

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761037Orig1s000

PRODUCT QUALITY REVIEW(S)

First Approval for Indication**Recommendation:****BLA: Approval****BLA 761037**
Review #2
Review Date April 21, 2017

Drug Name/Dosage Form	Kevzara (pending) (sarilumab)/ Injection
Strength/Potency	150 mg/ 1.14 ml (136.1 mg/ml) and 200 mg/1.14 ml (175 mg/ml) Injection in a pre-filled syringe
Route of Administration	Subcutaneous Injection
Rx/OTC Dispensed	Rx
Indication	Kevzara™ is indicated for the treatment of adults with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to one or more disease-modifying-antirheumatic drugs (DMARDs)
Applicant/Sponsor	Sanofi-aventis U.S. LLC
US agent, if applicable	N/A

Product Overview**Quality Review Team**

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Product Quality	Gerald Feldman	OBP/DBRRIV
Facilities	Laura Fontan	OPF/DIA
Microbiology	DMA-DS: Candace Gomez-Broughton DMA-DP: Lakshmi Narasimhan	OPF/DMA
Regulatory Business Process Manager	Melinda Bauerlien	OPQ/OPRO
Application Technical Lead	Joel Welch	OBP/DBRRIV

Multidisciplinary Review Team

DISCIPLINE	REVIEWER	OFFICE/DIVISION
Regulatory Project Manager	Christine Ford	OND/ODEII/DPARP
Cross-disciplinary Team Lead	Janet Maynard	OND/ODEII/DPARP
Clinical	Suzette Peng	OND/ODEII/DPARP
Non-Clinical	Eleni Salicru	OND/ODEII/DPARP
Clinical Pharmacology	Jianmeng Chen	OTS/OCP/DCPII
Clinical Statistics	Yongman Kim	OTS/OB/DBII

a. Names

1. Proprietary Name: Kevzara™ (pending)
2. Trade Name: Kevzara™ (pending)
3. Non-Proprietary/USAN: sarilumab
4. CAS name: 1189541-98-7
5. Common Name: REGN88, SAR153191
6. INN Name: sarilumab

b. Pharmacologic category

Therapeutic recombinant human monoclonal antibody (IgG1), anti-human interleukin 6 receptor (IL-6R)

Submissions Reviewed:

SUBMISSION(S) REVIEWED	DOCUMENT DATE
761037/0.53	March 22, 2017

Quality Review Data Sheet

1. LEGAL BASIS FOR SUBMISSION: 351(a)

2. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

No new information is provided. Sufficient data was provided in the BLA for review during the initial review cycle.

B. Other Documents:

None.

3. CONSULTS:

None

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

a. Recommendation

The Office of Pharmaceutical Quality, CDER, recommends approval for STN 761037 for KEVZARA (sarilumab) manufactured by Sanofi, Inc. The data submitted in this application support the conclusion that the manufacture of KEVZARA™ is well controlled and produces a product that is pure and potent. It is recommended that this product be approved for human use under conditions specified in the package insert.

The initial OPQ recommendation (dated October 19, 2016) proposed a CR based on the provisional official action indicated (pOAI) status of the Sanofi, Inc drug product manufacturing facility, Le Trait, France (FEI 3003259844). The status of this site is now acceptable per review of the Division of Inspectional Assessment (see separate review from DIA dated April 17 2017). The submission contains no new product quality data and the original conclusion of its adequacy remains unchanged.

b. Action letter language

1. Manufacturing Location

a. Drug Substance:

Regeneron Pharmaceutical, Inc., [REDACTED]
[REDACTED] Rensselaer, NY

(b) (4)

b. Drug Product:

Sanofi Winthrop Le Trait, Boulevard Industriel 76508 Le Trait, France

2. Fill Size and Dosage Form 150 mg/1.14 ml and 200 mg/1.14 ml in pre-filled syringe
3. Dating Period Drug Product: 24 months; 2-8C
4. [REDACTED] (b) (4)
5. Dating Period Drug Substance: (b) (4) months; (b) (4) C
6. Exempt from Lot Release Yes; rationale for exemption: Specified Product (exempted according to 21 CFR 601.2a)

(b) (4)

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None are recommended.

II. Summary of Quality Assessments

See original review dated October 21, 2016 for summary information on identification of CQAs and their control strategy, additional establishment information, and lifecycle management items.

APPEARS THIS WAY ON ORIGINAL



Lakshmi Rani
Narasimhan

Digitally signed by Lakshmi Rani Narasimhan
Date: 4/19/2017 03:31:10PM
GUID: 508da7160002976791592556d218b997



Candace
Gomez-
Broughton

Digitally signed by Candace Gomez-Broughton
Date: 4/19/2017 03:59:57PM
GUID: 508da7470002bfa96430b4eae8e26771



Laura
Fontan

Digitally signed by Laura Fontan
Date: 4/19/2017 02:51:45PM
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Zhihao Peter
Qiu

Digitally signed by Zhihao Peter Qiu
Date: 4/19/2017 02:26:03PM
GUID: 508da7480002bfb5825e149b2b4eb91d



Patricia
Hughes Troost

Digitally signed by Patricia Hughes Troost
Date: 4/19/2017 02:43:29PM
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Gibbes
Johnson

Digitally signed by Gibbes Johnson
Date: 4/19/2017 02:56:31PM
GUID: 508da6da00026559efc8cb7b82db48f8
Comments: thanks



Gerald
Feldman

Digitally signed by Gerald Feldman
Date: 4/19/2017 02:33:14PM
GUID: 508da6d7000262b8e01063de903db2bf

BLA-761037-ORIG-1-RESUB-53 Manufacturing Facility Inspection

Overall Manufacturing Inspection Recommendation

Edit Task Task Actions

- Task Summary
- Task Details
- Documents
- Approvals
- Updates
- Application Life Cycle
- Inspection Management Form

As of May 16, 2017 4:00 pm GMT

Inspection Management Form

BLA-761037-ORIG-1-RESUB-53

SANOFI WINTHROP INDUSTRIES | 3001259044 | SVS STERILE-FILLED SMALL VOLUME PARENTERAL DRUGS | Approve Facility

Overall Manufacturing Inspection Recommendation

- Approve
- Withhold
- No Evaluation Necessary

Cancel

Assigned To



Laura Fontan

IM - OPF Reviewer

Edit Assignment

This was done on

Mar 31, 2017

[View logs](#)

Status

Complete

Requested by



Zhihao Peter Qiu

Task tasks waiting on

- Facilities

Task waiting on this

- Upload Final Decision

Last Update

Apr 21, 2017

Submitted On

Mar 23, 2017

Reference Number

13866536

panorama.fda.gov/task/view?ID=5638613004761d14f9a55ab0a1cd243&activeTab=content-dashboard_542Reab000368cd550c56070c44a823

PANORAMA My Work Projects Reporting Timesheet

BLA-761037-ORIG-1 Manufacturing Facility Inspection

Overall Manufacturing Inspection Recommendation

FBI 3003259644, Sanofi Winthrop. Site is currently pOAI. Pending response and EIR evaluation.

Task Summary Task Details Documents Approvals Updates Application Life Cycle Inspection Management Form

As of Oct 18, 2015 12:46 AM GMT

Inspection Management Form

BLA-761037-ORIG-1

SANOFI-AVENTIS U.S. LLC | 1000117606 | SYS STERILE FILLED SMALL VOLUME PARENTERAL DRUGS | Approve Facility ▾

(b) (4) CTL CONTROL TESTING LABORATORY | Approve Facility ▾

REGENERON PHARMACEUTICALS INC | 1000514603 | (b) (4) Approve facility ▾

(b) (4) CTL CONTROL TESTING LABORATORY | Approve Facility ▾

(b) (4) CTL CONTROL TESTING LABORATORY | Approve Facility ▾

(b) (4) CTL CONTROL TESTING LABORATORY | Approve Facility ▾

SANOFI-AVENTIS DEUTSCHLAND GMBH | 3003195501 | CTL CONTROL TESTING LABORATORY | Approve Facility ▾

Sanofi Winthrop Industrial | 3003259044 | SYS STERILE-FILLED SMALL VOLUME PARENTERAL DRUGS | Withhold Approval ▾

(b) (4)

Overall Manufacturing Inspection Recommendation

Approve

Withhold

Cancel

Assigned To

 **Laura Fontan**

 Edit Assignment

This was done on
Oct 13, 2016
(14:12 EDT)

Status
Complete

This task is yielding on

Facilities

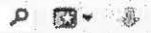
Last Update	Submitted On
Oct 13, 2016	Nov 3, 2015

