this time and that it may be possible to further discuss this at the late cycle meeting.

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/s/

CHRISTINE H CHUNG

04/19/2016

Christine Ford (formerly Chung)



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761037

**PROPRIETARY NAME REQUEST
ACKNOWLEDGEMENT/WITHDRAWAL**

Sanofi-aventis U.S. LLC 500 Kendall Street
Cambridge, MA 02142

ATTENTION: Sarah Feathers, PharmD
Global Regulatory Lead, Global Regulatory Affairs

Dear Dr. Feathers:

Please refer to your Biologics License Application (BLA) dated and received on October 30, 2015, submitted under section 351(a) of the Public Health Service Act for Sarilumab, 150 mg/1.14 mL and 200 mg/1.14 mL.

We also refer to your correspondence, dated and received on March 16, 2016, notifying us that you are withdrawing your request for a review of the proposed proprietary name (b) (4). Therefore, (b) (4) is considered withdrawn as of March 16, 2016.

Finally, we refer to your correspondence, dated and received on March 16, 2016, requesting review of your proposed proprietary name, Kevzara. Upon preliminary review of your submission, we have determined that it is a complete submission as described in the Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names*, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>.

Therefore, the user fee goal date is June 14, 2016.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Neil Vora, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-4845. For any other information regarding this application, contact Christine Ford, Regulatory Project Manager in the Office of New Drugs, at (301) 796-3420.

Sincerely,

{See appended electronic signature page}

Neil Vora, PharmD, MBA
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

NEIL VORA
03/31/2016

Ford, Christine

From: Ford, Christine
Sent: Tuesday, March 29, 2016 10:06 AM
To: 'Sarah.Feathers@genzyme.com'
Cc: Ford, Christine
Subject: Request for information BLA 761037 sarilumab: IFU for PFS-S

Dear Sarah,
BLA 761037 for sarilumab is currently under review, and we have the following request for information:

We acknowledge in your responses to the information requests, dated March 22 and 25, 2016, that while it is still under internal discussion, Sanofi currently intends to [REDACTED] (b) (4)

As the IFU for the PFS was tested in a human factors validation study, submitted on October 30, 2015 [REDACTED] (b) (4)
[REDACTED] we recommend that Sanofi revise the proposed IFU [REDACTED] (b) (4)

Please confirm receipt of this information request, and provide an official response to the BLA no later than April 4, 2016. If you have any questions, please contact me at 301-796-3420. Thank you for your cooperation.

Regards,
Christine

Christine Ford, MS, RPh
CDR, USPHS
Sr. Regulatory Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products
FDA/CDER/OND/ODE II
Phone 301-796-3420
Fax 301-796-9728
christine.ford@fda.hhs.gov

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/s/

CHRISTINE H CHUNG

03/29/2016

Christine Ford (formerly Chung)

Ford, Christine

From: Ford, Christine
Sent: Monday, March 21, 2016 2:07 PM
To: 'Sarah.Feathers@genzyme.com'
Cc: Ford, Christine
Subject: Request for information BLA 761037 sarilumab

Importance: High

Dear Sarah,
BLA 761037 for sarilumab is currently under review, and we have the following request for information:

You noted that there were 2 additional deaths between April 30 and July 31, 2015. Submit the narratives for these deaths. If they have previously been submitted, provide location where these files may be found.

Please confirm receipt of this information request, and provide an official response to the BLA no later than March 22, 2016, if possible. If you have any questions, please contact me at 301-796-3420. Thank you for your cooperation.

Regards,
Christine

Christine Ford, MS, RPh
CDR, USPHS
Sr. Regulatory Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products
FDA/CDER/OND/ODE II
Phone 301-796-3420
Fax 301-796-9728
christine.ford@fda.hhs.gov

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/s/

CHRISTINE H CHUNG

03/21/2016

Christine Ford (formerly Chung)

Vora, Neil

From: Vora, Neil
Sent: Tuesday, March 15, 2016 8:34 AM
To: 'Sarah.Feathers@genzyme.com'
Subject: RE: BLA 761037 Proprietary Name

Hi good morning Sarah,

Sorry for the delayed response.

In regards to your question, you can do either. However, for ease of the reviewer the labeling can be appended to the PNR submission **OR** you may insert a link in the new Proprietary Name submission to the new labeling in mod 1.14.

Hope this helps!

Thanks,
Neil

Neil Vora, PharmD, MBA

Safety Regulatory Project Manager | OSE | CDER | FDA | 240.402.4845 | Neil.Vora@fda.hhs.gov

From: Sarah.Feathers@genzyme.com [mailto:Sarah.Feathers@genzyme.com]
Sent: Thursday, March 10, 2016 12:44 PM
To: Vora, Neil
Subject: RE: BLA 761037 Proprietary Name

Dear Neil,

Sanofi has decided to move forward with submission of a new proposed proprietary name for sarilumab (BLA 761037 currently under review). Sanofi plans to withdraw conditional approval of (b) (4) and submit a new proprietary name review request early next week. With regard to the proprietary name review request, the "Guidance for Industry - Contents of a Complete Submission for the Evaluation of Proprietary Names," articulates the submission should include the proposed labeling (including PI, Med guide, instructions for use) and carton and containers. In order to facilitate ease of review for the division, I would like to confirm if the proposed labeling and carton and containers should be appended to the proprietary name request or should the labeling files located in module 1.14 in the BLA be replaced as part of the proprietary name request submission. I appreciate your assistance in this matter.

Kindly,
Sarah

Sarah Feathers, PharmD

Global Regulatory Affairs

Genzyme center, 500 Kendall Street, Cambridge, MA – 02142 |

Tel: +1 617-768-6099 | cell: (b) (6)

Email: sarah.feathers@genzyme.com



From: Vora, Neil [<mailto:Neil.Vora@fda.hhs.gov>]
Sent: Monday, February 29, 2016 10:27 AM
To: Feathers, Sarah GZ/US
Subject: RE: BLA 761037 Proprietary Name

Hi good morning Sarah,

Yes, if Genzyme wishes to submit a new PNR for review, then you would have to withdraw (b) (4). The new PNR request would have a 90-day review. In the event of a rejection, a new 90-day clock would start upon the submission of another name (either (b) (4) or other). I hope this helps.

Thanks,
Neil

From: Sarah.Feathers@genzyme.com [<mailto:Sarah.Feathers@genzyme.com>]
Sent: Friday, February 26, 2016 4:25 PM
To: Vora, Neil
Subject: RE: BLA 761037 Proprietary Name

Hi Dr Vora,

Thank you for your quick response. Currently, our team is assessing the possibility of a different trade name for sarilumab. However, as part of that assessment, we want to understand the implications to our current conditionally approved tradename. In the event that we do wish to submit an alternate name to the BLA, would we have to withdraw (b) (4) first (and therefore no longer have conditional approval)?

I am happy to discuss more via telephone if that is more convenient for you.

Kindly,
Sarah

Sarah Feathers, PharmD

Global Regulatory Affairs

Genzyme center, 500 Kendall Street, Cambridge, MA – 02142 |

Tel: +1 617-768-6099 | cell: (b) (6)

Email: sarah.feathers@genzyme.com



From: Vora, Neil [<mailto:Neil.Vora@fda.hhs.gov>]
Sent: Friday, February 26, 2016 3:32 PM
To: Feathers, Sarah GZ/US
Subject: RE: BLA 761037 Proprietary Name

Hi good afternoon Sarah, thank you for your email.

We have couple questions for your team. Per our records, Genzyme submitted the proposed proprietary name, (b) (4) to this BLA on Oct. 30, 2015 and DMEPA conditionally accepted the name on Dec. 21, 2015. Can you confirm if the team would like to withdraw the proposed name, (b) (4) and submit an alternate proprietary name?

Thank you again, and have a good weekend.

Kind Regards,
Neil

Neil Vora, PharmD, MBA

Safety Regulatory Project Manager | OSE | CDER | FDA | 240.402.4845 | Neil.Vora@fda.hhs.gov

From: Sarah.Feathers@genzyme.com [<mailto:Sarah.Feathers@genzyme.com>]

Sent: Friday, February 26, 2016 1:56 PM

To: Vora, Neil

Subject: BLA 761037 Proprietary Name

Dear Mr. Vora,

Christine Ford, regulatory project manager for Sarilumab (IND 100632; BLA 761037), suggested I reach out to you regarding conditional approval of the proprietary name (b) (4) as referenced in the attached communication dated April 23, 2015. Can you please advise, should Sanofi wish to use a different proprietary name, would the conditional approval for (b) (4) be withdrawn? If so, should the new proposed proprietary name be rejected, would (b) (4) need to be "re-reviewed" with a 90 day review clock as referenced in "Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names."

I appreciate your guidance with this matter.

Kind regards,
Sarah

Sarah Feathers, PharmD

Global Regulatory Affairs

Genzyme center, 500 Kendall Street, Cambridge, MA – 02142 |

Tel: +1 617-768-6099 | cell: (b) (6)

Email: sarah.feathers@genzyme.com



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/s/

NEIL VORA
03/29/2016

Ford, Christine

From: Ford, Christine
Sent: Thursday, March 10, 2016 4:26 PM
To: 'Sarah.Feathers@genzyme.com'
Cc: Ford, Christine
Subject: RE: BLA 761037 sarilumab biometrics information request

Hi Sarah,
We have the following response to your email below:

We derived the numbers submitted in the earlier information request (IR) with an approach that considered patients who had missing data to meet the lack of 20% improvement rescue criteria at that visit. Your proposed alternative approach to exclude from the denominator those patients with missing Week 12 or 16 data is reasonable. We also agree with your plan to respond to our IR based on the numbers you have generated and to include a detailed description of how the numerators and denominators for each group were defined.

Please contact me if there are additional questions. thanks
Christine

Christine Ford, MS, RPh
CDR, USPHS
Sr. Regulatory Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products
FDA/CDER/OND/ODE II
Phone 301-796-3420
Fax 301-796-9728
christine.ford@fda.hhs.gov

From: Sarah.Feathers@genzyme.com [<mailto:Sarah.Feathers@genzyme.com>]
Sent: Wednesday, March 09, 2016 3:03 PM
To: Ford, Christine
Subject: RE: BLA 761037 sarilumab biometrics information request

Hi Christine,
As we discussed via telephone, the stats team has not been able to replicate the patient numbers provided in the sarilumab biometrics information request received March 7th 2016 (below for reference; number of patients eligible for rescue in Cohort B of Study EFC11072). The Sanofi generated and Agency generated numbers are included in the table below. Sanofi included the following definition to calculate the denominator (number of patients eligible for rescue): Number of pts meeting criteria for rescue , <20% improvement in TJC or SJC at week 12 AND week 16 [Note: included subjects who met TJC criteria at one visit and SJC at the other; if week 12 or 16 is missing subject was treated as not qualified for rescue]

Sanofi plans to respond to the Agency request based on the numbers we have generated and include a detailed description of how the numerators and denominators for each group were defined. We would appreciate if the review team could advise how they derived the numbers of patients eligible for rescue for our understanding.

Study EFC11072 Cohort B: Number of patients who received rescue therapy/number of patients eligible for rescue

	Sanofi Generated	FDA Generated
Placebo	75/127 (59%)	75/140 (54%)
150mg	20/52 (38%)	19/79 (24%)
200mg	20/47 (43%)	20/71 (28%)

Please let me know if you or your team have any questions.

Kindly,

Sarah

Sarah Feathers, PharmD

Global Regulatory Affairs

Genzyme center, 500 Kendall Street, Cambridge, MA – 02142 |

Tel: +1 617-768-6099 | cell (b) (6)

Email: sarah.feathers@genzyme.com



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/s/

CHRISTINE H CHUNG

03/11/2016

Christine Ford (formerly Chung)

Ford, Christine

From: Ford, Christine
Sent: Monday, March 07, 2016 12:02 PM
To: 'Sarah.Feathers@genzyme.com'
Cc: Ford, Christine
Subject: BLA 761037 sarilumab biometrics information request

Dear Sarah,

BLA 761037 for sarilumab is currently under review, and we have the following request for information:

Your protocol for Study EFC11072 indicates that "from Week 16, patients with lack of efficacy defined as less than 20% improvement from baseline in either SJC or TJC for two consecutive visits, or any other clear lack of efficacy based on investigator judgment will be proposed to be rescued with open-label SAR153191 highest available dose..."

We calculate that, among patients in part B cohort 2 who were eligible for escape at Week 16 according to the swollen and tender joint count criteria, 75/140 (54%) of patients on placebo initiated rescue therapy, as compared to 19/79 (24%) and 20/71 (28%) of patients on sarilumab 150 mg and 200 mg, respectively. We calculated relatively similar results in Study EFC10832, with smaller differences between treatment arms in the proportions. Please clarify why such low proportions of patients on all treatment arms who met the escape criteria actually initiated escape therapy. In addition, while we recognize that the comparison between treatment arms is no longer a randomized comparison, provide any insight you may have into why a greater proportion of patients on placebo than sarilumab who met the rescue criteria actually initiated rescue therapy. (We note that a similar trend was observed for the proportions who initiated rescue by investigator judgment). The manner in which rescue is implemented is important because patients who initiated rescue were considered non-responders in the primary analysis of ACR20 at Week 24.

In addition, we remind you of our request for additional supportive and sensitivity analyses in the 74-day letter issued January 12, 2016.

Provide the requested analyses no later than Wednesday, March 16, 2016, and contact me if you have any questions at 301-796-3420. Thank you.

Regards,
Christine

Christine Ford, MS, RPh
CDR, USPHS
Sr. Regulatory Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products
FDA/CDER/OND/ODE II
Phone 301-796-3420
Fax 301-796-9728
christine.ford@fda.hhs.gov

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/s/

CHRISTINE H CHUNG

03/07/2016

Christine Ford (formerly Chung)



BLA 761037

INFORMATION REQUEST

Sanofi-aventis U.S. LLC
Attention: Jennifer Cairns, Ph.D.
Director, Global Regulatory Affairs
55 Corporate Drive, Mail Stop 55D-220B
Bridgewater, NJ 08807

Dear Dr. Cairns:

Please refer to your Biologics License Application (sBLA) dated and received October 30, 2015, submitted under section 351(a) of the Public Health Service Act for sarilumab (SAR153191/REGN88).

We are reviewing your submission and have the following request for information. We request a prompt written response by March 15, 2016 in order to continue our evaluation of your application.

I. Container closure integrity test

1. Please clarify and confirm if the PFS used for qualification of microbial immersion and dye ingress test methods are the same as the commercial PFS.
2. Please submit the following information regarding microbial ingress method for CCI testing performed after manufacturing operations:
 - a. details of the positive control preparation
 - b. sensitivity of the method (LOD) as a function of breach size.
 - c. describe how the final concentration of challenge organism was verified (b) (4)
3. Please implement a system suitability control with a small breach size, (b) (4) μm for the routine dye ingress CCI test at Regeneron and Sanofi.

II. Drug product manufacturing process

1. Please update the section 3.2.P.3 with
 - a. description (b) (4)
 - b. room, area and fill line used for syringe filling and also provide the list of other products filled on this line.
2. As stated in process validation section (P.3.5), revise Section P.3.3 to reflect that bioburden is monitored (b) (4) during the Sarilumab drug product manufacturing process and provide the bioburden acceptance criteria.

3. Please describe [redacted] (b) (4) and provide the exact location [redacted] (b) (4).
A diagram will be useful.
4. Please implement [redacted] (b) (4) during routine manufacturing.

III. Process Validation

1. During process validation, how many PFS were subjected to [redacted] (b) (4)?
2. Please provide the processing and hold time limits [redacted] (b) (4).
3. The [redacted] (b) (4) step has been validated [redacted] (b) (4). You have stated [redacted] (b) (4).
Please clarify and explain [redacted] (b) (4).

[redacted] (b) (4) validation:

4. Please provide a comparison of validated [redacted] (b) (4) parameters with that of routine production parameters.
5. The justification [redacted] (b) (4) does not appear to be acceptable. [redacted] (b) (4)

Hold time:

6. The time limit [redacted] (b) (4) is not clearly defined [redacted] (b) (4). Please clarify.

Sterilization Validation [redacted] (b) (4)

7. Please provide [redacted] (b) (4) validation data summaries for the assembly which contains [redacted] (b) (4). This information should include initial sterilization dose establishment report, dose mapping report, and quarterly dose audit report. Alternatively provide a Letter of Authorization to cross reference a DMF containing pertaining information.
8. Regarding the [redacted] (b) (4) provide a comparison [redacted] (b) (4) used for production and validation.

Media Fill:

9. You have provided information and data on media fills [redacted] (b) (4) performed [redacted] (b) (4). Please provide the three most recent media fills performed [redacted] (b) (4) used for Sarilumab product fill. Please include environmental monitoring summary data obtained during these runs and the results from the growth promotion verification tests.
10. Please clarify whether positive units in a media fill are identified to the genus/species level.

If you have questions, call me, at (301) 796-0906.

Sincerely,

Melinda J.