Reference Number:
6034542

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panorama.fda.gov: PanoramaExtendedFramework/extendedform.cpg?appFacilityIndex.projectId=null&responseId=5165442076481e7595de1852e4583108userId=502date=2007

Google



Facility Status	Completion Date	Project Name	FEI	DUNS	Facility ID	Facility Name	Profile Code	Association (per 356h)	Alert
Withhold Approval	10/13/2016	BLA-761037-ORIG-1	3003259844	297730488	110001799	SANOFI WINTHROP INDUSTRIES	SVS STERILE-FILLED SMALL VOLUM...	ACTIVE	Potential Official Action Indicated as of 7/27/2016
Approve Facility	6/24/2016	BLA-761037-ORIG-1	1000514603	945589711	110000630	REGENERON PHARMACEUTICALS INC	CBI BIOTECHNOLOGY DERIVED API...	ACTIVE	None
Approve Facility	4/7/2016	BLA-761037-ORIG-1	1000117606	011330857	110005690	SANOFI-AVENTIS U.S. LLC	SVS STERILE-FILLED SMALL VOLUM...	ACTIVE	None
(b) (4)									
Approve Facility	11/23/2015	BLA-761037-ORIG-1	(b) (4)				CTL CONTROL TESTING LABORATOR...	ACTIVE	None
Approve Facility	11/23/2015	BLA-761037-ORIG-1	(b) (4)				CTL CONTROL TESTING LABORATOR...	ACTIVE	None
Approve Facility	11/23/2015	BLA-761037-ORIG-1	2002199201	313218430	110004523	SANOFI-AVENTIS DEUTSCHLAND GMBH	CTL CONTROL TESTING LABORATOR...	ACTIVE	None
Approve Facility	11/23/2015	BLA-761037-ORIG-1	(b) (4)				CTL CONTROL TESTING LABORATOR...	ACTIVE	None
Approve Facility	11/23/2015	BLA-761037-ORIG-1	(b) (4)				CTL CONTROL TESTING LABORATOR...	ACTIVE	None

(b) (4)

Loading...

Integrated Quality Assessment Executive Summary

BLA Number: 761037

Recommendation: Complete Response

Drug Name / Dosage Form	Kevzara (sarilumab)/ Injection
Strength/Potency	150 mg/ 1.14 ml (136.1 mg/ml) and 200 mg/1.14 ml (175 mg/ml) Injection in a pre-filled syringe
Route of Administration	Subcutaneous
Rx/ORC Dispensed	RX
Indication	Kevzara™ is indicated for the treatment of adults with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to one or more disease-modifying-anti-rheumatic drugs (DMARDs)
Applicant / Sponsor	Sanofi-aventis U.S. LLC
US Agent, if applicable	Not applicable

Quality Review Team

Discipline	Reviewer	Branch / Division
Product Quality	Gerald Feldman	Division of Biotechnology Review and Research IV
Microbiology Quality Assessment	Lakshmi Narasimhan Candace Gomez-Broughton	Division of Microbiology Assessment
Manufacturing Facilities	Laura Fontan	Division of Inspectional Assessment
Business Regulatory Process Manager	Melinda Bauerlien	OPRO/OPQ
Quality Application Technical Lead	Michele Dougherty	Division of Biotechnology Review and Research IV

Multi Disciplinary Review Team

Discipline	Reviewer	Branch / Division
Regulatory Project Manager	Christine Ford	OND/ODEII /DPARP
Cross-disciplinary Team Lead	Janet Maynard	OND/ODEII /DPARP
Clinical	Suzette Peng	OND/ODEII /DPARP
Non-Clinical	Eleni Salicru	OND/ODEII /DPARP
Clinical Pharmacology	Jianmeng Chen	OTS/)CP/DCPII
Clinical Statistics	Yongman Kim	OTS/OB/DBII

Quality Review Team – Signature Page

Reviewer	Division	Signature

Gerald Feldman	Division of Biotechnology Review and Research IV	Gerald M. Feldman -S Digitally signed by Gerald M. Feldman -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000577813, cn=Gerald M. Feldman -S Date: 2016.10.19 17:08:09 -04'00'
Frederick Mills	Division of Biotechnology Review and Research IV	Frederick C. Mills -S Digitally signed by Frederick C. Mills -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000737256, cn=Frederick C. Mills -S Date: 2016.10.20 14:40:33 -04'00'
Lakshmi Narasimhan	Division of Microbiology Assessment	Lakshmi Narasimhan -S Digitally signed by Lakshmi Narasimhan -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000640223, cn=Lakshmi Narasimhan -S Date: 2016.10.20 10:48:03 -04'00'
Patricia Hughes	Division of Microbiology Assessment	Patricia F. Hughestroost -S Digitally signed by Patricia F. Hughestroost -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300096547, cn=Patricia F. Hughestroost -S Date: 2016.10.20 10:22:44 -04'00'
Candace Gomez-Broughton	Division of Microbiology Assessment	Candace Y. Gomez-broughton -A Digitally signed by Candace Y. Gomez broughton -A DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000640207, cn=Candace Y. Gomez broughton -A Date: 2016.10.20 11:11:10 -04'00'
Maria Reyes Candau-Chacon	Division of Microbiology Assessment	Maria D. Candauchaco n -S Digitally signed by Maria D. Candauchaco n -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000639745, cn=Maria D. Candauchaco n -S Date: 2016.10.20 11:39:38 -04'00'
Laura Fontan	Division of Inspectional Assessment	Laura Fontan -S Digitally signed by Laura Fontan -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Laura Fontan -S, 0.9.2342.19200300.100.1.1=2001525652 Date: 2016.10.20 11:59:33 -04'00'
Zhihao Qiu	Division of Inspectional Assessment	Zhihao Qiu -S Digitally signed by Zhihao Qiu -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Zhihao Qiu -S, 0.9.2342.19200300.100.1.1=2000438274 Date: 2016.10.20 07:52:48 -04'00'
Michele Dougherty	Division of Biotechnology Review and Research IV	Michele Dougherty -S Digitally signed by Michele Dougherty -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0010556865, cn=Michele Dougherty -S Date: 2016.10.19 15:33:59 -04'00'
Gibbes Johnson	Division of Biotechnology Review and Research IV	Gibbes R. Johnson -A Digitally signed by Gibbes R. Johnson -A DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000592128, cn=Gibbes R. Johnson -A Date: 2016.10.20 15:38:47 -04'00'

Quality Review Data Sheet

1. Legal Basis for Submission: 351(a)
2. Related Supporting Documents:

a. Submissions Reviewed

Submission	Date Received	Reviewed (Y/N)
761037.00	October 30, 2015	
761037.02 (response to IR)	December 14, 2015	Yes
761037.12 (response to IR)	March 15, 2016	Yes

761037.18 (response to IR)	May 04, 2016	Yes
761037.19 (response to IR)	May 26, 2016	Yes
761037.31 (response to IR)	July 21, 2016	Yes
761037. 33 (response to IR)	August 10, 2016	Yes
761037.35 (response to IR)	August 18, 2016	Yes
761037. 36 (response to IR)	August 23, 2016	Yes
761037.37 (response to IR)	September 01, 2016	Yes
761037. 38 (response to IR)	September 02, 2016	Yes
761037. 39 (response to IR)	September 08, 2016	Yes
761037.42 (response to IR)	September 12, 2016	Yes
761037.46 (response to IR)	September 30, 2016	Yes
761037. 47 (response to IR)	October 12, 2016	Yes
761037. 48 (response to IR)	October 14, 2016	Yes

b. DMFs

#	Holder	Item	Letter of Cross Reference	Comment / Status
(b) (4)			Yes	Review completed
			Yes	Review completed
			Yes	Review completed
			Yes	Review completed

3. Consults: None

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

i. Recommendation

The Office of Pharmaceutical Quality, CDER, recommends a complete response for STN 761037 for KEVZARA (sarilumab) manufactured by Sanofi, Inc. due to the provisional official action indicated (pOAI) status of the Sanofi, Inc drug product manufacturing facility, Le Trait, France (FEI 3003259844). When the compliance status of the Sanofi, Inc. Le Trait DP site is determined to be acceptable, OPQ will provide an updated recommendation on approval.

ii. Approval Action Letter Language

1. Manufacturing Location

Drug Substance: Regeneron Pharmaceutical, Inc., (b) (4)
Rensselaer, NY

Drug Product: Sanofi Winthrop Le Trait, Boulevard Industriel 76508 Le Trait, France

2. Fill Size and Dosage Form

150 mg/1.14 ml and 200 mg/1.14 ml in pre-filled syringe

3. Dating Period

Drug Product: 24 months; 2-8C

(b) (4)