Bauerlien -S

Digitally signed by Melinda J.
Bauerlien -S
DN: c=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=130017
8565, cn=Melinda J. Bauerlien -S
Date: 2016.03.03 11:37:32 -05'00'

Melinda Bauerlien, M.S.

Senior Regulatory Business Process Manager

Office of Program and Regulatory Operations

Office of Pharmaceutical Quality

Center for Drug Evaluation and Research

Vora, Neil

From: Sarah.Feathers@genzyme.com
Sent: Monday, February 29, 2016 10:41 AM
To: Vora, Neil
Subject: RE: BLA 761037 Proprietary Name

Follow Up Flag: Follow up
Flag Status: Flagged

Hi Neil,

Thank you for the feedback. This is very helpful.

Kindly,
Sarah

Sarah Feathers, PharmD

Global Regulatory Affairs
Genzyme center, 500 Kendall Street, Cambridge, MA – 02142 |
Tel: +1 617-768-6099 | cell: (b) (6)
Email: sarah.feathers@genzyme.com



From: Vora, Neil [<mailto:Neil.Vora@fda.hhs.gov>]
Sent: Monday, February 29, 2016 10:27 AM
To: Feathers, Sarah GZ/US
Subject: RE: BLA 761037 Proprietary Name

Hi good morning Sarah,

Yes, if Genzyme wishes to submit a new PNR for review, then you would have to withdraw (b) (4). The new PNR request would have a 90-day review. In the event of a rejection, a new 90-day clock would start upon the submission of another name (either (b) (4) or other). I hope this helps.

Thanks,
Neil

From: Sarah.Feathers@genzyme.com [<mailto:Sarah.Feathers@genzyme.com>]
Sent: Friday, February 26, 2016 4:25 PM
To: Vora, Neil
Subject: RE: BLA 761037 Proprietary Name

Hi Dr Vora,

Thank you for your quick response. Currently, our team is assessing the possibility of a different trade name for sarilumab. However, as part of that assessment, we want to understand the implications to our current conditionally

approved tradename. In the event that we do wish to submit an alternate name to the BLA, would we have to withdraw (b) (4) first (and therefore no longer have conditional approval)?

I am happy to discuss more via telephone if that is more convenient for you.

Kindly,
Sarah

Sarah Feathers, PharmD

Global Regulatory Affairs

Genzyme center, 500 Kendall Street, Cambridge, MA – 02142 |

Tel: +1 617-768-6099 | cell: (b) (6)

Email: sarah.feathers@genzyme.com



From: Vora, Neil [<mailto:Neil.Vora@fda.hhs.gov>]

Sent: Friday, February 26, 2016 3:32 PM

To: Feathers, Sarah GZ/US

Subject: RE: BLA 761037 Proprietary Name

Hi good afternoon Sarah, thank you for your email.

We have couple questions for your team. Per our records, Genzyme submitted the proposed proprietary name, (b) (4) to this BLA on Oct. 30, 2015 and DMEPA conditionally accepted the name on Dec. 21, 2015. Can you confirm if the team would like to withdraw the proposed name, (b) (4) and submit an alternate proprietary name?

Thank you again, and have a good weekend.

Kind Regards,
Neil

Neil Vora, PharmD, MBA

Safety Regulatory Project Manager | OSE | CDER | FDA | 240.402.4845 | Neil.Vora@fda.hhs.gov

From: Sarah.Feathers@genzyme.com [<mailto:Sarah.Feathers@genzyme.com>]

Sent: Friday, February 26, 2016 1:56 PM

To: Vora, Neil

Subject: BLA 761037 Proprietary Name

Dear Mr. Vora,

Christine Ford, regulatory project manager for Sarilumab (IND 100632; BLA 761037), suggested I reach out to you regarding conditional approval of the proprietary name (b) (4) as referenced in the attached communication dated April 23, 2015. Can you please advise, should Sanofi wish to use a different proprietary name, would the conditional approval (b) (4) be withdrawn? If so, should the new proposed proprietary name be rejected, would (b) (4) need to be "re-reviewed" with a 90 day review clock as referenced in "Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names."

I appreciate your guidance with this matter.

Kind regards,
Sarah

Sarah Feathers, PharmD

Global Regulatory Affairs

Genzyme center, 500 Kendall Street, Cambridge, MA – 02142 |

Tel: +1 617-768-6099 | cell: (b) (6)

Email: sarah.feathers@genzyme.com



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/s/

NEIL VORA
02/29/2016

Ford, Christine

From: Ford, Christine
Sent: Wednesday, February 24, 2016 4:46 PM
To: 'Sarah.Feathers@genzyme.com'
Cc: Ford, Christine
Subject: Request for information: BLA 761037 (b) (4) (sarilumab) - Nonclinical

Dear Sarah,

BLA 761037 for (b) (4) is currently under review, and we have the following request for information:

We note the protocol for "REGN844: 9-Week Subcutaneous Toxicity Study in the Juvenile Mouse Followed by a 13-Week Recovery Period" (Sanofi Reference #: JUV0030/Regeneron Reference #: REGN844-TX-1306) in your submission. If a draft or final report of this study is available, submit it to the BLA.

Provide your response no later than March 7, 2016. If you have any questions, please contact me at 301-796-3420. Thank you for your cooperation.

Regards,
Christine

Christine Ford, MS, RPh
CDR, USPHS
Sr. Regulatory Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products
FDA/CDER/OND/ODE II
Phone 301-796-3420
Fax 301-796-9728
christine.ford@fda.hhs.gov

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/s/

CHRISTINE H CHUNG

02/24/2016

Christine Ford (formerly Chung)



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

ELECTRONIC CORRESPONDENCE

Date: February 17, 2016

To: Sarah Feathers, PharmD Global Regulatory Affairs	From: Christine Ford, MS, RPh Regulatory Project Manager
Company: Sanofi-Aventis U.S. LLC	Division of Pulmonary, Allergy, and Rheumatology Products
Phone: 617-768-6099	Fax number: 301-796-9728
Email: sarah.feathers@genzyme.com	Phone number: 301-796-3420

Subject: BLA 761037 (b)(4) (sarilumab)
FDA request for information from Office of Scientific Investigations

Total no. of pages including cover: 4

Comments: *Information requested by no later than cob Friday, February 19, 2016*

Please call or send an email to confirm receipt at christine.ford@fda.hhs.gov

Document to be mailed: YES NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-3420. Thank you.

BLA 761037 for (b) (4) (sarilumab) prefilled syringes is currently under review, and we have the following request for information:

Submit the study subject data listing information requested below grouped as pdf files, stratified (organized) by clinical study investigator site separately (that is, all requested pdf information for a to f, in one pdf, for each principal investigator site) for Protocol EFC11072 (Part B) or Protocol EFC10832, as applicable, and for the following Principal Investigators:

- (1) Eric Lee, M.D., Site 840049 (Upland, CA),
- (2) Jacob Aelion, M.D., Site 840025 (Jackson, TN), and
- (3) Jeffrey Kaine, M.D., Site 840060 (Sarasota, FL).

- a. Subject discontinuations [if applicable, sorted by treatment group and including the following variables: site subject number, screening visit date, randomization date (if applicable), date of first dose/last dose, date of discontinuation, reason for discontinuation].
- b. Subject assignment per treatment arm (randomization group, if applicable).
- c. Concomitant medication list (non-study medications).
- d. All adverse events (if applicable, per treatment group: preferred term/investigator entry, date start/stopped, severity/resolution, serious adverse event (SAE [yes/no], death [yes/no]).
- e. Protocol deviations or violations.
- f. Primary study efficacy endpoint/s. [Note: Submit the actual raw item response per patient per study visit (that is, not derived/calculated data, not summed subscore or not the total score e.g., for each patient).

For example, provide the following individual item response for each visit (as applicable):

- i. actual individual item response of the VAS on a 100-mm horizontal VAS for the patient for that particular study visit;
- ii. Subject's/Investigator's Global Health Assessment (0 to 10) for each study visit, for the individual patient;
- iii. individual item response per patient, per visit for each of these individual items separately: [(dressing, grooming, arising, eating, walking), personal abilities(each patient score for hygiene, reach, grip, activity), use of aids, etc.],
- iv. joint swelling per joint site affected, and joint tenderness per joint site affected response item(s), per patient per visit.

Provide the following total score per patient per visit (as applicable): Van der Heijde total Sharp score.

Additionally, please submit adequate supportive documentations (between you as sponsor of the application and the study site, or your CRO and the clinical study site), IF these primary efficacy endpoint raw data from the clinical study site

(source documentation) were re-edited after data lock. Otherwise, submit any relevant documents, as deemed necessary.

Submit all versions and amendments of the informed consent documents (foreign and domestic versions), IF not submitted previously under the BLA.

The requested information should be submitted as official responses to the BLA no later than close of business Friday, February 19, 2016, or provide a timeline for when the information will be submitted.

If you have any questions, please contact Christine Ford at 301-796-3420.

APPEARS THIS WAY ON ORIGINAL

Drafted by: AOrencia/ 2.12.2016
cford/ 2.16.2016

Initialed by: SBarnes/ 2.16.2016
SPeng, JMaynard/ 2.17.2016

Finalized: cford/ 2.17.2016

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/s/

CHRISTINE H CHUNG

02/17/2016

Christine Ford (formerly Ford)



BLA 761037

**FILING COMMUNICATION -
NO FILING REVIEW ISSUES IDENTIFIED**

Sanofi US Services Inc.
55 Corporate Drive
Bridgewater, NJ 08807

Attention: Jennifer Cairns, Ph.D
Director, Global Regulatory Affairs

Dear Dr. Cairns:

Please refer to your Biologics License Application (BLA) dated and received October 30, 2015, submitted under section 351(a) of the Public Health Service Act for (b) (4) (sarilumab) injection, 150 mg and 200 mg pre-filled syringes (PFS).

We also refer to your amendment dated December 14, 2015.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 601.2(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is October 30, 2016. This application is also subject to the provisions of “the Program” under the Prescription Drug User Fee Act (PDUFA) V (refer to <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>).

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by September 6, 2016.

In addition, our internal mid-cycle review meeting is planned during the week of May 23, 2016. We are not currently planning to hold an advisory committee meeting to discuss this application.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

We request that you submit the following information:

1. For all endpoints proposed for inclusion on the product label, we request additional supportive analyses that include all observed data, including any outcomes collected after escape or discontinuation of study medication.
2. You have not provided sensitivity analyses that sufficiently evaluate the potential impact of missing data on the reliability of efficacy results. For co-primary endpoints, examine the potential effects of missing data and rescue on your results using tipping point sensitivity analyses. These tipping point analyses should include all observed data, including outcomes after patients discontinue study therapy or initiate rescue medications, and should vary assumptions about outcomes among the subsets of patients on the sarilumab and placebo arms who withdrew from the study prior to the planned endpoint. The varying assumptions should include scenarios where dropouts on sarilumab had worse future outcomes than dropouts on placebo. The goal is to identify assumptions under which the conclusions change, i.e., under which there is no longer evidence of a treatment effect. Then, the plausibility of those assumptions can be discussed.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [Pregnancy and Lactation Labeling Final Rule](#) websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances, and
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

During our preliminary review of your submitted labeling, we have identified the following labeling issues and have the following labeling comments:

Highlights (HL) section

All headings in HL (from Recent Major Changes to Use in Specific Populations) must be **bolded** and presented in the center of a horizontal line. *(Each horizontal line should extend over the entire width of the column.)*

Boxed Warning (BW) in Highlights

The BW title should be centered.

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by February 2, 2016. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), Medication Guide and Instructions for Use. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), Medication Guide and Instructions for Use, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

We acknowledge receipt of your request for a partial waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial waiver request is denied.

We acknowledge receipt of your request for a partial deferral of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial deferral request is denied.

If you have any questions, call Christine Ford, Regulatory Project Manager, at (301) 796-3420.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

BADRUL A CHOWDHURY
01/12/2016

Ford, Christine

From: Ford, Christine
Sent: Monday, December 28, 2015 12:05 PM
To: Jennifer Cairns (jennifer.cairns@sanofi.com)
Cc: Ford, Christine
Subject: Request for information: BLA 761037 (b) (4) (sarilumab) - Clinical Pharmacology

Dear Jennifer,
BLA 761037 for (b) (4) is currently under review, and we have the following request for information:

We refer to section 5.3.3.5, study report POH0455, "Empirical Exposure/Response Modeling of Selected Efficacy and Safety Endpoints for Sarilumab Phase 2/3 studies."

Submit the PK/PD analysis datasets and codes/scripts for reviewers to recreate all the results and figures described in Section 4, and Appendix 1-12 of study report POH0455. All model codes or control streams, output listings and scripts used to generate plots should be provided for all modeling performed. Files should be submitted as ASCII text files with *.txt extension (e.g., myfile_ctl.txt, myfile_out.txt).

Provide your response no later than January 20, 2016. If you have any questions, please contact me at 301-796-3420. Thank you for your cooperation.

Regards,
Christine

Christine Ford, RPh
CDR, USPHS
Sr. Regulatory Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products
FDA/CDER/OND/ODE II
Phone 301-796-3420
Fax 301-796-9728
christine.ford@fda.hhs.gov

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/s/

CHRISTINE H CHUNG

12/28/2015

IR drafted by clinpharm team Jianmeng Chen, Ping Ji; email cleared thru Sandy Barnes, CPMS

12/28/15

Christine Ford (formerly Chung)



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

BLA 761037

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Sanofi-aventis US LLC.
55 Corporate Drive
Mail Stop: 55D-220B
Bridgewater, NJ 08807

ATTENTION: Jennifer Cairns, PhD
Director, Global Regulatory Affairs

Dear Dr. Cairns:

Please refer to your Biologics License Application (BLA) dated and received on October 30 2015, submitted under section 351(a) of the Public Health Service Act for sarilumab, 150 mg/1.4 mL and 200 mg/1.4 mL.

We also refer to your correspondence, dated and received October 30, 2015, requesting review of your proposed proprietary name (b) (4)

We have completed our review of the proposed proprietary name, (b) (4) and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your October 30, 2015, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,
(<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Neil Vora, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-4845. For any other information regarding this application, contact Christine Ford, Regulatory Project Manager in the Office of New Drugs, at (301) 796-3420.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

LUBNA A MERCHANT on behalf of TODD D BRIDGES
12/21/2015



BLA 761037

INFORMATION REQUEST

Sanofi-aventis U.S. LLC
Attention: Marsha Miller, Ph.D.
Director, Global Regulatory Affairs
55 Corporate Drive, Mail Stop 55D-220B
Bridgewater, NJ 08807

Dear Dr. Miller:

Please refer to your Biologics License Application (sBLA) dated and received October 30, 2015, submitted under section 351(a) of the Public Health Service Act for sarilumab (SAR153191/REGN88).

We are reviewing your submission and have the following request for information. We request a written response by December 15, 2015 in order to continue our evaluation of your application.

1. Correction on 356H and S.2.1 Manufacturers for Regeneron Pharmaceuticals, Inc., 26 Tech Valley Drive, East Greenbush, NY 12061
 - a. FEI: 3010277405 is correct not (b) (4).
2. Correction for P.3.1 Manufacturers, Sanofi Winthrop Industrie, LeTrait France site, page 2 of 3:
 - a. FEI: 3003259844, currently DUNS number is listed.
3. Confirm current production schedule for the week of Jan 25th. Also provide detailed production schedule for week of February 1, 2016.
4. Please provide evidence that the drug product formulation does not interfere with endotoxin recovery in the LAL test. Conduct spiking studies on the undiluted drug product with known amount of endotoxin standard (CES or RSE) and simulate the worst-case hold conditions to evaluate endotoxin masking over time. The studies should be conducted using containers of similar composition as those used for the drug product.
5. For the rabbit pyrogen test, please provide the dose used for testing the rabbits, in terms of mg/kg.

If you have questions, call me at (301) 796-0906.

Sincerely,

**Melinda J.
Bauerlien -S**

Digitally signed by Melinda J. Bauerlien -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=1300178565,
cn=Melinda J. Bauerlien -S
Date: 2015.12.01 13:44:52 -05'00'

Melinda Bauerlien, M.S.
Senior Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



BLA 761037

BLA ACKNOWLEDGMENT

Sanofi US Services Inc.
55 Corporate Drive
Bridgewater, NJ 08807

Attention: Jennifer Cairns, Ph.D
Director, Global Regulatory Affairs

Dear Dr. Cairns:

We have received your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for the following:

Biological Product: (b) (4) (sarilumab) injection, 150 and 200 mg pre-filled syringes

Date of Application: October 30, 2015

Date of Receipt: October 30, 2015

Our Reference Number: BLA 761037

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on December 29, 2015, in accordance with 21 CFR 601.2(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 601.14(b) in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action. The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The BLA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Pulmonary, Allergy, and Rheumatology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me at (301) 796-3420.

Sincerely,

{See appended electronic signature page}

Christine Ford, R.Ph.
CDR, U.S. Public Health Service
Sr. Regulatory Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

CHRISTINE H CHUNG

11/06/2015

Christine Ford (formerly Chung)



IND 100632

MEETING MINUTES

Sanofi US Services, Inc.
Attention: Marsha J. Miller, Ph.D.
Director, Global Regulatory Affairs
55 Corporate Drive
Mailstop: 55D-220B
Bridgewater, NJ 08807

Dear Dr. Miller

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for sarilumab.

We also refer to the meeting between representatives of your firm and the FDA on December 16, 2014. The purpose of the meeting is to gain the Agency's concurrence on specific aspects related to CMC topics.

A copy of the official minutes is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, contact me.

Sincerely,

{See appended electronic signature page}

Marjorie Shapiro, Ph.D.
Chief, Laboratory of Molecular and Developmental Immunology
Division of Biotechnology Review and Research I
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: CMC Only

Meeting Date and Time: December 16, 2014 at 1:00 P.M.
Meeting Format: Face to Face

Application Number: 100632
Product Name: sarilumab
Sponsor/Applicant Name: Sanofi U.S. Services, Inc.

Meeting Chair: Marjorie Shapiro
Meeting Recorders: Andrew Shiber

FDA ATTENDEES:

Center for Drug Evaluation and Research

Office of Biotechnology Products (OBP)

Marjorie Shapiro, Ph.D. Team Leader, Division of Monoclonal Antibodies (DMA)
Gerald Feldman, Ph.D. Product Quality, DMA
Andrew Shiber, Pharm.D. Regulatory Project Manager, OBP

Office of Compliance/Biotech Manufacturing Assessment Branch (BMAB)

Patricia Hughes, Ph.D. Team Leader, BMAB
Colleen Thomas, Ph.D. Microbiologist
Lakshmi Narasimhan, Ph.D. Microbiologist

Center for Devices and Radiological Health

Combination Products III

Ryan McGowan Team Leader, Biomedical Engineer

SPONSOR ATTENDEES

Sanofi

Isabelle Baillon Regulatory Site Officer, PSO LeTrait
Farida Laadani Validation Department Representative, Le Trait
Fabrice Leydet, Ph.D. Industrial Affairs Project Leader
Joseph Mezzatesta, Ph.D. Associate Director, Global Regulatory CMC
Marsha Miller, Ph.D. Director, Global Regulatory Affairs
Peter Noolandi Global Device Project Leader
Deborah Thomas, Ph.D. Senior Director, Global Regulatory Devices
Pierre Wils, Ph.D. CMC project leader
Stephen Fitzpatrick, Ph.D. Senior Director, Global Regulatory CMC Biologic Products
Geary E. MacQuiddy Associate Director, Program Management

Regeneron

Rajesh Ahuja, M.S.	Senior Director, Validation
Matthew Elliott, Ph.D.	Associate Director, Quality Control
Jennifer McNay, Ph.D.	Senior Director, Process Sciences
Michele Lastro, Ph.D.	Associate Director, CMC Regulatory Sciences (She is attending in place of Michael Lennick)
Laura Pologe, Ph.D.	Associate Director, Regulatory Affairs
Pat Reilly, Ph.D.	Senior Director, Regulatory Affairs
Gene Zhu, Ph.D.	Senior Director, CMC Regulatory Affairs

1.0 BACKGROUND

Name of drug: sarilumab

Objectives: To gain the Agency's concurrence on specific aspects related to CMC topics.

2.0 DISCUSSION

Prefilled Syringe (PFS)

Question 1:

- a) Does the Agency agree with the proposed strategy for the validation of the commercial filling and assembly process as applied to the PFS?

FDA Response to Question 1a:

The proposed strategy for the validation of the commercial filling and assembly process for the PFS appears to be acceptable.

- b) Does the Agency agree with the Sponsor's conclusion of comparability between the industrial and clinical filling lines?

FDA Response to Question 1b:

Comparability between products made with the industrial versus the clinical filling lines appears to be demonstrated.

No Meeting Discussion.

Question 2:

- a) Does the Agency agree with the control testing strategy for release of Bulk PFS and final assembled PFS?

FDA Response to Question 2a:

The testing strategy for release of Bulk PFS and final assembled PFS appears to be acceptable.

b) Does the Agency agree that the qualification package demonstrates the suitability of the dye ingress method for container closure integrity testing of commercial PFS (b) (4)?

FDA Response to Question 2b:

The general approach of using the dye ingress method for container closure integrity testing of commercial PFS (b) (4) appears to be acceptable. However, the qualification for the dye ingress method and its comparison to microbial ingress method will be assessed during the review of the BLA.

No Meeting Discussion.

Question 3:

Does the Agency agree with the Sponsor's approach for supporting the expiration date of 24 months for the commercial PFS presentation using data from Bulk PFS validation lots and PFS lots representative of the commercial PFS, which will be provided during BLA review as a simple stability update within 7 months of anticipated initial BLA submission in October 2015?

FDA Response to Question 3:

Your proposal to assign an expiration date to the sarilumab PFS presentation (b) (4) is acceptable.

Within your briefing package, you state that you will provide (b) (4) months of stability data for the Primary PFS 131.6 mg/mL configuration and (b) (4) months of stability data for the Primary PFS 175mg/mL configuration. You state that at the time of the submission you will provide (b) (4) months of stability data for commercially representative product and (b) (4) months of stability data for the clinically used product. After the submission review has commenced, you propose that you will submit 24 months of stability data for both Primary PFS configurations and (b) (4) months for the commercially representative product. Please note - if you are in the PDUFA V program the Agency cannot accept any unrequested stability updates. However, you may be allowed to submit an update upon request by the Agency.

You further state that you will provide stability information for the Primary PFS under artificially aged conditions.

The Agency has the following advice regarding the proposed aging program:

Within the stability program description, you do not appear to include stability testing which demonstrates that device constituent parts of the final finished (commercially representative) combination product are able to meet essential performance requirements after aging to period constituent with proposed expiration. If you intend to submit information to support stability of the final finished (commercially representative) combination product using a real time period less than the labeled expiration, the Agency expects that you will provide results of artificially aged final finished combination product. The Agency further expects that you will validate the artificial aging process by comparing artificially aged samples to real time aged samples of an identical time point.

As the device constituent parts of the final finished (commercially representative) combination product include features not present on the bulk product, you are advised to create performance tests specifically for those features to assure they perform as intended after aging.

For the long term aging studies of the bulk product, it appears that you do not plan to perform assessments of device constituent part functionality or fluid path sterility. These are critical elements of combination product performance and should be assessed within the program.

It may be possible that device constituent fluid path sterility is assured after aging by means of the dye ingress study however based on information provided in the meeting package this is not clear.

For the accelerated aging studies of the bulk product, it appears that you do not plan to perform assessments of device constituent part fluid path sterility. These are critical elements of combination product performance and should be assessed within the program.

Sponsor Response:

The Sponsor would like to clarify the following points in the Agency's preliminary comments:

- a. Submission of a simple stability update during the BLA review*
- b. Performance testing of the final finished (commercially representative) PFS*
- c. Fluid path sterility*

a. Submission of a simple stability update during the review of BLA

The Sponsor would like to provide additional stability data during the BLA review (within 7 months after submission of the BLA) as summarized in the briefing package. Does the Agency anticipate requesting a simple stability update, as noted in the preliminary response, during the BLA review to support 24-month shelf life at approval?

Meeting Discussion: The Agency explained that per the PDUFA V agreement that the BLA submission should be complete when submitted. The Agency also noted there will be additional requests at the 74 day letter for updated stability data.

b. Performance testing of final finished PFS

The Agency commented that the proposed stability program does not demonstrate that device constituent parts of the final finished PFS are able to meet essential performance requirements after aging. In the BLA, the Sponsor will provide design verification data to qualify the device components. Device components (including the glass barrel, finger flange, piston rod, and needle shield) will be evaluated during design verification through a combination of dimensional, visual and functional testing to demonstrate that the device constituent parts are functioning as intended. Design verification also includes functional testing of the final finished PFS. The Sponsor's current plan for performance testing during design verification includes deliverable volume, break loose and glide force, and needle shield removal force.

The final finished PFS is put under real time, accelerated, and stressed stability testing which includes performance tests of break loose and glide force. Additional tests that could be added are deliverable volume and needle shield removal force going forward in the stability program.

The Sponsor believes that the combination of these tests demonstrates that the final finished combination product meets essential performance requirements. Does the Sponsor's approach adequately address the Agency's concerns regarding assessment of the device constituent parts in the stability program?

Meeting Discussion: The Agency wanted to make sure that the removal force from the staked needle was accounted for in an aging study. The Sponsor noted that during design verification the supporting data for the performance of the device and its components will be acquired. The sponsor noted that a Master File would be referenced in the BLA to support design verification performed by suppliers. The Agency noted that because the Prefilled Syringe (PFS) is a Combination Product and as such the Sponsor would be responsible for the design control for device constituent parts.

c. Fluid path sterility

Regarding the Agency's comment that there is no assessment for fluid path sterility, the Sponsor would like to clarify that the sterility is assessed at time 12, 24, and 36 months in the current long term stability study of the bulk PFS and final finished (commercially representative) PFS. In addition, CCIT is performed at time 0, 12, 24, and 36 month time point to ensure that there is no breach of integrity of the bulk PFS and the commercially representative PFS over the expiry. The Sponsor considers the long term stability to be the most representative for assessing long term integrity of the bulk PFS and final finished PFS. Consequently the Sponsor is not assessing sterility and CCIT in accelerated aging studies of the bulk PFS and the final finished PFS, but rather the Sponsor plans to provide the integrity (sterility and CCIT) data for the long term (real storage conditions) stability studies.

Does the Sponsor's sterility testing plans address the Agency's concern regarding fluid path sterility for the bulk PFS and final finished PFS?

Meeting Discussion: The Agency explained that fluid path sterility assessment should include the interior surface area of the needle which is the empty space. This empty space should be adequately monitored during stability testing. The sponsor confirmed that this is completed using container closure integrity testing (CCIT).

Question 4:

Does the Agency agree with the proposed shipping validation for PFS?

FDA Response to Question 4:

The analytical studies proposed for validation of shipping are acceptable. However, the proposed shipping validation as described is unacceptable for the combination product due to the lack of appropriate device constituent parts performance testing after exposure to shipping conditions.

Within submission Appendix 2, you include a listing of tests the product will undergo

after shipping studies are completed. Table 1 of this appendix does not appear to include a comprehensive analysis of essential device constituent part performance, such as an evaluation of the flange features or an assessment of fluid path sterility. Please refer to question 3 for additional detail for device constituent part fluid path sterility.

Additionally Table 1 of this appendix includes reference to “Break Loose and Glide Force Report results”, however the acceptance criteria for these tests is shown as “report results”. The Agency expects that you have developed specific requirements for these attributes and will assure that they are satisfied after exposure to shipping conditions.

Sponsor Response: For shipping validation, the Sponsor is conducting performance tests of break loose and glide force, deliverable volume, and visual inspection, which includes confirmation of no visual defects and correct color of plunger rod and finger flange. An additional test that could be added is needle shield removal force.

Regarding the Agency’s comment that there is no assessment for fluid path sterility, the Sponsor would like to clarify that the sterility and CCIT are assessed in the shipping validation study of the bulk PFS and commercially representative PFS.

Also the Sponsor would like to confirm to the Agency that the acceptance criteria for the break loose and glide force tests will be defined before the shipping validation study of the final finished PFS is conducted.

Has the Sponsor adequately addressed the Agency’s concerns regarding device constituent parts performance testing after exposure to shipping conditions?

Meeting Discussion: The Agency told the sponsor that verification studies conducted for the device constituent parts of the combination product, as well as acceptability criteria for those verification studies, should follow from product design requirements, which have been developed with intended use, environment of use, and patient population in mind. The Agency noted that the verification tests conducted after shipping should be similar to those conducted after aging. The sponsor confirmed that the performance tests for the shipping validation mirrored those performed in the stability program. The sponsor also agreed to include a specification for break loose and glide force in the shipping studies.

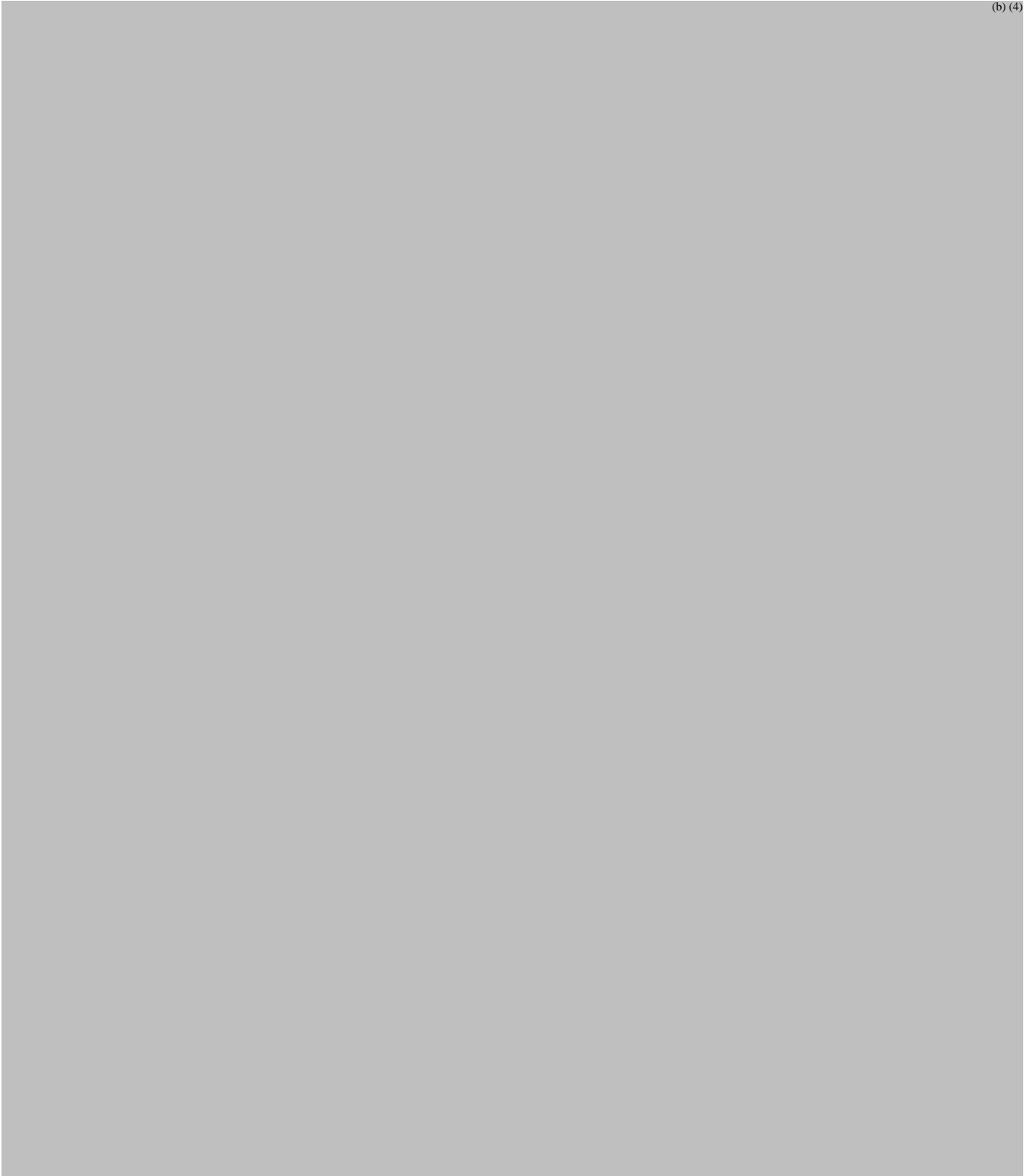
Question 5:

The Sponsor’s activities for the design development and manufacturing of the finished PFS combination product will be conducted in accordance with 21 CFR Part 4. The Sponsor has proposed that the finished combination product will fall under the current drug Good Manufacturing Practices (21 CFR 210 and 21 CFR 211) and relevant sections of the Quality System Regulation (21 CFR 820). Does the Agency agree with the Sponsor’s proposed quality systems strategy?

FDA Response to Question 5:

The Agency agrees overall with the Sponsor’s strategy of complying with 21 CFR Part 4 requirements for the combination product. Also see FDA response to Question-10 for the type and location of information to support the manufacturing requirements.

5 Pages have been Withheld in Full as B4 (CCI/TS) immediately following this page



REGULATORY

Question 11:

Does the Agency agree that CMC information relating to manufacture, control and stability (b) (4) (b) (4) can be filed in Module 3 Drug Substance sections (3.2.S) of the submission?

FDA Response to Question 11:

We agree that the CMC information relating to manufacture, control and stability (b) (4) (b) (4) can be filed in Module 3 Drug Substance sections (3.2.S) of the submission, however a determination of the file ability will be made after the BLA has been submitted.

No Meeting Discussion.