Drug Substance: (b) (4) months; (b) (4) C

4. Exempt from Lot Release

Yes; rationale for exemption: Specified Product (exempted according to 21 CFR 601.2a)

B. Recommendation on Phase 4 Marketing Commitments, Agreements, and/or Risk Management Steps, if approvable: Product Quality (OPQ)

Office of Biotechnology Products: Not applicable

Office of Process and Facilities: Not applicable

II. Summary of Quality Assessments

A. Product Overview

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

i. Names:

1. **Proprietary Name:** Kevzara™

2. **Trade Name:** Kevzara™

3. **Non-Proprietary/USAN:** sarilumab

4. **CAS name:** 1189541-98-7

5. **Common Name:** REGN88, SAR153191

6. **INN Name:** sarilumab

7. OBP Systematic Name: MAB HUMAN (IGG1) ANTI P08887 (IL6R_HUMAN) [REGN88]

ii. Pharmacologic Category: Therapeutic recombinant human monoclonal antibody (IgG1), anti-human interleukin 6 receptor (IL-6R)

B. Drug Substance [sarilumab] Quality Assessment

i. CQA Identification, Risk, and Lifecycle Knowledge Management

Table 1 below provides a summary of product-related critical quality attributes that are relevant to both drug substance (DS) and drug product (DP). The table includes the identification of the various attributes along with their risk management. For additional information see Appendix A for the OBP product quality review and Appendix B-D for the OPF product quality microbiology and facility review.

Table 1: Drug Substance and Drug Product CQA Identification, Risk and Lifecycle Knowledge Management

CQA	Type	Risk	Origin	Control Strategy	Other
a ,b, c Binding to target (IL-6R)	Potency	Lower potency impacts efficacy, increased potency impacts safety	Structure may be impacted during all stages of the manufacturing process, as well as on stability	(b) (4)	
a ,b, c Binding to effector cells for ADCC activity	Potency	Impacts Safety	Structure may be impacted during all stages of the manufacturing process, as well as on stability		
a ,b, c Aggregates (High Molecular Weight species; primarily (b) (4))	Size variants, Product-related impurity	Immunogenic response. (Unknown if some variants may impact efficacy or PK)	Aggregates may form during all stages of the manufacturing process. Increased aggregates were observed under certain stress		

			conditions including (b) (4)	(b) (4)	
a ,b, c Fragments/ Low molecular weight species (Fragmented heavy chain – loss of a single Fab arm)	Size variants, Product-related impurities	Might impact PK and Efficacy	Originate in the (b) (4) process. May increase following (b) (4)		
a Glycosylation N-linked at Asn 296	Product variants and product impurities.	Glycosylation, such as mannose forms may impact PK; ADCC is not an MOA for sarilumab so changes in fucosylation would not impact ADCC activity.	Manufacturing process. Variability is mainly from the (b) (4).		
a ,b, c Charge Heterogeneity; most common or predominant charge isoforms include: neutral isoform, followed by acidic isoforms	Product Variants and product impurities	No impact on potency, might impact PK through absorption	Manufacturing process and stability. Charge isoform changes due to (b) (4)		

a, b, c Bioburden	Microorg anisms	Safety, Purity and Efficacy (degradatio n or modification of the product by contaminati ng microorgani sms	Raw materials and contamination during manufacturing	(b) (4)	
c DP Sterility	Sterility	Safety Safety (infection) Purity and Efficacy (degradatio n or modification of the product by contaminati ng microorgani sms)	Contamination could be introduced throughout DP manufacturing or through a container closure integrity failure		
a, b, c Clarity	General	Safety	Formulation and on stability, from protein, excipients, interaction		

			with container closure system		
a ,b, c Endotoxin	Process-related impurity	Immunogenicity, Safety, and Purity	Raw materials or contamination during manufacturing process or due to container closure integrity failure	(b) (4)	
a ,b, c Appearance	General	Safety: Immunogenic response (with visible particles)	In-process & stability		
a ,b, c Protein Concentration	Product	Potency and Efficacy	In-process (& stability)		
a ,b, c Osmolality	General	Safety (site reaction), on product stability	In-process		
a ,b, c pH	General	Potency and Efficacy	In-process		
a Host Cell Protein	Process-related impurity	Safety (immunogenicity)	CHO Host cell line		

				(b) (4)	
a (b) (4)	Process-related impurity	Safety	(b) (4) step.		No longer tested as part of lot release
a Host cell DNA	Process-related impurity	Safety	CHO Host cell line		
a Mycoplasma	Process-related impurity	Safety	CHO Host cell line, raw materials		
a Viruses	Process-related impurity	Safety	CHO Host cell line, raw materials		
a Other impurities: (b) (4)	Process-related impurities	Safety	From raw materials used in the manufacturing process, and exposure to components of that process (b) (4)		
b ,c PS20 concentration	Formulation component	(b) (4)	Manufacturing process		
b ,c PS20 quality	Formulation component	(b) (4)	Quality of raw material (b) (4) and storage.		
c Container	Safety Leachabl	Maintanance of sterility.	Container closure		

closure systems (for both DS and DP)	es from containe r closure systems	Glass delamination, Leachables from the stopper.	system.	(b) (4)
^c Particulate Matter	Product and process related impurity	Safety. product stability	Manufacturing process and stability	
^{a, b, c} Non-critical molecule attributes: Methionine oxidation - Met4,34,83, 111, 251, and 427 (non-CDR), C-terminal lysine, N-terminal pyroglutamate, Lys 98 glycation, and Asn 84, 314, and 383 deamidation	Product-related impurity	Reduction in FcRn binding and PK	Manufacturing process and Stability (b) (4)	
				(b) (4)

ii. Drug Substance [sarilumab] Quality Summary

- 1. Description:** Sarilumab is a human monoclonal antibody (mAb) of the IgG kappa isotype that binds the interleukin 6 receptor (IL-6R). Sarilumab has a molecular weight of approximately 150 kDa.
- 2. Mechanism of Action:** The primary mechanism of action is the inhibition of the binding of interleukin 6 (IL-6) to the IL-6R. Sarilumab binds to the IL-6R with a dissociation constant of 60.2 pM. Binding of sarilumab to IL-6R prevents ligand-induced receptor activation and subsequent signaling through downstream signaling pathways.
- 3. Potency Assay:** The potency assay used to assess the biological activity of sarilumab for release and stability is a cell-based assay that assesses the ability of sarilumab to block IL-6-induced proliferation of human DS-1 cells in vitro. The potency is reported as % relative potency to that of a qualified reference standard.

4. Reference Materials:

(b) (4)

[Redacted]

5. Critical Starting Materials or Intermediates:

(b) (4)

[Redacted]

6. Manufacturing Process Summary: Sarilumab manufacturing begins with

(b) (4)

[Redacted]

- 7. Container Closure:** The container closure for (b) (4) sarilumab DS (b) (4)
- 8. Dating Period and Storage Conditions:** The data provided in the BLA support a shelf life of (b) (4) months for the drug substance when stored at (b) (4) C. (b) (4)
- C. Drug Product [KEVZARA™] Quality Assessment**
- i. CQA Identification, Risk, and Lifecycle Knowledge Management**
See Table 1, above
- ii. Drug Product [KEVZARA™] Quality Summary**
- 1. Potency and Strength:** KEVZARA is supplied as a 150 mg/1.14 ml (131.6 mg/ml) or 200 mg/1.14 ml (175 mg/ml)
- 2. Description/Commercial Image:** KEVZARA is a sterile, preservative free, clear, colorless to slightly yellow solution. KEVZARA is provided in sterile, (b) (4) glass, (b) (4) syringes with staked-in-place needles, (b) (4) plungers with a (b) (4) elastomeric plunger tip with a (b) (4), and an elastomeric needle shield that is a non-product contact safety device.
- 3. List of Excipients:** Each milliliter of KEVZARA contains sarilumab (131.6 mg or 175 mg) and 3.71 mg (b) (4) histidine, 8.94 mg (b) (4) arginine, 57 mg sucrose, and 2.28 mg polysorbate 20
- 4. Reference Materials:** Same as Drug Substance
- 5. Manufacturing Process:** Sarilumab drug product is manufactured at Sanofi Le Trait. For the manufacture of KEVZARA, (b) (4)
- 6. Container Closure:** The container closure system of KEVZARA drug product is (b) (4) mL clear glass syringe barrel with a 27 Gauge (G) (b) (4) staked needle, protected by a soft elastomeric needle shield closed with (b) (4) plunger stopper with (b) (4).
- 7. Expiration Date and Storage Conditions:** The data provided in the BLA support an expiry of 24 months for the drug product when stored at the recommended storage conditions of 2-8°C. The data provided in the BLA do support storage of the drug product for up to 14 days at (b) (4)°C once removed from the refrigerator.
- 8. List of co-packaged components:** not applicable
- D. Novel Approaches/Precedents:** None
- E. Special Product Quality Labeling Recommendations:**
Store in a refrigerator at 2-8°C
Protect from Light
Do not freeze
Do not shake
- F. Establishment Information:**
A pre-approval inspection of the drug substance manufacturing site was conducted from 02/01/16 to 02/05/16. The compliance status of the manufacturing site was found to be acceptable.