Question 12:

Does the Agency agree that summary of the results of the simulated shipping validation study will be provided within 30 days after BLA submission?

FDA Response to Question 12:

BLAs that are in the PDUFA V program should be complete at the time of submission; however, the simulated shipping validation study data can be provided within 30 days after BLA submission. Please clarify if simulated shipping validation study data (b) (4) will be submitted within 30 days after BLA submission.

On page 59 of the submission, referencing table 20, you state, “The device performance tests were selected as they are an integral part of the injection sequence experienced by the patients. All other device performance characteristics have been confirmed as part of the Design Verification performed (b) (4) The Agency expects that you, as the combination product developer, are responsible for development of device constituent part requirements and specifications, and the verification and validation of those specifications. The future marketing application should include all design control information for the final finished combination product. If some low-level performance tests of the sub- components of the combination product are determined to be unaffected by medication and intended use of the product, are considered to be proprietary to a third party sponsor developing those subcomponents, then it may be acceptable to submit such information in the form of a master file.

On page 59 of the submission, you provide rationale for select device constituent part acceptance criteria. Specifically you state that a formative usability study contribute to the selection of device activation force and injection time, and separate design decisions contributes to the selected injection depth specification. The Agency notes that these rationale elements alone are not sufficient to justify the selection of a the relatively wide range of device specifications (e.g. activation time may range from 3 to 20 seconds). Additionally, if you wish to retain such die ranges of device specifications, performance information from samples within the furthest extent of these ranges should be validated.

Additional comments:

We are providing additional product quality microbiology comments for you to consider during development of your commercial manufacturing process and preparation of your BLA submission.

All facilities should be registered with FDA at the time of the BLA submission and ready for inspection in accordance with 21 CFR 600.21 and 601.20(b)(2). Please include in the BLA submission a complete list of the manufacturing and testing sites with their corresponding FEI numbers. A manufacturing schedule for both the drug substance and drug product should be included in Module 1 of the BLA.

The CMC Drug Substance section of the BLA (Section 3.2.S) should contain the following product quality microbiology information:

- *Bioburden and endotoxin levels at critical manufacturing steps should be monitored using qualified bioburden and endotoxin tests. Bioburden samples should be collected (b) (4) The pre-established bioburden and endotoxin limits should be provided (3.2.S.2.4).*
- *Microbial data from three successful product (b) (4) hold time validation runs at manufacturing scale should be provided. Bioburden and endotoxin levels before and after the maximum allowed hold time should be monitored and bioburden and endotoxin limits provided (3.2.S.2.5).*
- *Data demonstrating microbial control (b) (4) (3.2.S.2.5).*
- *Bioburden and endotoxin data obtained during manufacture of at least three process qualification lots (3.2.S.2.5).*
- *Information and summary results from the shipping validation studies (3.2.S.2.5).*
- *Drug substance bioburden and endotoxin release specifications (3.2.S.4). Bioburden specifications should be (b) (4) CFU/ (b) (4) mL for bulk materials stored at (b) (4)*
- *Summary report and results from bioburden and endotoxin test methods qualification performed for (b) (4) the drug substance (3.2.S.4).*

The CMC Drug Product section of the BLA (Section 3.2.P) should contain validation data summaries to support the (b) (4) operations. For guidance on the type of data and information that should be submitted, refer to the 1994 “FDA Guidance for Industry, Submission

Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products”

Provide information and validation data summaries in Section 3.2.P.3.5 for the following:

- *(b) (4) retention study (b) (4)*
- *Sterilization and depyrogenation of equipment and components that contact the sterile drug product. Provide summary data for the three most recent requalification studies and describe the equipment requalification program.*
- *Three successful consecutive product (b) (4) hold time validation runs at manufacturing scale. Bioburden and endotoxin levels (b) (4) should be monitored and bioburden and endotoxin limits provided.*
- *(b) (4) if applicable.*
- *Three successful consecutive media fill runs, including summary environmental monitoring data obtained during the runs.*
- *A description of the routine environmental monitoring program.*
- *Qualification of the bioburden, sterility and endotoxin test methods performed (b) (4) (if applicable) and the drug product, as appropriate.*
- *Rabbit Pyrogen Test conducted on three batches of drug product in accordance with 21 CFR 610.13(b).*
- *Formulations with certain excipient and polysorbate combinations have been reported to interfere with endotoxin recoverability in the USP LAL test methods over time. The effect of hold time on endotoxin recovery should be assessed by spiking a known amount of endotoxin into undiluted drug product and then testing for recoverable endotoxin over time. The studies should be conducted using containers of similar composition as those used for drug product during hold.*
- *Shipping validation study results, including container closure integrity data.*
- *Container closure integrity testing (3.2.P.2.5). System integrity (including maintenance of (b) (4)) should be demonstrated initially and during stability. Container closure integrity methods validation should demonstrate that the assay is sensitive enough to detect breaches that could allow microbial ingress. We recommend that container closure integrity testing be performed in lieu of sterility testing for stability samples every 12 months (annually) until expiry (3.2.P.8.2).*

Sponsor response:

(b) (4)
The simulated shipping validation study data for the PFS will be included in the initial BLA.

Meeting Discussion: The Agency told the sponsor (b) (4)

(b) (4)

(b) (4)

Meeting Discussion: The specifications for device performance tests need to be justified and that should include usability aspects. Devices have more established criteria and all should be listed. Be sure to use clinical trials, human factor studies (b) (4)

(b) (4)

(b) (4) **The sponsor concluded that further clarifications will be submitted in comments to the Human Factors protocol that is under review with the Agency.**

The meeting ended amicably.

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/s/

MARJORIE A SHAPIRO
02/09/2015



IND 100632

MEETING MINUTES

Sanofi US Services Inc.
55 Corporate Drive
Bridgewater, NJ 08807

Attention: Marsha Miller, Ph.D
Director, Global Regulatory Affairs

Dear Dr. Miller:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for sarilumab.

We also refer to the meeting between representatives of your firm and the FDA on October 22, 2014. The purpose of the meeting was to discuss the BLA submission for sarilumab.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-3420.

Sincerely,

{See appended electronic signature page}

Christine Ford, R.Ph.
CDR, U.S. Public Health Service
Sr. Regulatory Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-BLA

Meeting Date and Time: October 22, 2014 4:00 – 5:30 P.M.
Meeting Location: White Oak Building 22, Conference Room: 1419

Application Number: IND 100632
Product Name: sarilumab
Indication: Rheumatoid Arthritis
Sponsor/Applicant Name: Sanofi US Services Inc. (Sanofi)

Meeting Chair: Sarah Yim, Supervisory Associate Director
Meeting Recorder: Christine Ford, Regulatory Project Manager

FDA ATTENDEES:

Sarah Yim, M.D., Supervisory Associate Director, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Nikolay Nikolov, M.D., Clinical Team Leader, DPARP
Rachel Glaser, M.D., Clinical Reviewer, DPARP
Christine Ford, R.Ph., Regulatory Project Manager, DPARP
Ruthanna Davi, Ph.D., Biometrics Team Leader, Division of Biometrics II
Gregory Levin, Ph.D., Biometrics Reviewer, Division of Biometrics II
Satjit Brar, Ph.D., Team Leader, Division of Clinical Pharmacology II (DCP II)
Ping Ji, Ph.D., Clinical Pharmacology Reviewer, DCP II
Robert G. Pratt, Pharm.D., Division of Risk Management/OSE
Teresa Mcmillan, Pharm.D., Safety Evaluator, Division of Medication Error and Prevention Analysis/OSE
Margie R. Goulding, Ph.D., Epidemiology Team Leader, Division of Epidemiology II/OSE
Laura Fontan, Consumer Safety Officer, Office of Manufacturing and Product Quality, OC

EASTERN RESEARCH GROUP ATTENDEES:

SoHyun Kim, Eastern Research Group, Inc.

SPONSOR ATTENDEES:

Sanofi attendees:

Alex Boddy, MS, Senior Director, Biostatistics
Simon Cooper, MD, Vice President, Global Project Head, Immunology & Inflammation
Development Franchise
Anju Garg, MD, Senior Director, Global Pharmacovigilance and Epidemiology
Tian Luo, Operations Director, Immunology & Inflammation Development Franchise
Marsha Miller, PhD, Director, Global Regulatory Affairs
Bart van Hoogstraten, MD, PhD, Senior Director, Clinical Leader, Immunology &
Inflammation Development Franchise
Christine Xu, PhD, Senior Manager, DSAR/Pharmacokinetics Modeling & Simulation
Ying Liu, Associate Director, Biostatistics

Regeneron attendees:

Neil Graham, MD, MPH Vice President, Program Direction, Immunology & Inflammation
Janie Parrino, MD Director, Clinical, Immunology and Inflammation
Patricia Reilly, PhD Senior Director, Regulatory Affairs
Janet van Adelsberg, MD Senior Director, Clinical, Immunology and Inflammation

BACKGROUND:

Sarilumab is currently in phase 3 clinical development for use in treatment of rheumatoid arthritis (RA). There have been numerous interactions with the sponsor, including the EOP2 meetings held September 15 and October 26, 2011 (CMC). An Agreed Pediatric Study Plan letter was issued January 13, 2014. Sanofi submitted a request for a pre-BLA meeting to discuss aspects related to the presentation of data, overall format of the BLA, and specific clinical, nonclinical, and regulatory questions. The briefing package was received September 8, 2014. On a related note, Sanofi submitted a request for a separate CMC pre-BLA meeting on October 2, 2014.

After review of the briefing package, FDA sent preliminary responses to Sanofi's questions in an emailed letter dated October 17, 2014. Sanofi emailed areas for discussion and clarification on Tuesday, October 21, 2014. The sponsor's comments or additional questions are incorporated into the body of the minutes as well as provided as an Attachment at the end of the minutes.

The content of the letter is printed below, with the sponsor's questions from the briefing package in *italics*; FDA's responses (meeting preliminary comments) in normal font; and Sanofi's October 17, 2014, emailed areas for discussion also in noted in *italics*. Summary of meeting discussions, if any, are found in **bold normal font** following the specific area of discussion.

QUESTIONS AND RESPONSES

Question 1

Does the Agency agree that there are no outstanding or unresolved topics in the sarilumab nonclinical development program, that the requirements for registration have been met, and that the planned content of the nonclinical sections of the BLA is acceptable?

FDA response:

The sarilumab nonclinical program appears to be sufficient to support submission and review of a BLA.

Question 2

Does the Agency agree that the clinical studies and patient exposure in the sarilumab clinical development program are adequate to support review and approval of the BLA for the proposed indication?

FDA response:

The clinical studies and the extent of patient exposure in the sarilumab clinical development program appear reasonable to support submission and review of your application. Whether or not the submitted data are adequate to support approval of the BLA for the proposed indication will be a review issue.

Question 3

Does the Agency agree with the Sponsor's proposal for studies to be considered "covered clinical studies" for the purposes of providing financial disclosures and summary level clinical site data for BIMO requirements?

FDA response:

You propose to include financial disclosures and summary level clinical site data for BIMO requirements from the pivotal studies (EFC11072 and EFC10832) and not include data from the safety extension study (LTS11210). We agree with your proposal to not include data from the safety extension study (LTS11210). However, we note that study SFY13370 evaluated the safety of sarilumab compared to tocilizumab. Since this phase 3 study makes a significant contribution to the evaluation of safety, it would also be considered a covered clinical study. Thus, submit financial disclosure information and summary level clinical site data for this study.

Question 4

Does the Agency agree with the proposed location of the efficacy results in the BLA?

FDA response:

If you believe section 2.7.3 (Summary of Clinical Efficacy) would be sufficiently detailed to serve as the summary portion of the ISE, then you may place the summary portion of your integrated assessment in Module 2 and place the appendices of tables, figures, and datasets in section 5.3.5.3. In this case, an explanation should be placed in both Module 2 and Module 5.

Question 5

Does the Agency agree with the proposed content, analyses, and presentation for the Summary of Clinical Efficacy?

FDA response:

In general, the proposed content, analyses, and presentation for the Summary of Clinical Efficacy appears reasonable. We agree that the efficacy results from EFC11072, Part B and EFC10832 should be presented side-by-side to facilitate an evaluation of the consistency of the response, as well as to identify any differences in response in the populations.

Regarding your proposals to support “durability of response,” we do not believe that specific labeling in this regard is necessary. If approved without specific time limitations, your product would be considered appropriate for chronic use. In any case, conclusions regarding “durability of response” cannot be drawn due to limitations of the data, including lack of a control group in study LTS11210 and potential “survivor bias” as patients who remain in the study tend to be experiencing the most benefit from the study drug.

Sanofi’s 10/21/14 emailed request for clarification

*The Sponsor did not intend to imply a label claim in the section of briefing document related to durability of response. The intent of the proposed analyses was to evaluate response, especially progression of structural damage, over a duration longer than 1 year. While we acknowledge the potential for survivor bias, it is informative to assess the percentage of patients as initially randomized who experienced no progression of structural damage based on the X-ray data at 2 years. The proposed statistical analyses of the radiographic endpoints were provided in Section 2.6.2.3 of the Summary of Clinical Efficacy SAP (Appendix 2 of the briefing document). **Are there additional analyses beyond those proposed by the Sponsor that would aid the Agency in the review and evaluation of these data?***

Discussion:

FDA responded that there are no additional analyses that would be helpful. The lack of control group at this time point makes any outcome difficult to interpret. It would not be clear whether patients who stayed in the study would have progressed without treatment, as they may have just stayed in because they continued to do well. Therefore, these extended uncontrolled results may be at best unreliable, and at worst, misleading. Even if groups were maintained as initially randomized, there would still be concerns about bias that would make it difficult to draw definitive conclusions in the subgroups that remain in the study at 2 years. FDA noted that the sponsor can still submit the data.

Question 6

The ISS SAP is provided in [Appendix 3](#) and table shells representing output for a subset of the analyses are provided in [Appendix 4](#). The Sponsor plans to pool safety data from the Phase 2 and Phase 3 studies and does not plan to pool the safety data from the Phase 1 studies conducted

in patients with rheumatoid arthritis. The Sponsor plans to conduct subgroup analyses on the placebo-controlled population.

- a. *Does the Agency agree with the proposed pooling strategy for Phase 2 and Phase 3 studies, as well as with the proposal for not pooling the safety data from the Phase 1 studies?*

FDA response:

We agree with the proposal for not pooling the safety data from the phase 1 studies, but we do not agree to the proposed pooling strategy. In general, limited conclusions will be possible from pooled safety data given important differences in study design, including study duration and timing of escape provisions. We have the following recommendations regarding your pooling strategy:

1. For Pool 1, we agree that it is reasonable to pool the data from the patients from placebo-controlled studies EFC11072 and EFC10832 who received doses selected for Phase 3 (150mg Q2W or 200mg Q2W) or placebo. In addition to the proposed data pools, include a data pool from the patients from placebo-controlled studies EFC11072 and EFC10832 (Part B: Cohort 2).

Sanofi's 10/21/14 emailed request for clarification

- i. *FDA has provided feedback on the analyses of the placebo controlled data (Pool 1). The Sponsor would like to confirm that the FDA agrees with the Sponsor's proposals with regard to long term data in Pool 2 (sarilumab + DMARD population) and Pool 3 (sarilumab monotherapy population) as these were not explicitly mentioned in the response. Does the Agency agree with the Sponsor's proposals for Pool 2 and Pool 3?*

Discussion:

FDA replied that in general, the Pool 2 and Pool 3 proposals are acceptable. However, if conducted as proposed, the pooled analyses may blur differences between the 150 mg q2wk and 200 mg q2wk dosing regimens, as patients initially assigned to 150 mg q2wk but who escaped or rolled over into the 200 mg q2wk regimen would still be counted as 150 mg q2wk in the pooled analyses. FDA would also be interested in analyses that evaluate patients who received only 150 mg q2wk and patients who received only 200 mg q2wk to facilitate assessment of dose-related adverse effects.

- ii. *Based on the Agency response, the Sponsor understands that the Agency is in agreement with the proposed Pool 1 (EFC11072, Parts A [selected doses] and B, Cohort 1 [selected doses] and Cohort 2 and EFC10832). Also, the Sponsor understands the Agency requests an additional pool comprised of EFC11072, Part B, Cohort 2 and EFC10832 only, hereafter referred to as Pool 1a. Is the Sponsor's understanding correct?*

Discussion:

FDA agreed.

- iii. *The Sponsor would like to understand the Agency's rationale for requesting Pool 1a, which would exclude patients from EFC11072 (Part A and Part B, Cohort 1). All parts of Study EFC11072 were randomized, placebo-controlled, and double-blind. Moreover, patients who received sarilumab 150 mg q2w, sarilumab 200 mg q2w, or placebo in EFC11072, Part B, Cohort 1 had the same treatment duration as the patients randomized in Part B, Cohort 2. The number of patients in EFC11072 (Part A and Part B: Cohort 1 [selected doses]) is small (~50 per group for Part A and <30 per group for Part B, Cohort 1) and only accounts for about 10% of the total sample size of Pool 1. Results from Pool 1a are expected to be very similar to the results of Pool 1. Could the Agency clarify the rationale for requesting Pool 1a?*

Discussion:

FDA stated that presuming that there are no major differences between analyses, an analysis limited to the primary Phase 3 study population could potentially be helpful as a simplifying option for labeling.

- iv. *For Pool 1a, the Sponsor proposes to provide assessment of common AEs and AEs of interest (ie, SAEs, AESIs, discontinuation due to AEs, and deaths). Does the Agency agree?*

Discussion:

FDA agreed.

2. Also, we have the following recommendations regarding the presentation of the data from these studies:

For the assessment of common AEs and AEs of interest (i.e., targeted events, such as serious adverse events, adverse events of special interest, discontinuations secondary to adverse events, and deaths), we request the following additional analyses for studies EFC11072 and EFC10832 (for each study and for the pooled studies):

- a. For the common AEs, we recommend analyses of data by the following interval: 0 to 12 weeks.
- b. For targeted events, we recommend analyses of the data by the following intervals: 0 to 12 weeks, 0 to 24 weeks, and 0 to 52 weeks. For targeted and common AEs, provide exposure adjusted incidence rates from 0 to 12 weeks and 0 to 16 weeks for studies EFC10832 and EFC11072, respectively.
- c. For all analyses of safety data, in addition to raw cumulative incidence proportions, also provide exposure adjusted incidence rates. Include in your tables the exposure years for each adverse event. For all analyses, report estimated differences and confidence intervals for all pairwise treatment arm comparisons. In addition, for all integrated analyses, you should appropriately account for study differences¹, either by adjusting for study in a model or carrying out meta-analyses of within-study results.

¹ Chuang-Stein, C. and Beltangady, M. (2011), Reporting cumulative proportion of subjects with an adverse event based on data from multiple studies. *Pharmaceutical Statistics*, 10: 3–7.

In addition to the planned summaries of safety data from the double-blind treatment periods, sensitivity analyses should be conducted including safety data after escape in patients who transitioned from placebo to sarilumab at week 16 or week 12 for studies EFC11072 and EFC10832, respectively. In other words, patients who escaped to sarilumab should be counted in the denominator in both groups based on their actual on-treatment time. The numerator count will depend on the timing of the event.

Hypothetical example:

Patient A was on placebo for the first 4 months and escaped to sarilumab, and was then diagnosed with certain adverse event at Month 5. Patient A would be double-counted in the denominator of the 0 to 12 week interval, with 0 events in the placebo numerator and 1 adverse event in the sarilumab numerator with the exposure time being counted at month 1. The patient would be counted in the placebo denominator in the 0 to 12 week and 0 to 24 week interval displays. That patient would also be counted in the sarilumab denominator in the 0 to 12 and 0 to 24 week interval analyses.

Example Tables:

Table 1:

0 to ≤12 week Period	Placebo	Sarilumab 150mg Q2W	Sarilumab 200mg Q2W

Table 2:

0 to ≤24 week period	Placebo	Sarilumab 150mg Q2W*	Sarilumab 200mg Q2W*

* Includes randomized patients and patients who escaped and are within the first 24 weeks of treatment with this regimen

Table 3:

0 to ≤52 week period	Placebo**	Sarilumab 150mg Q2W*	Sarilumab 200mg Q2W*

* Includes randomized patients and patients who escaped and are within the first 52 weeks of treatment with this regimen

**Includes all placebo patients (whether they stayed on placebo or escaped)

When attributing adverse events to either drug or placebo, the period of drug exposure will vary depending on the treatment regimen. For patients on placebo, the exposure period is only the period during which the patient received placebo. For patients on investigational drug, the exposure period will include some period after the investigational drug was stopped, such as 30-60 days. Clarify how long patients were followed after discontinuation of study drug.

For targeted AEs of interest, we also recommend that you perform additional model-based analyses that utilize all safety data from the integrated studies (including data after cross-over from placebo to sarilumab) and appropriately account for the study designs. These analyses should, at a minimum, account for the following: (1) the time the patient is receiving a particular treatment (e.g., with a Poisson or Cox model); (2) possible differences between studies (e.g., through stratification by study in a meta-analysis or adjustment for study in a model); and (3) the correlation between outcomes within a patient (e.g., with a GEE or mixed effects model). It may also be important to account for important baseline prognostic factors and time in study, given the non-randomized nature of comparisons based on such analyses. We also recommend that you present Kaplan Meier curves that (1) only include data prior to escape; and (2) include all safety data, where patients enter the sarilumab risk set at the time of cross-over from placebo to sarilumab.

Sanofi's 10/21/14 emailed request for clarification

For the assessment of common AEs and AEs of interest (ie, targeted events, such as serious adverse events, adverse events of special interest, discontinuation secondary to adverse events and deaths), the Agency requested some additional analyses for studies EFC11072 and EFC10832 (for each study and for the pooled studies). The additional analyses, as shown in Sponsor Table 1, will be performed for Study EFC11072 (Part B, Cohort 2), Study EFC10832, and Pool 1 (ie, EFC11072 (Part A [selected doses] and Part B Cohort 1 [selected doses] and Cohort 2) and EFC10832), and Pool 1a (EFC11072, Part B, Cohort 2 and EFC10832). For each time period and study/pool in Sponsor Table 1 the Sponsor will:

- *Provide raw incidence rates and exposure adjusted incidence rates (ie, number of patients with at least one event per 100 patient-years);*
- *Provide estimated incidence rate differences and 95% CIs for the difference between sarilumab 200 mg q2w and placebo, between sarilumab 150 mg and placebo, and between sarilumab 150 mg q2w and Sarilumab 200 mg q2w. The estimated differences and 95% CIs of the differences will be derived using M&N method^(1,2) stratified by the study, using the CMH weight.*

1. *Miettinen O, Nurminen M. Comparative analysis of two rates. Statistics in Medicine 1985;4:213-26.*
2. *Kaifeng Lu. Cochran-Mantel-Haenszel weighted Miettinen & Nurminen method for confidence intervals of the difference in binomial proportions from stratified 2x2 samples. ASA Proceedings of the Joint Statistical Meetings, American Statistical Association (Alexandria, VA), 2008.*

Sponsor Table 1: Analyses on Placebo-controlled studies as requested by Agency

Endpoints	EFC11072 (Part B, Cohort 2)	EFC10832	Pool 1 and 1a
<i>Common AEs</i>	<i>0-12 weeks; 0-16 weeks</i>	<i>0-12 weeks</i>	<i>0-12 weeks</i>
<i>Targeted events (SAEs, AESIs, discontinuations due to AEs, and deaths)</i>	<i>0-12 weeks; 0-16 weeks; 0-24 weeks; 0-52 weeks</i>	<i>0-12 weeks; 0-24 weeks</i>	<i>0-12 weeks; 0-24 weeks; 0-52 weeks</i>

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)

- i. *Does the Agency agree that the by study analysis for EFC11072 is specific to Part B, Cohort 2 only?*

Discussion:
FDA agreed.

- ii. *Does the Agency agree with the Sponsor's approach to the additional analyses requested by the Agency, including our understanding that the Agency is requesting a comparison of the two sarilumab doses?*

Discussion:
FDA agreed and stated that one additional analysis would be preferable: exposure-adjusted incidence rates using all of the pre-escape data for pools 1 and 1a (i.e., integrated 0-16 week data from Study EFC11072 and 0-12 week data from Study EFC10832).

Sanofi noted agreement.

- iii. *In the briefing package and ISS SAP, the Sponsor had proposed a 0-24 week data analysis for common AEs for the pooled population from EFC11072 Part B, Cohort 1 (selected doses) and Cohort 2 and EFC 10832. The Sponsor had intended that these 0-24 week data would be presented in the BLA to support the presentation of the common AEs that the Sponsor expects to recommend in the prescribing information. The rationale for the 24 week data cut was that this period corresponds to one of the co-primary endpoints (ACR20) and contains the entire study period for one of the pivotal studies (EFC10832). Can the Agency clarify whether the Sponsor should perform only the 0-12 week data analysis for common AEs or whether the Sponsor should perform both the 0-12 and 0-24 week data analysis for common AEs? If the Agency agrees that analyses should be done on the 0-24 week data, the Sponsor proposes conducting these analyses on Pool 1a rather than the pooled population from EFC11072 Part B, Cohort 1 (selected doses) and Cohort 2 and EFC 10832. Does the Agency agree?*

Discussion:

FDA responded that the 0-12 week analysis simplifies the assessment because no patients have yet escaped to sarilumab. However, they agreed that it is reasonable to provide a 0-24 week analysis for the reasons described by the sponsor. FDA stated that they preferred both analyses be performed. They agreed that these analyses may be conducted on Pool 1a.

*Sanofi's 10/21/14 emailed request for clarification- **Sensitivity analyses***

With regard to the sensitivity analyses requested by Agency for Studies EFC11072 and EFC10832 the Sponsor would like to clarify the following points:

- i. The Sponsor would like to clarify the objective of this sensitivity analyses. If the purpose is to compare between sarilumab doses and placebo, the Sponsor believes the comparisons are potentially biased due to the rescue being a selective process based on patients' efficacy response. Not all the placebo patients were rescued and after rescue patients took open-label sarilumab. If the purpose is to integrate all data while patients received sarilumab, including open label, then the Sponsor believes this is addressed by the analysis proposed for Pool 2. **Can the Agency clarify the purpose of the proposed sensitivity analysis?***

Discussion:

FDA responded that the purpose of these sensitivity analyses is to reassure that escape-patient data are not being diluted out and missed by simply including their post-treatment-change data in the extension study data. These analyses allow for an accounting of all patient data for the selected time period (e.g., 0 to 12 wks), and assigns that data to the treatment actually being received for that time period.

- ii. The sensitivity analyses proposed by the Agency can be performed for EFC11072, Part B. In Study EFC10832, patients who escaped to rescue therapy did not continue in the study and were enrolled in the long-term extension study LTS11210. Therefore the Sponsor believes these analyses would not be applicable for EFC10832. **Does the Agency agree?***

Discussion:

FDA stated that they did not agree; the intent of the sensitivity analyses is to capture data from patients who escape or cross over to sarilumab. Therefore the analyses are applicable to EFC10832 as well.

- iii. The safety data for sarilumab patients in Study EFC11072, Part B after escape will also be included (ie, patients who transitioned from sarilumab 150 mg q2w to sarilumab 200 mg q2w, and from sarilumab 200 mg q2w to sarilumab 200 mg q2w). The Sponsor proposes that events occurring after the first dose of 200mg q2w should be assigned to this dose group and not the 150mg q2w group. **Does the Agency agree?***

Discussion:

FDA agreed.

- iv. *Prior to Phase 3 dose selection, patients in EFC11072, Part B, Cohort 1 were rescued to sarilumab 150 mg weekly. **Should the sensitivity analyses be performed on EFC11072 (Part B, Cohort 2)?***

Discussion:

FDA responded that although there is no reason to exclude the data, it is acceptable to limit the sensitivity analyses of EFC11072 to Part B Cohort.

Sanofi's 10/21/14 emailed request for clarification: Follow-up period/period of drug exposure

The Sponsor would like to provide clarification for the follow-up period and the period of drug exposure. All completed patients were followed 8 weeks (+/- 3 days) after their last IMP (6 weeks after the EOS visit); or 6 weeks after the last IMP for patients who prematurely discontinued from the study. Regarding the planned period of drug exposure, since all the patients were followed in the same way irrespective their treatments, the period of drug exposure was defined in the same way for both placebo and active treatment groups.

- *For patients who rescued or participated in the long term extension study, the drug exposure period ends at the first open-label rescue or LTS sarilumab dose (usually 2 weeks [+/- 3 days] after the last IMP). For instance, for patients who transitioned from placebo to sarilumab 200 mg q2w, the events (new or worsened) observed after the first open-label dose will be counted in the sarilumab 200 mg q2w group; for patients who transitioned from sarilumab 150 mg q2w to 200 mg q2w, the events (new or worsened) observed after the first open-label dose will be counted in the sarilumab 200 mg q2w group.*
- *For patients who were unwilling or unable to continue in the long term extension study (including the discontinued patients), the drug exposure period ends at last IMP date+60 days OR last contact date (usually the follow-up visit), whichever came first.*

Does the Agency agree that the Sponsor's approach for defining drug exposure is consistent with the Agency's recommendations?

Discussion:

FDA responded that the sponsor's approach for defining drug exposure is acceptable.

Sanofi's 10/21/14 emailed request for clarification: Model based analyses

With regard to the model-based analyses recommended by the Agency, since the analyses referred to include all sarilumab data (including uncontrolled open-label), the Sponsor would like to confirm our understanding that they are for the purpose of estimation and examination of subgroups/ predictors and not intended to be comparative to placebo.

Discussion:

FDA stated that they did not agree. While these analyses will be for sensitivity purposes and exploratory in nature because of the possibility of confounding, the interest is not only in estimation of within-group rates on sarilumab, but also in

comparing rates between different treatments (placebo versus each sarilumab dose, and sarilumab 150 versus 250).

- i. *In term of the estimation of the sarilumab effect on targeted AEs of interest, the Sponsor believes that the All Sarilumab Pool (ie, Pool 2) is more appropriate for this purpose as it includes all patient exposure to sarilumab. Does the Agency agree?*

Discussion:
FDA agreed.

- ii. *Could the Agency clarify whether the unit of interest in these analyses is the patient (e.g. patients with an event per 100 patient years), or events (e.g. number of events per 100 patient years)?*

Discussion:
FDA noted that the unit of interest depends on the AE being described. For example, for the laboratory abnormalities it is not necessary to count additional reported events per patient; however for serious infections and malignancies, both analyses (by patient and by event) may be helpful. Also, different models might be used for each approach, e.g., a Kaplan Meier plot or Cox model for time to first event, versus a Poisson model for incidence rates per 100 person-years (allowing for multiple events per person).

FDA acknowledged the challenges of performing the requested analyses and noted that similar analyses will be performed internally during review in assessing safety. Events to consider are AEs of special interest and rare events (not restricted to those mentioned). FDA stated that it is open to proposals for the statistical approach.

For defining an event, Sanofi gave the following example: diagnosis of pneumonia, 6 months later sepsis, clearly temporally separated → acceptable to count as 2 separate events? They asked about the acceptability of adopting definition of a “new (or another separate) event” as an event that occurs 30 days after resolution of the first (or previous) event?

FDA responded that the sponsor’s proposal appeared to be reasonable, but clinical judgment should also be used regarding the determination about whether events are convergent or separate.

b. *Does the Agency agree with the proposed subgroups to be analyzed for safety?*

FDA response:

The proposed format and content of the narratives for the phase 3 studies appear reasonable.

Sanofi's 10/21/14 emailed request for clarification

Can the Agency confirm that in the Agency response above the Agency is referring to subgroups and not narratives?

Discussion:

FDA responded that the proposed subgroups (age, gender, race, ethnicity, BMI, and weight) are acceptable.

c. *Does the Agency have any comments on the additional analyses provided in the ISS SAP or on the table shells?*

FDA response:

See our response to Question 6. We do not have any additional comments regarding the additional analyses provided in the ISS SAP or on the table shells.

Question 7

Does the Agency agree with the list of adverse events of special interest and the search criteria that will be used to identify them as described in the briefing document?

FDA response:

The proposed criteria used to identify selected adverse events of special interest that are non-serious adverse events and do not lead to permanent treatment discontinuation and for which a narrative will be provided appear reasonable.

Question 8

CSR narratives will be provided for deaths, SAEs, and adverse events leading to permanent treatment discontinuation for all studies. In addition, for the Phase 3 studies, the Sponsor plans to submit narratives for selected non-serious AESIs that did not lead to permanent treatment discontinuation.

a. *Does the Agency agree with the criteria the Sponsor is using to identify selected AESI that are non-serious adverse events and do not lead to permanent treatment discontinuation and for which a narrative will be provided?*

FDA response:

Your proposal for submission of patient narratives appears reasonable.

b. Does the Agency agree with the format and content of the narratives for the Phase 3 studies?

FDA response:

Your proposal for the format and content of the narratives for the phase 3 studies appear reasonable.

Question 9

Does the Agency agree with the proposal for data extraction dates, data cut-off dates and outputs to be included in the initial BLA for ongoing studies?

FDA response:

The proposal for data extraction dates, data cut-off dates and outputs to be included in the initial BLA for ongoing studies appears reasonable.

Question 10

Does the Agency agree with the Sponsor's proposal for the day 120 safety update report?

FDA response:

There appears to be a typographical error in your briefing book on page 63, and we believe that it intended to state that the 120-day safety update would include the "final CSR for EFC13752" rather than the (b) (4). See our response to Question 14 regarding our lack of agreement with inclusion of the data from EFC13752 in the 120-day safety update.

Question 11

Does the Agency agree with the planned content of the Clinical Pharmacology section of the BLA?