The compliance status of the drug product manufacturing site is currently under assessment. A GMP inspection was conducted from 07/07/16 to 07/19/16. The inspection resulted in multiple 483 observations and a “provisional official action indicated” recommendation. The status of the facility is currently under review with the CDER Office of Compliance. In the absence of an acceptable compliance status, OPQ recommends a complete response for the application.

Table 2 and 3 below list the DS and DP manufacturing sites and responsibilities:

Table 2: Drug substance manufacturing sites:

Site	Location	FEI	Use
Regeneron Pharmaceuticals	Rensselaer, NY	1000514603	Manufacture of DS (b) (4) Release and stability testing
Regeneron Pharmaceuticals	East Greenbush, NY		Primary site for testing for adventitious agents
(b) (4)			

Table 3: Drug product manufacturing sites:

Site Name	Regeneron Pharmaceuticals, Inc.	Sanofi Winthrop Industrie	Sanofi - Aventis U.S. LLC
Address	81 Columbia Turnpike Rensselaer, NY 12144	1051 Boulevard Industriel, 76580 LeTrait, France	6239-6244 Lemay Ferry Road, Saint Louis, MO 63129
FEI #	1000514603	3003259844	1000117606

DP Manufacturing Process Step (s) and Responsibilities	• Supplier of (b) (4) • Bulk PFS primary stability studies • PFS primary stability studies • Release and stability analytical testing site	• Manufacture of bulk PFS and PFS • Labeling and packaging of PFS • PFS post-approval stability studies • Release and stability analytical testing site • Secondary packaging and release for distribution of PFS	Secondary packaging and release for distribution of PFS
--	---	---	---

Table 4: Extra locations where DP testing is performed include the following:

Site Name	(b) (4)		Sanofi-Aventis Deutschland GmbH
Address			Brüningstrasse 50 Industriepark Höchst 65926 Frankfurt am Main, Germany
FEI #			3003195501
DP Manufacturing Process Step (s) and Responsibilities	Bulk PFS and PFS Primary stability analytical testing site		Release and stability analytical testing site

G. Life Cycle Knowledge Management

i. Drug Substance

1. Protocols approved: Annual GMP stability protocols, (b) (4)
2. Outstanding Review Issues: See PMCs
3. Future inspection points to consider: not applicable

ii. Drug Product

1. Protocols Approved: Annual GMP stability protocol, (b) (4)
2. Outstanding Review Issues: See PMCs
3. Future Inspection Points to Consider: N/A

Quality Assessment Summary Tables
Table 1: Noteworthy Elements of the Application

#	Checklist		Yes	No	N/A
Product					
1.	Recombinant Product		X		
2.	Naturally Derived Product			X	
3.	Botanical			X	
4.	Human Cell Substrate/Source Material			X	
5.	Non-Human Primate Cell Substrate/Source Material			X	
6.	Non- Primate Mammalian Cell Substrate/Source		X		
7.	Non-Mammalian Cell Substrate/Source Material			X	
8.	Transgenic Animal Sourced			X	
9.	Transgenic Plant Sourced			X	
10.	New Molecular Entity		X		
11.	PEPFAR Drug			X	
12.	PET Drug			X	
13.	Sterile Drug Product		X		
14.	Other_____				N/A
Regulatory					
15.	Citizen Petition and/or Controlled Correspondence Linked to the Application (#_____)			X	
16.	Comparability Protocol(s)			X	
17.	End of Phase II/Pre-NDA Agreements tem)			X	
18.	SPOTS (Special Products On-line Tracking System			X	
19.	USAN Name Assigned		X		
20.	Other_____				
Quality Considerations					
21.	Drug Substance Overage			X	
22.	Design Space	Formulation		X	
23.		Process		X	
24.		Analytical Methods		X	
25.		Other		X	N/A
26.	Other QbD Elements			X	
27.	Real Time Release Testing (RTRT)			X	
28.	Parametric Release in lieu of Sterility Testing			X	
29.	Alternative Microbiological Test Methods			X	
30.	Process Analytical Technology in Commercial			X	
31.	Non-compendial Analytical Procedures	Drug Product	X		
32.		Excipients		X	
33.		Drug Substance	X		
34.	Excipients	Human or Animal		X	
35.		Novel		X	
36.	Nanomaterials			X	

37.	Genotoxic Impurities or Structural Alerts		X	
38.	Continuous Manufacturing		X	
39.	Use of Models for Release		X	
40.	Other _____			N/A

APPEARS THIS WAY ON ORIGINAL

BLA STN 761037

KEVZARATM (Sarilumab)

Manufacturer:

Sanofi-Aventis U.S. LLC

55 Corporate Drive

Bridgewater, NJ 08807

Frederick Mills, Ph.D., Quality Reviewer

(Immunogenicity Assay Validation)

Gerald M Feldman, Ph.D., Quality Reviewer (DS and DP)

Michele Dougherty, Ph.D., Review Chief

Division of Biotechnology Research and Review IV

Office of Biotechnology Products

Office of Pharmaceutical Quality

Center for Drug Evaluation and Research

OBP CMC Review Data Sheet

1. **BLA#:** STN 761037

2. **LEGAL BASIS FOR SUBMISSION:** 351(a)

3. **REVIEW DATE:** October 19, 2016

4. **PRIMARY REVIEW TEAM:**

Medical Officer: Suzette Peng / Janet Maynard
Pharm/Tox: Eleni Salicru / Tim Robison
Product Quality: Gerald M. Feldman/Michele Dougherty
Immunogenicity: Fred Mills
BMT: Candace Gomez Broughton (DS), and Lakshmi Narasimhan (DP)
Facilities: Laura Fontan
Micro QAL: Maria Reyes Candau-Chacon
Clin Pharm: Sheetal Agarwal / Jianmeng Chen / Ping Ji / Yaning Wang
Statistics: Yongman Kim / Greg Levin
OBP Labeling: Jibril Abdus-Samad
RBPM: Melinda Bauerlien

5. **MAJOR GRMP DEADLINES**

Filing Meeting: December 17, 2015
Filing Date: December 29, 2015
Mid-Cycle Meeting: May 23, 2016
Wrap-Up Meeting: September 12, 2016
Primary Review Due: August 29, 2016
Secondary Review Due:
CDTL Memo Due:
PDUFA Action Date: October 30, 2016

6. **COMMUNICATIONS WITH SPONSOR AND OND:**

IR #	Information Request (IR) Submitted	Date Sent
1	Information request regarding CCI tests on the PFS	March 3, 2016
2	Information request for updated stability reports	April 19, 2016
3	Information request regarding process controls	July 14, 2016
4	Information request regarding WCB protocols	August 2, 2016
5	Information request for raw data reports on leachables and extractables	August 11, 2016
6	Information request regarding (b) (4) and hold times	August 17, 2016
7	Information request regarding failed (b) (4) batch	August 19, 2015
8	Request to (b) (4) limit to ensure sterility of the product.	August 17, 2016
9	Request to update section P.3.4 and other relevant sections to reflect the (b) (4)	September 7, 2016
10	Information request regarding transfer reports for analytical tests, full comparative test results, and (b) (4) test results	September 8, 2016
11	Request to update the BLA based on commitments stated in IR#3	September 27, 2016
12	Information request regarding (b) (4)	October 7, 2016
13	Follow up regarding the Sponsor's proposal to allow (b) (4)	October 13, 2016

7. SUBMISSION(S) REVIEWED:

Submission	Date Received	Review Completed (Yes/No)
761037.00	October 30, 2015	Yes
761037.12 (response to IR1)	March 15, 2016	Yes
761037.19 (response to IR2)	May 4, 2016	Yes
761037.32 (response to IR3)	July 21, 2016	Yes
761037.35 (response to IR5)	August 15, 2016	Yes
761037.36 (response to IR4)	August 18, 2016	Yes
761037.37 (response to IR6)	August 23, 2016	Yes
761037.38 (response to IR7)	September 1, 2016	Yes
761037.39 (response to IR8)	September 2, 2016	Yes
761037.40 (response to IR9)	September 8, 2016	Yes
761037.41 (response to IR10)	September 12, 2016	Yes
761037.46 (response to IR11)	September 30, 2016	Yes
761037.47 (response to IR12)	October 12, 2016	Yes
761037.48 (response to IR13)	October 14, 2016	Yes