FDA response:

The planned content of the clinical pharmacology section appears reasonable. However, the acceptance of the data will be a review issue.

Question 12

Does the Agency agree with the Sponsor's approach to analysis of ADA data across the Phase 3 studies?

FDA response:

Your proposal to establish a patient specific cut-point is acceptable. However, the assay validation report should contain data demonstrating that the observed increase in background is not due to true positives in the population. Rheumatoid arthritis patient serum samples may have background from Rheumatoid Factor that needs to be taken into account when determining background.

Question 13

Based on the data from nonclinical and clinical studies conducted to date, as well as an evaluation of the mechanism of action of sarilumab, there is no evidence of CNS activity or signs

associated with drugs of abuse. Does the FDA agree that, for sarilumab, Drug Abuse Liability Assessment (DALA) studies and abuse liability assessment analysis are not required?

FDA response:

We agree that it is reasonable not to perform Drug Abuse Liability Assessment (DALA) studies and abuse liability assessment analyses.

Question 14

Does the Agency agree with the Sponsor's proposal for submission of data from the EFC13752 monotherapy safety study in support of the use of sarilumab as monotherapy at the time of initial approval?

FDA response:

We do not agree with your proposal to submit data from approximately (b) (4)% of patients in study EFC13752 (monotherapy safety study) at the time of initial BLA submission, followed by submission of the complete study report at the time of the day 120 safety update. As noted in FDA's response dated September 30, 2013, the evaluation of sarilumab monotherapy is not a requirement, but is of interest primarily from the perspective of immunogenicity and safety. Thus, the data are not required at the time of BLA submission. However, if you plan to include information in the proposed labeling regarding sarilumab monotherapy, then submit these data with the initial BLA submission.

Question 15

The initial BLA submission planned for fourth quarter 2015 provides for the sarilumab drug product in a prefilled syringe. This is the drug product used in pivotal registrations studies. (b) (4)

a. (b) (4)

FDA response:

b. *Does the Agency agree with the proposed organization of the Module 3.2 Body of Data* (b) (4) ?

FDA response:

Your proposal is acceptable.

Question 16

Does the Agency agree with the proposed overall Table of Contents for the BLA?

FDA response:

The overall proposed Table of Contents (TOC) for the BLA appears reasonable. See additional comments from Office of Compliance/Biotech Manufacturing Assessment Branch (BMAB) under “Product Quality Microbiology Additional Comments.”

Question 17

[Redacted] (b) (4)

FDA response:

[Redacted] (b) (4)

FDA REMS comment:

Based on your submission, it is unclear whether you plan to submit a risk evaluation and mitigation strategy (REMS). Given the potential serious risks associated with sarilumab and the existence of a REMS for another IL-6 inhibitor, you should consider whether or not a REMS is needed for sarilumab. At this time, the Office of New Drugs and the Office of Surveillance and Epidemiology have insufficient information to determine whether a REMS will be necessary to

ensure that the benefits of the drug outweigh the risks, and if it is necessary, what the required elements will be. We will determine the need for a REMS during the review of your application.

Product Quality Microbiology Additional Comments (continued response Question 16 - TOC):

A. CMC Drug Substance section (Section 3.2.S):

Section 3.2.S should contain the following product quality microbiology information:

1. Evidence of monitoring of bioburden and endotoxin levels at critical manufacturing steps using qualified bioburden and endotoxin tests. Bioburden samples should be collected (b)(4) Pre-determined bioburden and endotoxin limits should be provided (3.2.S.2.4).
2. Three successful product (b)(4) hold time validation runs at manufacturing scale. Bioburden and endotoxin levels before and after the maximum allowed hold time should be monitored and bioburden and endotoxin limits provided (3.2.S.2.5). Bioburden samples should be collected (b)(4)
3. (b)(4) storage validation data and information (3.2.S.2.5).
4. Bioburden and endotoxin data obtained during manufacture of the three conformance or PPQ batches (3.2.S.2.5).
5. Summary of shipping validation studies and data (3.2.S.2.5).
6. Drug substance bioburden and endotoxin release specifications. The bioburden limit should be (b)(4) CFU/ (b)(4) mL for bulk materials allowed to be stored (b)(4) (3.2.S.4).
7. Qualification data for bioburden and endotoxin test methods performed for (b)(4) drug substance (3.4.S.4).

B. CMC Drug Product section (Section 3.2.P):

Section 3.2.P should contain validation data summaries supporting the (b)(4) sterility assurance. For guidance on the type of data and information that should be submitted, refer to the 1994 FDA Guidance for Industry, "Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products."

1. The following study protocols and validation data summaries should be included in Section 3.2.P.3.5:
 - a. (b)(4) retention study (b)(4)
 - b. Sterilization and depyrogenation of equipment and components that contact the sterile drug product. The equipment requalification program should be described.
 - c. (b)(4) hold times. Hold times should be validated at manufacturing scale.
 - d. (b)(4) if applicable.
 - e. Three successful consecutive media fill runs, including summary environmental monitoring data obtained during the runs. Media fill and environmental monitoring procedures should be described.

- f. A description of the routine environmental monitoring program.
- g. Summary of shipping validation studies and data.
2. The following method validation information should be provided:
 - a. Container closure integrity testing (3.2.P.2.5). System integrity (including maintenance of the (b)(4)) should be demonstrated during the qualification of the process and during stability. Maintenance of PFS container closure integrity (b)(4) and shipment should be demonstrated. Container closure integrity methods validation should demonstrate that the assay is sensitive enough to detect breaches that could allow microbial ingress and should include routine manufacturing process defects as controls. We recommend that container closure integrity testing be performed *in lieu* of sterility testing for stability samples every 12 months (annually) and at expiry (3.2.P.8.2).
 - b. Qualification data for bioburden, sterility and endotoxin test methods performed for (b)(4) (where applicable) and the drug product, as appropriate (3.2.P.5).
 - c. Rabbit Pyrogen Test data for three batches of drug product in accordance with 21 CFR 610.13(b).

Formulations with certain excipient and polysorbate combinations have been reported to interfere with endotoxin recoverability in the USP LAL test methods over time. The effect of hold time on endotoxin recovery should be assessed by spiking a known amount of endotoxin into undiluted drug product and then testing for recoverable endotoxin over time. The studies should be conducted using containers of similar composition as those used for drug product during hold.

C. Inspection Readiness:

All facilities should be registered with FDA at the time of the BLA submission and ready for inspection in accordance with 21 CFR 600.21 and 601.20(b)(2). Please include in the BLA submission a complete list of manufacturing and testing sites with their corresponding FEI numbers. An updated manufacturing schedule for the bulk drug substance and drug product fill finish sites should be included in Module 1 of the BLA.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our August 13, 2014, communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to “the Program” under PDUFA V. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Finally, in accordance with the PDUFA V agreement, FDA has contracted with an independent contractor, Eastern Research Group, Inc. (ERG), to conduct an assessment of the Program. ERG will be in attendance at this meeting as silent observers to evaluate the meeting and will not participate in the discussion. Please note that ERG has signed a non-disclosure agreement.

Information on PDUFA V and the Program is available at <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>.

In addition, we note that a chemistry pre-submission meeting is planned. A summary of agreements reached at that meeting will be documented in the respective meeting minutes.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e. phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the *application and/or supplement review process*.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

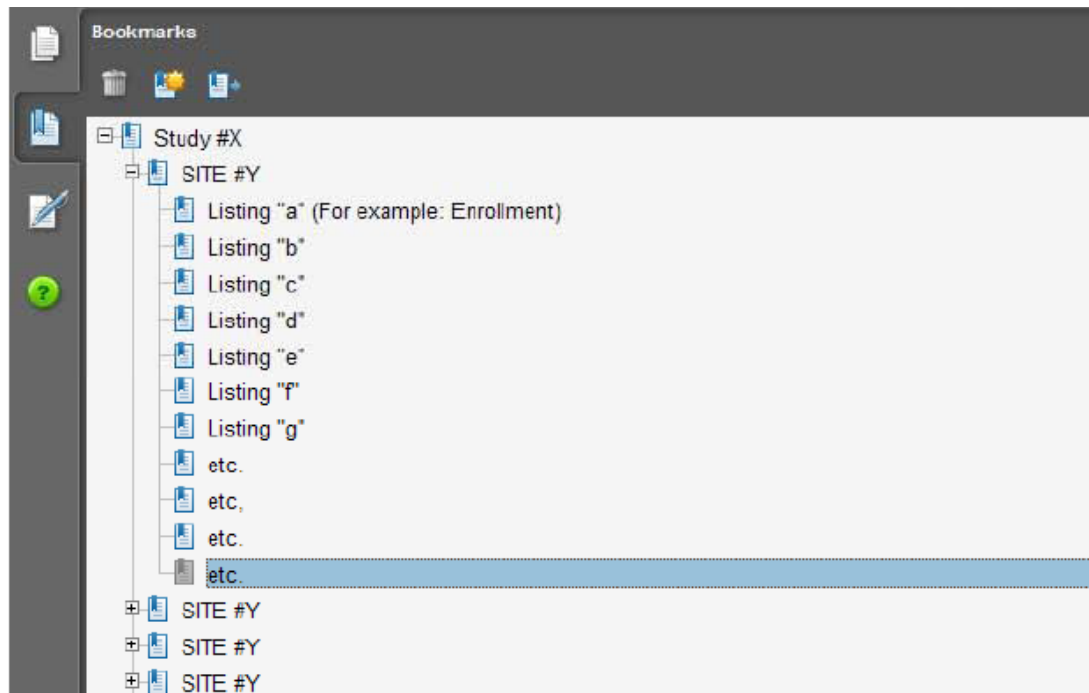
I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
 - a. Site number
 - b. Principal investigator
 - c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - d. Location of Principal Investigator: Address (e.g. Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.
2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
 - a. Number of subjects screened at each site
 - b. Number of subjects randomized at each site
 - c. Number of subjects treated who prematurely discontinued for each site by site
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
 - a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
 - b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g. as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
 - c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as “line listings”). For each site, provide line listings for:
 - a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
 - b. Subject listing for treatment assignment (randomization)
 - c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
 - d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
 - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
 - f. By subject listing, of AEs, SAEs, deaths and dates
 - g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
 - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
 - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
 - j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft “Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning” (available at the following link <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>) for the structure and format of this data set.

Attachment 1

Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

DSI Pre-NDA Request Item ¹	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

¹ Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page
(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: ESUB@fda.hhs.gov

ISSUES REQUIRING FURTHER DISCUSSION:

There were no issues requiring further discussion.

ATTACHMENTS AND HANDOUTS:

Sanofi's October 21, 2014, emailed areas for discussion.

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/s/

CHRISTINE H CHUNG
11/21/2014



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Meeting Type: Type B

Meeting Category: EOP2 CMC Only

Meeting Date and Time: October 26, 2011

Meeting Location: Building 22, Room 1419

Application Number: 100632

Product Name: SAR153191

Received Briefing Package August 16, 2011

Sponsor Name: Sanofi-Aventis

Meeting Requestor: Marsha Miller

Meeting Chair: Sarah Yim, M.D.

Meeting Recorder: Miranda J. Raggio, BA, BSN, MA, RPM

Meeting Attendees:

FDA Attendees: Sarah Yim, M.D., Clinical Team Leader, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

Susan Limb, M.D., Clinical Team Leader, DPARP

Rosemarie Neuner, M.D., Clinical Reviewer, DPARP

Miranda Raggio, Senior Regulatory Project Manager, DPARP

Christine Chung, RPh, Sr. Regulatory Management Officer, DPARP

Lana Hann, Regulatory Project Manager, DPARP

Gerald Feldman, Ph.D., Product Quality Reviewer, Office of Biotechnology Products Division of Monoclonal Antibodies

Marjorie Shapiro, Ph.D., Product Quality Team Leader, OBP, DMA

Jacqueline Ryan, M.D., Combination Product Team Leader, Office of Device Evaluation, Division of Anesthesiology, General Hospital, Infection Control and Dental Devices, General Hospital Devices Branch. CDRH

Lt. Quynh Nguyen, Human Factors Expert, Office of Device Evaluation, Division of Anesthesiology, General

Hospital, Infection Control and Dental Devices, General
Hospital Devices Branch, CDRH

Patricia Y, Love, M.D., MBA, Deputy Director, Office of
Combination Products

Lana Shiu, M.D., Commander, U.S. Public Health, Senior Medical
Advisor, Office of Combination Products

Sponsor Attendees:

Sanofi-Aventis

Judy Plon, MBA, RAC, Senior Director, Regulatory Affairs

Marsha J. Miller, Ph.D., Director, Regulatory Affairs

Joseph R. Mezzatesta, Ph.D., Assistant Director, RCMC

Serpil Heger Global Device Project Leader

Anke Liewald, Head of Usability and Risk-Management

Ghislaine Pisapia, MSc, Project Leader, Clinical, District Project Unit
Anti-IL-6R

Regeneron

Kris Ghosh, Director, CMC Regulatory Affairs, Clinical Development
& Regulatory Affairs

Agnieszka Brzoska-Leckonby, Manager, CMC Project Management

Jenny McNay, Sr Director, Process Sciences, Manufacturing

BACKGROUND

Sanofi-Aventis (Sanofi) requested a Type B Pre-IND meeting in correspondence dated July 19, 2011. The stated purpose of this meeting was to discuss the planned CMC development program for a sarilumab pre-filled syringe (b) (4)

Upon review of the meeting package, received on September 26, 2011, the Division provided responses to Sanofi's questions via a telephone facsimile on October 21, 2011. The content of the telephone facsimile is printed below, with the Sanofi's questions in *bold italics*, the Division's responses in *italics*, and the requests for clarification and discussion in normal font. Marsha Miller, Sanofi Global Regulatory Affairs sent an email on October 24, 2011, to notify the Division that Sanofi would like further clarification on Questions 1, 2 and 4 included specific clarification requests in the email. Summary comments of the meeting discussion are found in normal font following the specific questions.

QUESTIONS, RESPONSES, AND DISCUSSION

Question 1: Stability program: Does the Agency agree that should acceptable stability be demonstrated, the program would support a (b) (4) month shelf life (b) (4)

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/s/

MIRANDA B RAGGIO
11/14/2011



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Meeting Type: Type B
Meeting Category: IND
Meeting Date and Time: September 15, 2011
Meeting Location: Building 22, Room 1419
Application Number: 100632
Product Name: SAR153191
Received Briefing Package August 16, 2011
Sponsor Name: Sanofi-Aventis
Meeting Requestor: Marsha Miller
Meeting Chair: Sarah Yim, M.D.
Meeting Recorder: Miranda J. Raggio, BA, BSN, MA, RPM
Meeting Attendees:
FDA Attendees: Sarah Yim, M.D., Clinical Team Leader, Division of Pulmonary, Allergy, and and Rheumatology Products (DPARP)
Susan Limb, M.D., Clinical Team Leader, DPARP
Rosemarie Neuner, M.D., Clinical Reviewer, DPARP
Tim Robison, Ph.D., Nonclinical Team Leader, DPARP
Grace Lee, Ph.D., Nonclinical Reviewer, DPARP
Partha Roy, Ph.D., Clinical Pharmacology Reviewer, Division of Clinical Pharmacology II, Office of Clinical Pharmacology
Gerald Feldman, Ph.D., Product Quality Reviewer, Office of Biotechnology Products Division of Monoclonal Antibodies
Ruthie Davi, Ph.D., Office of Biostatistics, Division of Biometrics II
Joan Buenconsejo, Ph.D, Acting Biostatistics Team Leader, Office of Biostatistics, Division of Biometrics II
Miranda Raggio, Senior Regulatory Project Manager, Division of Pulmonary and Allergy Products

Sponsor Attendees:**Sanofi-Aventis**

Judy Plon, MBA, RAC, Senior Director, Regulatory Affairs

Marsha J. Miller, Ph.D., Director, Regulatory Affairs

Tanya Momtahn, Vice President, Head, District Project Unit Anti-IL-6R

Hubert van Hoogstraten, M.D., Ph.D., Senior Director, Clinical, District Project Unit Anti-IL-6R

Stefano Fiore, M.D., Associate Director, Clinical, District Project Unit Anti-IL-6R

Ghislaine Pisapia, MSc, Project Leader, Clinical, District Project Unit Anti-IL-6R

Christina (Yongtao) Li, Ph.D., Dedicated Project Expert, Drug Disposition (Pharmacokinetics)

Leah Teoh, Assistant Director, Statistics

Catherine Ortemann-Renon, Pharm.D. Director, Clinical and Exploratory Pharmacology

Nabil Said, M.D., Director, Global Pharmacovigilance and Epidemiology

Peter Glascott, Ph.D., Director, Disposition, Safety and Animal Research

Regeneron

Ned Braunstein, M.D., Executive Director and Head, Regulatory Affairs

Neil Graham, M.D., Ph.D., Vice President, Program Direction, Immunology and Inflammation

Steve Weinstein, M.D., Ph.D., Clinical Sciences, Immunology and Inflammation

BACKGROUND

Sanofi-Aventis (Sanofi) requested a Type B Pre-IND meeting in correspondence dated May 17, 2011. The stated purpose of this meeting was to discuss the planned Phase 3 clinical and nonclinical programs for SAR153191 for the treatment of adult patients with moderate to severe active rheumatoid arthritis (RA) who have had an inadequate response to previous therapy and for the treatment of ankylosing spondylitis in adult patients. Upon review of the meeting package, received on August 16, 2011, the Division provided responses to Sanofi's questions via a telephone facsimile on September 12, 2011. The content of the

telephone facsimile is printed below, with the Sanofi's questions in ***bold italics***, the Division's responses in *italics*, and the requests for clarification and discussion in normal font. Marsha Miller, Sanofi Global Regulatory Affairs sent an email on September 13, 2011, to notify the Division that Sanofi would like further clarification on Introductory Comments and Questions 1, 2, 3, 8, 11, 12, and 13 and included specific clarification requests in the email. Summary comments of the meeting discussion are found in normal font following the specific questions.

QUESTIONS AND RESPONSES

Introductory Comment

As discussed at the Type C meeting held on February 23, 2011, we have concerns regarding what appears to be a narrow therapeutic window for sarilumab. We agree that the available data suggest that a dose of 100 mg q2weeks or less lacks efficacy. However, the safety data indicate several dose-related toxicities for the proposed doses of 150 mg q2weeks and 200 mg q2weeks, including neutropenia, lipid abnormalities, and elevated transaminases. Therefore, while dose ranging from an efficacy perspective appears adequate, we have concerns regarding the proposed doses from a safety perspective. These safety concerns may impact the viability of the overall clinical program. We suggest that you consider incorporating an active comparator in the Phase 3 program for the purpose of safety comparison.

Sanofi Clarification Request: The Sponsor requests that the Agency clarify the recommendation for an active comparator in Phase 3.

1. The Sponsor interprets the Agency's recommendation to either conduct an additional study or incorporate an active comparator arm in one of the planned Phase 3 efficacy or safety studies. Is the Sponsor's understanding correct?

Discussion: The Division clarified that it is not recommending that Sanofi necessarily do an additional study, but rather that an active comparator arm be incorporated into one of the planned Phase 3 studies. As noted above, although dose ranging information from an efficacy standpoint seems reasonable, safety signals associated with the proposed Phase 3 doses raise concerns. Therefore, it would be helpful to have data from another product with a similar mechanism of action to determine if these toxicities are class related.

2. Does the Agency recommend a specific class of drug to be used as the active comparator?

Discussion: The Division clarified that Actemra (tocilizumab) would be an appropriate comparator, noting that Sanofi would want to use the U.S. approved dosing regimen for this product in the trial. Sanofi asked if the Division is recommending a non-inferiority trial, to which the Division responded that the purpose of the comparison is not for a marketing claim, nor to establish superiority to another product, but rather to gather data to aid in the assessment of sarilumab's toxicity profile compared to that of other products in the same drug class. Therefore, a non-inferiority trial is not recommended.

3. Does the Agency have a recommendation regarding the number of patients receiving this active comparator to be included in the Phase 3 program for the purpose of safety comparison?

Discussion: The Division stated that it does not expect that this active comparator trial to be powered for statistical significance, but noted that the trial should be large enough and of adequate duration to provide the data necessary to make a reliable comparison to the safety profile of sarilumab. The Division went on to note that although the Actemra label limits its use to the TNF inhibitor refractory population, it would be

possible to use it in other RA populations in studies conducted under the IND. Sarilumab should be studied in the population intended for marketing.

Question 1a: With regard to the clinical program to evaluate sarilumab in patients with RA, does the Agency agree that the study program outlined below, including study designs and proposed statistical analyses for the Phase 3 studies in patients with RA, supports registration with the proposed indication?

Division Response: We agree, in principle, that positive results from your two proposed pivotal Phase 3 studies, in conjunction with an acceptable safety profile, should be adequate to support filing a BLA for sarilumab for the claims of improvement in signs and symptoms, improvement in physical function, and induction of major clinical response. The proposed program is also adequate to support a claim for the prevention of structural damage in patients with RA, provided that a similar benefit is observed in patients with psoriatic arthritis. The final determination of the efficacy and safety of the product as well as the exact wording of the indication will be a review issue.

Sanofi Clarification Request: The Sponsor requests that the Agency confirm that if the Sponsor submits the BLA with clinical studies in an RA population only, the claim for the prevention of structural damage in patients with RA will be fully supported from the single RA study EFC11072 (MOBILITY) assessing x-ray data in support of the structural damage claim.

Discussion: The Division stated that the adequacy of the data generated from the single RA study in support of a claim for the prevention of structural damage in patients with RA will be a review issue. However, if the data from this single study is less than compelling, supporting data from a second trial in the same or a related disease (e.g., psoriatic arthritis) would need to be submitted to support a prevention of structural damage claim for sarilumab.

b) The Sponsor has proposed a strategy to demonstrate that with the selection of 2 doses for Phase 3, 150 mg 2qw and 200 mg 2qw, there will be adequate dose ranging for the drug product to be used in the Phase 3 Program and for registration. Does the Agency agree?

Division Response: Refer to our Introductory Comment.

c) The Sponsor would like confirmation of the advice given by the Agency at the September 2009 Type C Meeting that Part B2 of EFC11072 (MOBILITY), along with a second pivotal study (EFC10832), will support the claim of improvement of signs and symptoms and claim of improvement in physical function, and that EFC11072 (MOBILITY) is acceptable as the sole study to support the claims of prevention of structural damage and induction of major clinical response in patients with RA.

Division Response: Refer to our response to Question 1a.

Question 2: The Sponsor is considering amending the EFC11072 (MOBILITY) protocol to unblind the study prior to study completion and to perform the primary endpoint analysis at Week 24 in support of an initial registration based on signs and symptoms data, including ACR20, and to have the currently planned final analysis as a secondary analysis for a subsequent supplemental filing. Top line results would be publicly released at that time due to the fiduciary responsibility of Regeneron.

a) Does the Agency agree with the Sponsor's proposed analysis plan, including the multiplicity adjustment?

Division Response: Endpoints that incorporate subjective assessments, such as ACR Responses, or HAQ-DI, may be subject to bias if assessed at timepoints that are known to occur after the controlled period has ended. Therefore you should report results for the HAQ-DI at Week 24, along with your primary endpoint.

The Division is re-evaluating the Major Clinical Response claim, given that extended controlled periods using placebo comparisons may no longer be justifiable given the number and availability of highly effective therapies for RA.

The proposed analysis plan for the radiographic endpoint is generally acceptable. However, measures should be taken to protect the reliability of the radiographic endpoint, for example, those evaluating the radiographic endpoint should remain blinded to treatment through week 52, be external to the conduct of the study, and not be aware of the efficacy results obtained at week 24. In addition, you should continue to obtain radiographs on patients who escape or drop out of the study in order to be able to provide a sensitivity analysis based on these data (i.e., a "retrieved dropout" analysis). If sensitivity analyses are not consistent with the primary analysis using linear extrapolation, then it may not be possible to draw a definitive conclusion regarding treatment effect on radiographic outcomes.

The multiplicity adjustment is acceptable.

b) Does the Agency agree with the Sponsor's proposed internal procedure to protect the integrity of the subsequent endpoints through Week 52 of the study?

Division Response: *The proposed internal procedure is generally acceptable, however, the Division has concerns regarding endpoints using subjective assessments, as noted in the response to Question 2a above.*

Sanofi Clarification Request: *The radiographic readers will be independent of study team and will remain blinded to study treatment and the order of the x-rays when assessing x-ray results through the Week 52 database lock. They are external to the conduct of the study and will not be directly notified by the Sponsor of any study results obtained at Week 24. The press release will contain the ACR results and major comments regarding safety and the Sponsor cannot rule out that the radiographic readers would become aware of these results. Is this an acceptable approach?*

Discussion: *The Division stated that the proposed approach seems reasonable, and reminded Sanofi to include detailed information on and rationales for the internal procedures and steps taken to maintain blinding throughout the 52 week duration.*

Question 3: Does the Agency agree that the study program outlined below, including study designs and proposed statistical analyses for the Phase 3 studies in patients with PsA, supports registration with the proposed indication?

Division Response: *We agree, in principle, that positive results from these two studies in conjunction with an acceptable safety profile should be adequate to support filing a supplemental BLA for sarilumab for claims of improvement in signs and symptoms and improvement in physical function.*

(b) (4)

Sanofi Clarification Request:

(b) (4)

Discussion:

(b) (4)

Question 4:

a) Does the Agency agree that the proposed size of the safety database expected to be available at the time of registration, is sufficient for assessment of patient safety and for registration of sarilumab in the RA indication based on the data from the RA patients alone?

Division Response: The proposed safety database appears adequate, in principle. Additional safety data may be necessary depending on the safety profile observed.

b) Does the Agency agree that the proposed size of the safety database expected to be available at the time of registration of RA, or in a later supplemental BLA, is sufficient for assessment of patient safety and for registration of sarilumab in the PsA indication?

Division Response: The proposed safety database appears adequate, in principle. Additional safety data may be necessary depending on the safety profile observed.

Question 5: Does the Agency agree that the proposed safety assessments will sufficiently document the safety of sarilumab for the initial registration for the RA and PsA indications?

Division Response: We concur, in principle, that the adverse events of interest (e.g., hematologic, hepatobiliary, lipid parameter abnormalities, cardiovascular events, infections, malignancies, gastrointestinal perforations, demyelinating disorders and systemic hypersensitivity) have been appropriately identified. However, we have the following recommendations for your proposed safety assessments:

- 1. We recommend that you use the definition for anaphylaxis as described by the article by Sampson et al¹ when you classify these types of events in your safety database.*
- 2. In addition to the independent Data Monitoring Committee that will oversee the safety data generated from the Phase 3 trials and serial ECG monitoring of subjects participating in the Phase 3 trials, consider having an independent external clinical events committee (CEC) composed of external specialists blinded to treatment to review and prospectively adjudicate cases of major cardiovascular events (MACE) which are defined as myocardial infarction, stroke, death, hospitalizations for both unstable angina and transient ischemic attack.*

Reference:

¹Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF, 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* 117(2):391-397.

Question 6:

a) Does the Agency agree that the completed and planned clinical pharmacology studies, including the Sponsor's proposed plans to assess the drug interaction potential of sarilumab, are adequate to support registration?

*Division Response: The issue of drug interaction potential of therapeutic proteins with small molecule drugs that are substrates of CYP450 enzymes and/or transporters is still evolving. We refer you to a recent publication which may provide insight into our current thinking [Huang S-M et al. *Clin. Pharmacol. Ther.* 87 (4): 497-503 (2010)]. Although the utility of using in vitro models of CYP450 modulation via cytokines to accurately predict in vivo effect is unclear at this time, it may still be worthwhile to conduct such experiments to understand the impact of your drug on drug metabolizing enzyme and/or transporter*

expression levels. We may recommend conducting additional clinical drug-drug interaction studies based on the data you submit and the regulatory position at the time of data review.

In addition to the completed (5 Phase 1 trials) and planned (simvastatin interaction study) clinical pharmacology trials, we note that you are planning to use population PK analyses to determine the impact of intrinsic (renal and hepatic impairment) and extrinsic (concomitant medications) factors on the PK of sarilumab. In addition, we recommend that you also investigate the effect of age, gender and race on sarilumab PK. We generally agree that the proposed clinical pharmacology package may be sufficient for BLA filing, provided no unexpected findings are uncovered that would need further investigations.

b) Does the Agency agree that no other clinical pharmacology or drug interaction studies are necessary for registration?

Division Response: Refer to our response to Question 6a.

Question 7: Does the Agency agree with the Sponsor’s proposed plans to assess the immunogenicity of sarilumab?

Division Response: Your proposal to collect serum samples to test for anti-sarilumab antibodies and to correlate ADA status on PK, efficacy, and safety, appears reasonable. However, additional information is required. See the CMC Additional Comments at the end of this document.

Question 8: The Sponsor intends to (b) (4)

[Redacted]

a) Does the Agency agree (b) (4)

[Redacted] ?

b) Does the Agency agree (b) (4)

[Redacted]

c) Based on the Sponsor’s previous device experiences (b) (4)

[Redacted] can the Agency provide feedback (b) (4)

[Redacted] ?

Division Response to a, b, and c: (b) (4)

[Redacted]

[Redacted]

(b) (4)

Sanofi Clarification Request 1.

(b) (4)

[Redacted]

(b) (4)

Discussion:

(b) (4)

(b) (4)

[Redacted]

Sanofi Clarification Request 2.

(b) (4)

(b) (4)

[Redacted]

Discussion:

(b) (4)

(b) (4)

[Redacted]

(b) (4)

Sanofi Clarification Request 3.

(b) (4)

Discussion:

(b) (4)

Question 9:

a) *The Sponsor plans to begin pediatric studies in juvenile idiopathic arthritis (JIA) prior to the initial registration; however the Sponsor expects that these studies will not be completed until after the initial registration. The Sponsor, therefore, requests a deferral with regard to completing pediatric studies prior to initial registration. Does the Agency agree with the request for a deferral for JIA?*

b) *The Sponsor will not conduct pediatric studies for the RA indication and, therefore, requests a waiver for these studies. Does the Agency agree?*

c)

(b) (4)

Division Response to a, b, and c: Approval of sarilumab for the treatment of RA in adults will trigger a requirement for pediatric studies in polyarticular JIA under PREA. Decisions regarding deferral or waiver are made at the time of BLA action. That being said, the proposal to evaluate sarilumab in children following initial evaluation in adults appears reasonable.

Question 10: *The general toxicity studies include a duration of sarilumab treatment in monkeys of up to 3 months SC and 6 months intravenously (IV). Does the Agency agree that the general toxicity program is sufficient to support the initial registration of sarilumab by SC route?*

Division Response: Yes, we agree.

Question 11: *Does the Agency agree that the 2 reproductive studies (fertility study in mice with the fully-murine surrogate against mouse IL-6R and enhanced pre/postnatal developmental study in monkeys) plus the available data in the public domain on IL-6 inhibition (including a) are sufficient for the initial registration?*

Division Response: It appears that the information that could not be used to support your application. We have some concerns about the adequacy of the enhanced pre/postnatal developmental study

in monkeys using sarilumab. First, numbers of neonates in each group were relatively small. Second, immune function testing in the offspring during the postnatal phase was not conducted (e.g., TDAR). Last, sarilumab was not totally cleared from the circulation of F1 offspring at the time of necropsy (around postnatal day 30) and therefore the drug may have uncharacterized effects beyond the one month of age in monkeys. We are aware that sarilumab has been shown to be immunosuppressive in adult monkeys (e.g., decreased neutrophil counts, decreased effects in the TDAR assay in the 6-month study) as well as in adult humans. The investigator's brochure, informed consent, and potential product labeling will need to use existing knowledge on sarilumab and the IL-6 pathway to report the potential immunosuppressive effects of sarilumab in infants of mothers exposed to sarilumab.

Sanofi Clarification Request: The Sponsor acknowledges the Agency's comments. To address the Agency's concerns, the Sponsor proposes to conduct a GLP subcutaneous pre- /postnatal toxicity study in mice using the murine surrogate against IL-6R, REGN844. This is the same molecule used in the fertility study in mice. The pre-/postnatal study would include TDAR evaluation and be of sufficient duration to clear the test-article from the F1 offspring. This study would be conducted for BLA submission. Upon completion of this mouse pre-postnatal study, the Sponsor would consider the Agency's concerns addressed and that the reproductive toxicity package would have appropriately evaluated the target for registration. Does the Agency agree that after completion of this pre-/postnatal toxicity study in mice that no additional reproductive toxicity studies are needed for registration?

Discussion: The Division reiterated concerns about the adequacy of the enhanced pre/postnatal developmental study in monkeys using sarilumab, but stated that additional developmental toxicity studies are not necessarily required if Sanofi agrees to incorporate information regarding the potential immunosuppressive effects of the product in infants in the Informed Consent(IC), the Investigator's Brochure(IB), and the potential product label as follows: "Infant monkeys were evaluated up to 1 month of age in the enhanced PPND study with monkeys and immune functional testing was not performed. Based on the findings from the 6-month toxicity study in adult monkeys and available adult human clinical data, sarilumab possesses the potential to cause immunosuppressive effects in the infants of mothers treated with sarilumab". Sanofi asked if it would be acceptable to include this information in the documents noted above

(b) (4)
The Division noted that it is Sanofi's choice to take this approach. However, (b) (4)
Sanofi asked whether
the statement can be (b) (4) It was stated that the agency is not
recommending (b) (4)

Question 12: *Does the Agency agree that, given the available nonclinical data with sarilumab (including general toxicity and reproductive studies in animals) and available information on molecules with the same mechanism of action in terms of inhibition of IL-6R,* (b) (4)

Division Response: No, we do not agree. (b) (4)

Sanofi Clarification Comment: Thank you for the response. Should it be decided that (b) (4)

Question 13: *The Sponsor conducted a weight-of-evidence based carcinogenicity risk assessment based on results from toxicology studies with sarilumab and REGN844 (the fully-murine surrogate against*

mouse IL-6R), effects of sarilumab in antitumor pharmacology models, and a review of published literature following IL-6R activation and inhibition. Does the Agency agree that, given the available data with sarilumab and data in the literature on IL-6 inhibition, no additional in vitro and in vivo studies (eg, in vitro cell-based assays, xenograft models, tumor promotion models, 2-year bioassays) with sarilumab are necessary for registration?