8. DRUG PRODUCT NAME/CODE/TYPE:

- a. Proprietary Name: Kevzara (formerly (b) (4))
- b. Trade Name: Kevzara (formerly (b) (4))
- c. Non-Proprietary/USAN: Sarilumab
- d. Common name: REGN88, SAR153191
- e. INN Name: Sarilumab
- f. OBP systematic name: MAB HUMAN (IGG1) ANTI P08887 (IL6R_HUMAN)
[REGN88]
- g. Other Names: Recombinant human anti-IL-6 receptor monoclonal antibody

9. PHARMACOLOGICAL CATEGORY: Therapeutic recombinant human IgG1 mAb**10. DOSAGE FORMS:** Pre-filled syringe (PFS) containing 150 mg or 200 mg of drug product (DP) in a 1.14 ml deliverable volume**11. STRENGTH/POTENCY:** 150 mg single-use PFS; 131.6 mg/ml DP
200 mg single-use PFS: 175 mg/ml DP**12. ROUTE OF ADMINISTRATION:** Subcutaneous injection**13. REFERENCED MASTER FILES:**

DMF #	HOLDER	ITEM REFERENCED	Letter of Cross-Reference	COMMENTS (STATUS)
(b) (4)			Yes	Review completed
			Yes	Review completed
			Yes	Review completed
			Yes	Review completed

14. INSPECTIONAL ACTIVITIES

Drug substance site inspection (Rensselaer, NY) initiated February 1, and completed February 5, 2016. No 483 items provided.

15. CONSULTS REQUESTED BY OBP

None

16. QUALITY BY DESIGN ELEMENTS

None

17. PRECEDENTS

None

18. PROTOCOLS APPROVED WITHIN THE BLA

The only Protocols approved within this BLA provide for manufacturing a new Working Cell Bank [REDACTED] (b) (4), and for manufacturing a new Reference Standard when the current Reference Standard is near depletion.

19. COMMITMENTS APPROVED WITHIN THE BLA

The Sponsor has committed to place one lot of DS, (b) (4) and DP on stability annually each year they are manufactured. The Sponsor has also committed to [REDACTED] (b) (4)

[REDACTED]

[REDACTED]

20. ADMINISTRATIVE

A. Signature Block

Name and Title	Signature and Date
Michele Dougherty, Ph.D., Review Chief Division of Biotechnology Research and Review IV	Michele Dougherty -S Digitally signed by Michele Dougherty -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0010556865, cn=Michele Dougherty -S Date: 2016.10.19 15:29:23 -04'00'
Gerald M. Feldman, Ph.D., CMC Reviewer Division of Biotechnology Research and Review IV	Gerald M. Feldman -S Digitally signed by Gerald M. Feldman -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000577813, cn=Gerald M. Feldman -S Date: 2016.10.19 15:27:20 -04'00'
Frederick Mills, Ph.D., Immunogenicity, Division of Biotechnology Research and Review IV	Frederick C. Mills -S Digitally signed by Frederick C. Mills -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000737256, cn=Frederick C. Mills -S Date: 2016.10.20 09:32:26 -04'00'

B. CC Block

Recipient	Date
Clinical Division BLA RPM	
Division of Biotechnology Research and Review - IV File/BLA STN 761037	

SUMMARY OF QUALITY ASSESSMENTS

I. Primary Reviewer Summary Recommendation

From the Chemistry, Manufacturing Controls perspective, BLA 761037 is recommended for approval.

II. List of Deficiencies To Be Communicated

None

III. List of Post-Marketing Commitments/Requirement

None

IV. Review of Common Technical Document-Quality Module 1

1. Environmental Assessment or Claim Of Categorical Exclusion (BLA section 1.12.14)

The Sponsor claims a categorical exclusion from the requirements of environmental assessment pursuant to the provisions provided under 21 CFR 25.31(c). Thus, no environmental assessment needs to be performed.

The Sponsor's claim for Categorical Exclusion is appropriate for this product and should be granted.

2. Primary Container Labeling Review (BLA section 1.14.13)

Draft package labeling review provided by Jibril Abdus-Samad. See separate review.

V. Review of Common Technical Document-Quality Module 3

Review of CTD Module 3 provided. See below.

VII. Review of Immunogenicity Assays – Module 5.3.1.4

Review of immunogenicity assays provided by Fred Mills. See attached.

BLA EDR Location: [STN 761037](#)

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S. DRUG SUBSTANCE

3.2.S.1 General Information

3.2.S.1.1 Nomenclature

Product Name:	Kevzara™
INN Name:	Sarilumab
Compendial Name:	<i>Not Applicable</i>
Chemical Name:	Recombinant humanized immunoglobulin G1 mAb
Company Codes:	REGN88, SAR153191
USAN Name:	Sarilumab
CAS Registry Number:	1189541-98-7
WHO Number:	<i>Not Applicable</i>
Other Names:	Recombinant humanized anti-IL-6 receptor monoclonal antibody

3.2.S.1.2 Structure

Sarilumab is a humanized IgG1 kappa antibody, consisting of two 446 amino acid heavy chains and two 214 amino acid light chains. It is produced in Chinese Hamster Ovary cells and has an H₂L₂ structure typical of the IgG1 subclass. The amino acid sequence of the heavy and light chain was deduced from the cDNA, and confirmed by LC-MS peptide mapping: the light chain contains 5 cysteine residues that are involved in two intra-chain disulfide linkages and one inter-chain disulfide linkage. The intra-chain disulfide bonds exist between Cys_{L23}-Cys_{L88} and between Cys_{L134}-Cys_{L194}. Inter-chain disulfide linkage occurs at Cys_{L214}-Cys_{H219}. These assignments were confirmed by LC-MS peptide mapping. There are eleven cysteine residues in the heavy chain that are involved in four intra-chain disulfide linkages (Cys_{H22}-Cys_{H96}, Cys_{H143}-Cys_{H199}, Cys_{H260}-Cys_{H320} and Cys_{H366}-Cys_{H424}), two inter-chain disulfide linkages (Cys_{H225}-Cys_{H225} and Cys_{H228}-Cys_{H228}) between the two heavy chains, and a third inter-chain disulfide linkage between the heavy chain and the light chain of each heterodimer (Cys_{L214}-Cys_{H219}). These assignments were confirmed by LC-MS peptide mapping.

There is one N-linked glycosylation site at Asn²⁹⁶ of the heavy chain.

The amino acid sequence of the heavy and light chain is provided below (figure copied from submission). The sequences of sarilumab CDR regions are highlighted in blue. The cysteine residues (in red) that form the predicted disulfide bonds are connected by solid orange lines. The N-linked glycosylation site at Asn²⁹⁶ is highlighted in green. The heavy chain C-terminal Lys⁴⁴⁶ is in pink:

Sarilumab Heavy Chain Amino Acid Sequence

EVQLVESGGG LVQPGRSLRL SCAASRFTFD DYAMHWVRQA PGKGLEWVSG ISWNSGRIGY⁶⁰
ADSVKGRFTI SRDNAENSLF LQMNGLRAED TALYYCAKGR DSFDIWQGT MVTVSSASTK¹²⁰
GPSVFPLAPS SKSTSGGTAA LGCLVKDYFP EPVTVSWNSG ALTSGVHTFP AVLQSSGLYS¹⁸⁰
LSSVVTVPSS SLGTQTYICN VNHKPSNTKV DKKVEPKSCD KTHTCPPCPA PELLGGPSVF²⁴⁰
LEFPPKPKDTL MISRTPEVTC VVVDVSHEDP EVKFNWYVDG VEVHNAKTKP REEQYNSTYR³⁰⁰
VVSVLTVLHQ DWLNGKEYKC KVSNAKALPAP IEKTISKAKG QPREPQVYTL PPSRDELTKN³⁶⁰
QVSLTCLVKG FYPSDIAVEW ESNGQPENNY KTTTPVLDSG GSFFLYSKLT VDKSRWQQGN⁴²⁰
VFSCSVMHEA LHNHYTQKSL SLSPGK⁴⁴⁶

CPPC of heavy chain

Sarilumab Light Chain Amino Acid Sequence

DIQMTQSPSS VSASVGDRVT ITCRASQGIS SWLAWYQKP GKAPKLLIYG ASSLESGVPS⁶⁰
RFGSGSGTD FTLTISSLQP EDFASYCQQ ANSFYTFGQ GTKLEIKRTV AAPSVFIFPP¹²⁰
SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSTLT¹⁸⁰
LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGE²¹⁴

The heavy chain C-terminal lysine is mostly clipped during protein expression.