Division Response: *Your carcinogenicity assessment position paper is being reviewed by DPARP. In order to complete the review of your carcinogenicity assessment position paper, we need the study report on characterization of the effects of sarilumab (REGN88) on STAT3 activation and tumor xenograft growth (Report Number REGN88-MX-11050-SR-01V1). Your proposal on the carcinogenicity assessment will be also discussed with the Executive Carcinogenicity Assessment Committee at which time we will address whether further carcinogenicity assessment for sarilumab is needed. After this issue is discussed with the Executive Carcinogenicity Assessment Committee, we will respond to this question.*

Sanofi Clarification Request: The Sponsor appreciates the review of the position paper by DPARP at this time. Please note that on 12 September 2011 the requested study report on the characterization of the effects of sarilumab (REGN88) on STAT3 activation and tumor xenograft growth (Report Number REGN88-MX-11050-SR-01V1) was submitted to the IND 100632(Serial No. 0125).

As noted in the Agency's response, prior to responding to Question 13, the Division will discuss the sponsor's carcinogenicity assessment position paper with the Executive Carcinogenicity Assessment Committee. Can the Division provide feedback on the timeline when the sponsor can expect to receive a definitive response on whether an additional carcinogenicity assessment for sarilumab is required in support of registration?

Discussion: The Division clarified that discussion of a carcinogenicity assessment position paper with the Executive Carcinogenicity Assessment Committee is a routine occurrence, but that definitive timeline for a response cannot be given. The Division assured Sanofi that review and feedback will be accomplished in as timely manner as possible, given the resources available.

Additional CMC Comments

- 1. Insufficient information was provided describing the method and validation of Immunogenicity Assay II. Please refer to the Draft Guidance for Industry: "Assay Development for Immunogenicity Testing of Therapeutic Proteins" (2009) for recommendations regarding the approach, design and validation of immunogenicity assays. Steps taken to reduce interference by RF and ligand in Immunogenicity Assay II are appropriate and the sensitivity of the assay within an appropriate range. We recommend that results be reported as a titer rather than positive versus negative.*
- 2. The immunogenicity assays should be properly validated for their intended use in phase 3 studies. Patient samples should be collected at a time point when the concentration of sarilumab will not interfere with the assay and appropriately banked. Stability of patient samples should be assessed. The validation of the immunogenicity assays will be a review issue during the BLA. However, if there are specific questions or concerns regarding your approach, we recommend that you submit an amendment to the IND with sufficient data to review the assay so we can provide adequate guidance.*

Discussion: Sanofi pointed out that validation of immunogenicity assay reports were submitted to the FDA on January 11, 2011, and asked that the Division review these reports. The Division acknowledged this oversight and thanked Sanofi for this information. Sanofi stated that the neutralizing antibody reports would be submitted to the IND, when available.

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at the following link:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

APPEARS THIS WAY ON ORIGINAL

Drafted: M. Raggio/9-15-11

Initialed: Partha Roy/9/23/11

Suresh Doddapaneni/9-23-11

Grace Lee/9-19-11

Tim Robison/9-19-11

Rosemarie Neuner/9-16-11

Susan Limb/9-19-11

Sarah Yim/9-26-11

Finalized: M. Raggio/9-26-11

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/s/

MIRANDA B RAGGIO
09/26/2011

LATE-CYCLE COMMUNICATION
DOCUMENTS



BLA 761037

LATE-CYCLE MEETING MINUTES

Sanofi US Services Inc.
55 Corporate Drive
Bridgewater, NJ 08807

Attention: Sarah Feathers, PharmD
Global Regulatory Affairs

Dear Dr. Feathers:

Please refer to your Biologic License Application (BLA) submitted under the Public Health Service Act for Kevzara (sarilumab) injection, 150 mg and 200 mg pre-filled syringes (PFS).

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on July 25, 2016.

A copy of the official minutes of the LCM is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Christine Ford, Regulatory Project Manager at (301) 796-3420.

Sincerely,

{See appended electronic signature page}

Janet Maynard, MD, MHS
Cross-Discipline Team Leader (CDTL)
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: July 25, 2016 1:00 – 2:00 P.M.
Meeting Location: Teleconference

Application Number: BLA 761037
Product Name: Kevzara (sarilumab) injection, 150 mg and 200 mg pre-filled syringes (PFS)
Indication: Rheumatoid arthritis
Applicant Name: Sanofi US Services Inc. (Sanofi)

Meeting Chair: Dr. Janet Maynard, Cross-Discipline Team Leader
Meeting Recorder: Christine Ford, Regulatory Project Manager

FDA participants:

Curtis Rosebraugh, MD, MPH, Director, Office of Drug Evaluation II
Badrul A. Chowdhury, MD, PhD, Director, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Sarah Yim, MD, Supervisory Associate Director, DPARP
Janet Maynard, MD, MHS, Clinical Team Leader, DPARP
Suzette Peng, MD, Clinical Reviewer, DPARP
Timothy Robison, PhD, Nonclinical Team Leader, DPARP
Eleni Salicru, PhD, Nonclinical Reviewer, DPARP
Christine Ford, MS, RPh, Regulatory Project Manager, DPARP
Gregory Levin, PhD, Biometrics Team Leader, Division of Biometrics II (DBII)
Gerald Feldman, PhD, Product Quality Reviewer, Division of Biotechnology Review and Research IV (DBRRIV)
Frederick Mills, PhD, Immunogenicity Reviewer, DBRRIV
Anshu Marathe, PhD, Team Leader, Division of Clinical Pharmacology II (DCPII)
Jianmeng Chen, PhD, Clinical Pharmacology Reviewer, DCPII
Teresa Mcmillan, PharmD, Safety Evaluator, Division of Medication Error & Prevention Analysis (DMEPA)
Nichelle Rashid, Team Leader Project Management Staff, Office of Surveillance & Epidemiology (OSE)
Michael Sinks, PharmD, Safety Regulatory Project Manager, OSE

EASTERN RESEARCH GROUP (ERG) participant:

Marc Goldstein, independent assessor of The Program under PDUFA V

APPLICANT participants:

Sanofi

Jonathan Sadeh, Global Project Lead
Alex Boddy, Lead Statistician
Yong Lin, Clinical Lead
Rachpal Malhotra, Pharmacovigilance
Christine Xu, Clinical Pharmacology
Pierre Wils, CMC
Sarah Feathers, Regulatory Lead
Debbie Thomas, Regulatory Device/CMC

Regeneron

Neil Graham, Global Project Lead
Janet Van Adelsberg, Clinical Lead
Janie Parrino, Clinical
Pat Reilly, Regulatory Lead
Matthew Elliott, Regulatory CMC
Albert Torri, Bioanalytical Sciences

BACKGROUND:

BLA 761037 was submitted on October 30, 2015, for sarilumab injection, 150 mg and 200 mg pre-filled syringes (PFS).

Proposed indication(s): Rheumatoid arthritis (RA)

PDUFA goal date: October 30, 2016

FDA issued a Background Package in preparation for this meeting on July 13, 2016.

AGENDA:

1. Introductory Comments – 5 minutes

Welcome, Introductions, Ground rules, Objectives of the meeting

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle.

2. Discussion of Substantive Review Issues – 10 minutes

Each issue will be introduced by FDA and followed by a discussion.

Clinical: Safety and Risk/Benefit Considerations

- a. Proposed doses: You propose use of 200 mg of sarilumab once every 2 weeks by subcutaneous (SC) injection for the treatment of moderately to severely active rheumatoid arthritis. Reduction of dose from 200 mg every 2 weeks to 150 mg every 2 weeks is recommended for management of neutropenia, thrombocytopenia, and elevated liver enzymes. We continue to review the overall safety and efficacy of each dose to determine whether data are adequate to support one or two doses or a weight-tiered starting dose. No additional information or analyses are requested from you at this time.
- b. Cardiovascular: Treatment with sarilumab is associated with increases in lipid parameters, such as LDL cholesterol, HDL cholesterol, and triglycerides. Whether additional data are needed to assess potential risks associated with increases in lipid parameters, such as serious cardiovascular events, remains under review. While no additional analyses are requested at this time, it is still under discussion whether post-marketing data will be requested to address this issue.

Discussion:

Sanofi stated that they would like to submit a white paper analysis regarding cardiovascular risk in RA patients and the association with inflammation and lipids. Sanofi asked if the Agency would find it useful.

FDA responded that they are familiar with the issues, and a white paper analysis on the general concepts may not add any additional information. However, it would be at Sanofi's discretion whether to submit the white paper. The Agency reiterated that there are internal discussions occurring on the need for additional postmarketing data. Any decision will be conveyed to the applicant no later than September 6, 2016.

Sanofi indicated that they would probably not submit the white paper.

FDA post-meeting note:

Refer to minutes of August 10, 2016, teleconference which will be forwarded as a separate correspondence.

- c. Prescribing information: The proposed prescribing information is still under review. You have proposed inclusion of safety information from the 12-week placebo-controlled population from the 2 phase 3 efficacy studies. Given the complexities in the study design of the phase 3 studies and the differences in the study, the optimal presentation of the safety data is under review. It may be preferable to display the safety data for the pre-rescue period, containing data from 0-16 weeks from EFC11072 Part B and 0-12 weeks from EFC10832.

3. Additional Applicant Data

No additional data needed at this time.

4. Information Requests – 5 minutes

Product Quality

- a. Microbiology: The microbial retention studies (b) (4) are still under review, and a follow-up information request will be sent.
- b. Remaining components of the CMC sections are still under review, and a follow-up information request is being prepared.

5. Postmarketing Requirements/Postmarketing Commitments – 5 minutes

PREA PMR

PK/PD study in children ages ≥ 2 years to ≤ 17 years with polyarticular juvenile idiopathic arthritis (pJIA) and an efficacy and safety study in children ages ≥ 2 years to ≤ 17 years with pJIA

(b) (4)



6. Major labeling issues – 5 minutes

- Hypersensitivity: need warning about hypersensitivity events
- Other edits to sections 6 and 14 will be forthcoming

Discussion:

FDA stated that the goal date for the Agency to provide labeling comments, including the warning about hypersensitivity events, is September 6, 2016.

7. Review Plans – 5 minutes

Reviews ongoing and on target with PDUFA goals

8. Wrap-up and Action Items – 5 minutes

LCM is scheduled for July 25, 2016, and the PDUFA goal date is October 30, 2016.

This application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, this meeting did not address the final regulatory decision for the application.

APPEARS THIS WAY ON ORIGINAL

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/s/

SARAH K YIM
08/19/2016
Signing for Janet Maynard, MD, MHS



BLA 761037

**LATE CYCLE MEETING
BACKGROUND PACKAGE**

Sanofi US Services Inc.
55 Corporate Drive
Bridgewater, NJ 08807

Attention: Sarah Feathers, PharmD
Global Regulatory Affairs

Dear Dr. Feathers:

Please refer to your Biologic License Application (BLA) submitted under the Public Health Service Act for Kevzara (sarilumab) injection, 150 mg and 200 mg pre-filled syringes (PFS).

We also refer to the Late-Cycle Meeting (LCM) scheduled for July 25, 2016. Attached is our background package, including our agenda, for this meeting.

If you have any questions, call Christine Ford, Regulatory Project Manager, at (301) 796-3420.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, MD, PhD
Director,
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:
Late-Cycle Meeting Background Package

LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time: July 25, 2016 1:00 – 2:00 P.M.
Meeting Location: White Oak Building 22 Conference Room 1415

Application Number: BLA 761037
Product Name: Kevzara (sarilumab) injection, 150 mg and 200 mg pre-filled syringes (PFS)
Indication: Rheumatoid arthritis
Applicant Name: Sanofi US Services Inc. (Sanofi)

FDA ATTENDEES (tentative):

Curtis Rosebraugh, MD, MPH, Director, Office of Drug Evaluation II
Badrul A. Chowdhury, MD, PhD, Director, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Sarah Yim, MD, Supervisory Associate Director, DPARP
Janet Maynard, MD, MHS, Clinical Team Leader, DPARP
Suzette Peng, MD, Clinical Reviewer, DPARP
Timothy Robison, PhD, Nonclinical Team Leader, DPARP
Eleni Salicru, PhD, Nonclinical Reviewer, DPARP
Christine Ford, MS, RPh, Regulatory Project Manager, DPARP
Gregory Levin, PhD, Biometrics Team Leader, Division of Biometrics II (DBII)
Yongman Kim, PhD, Biometrics Reviewer DBII
Anshu Marathe, PhD, Team Leader, Division of Clinical Pharmacology II (DCPII)
Jianmeng Chen, PhD, Clinical Pharmacology Reviewer, DCPII
Sheetal Agarwal, PhD, Clinical Pharmacology Reviewer, DCPII
Michele Dougherty, PhD, Team Leader, Division of Biotechnology Review and Research IV (DBRRIV)
Gerald Feldman, PhD, Product Quality Reviewer, DBRRIV
Frederick Mills, PhD, Immunogenicity Reviewer, DBRRIV
Patricia Hughes, PhD, Branch Chief, Division of Microbiology Assessment (DMA), Branch IV
Collen Thomas, PhD, Product Quality Microbiology Reviewer, DMA, Branch IV
Representative from the Eastern Research Group, Inc. (for applications under the Program)

INTRODUCTION:

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal

date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE:

1. Discipline Review Letters

No Discipline Review letters have been issued to date.

2. Substantive Review Issues

The following substantive review issues have been identified to date:

Clinical

- a. **Proposed doses:** You propose use of 200 mg of sarilumab once every 2 weeks by subcutaneous (SC) injection for the treatment of moderately to severely active rheumatoid arthritis. Reduction of dose from 200 mg every 2 weeks to 150 mg every 2 weeks is recommended for management of neutropenia, thrombocytopenia, and elevated liver enzymes. We continue to review the overall safety and efficacy of each dose to determine whether data are adequate to support one or two doses or a weight-tiered starting dose. No additional information or analyses are requested from you at this time.
- b. **Cardiovascular:** Treatment with sarilumab is associated with increases in lipid parameters, such as LDL cholesterol, HDL cholesterol, and triglycerides. Whether additional data are needed to assess potential risks associated with increases in lipid parameters, such as serious cardiovascular events, remains under review. While no additional analyses are requested at this time, it is still under discussion whether post-marketing data will be requested to address this issue.
- c. **Prescribing information:** The proposed prescribing information is still under review. You have proposed inclusion of safety information from the 12-week placebo-controlled population from the 2 phase 3 efficacy studies. Given the complexities in the study design of the phase 3 studies and the differences in the study, the optimal presentation of the safety data is under review. It may be preferable to display the safety data for the pre-rescue period, containing data from 0-16 weeks from EFC11072 Part B and 0-12 weeks from EFC10832.

3. ADVISORY COMMITTEE MEETING:

An Advisory Committee meeting is not planned.

4. REMS OR OTHER RISK MANAGEMENT ACTIONS

No issues related to risk management have been identified to date.

LCM AGENDA:

1. Introductory Comments – 5 minutes

Welcome, Introductions, Ground rules, Objectives of the meeting

2. Discussion of Substantive Review Issues – 10 minutes

Each issue will be introduced by FDA and followed by a discussion.

Clinical: Safety and Risk/Benefit Considerations

- a. Proposed doses
- b. Cardiovascular
- c. Prescribing information

3. Additional Applicant Data

No additional data needed at this time.

4. Information Requests – 5 minutes

Product Quality

- a. Microbiology: The microbial retention studies (b) (4) are still under review, and a follow-up information request will be sent.
- b. Remaining components of the CMC sections are still under review, and a follow-up information request is being prepared.

5. Postmarketing Requirements/Postmarketing Commitments – 5 minutes

PREA PMR

PK/PD study in children ages ≥ 2 years to ≤ 17 years with polyarticular juvenile idiopathic arthritis (pJIA) and an efficacy and safety study in children ages ≥ 2 years to ≤ 17 years with pJIA

(b) (4)

6. Major labeling issues – 5 minutes

- Hypersensitivity: need warning about hypersensitivity events
- Other edits to sections 6 and 14 will be forthcoming

7. Review Plans – 5 minutes

Reviews ongoing and on target with PDUFA goals

8. Wrap-up and Action Items – 5 minutes

LCM is scheduled for July 25, 2016, and the PDUFA goal date is October 30, 2016.

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/s/

BADRUL A CHOWDHURY
07/13/2016