The glycosylation site at Asn²⁹⁶ of the heavy chain is expected to show mostly full site occupancy (92-94%) with a range of core-fucosylated bi-antennary N-linked oligosaccharides. Based on the primary sequence, the antibody without glycans has a predicted molecular weight of 143,873.7 Da, assuming the formation of 16 canonical disulfide bonds, and removal of Lys⁴⁴⁶ from each heavy chain C-terminus. The expected molecular mass of the glycosylated protein averages to about 149,600 Da based on the predicted amino acid sequence and the expected glycosylation profiles. Post-translational modifications of both the heavy and light chains result in multiple isoforms of sarilumab. Each of these was individually separated by ion exchange chromatography and biochemically and biologically characterized. All retained full biological activity.

3.2.S.1.3 General Properties

DS is a colorless to pale yellow liquid with a concentration of (b) (4)

(b) (4)

(b) (4)

3.2.S.2 Manufacture

3.2.S.2.1 Manufacturer(s)

Production, release, and testing are performed at the following locations (table modified from submission):

Site	Location	FEI	Use
Regeneron Pharmaceuticals, Inc.	Rensselaer, NY	1000514603	Manufacture of DS and (b) (4) Release and stability testing
Regeneron Pharmaceuticals, Inc.	East Greenbush, NY		Primary site for testing for adventitious agents

(b) (4)

Reviewer's comment: The use of the identical FEI for two distinct addresses is unusual and should be checked out. Preliminary assessment is that these addresses are for facilities within the same location. DMA is verifying this. Should also verify and review the Transfer Reports for the remote testing sites.

47 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

3.2.R.2 Method Validation Package

Detailed descriptions, including validation and system suitability assessment of each method of analysis for sarilumab drug substance and drug product release specification were provided. Since DP can be analyzed at either Regeneron or Sanofi companies, assessments of each specific method of analysis for testing of sarilumab 150 mg and 200 mg PFS were provided for all testing locations.

Reviewer's comment: *This section of the BLA merely reproduced data provided elsewhere in the BLA.*

3.2.R.3 Comparability Protocols

None

5.3.1.4: Immunogenicity Assay Validation

(Review by Fred Mills, Ph.D., Staff Scientist, CDER, OPS, OBP, Division IV)

Executive Summary on Immunogenicity

The rates of persistent anti- sarilumab antibodies, which are likely to affect therapy, are low in the range 4-5.6%, but above a placebo background of 2%. Antibody titers are also low; i.e. a signal below the cutpoint was reached after 1/30-1/60 dilutions. There is some effect of persistent antibodies on PK. Neutralizing antibodies incidence is also low, in the range 1.8-3.3%, above a placebo background of 0.2%. The incidences of anti-sarilumab antibody formation and hypersensitivity are consistent with actemra, the licensed anti-IL6R α therapy for rheumatoid arthritis.

Binding antibodies (ADA) have been measured with the widely used electrochemiluminescence (ECL) technology in a bridging assay format, so that anti-sarilumab antibodies can bind and be detected with labeled sarilumab, giving rise to a readout of light emission. The sensitivity of this assay is 116.3 ng/ml, which is very close to the 100 ng/ml sensitivity recommended in the current FDA guidance (Guidance for Industry, 2016: Assay Development and Validation of Immunogenicity Testing of Therapeutic Protein Products), and The drug tolerance values of 336 μ g/mL and 409 μ g/mL are well above expected sarilumab serum concentrations of 6.63-16.5 μ g/ml. Overall the ADA assay is appropriately validated according to guidance, and I find the validation to be acceptable

Neutralizing antibodies (Nabs) have been assessed with a ligand binding assay, so that sarilumab is immobilized on an assay plate and can bind labeled IL6R- α , with neutralizing antibody activity inhibiting this binding. The Nab assay has overall been appropriately validated, with a sensitivity of 150-257 ng/ml that is within the typical range for neutralizing antibody assays, and

is able to detect patient neutralizing antibody activity. However, the validated drug tolerance for sarilumab levels in serum is low (b) (4)

As sarilumab is not an endogenous protein, this problem with the Nab assay may potentially affect evaluation of changes in efficacy, but is not a safety issue. Therefore, I find no immunogenicity issues to prevent approval of BLA 761037.

Clinical Immunogenicity Summary

Antibody incidence

For Treatment Emergent Adverse Event data, which broadly consists of data derived when patients participated in a given study, either to completion or discontinuation, the Sponsor observed the following incidences:

Table 55 - Overview of ADA assay response during the entire TEAE period - Placebo-controlled immunogenicity population (Pool 1)

	Placebo + DMARD (N=608)	Sarilumab + DMARD	
		150 mg q2w (N=607)	200 mg q2w (N=609)
Number of patients with ADA assay results available	608/608 (100%)	607/607 (100%)	607/609 (99.7%)
Patients with an ADA positive sample at baseline	9/606 (1.5%)	14/599 (2.3%)	10/599 (1.7%)
ADA positive patients ^a during the TEAE period	21/608 (3.5%)	117/607 (19.3%)	85/607 (14.0%)
Neutralizing ^b	1/608 (0.2%)	20/607 (3.3%)	11/607 (1.8%)
Non-Neutralizing	20/608 (3.3%)	97/607 (16.0%)	74/607 (12.2%)

For persistent antibody responses, where persistent ADA status is defined as positive ADA status for two or more sampling time points, the incidence was 4.0% in the sarilumab 200 mg q2w group and 5.6% in the sarilumab 150 mg q2w group; however persistent ADA responses were also observed in 2.0% of patients in the placebo group, suggesting a 2% false positivity rate in the ADA assay in this population. The percentage of patients who exhibited both persistent and neutralizing antibody responses was 1.0% in the 200 mg q2w group, 1.6% in the 150 mg q2w group, and 0.2% in the placebo group. Titers were observed to be low in the range 30-60, meaning 1/30 to 1/160 dilutions. Nab incidence was in the range 1.8-3.3%, and like the ADA incidence, the Nab incidence was actually lower with the higher sarilumab dosing regimen. The Sponsor considers that presentation of the incidence rates of persistent ADA (rather than any positive ADA or transient ADA) and Nab do provide useful information for physicians because of persistent ADA is associated with lower sarilumab exposure.

Reviewer comments

Because the overall ADA incidence rates are appreciable (19.3-14%), the rates of persistent antibodies, which are likely to affect therapy, are low in the range 4-5.6%. I also note that the ADA incidence is higher for patients receiving 150 mg q2w dosing, versus the 200 mg q2w treatment, suggesting the possibility of some tolerization resulting from higher doses. Finally, from a safety standpoint, it is reassuring that titers are low; i.e. a signal below the cutpoint was reached after 1/30-1/60 dilutions. However in this situation, low titers were not completely innocuous, since as discussed in the section below on Pharmacokinetics, there is a clear impact of ADA on PK; i.e. reduced exposure.

Effect on PK

In summary for Phase 3 study POH0428,

- ADA patients showed 24-28% lower exposure
- Exposure was lower in Nab positive patients by 49-59%
- Patients with persistent ADA showed 32-41% lower exposure

The Sponsor states that NAb and persistent ADA positive response were considered to be most clinically relevant to assess for an impact on efficacy. In the sarilumab+DMARD long-term safety population, one patient on sarilumab+DMARD with persistent antibody response, and no patients with NAb, discontinued due to lack or loss of efficacy

Reviewer comments

These data show that ADA formation clearly reduces sarilumab exposure. I defer to the Clinical and Clinical Pharmacology review teams as to whether this reduced exposure has an impact on sarilumab therapy. However, I would note that these data extend for one year, and with at least one other chronic biologic therapy (Betaseron for MS) immune mediated loss of efficacy becomes more pronounced after a year of treatment.

Hypersensitivity

Overall, there was an ~ two fold increase in reported for hypersensitivity in sarilumab-treated patients versus those treated with placebo; i.e.

200 mg q2w	7.3% of 661 patients
150 mg q2w	6.8% of 660 patients
placebo	3.9% of 661 patients.

There was a lack of observed ADA for 25 out of 27 patients who discontinued due to hypersensitive reactions: a finding that is not necessarily surprising. Particularly in the case of IgE mediated hypersensitivity, serum antibody levels may not correlate with hypersensitive reactions, which are often local rather than systemic.

Injection site reactions showed the clearest hypersensitive signal above the placebo background, being observed in 9.5% of 200 mg q2w patients and 8% of 150 q2w patients versus only 1.4% of placebo patients. However, there was a potentially modest beneficial adaptation to dosing resulting in a decline in injection site reactions,

Reviewer comments

On the basis of the available data, there appears to be a lack of overall concern regarding hypersensitivity. The incidence of hypersensitivity with sarilumab, including injection sites reactions, is consistent with actemra, the licensed anti-IL6R α therapy for rheumatoid arthritis.

The immunogenicity assay strategy involves three tiers in evaluation of a sample: an initial screening assay to identify samples that are potentially positive for anti-drug antibodies (ADA); a confirmation assay to determine if the observed positive response in the screening can be inhibited by the presence of excess drug and a titer assay to assess levels of ADA in positive samples.

Antibody assay descriptions

Anti-Drug (ADA) Assay

The ADA assay employs electrochemiluminescence (ECL) technology in a bridging assay format, in which REGN88 is immobilized in wells of an assay plate, patient serum or control samples are incubated in the wells allowing anti-REGN88 to antibodies to bind, and then bound complexes are in turn detected by incubation with ruthenium labeled REGN88, giving rise to a readout of light emission. ECL is widely used for biologic immunogenicity testing due to its low background and generally high sensitivity. Important modifications to enhance assay performance were use of an acid dissociation step to reduce on board product interference from REGN88, inclusion of exogenous human IgG in assay samples in order to block potential confounding effects of rheumatoid factor (complexing with serum IgGs), and development of a screening assay cutpoint using sera from commercially available RA serum samples.

Rheumatoid factor binds nonspecifically to the Fc region of antibodies, and as such has the potential to generate a false positive signal in the assay by mimicking the bridge created by an ADA. Therefore, exogenous human immunoglobulin G (IgG) was also included in the validated assay. The addition of exogenous human IgG was demonstrated to reduce the assay signal caused by this RF-mediated bridge

Using this study specific screen cut point of 4.19, the sensitivity of the assay based on the mouse monoclonal positive control was approximately 116.3 ng/mL in neat undiluted serum. The Drug Tolerance Limit (DTL) was approximately 336 μ g/mL and 409 μ g/mL at 500 ng/mL of the mouse monoclonal positive control and a rabbit polyclonal antibody, respectively. Confirmatory cutpoint has been appropriately validated at a 99.1% confidence level, and a high degree of precision was demonstrated for titer determinations, where titer was determined as the highest reciprocal dilution with a signal above the assay cut point.

Reviewer comments

The sensitivity of 116.3 ng/ml is very close to the 100 ng/ml sensitivity recommended in the current FDA draft guidance (Guidance for Industry, 2016: Assay Development and Validation of Immunogenicity Testing of Therapeutic Protein Products), and is therefore acceptable. Moreover the DTL values of 336 μ g/mL (336 mg/L) and 409 μ g/mL are well above expected sarilumab serum concentrations of 6.63-16.5 μ g/ ml.

Overall the ADA assay is appropriately validated according to guidance, and I find the validation to be acceptable.

Neutralizing Antibody (Nab) Assay

The Nab assay uses the same ECL technology as the ADA assay, but in a competitive ligand format so that sarilumab is immobilized on the ECL plates as the capture reagent, which in the absence of neutralizing antibody, can bind ruthenium-labeled IL-6R α , generating an ECL signal. The presence of neutralizing antibodies in control samples or patient serum samples blocks binding of the labeled IL-6R α to immobilized sarilumab, so Nab activity is scored as an inhibition of the ECL signal. Again, measures are used to reduce assay interference; i.e. (1) acid treatment dissociates NAb:drug and drug:target complexes present in serum samples, reducing drug interference in the assay (2) an anti-IL6R monoclonal antibody (REGN17) is used to bind free target released by the acid treatment, mitigating target interference.

Using specific assay cut points derived from untreated RA patient samples, the sensitivity of the assay based on the monoclonal positive control antibody and the rabbit polyclonal antibody was approximately 150 ng/mL (0.15 mg/L) and 257 ng/mL (0.257 mg/L), respectively. The drug tolerance limit was 500 ng/mL (0.5 mg/L) of the monoclonal antibody positive control and the rabbit polyclonal antibody was 509 ng/mL (0.509 mg/L) and 224 ng/mL (0.224 mg/L) of sarilumab, respectively. The Nab assay has also been validated for precision, recovery, analyte stability, robustness, and ruggedness.

Reviewer comments

The Nab assay has overall been appropriately validated, with a sensitivity of 150-257 ng/ml that is within the typical range seen for neutralizing antibody assays. However, the expected sarilumab concentrations in patient samples are in the range of 6.63-16.5 μ g/ml, well above the validated 509 ng/ml REGN88 Drug Tolerance Limit. I would suggest

(b) (4)

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Detailed Summaries of Immunogenicity Results and Assays

Clinical Immunogenicity Results

Results and correlation with safety

The Sponsor states that ADA positivity nor persistent ADA positivity appeared to have an impact on safety or treatment discontinuation due to lack or loss of efficacy; however, an association between persistent ADA status and/or neutralizing ADA and reduced sarilumab exposure is evident from observed and modeled PK analyses. In order to place the incidence of ADA response in the sarilumab groups in appropriate context, the incidence in the placebo group must also be considered. The percent of patients exhibiting a persistent ADA response over 52 weeks was 4.0% in the sarilumab 200 mg q2w group and 5.6% in the sarilumab 150 mg q2w group; however persistent ADA responses were also observed in 2.0% of patients in the placebo group, suggesting a 2% false positivity rate in the ADA assay in this population. The percentage of patients who exhibited both persistent and neutralizing antibody responses was 1.0% in the 200 mg q2w group, 1.6% in the 150 mg q2w group, and 0.2% in the placebo group.

The Sponsor considers that presentation of the incidence rates of persistent ADA (rather than any positive ADA or transient ADA) and NAb do provide useful information for physicians because of greater impact on the associations with lower sarilumab exposure.

From Summary of Clinical Safety 2.7.4

In discussion of these results, persistent ADA status is defined as positive ADA status for two or more sampling time points, while transient is defined as “non-persistent”. Shown in Table 55 are summary results for the TEAE period. The TEAE period is defined specifically for each study population, but broadly consists of data derived when patients participated in a given study, either to completion or discontinuation.

Table 55 - Overview of ADA assay response during the entire TEAE period - Placebo-controlled immunogenicity population (Pool 1)

	Placebo + DMARD (N=608)	Sarilumab + DMARD	
		150 mg q2w (N=607)	200 mg q2w (N=609)
Number of patients with ADA assay results available	608/608 (100%)	607/607 (100%)	607/609 (99.7%)
Patients with an ADA positive sample at baseline	9/606 (1.5%)	14/599 (2.3%)	10/599 (1.7%)
ADA positive patients ^a during the TEAE period	21/608 (3.5%)	117/607 (19.3%)	85/607 (14.0%)
Neutralizing ^b	1/608 (0.2%)	20/607 (3.3%)	11/607 (1.8%)
Non-Neutralizing	20/608 (3.3%)	97/607 (16.0%)	74/607 (12.2%)

	Placebo + DMARD (N=608)	Sarilumab + DMARD	
		150 mg q2w (N=607)	200 mg q2w (N=609)
Treatment-boosted ADA positive patients	0/608	1/607 (0.2%)	1/607 (0.2%)
Treatment-emergent ADA positive patients	21/608 (3.5%)	116/607 (19.1%)	84/607 (13.8%)
Patients with a persistent ^c positive response	12/608 (2.0%)	34/607 (5.6%)	24/607 (4.0%)
Neutralizing ^b	1/608 (0.2%)	10/607 (1.6%)	6/607 (1.0%)
Non-Neutralizing	11/608 (1.8%)	24/607 (4.0%)	18/607 (3.0%)
Patients with a transient ^c positive response	9/608 (1.5%)	82/607 (13.5%)	60/607 (9.9%)
Neutralizing ^b	0/608	9/607 (1.5%)	5/607 (0.8%)
Non-Neutralizing	9/608 (1.5%)	73/607 (12.0%)	55/607 (9.1%)
Peak titers for treatment-emergent ADA positive patients			
Median	60.00	60.00	60.00
Q1 : Q3	30.00 : 60.00	30.00 : 120.00	30.00 : 120.00
Min : Max	30.0 : 120.0	30.0 : 3840.0	30.0 : 7680.0

The Sponsor notes that the incidence of patients who discontinued due to loss or lack of efficacy was similar in patients who were positive for ADA to those who were negative. No patients with NAb responses discontinued due to loss or lack of efficacy.

In addition, shown below in Table 56 are summary results for the long-term safety populations, consisting of patients still on treatment at the time of data extraction.

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Table 56 - Overview of ADA assay response during the entire TEAE period - Sarilumab+DMARD immunogenicity population (Pool 2)

	Sarilumab+DMARD		
	150 mg q2w Initial Dose (N=1099)	200 mg q2w Initial Dose (N=1248)	Any Dose (N=2559)
Number of patients with ADA assay results available	1099/1099 (100%)	1244/1248 (99.7%)	2555/2559 (99.8%)
Patients with an ADA positive sample at baseline	19/1082 (1.8%)	20/1236 (1.6%)	40/2426 (1.6%)
ADA positive patients ^a during the TEAE period	237/1099 (21.6%)	148/1244 (11.9%)	417/2555 (16.3%)
Neutralizing ^b	30/1099 (2.7%)	17/1244 (1.4%)	52/2555 (2.0%)
Non-Neutralizing	207/1099 (18.8%)	131/1244 (10.5%)	365/2555 (14.3%)
Treatment-boosted ADA positive patients	1/1099 (<0.1%)	1/1244 (<0.1%)	3/2555 (0.1%)
Treatment-emergent ADA positive patients	236/1099 (21.5%)	147/1244 (11.8%)	414/2555 (16.2%)
Patients with a persistent ^c positive response	77/1099 (7.0%)	40/1244 (3.2%)	114/2555 (4.5%)
Neutralizing ^b	18/1099 (1.6%)	8/1244 (0.6%)	31/2555 (1.2%)
Non-Neutralizing	59/1099 (5.4%)	32/1244 (2.6%)	83/2555 (3.2%)
Patients with a transient ^d positive response	159/1099 (14.5%)	107/1244 (8.6%)	300/2555 (11.7%)
Neutralizing ^b	11/1099 (1.0%)	9/1244 (0.7%)	20/2555 (0.8%)
Non-Neutralizing	148/1099 (13.5%)	98/1244 (7.9%)	280/2555 (11.0%)
Peak titers for treatment-emergent ADA positive patients			
Median	30.00	60.00	30.00
Q1 : Q3	30.00 : 120.00	30.00 : 120.00	30.00 : 120.00
Min : Max	30.0 : 3840.0	30.0 : 7680.0	30.0 : 15360.0

Reviewer comments

As also seen in the Table 55 for the TEAE population, the ADA incidence is higher for patients receiving the 150 mg q2w dosing, versus the 200 mg q2w treatment, suggesting the possibility of some tolerization resulting from higher doses. From a safety standpoint, it is reassuring that titers are low; i.e. a signal below the cutpoint was reached after 1/30-1/60 dilutions. However in this situation, low titers were not completely innocuous, since as discussed in the section below on Pharmacokinetics, there is a clear impact of ADA on PK; i.e. reduced exposure.

Impact of formulation on ADA

from Summary of Biopharmaceutical studies

The Sponsor did assess the impact of formulation changes on ADA. In study TDU11373 (SC administration in healthy subjects) comparison of the (b) (4) F2 vial formulation with (b) (4) F3 (proposed commercial) vial formulation showed similar ADA incidence and titer between the

two formulations. In study PKM12058 SC (administration in RA patients) comparison of (b) (4) F2 in vials vs (b) (4) F3 in prefilled syringes showed similar ADA incidence similar, with 3 ADA positive patients in each treatment group.

Reviewer comment

These data suggest that within the range of formulation change from (b) (4) F2 to (b) (4) F3 there are no changes in parameters that affect immunogenicity, providing support for interpreting immunogenicity data across this formulation change.

Impact of ADA on Pharmacokinetics

Shown below are Figures 26 and 27 from 2.7.2 Summary of Clinical Pharmacology Studies. Boundaries of boxes indicate the 25th and the 75th percentiles. Lines within boxes mark the median. Whiskers indicate minimum and maximum values. Outlier data points are plotted individually. Numbers inside the plot panels indicate numbers of patients within covariate categories.

In summary:

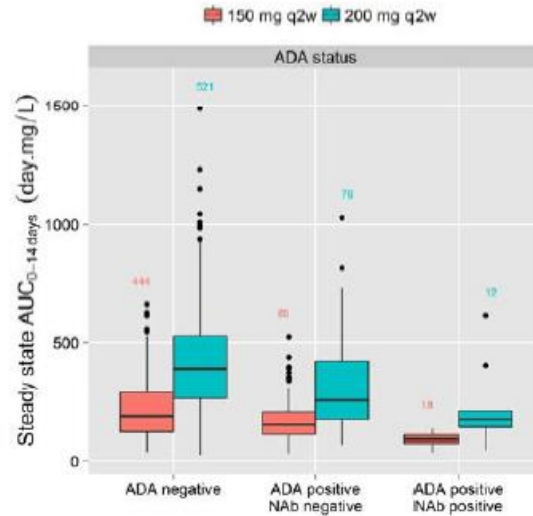
- d. ADA patients showed 24-28% lower exposure
- e. Exposure was lower in Nab positive patients by 49-59%
- f. Patients with persistent ADA showed 32-41% lower exposure

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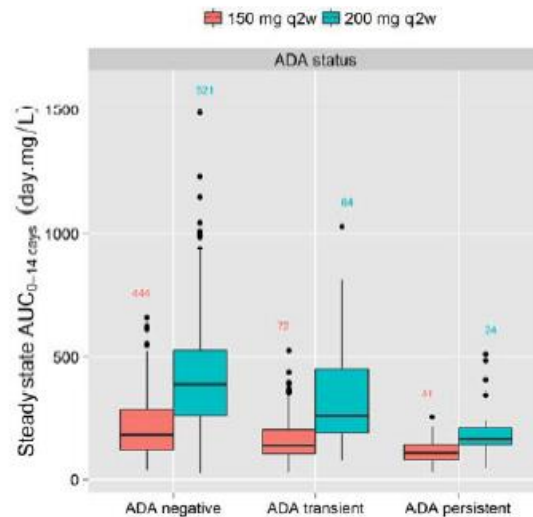
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Figure 26 - Functional sarilumab steady state exposure ($AUC_{0-14 \text{ days}}$) as a function of anti-antibody status in patients with rheumatoid arthritis in Phase 3 studies (Study POH04:

ADA positive (NAb positive or NAb negative) versus ADA negative

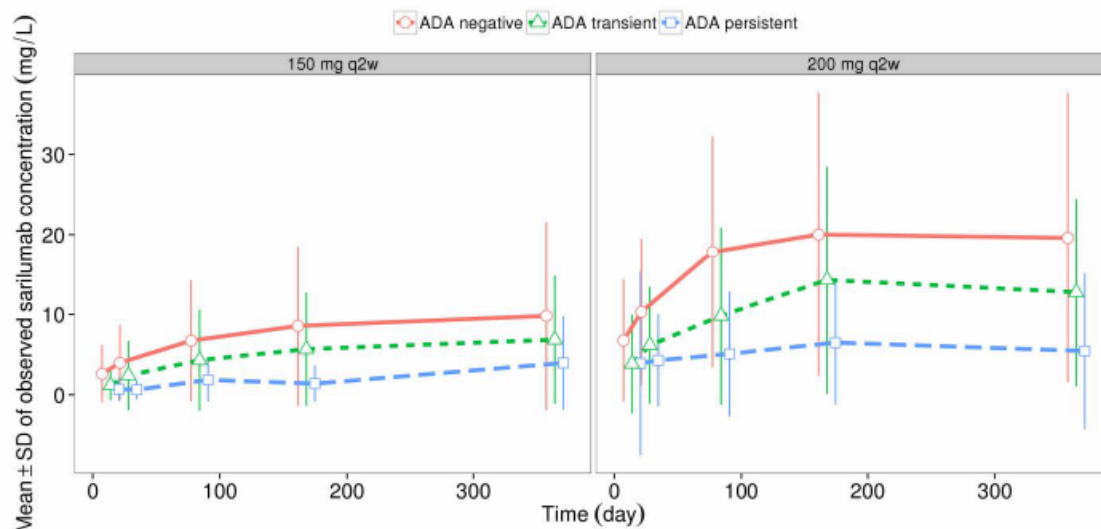


ADA positive (persistent or transient) versus ADA negative



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Figure 27 - Serum trough concentrations of functional sarilumab following repeated doses of sarilumab by antidrug antibody status in patients with rheumatoid arthritis (Study POH0428)



ADA: antidrug antibody; q2w: every 2 weeks; SD: standard deviation

Observed concentrations from Phase 3 Studies EFC11072 Part B and EFC10832

Therefore, the Sponsor states that NAb and persistent ADA positive response were considered to be most clinically relevant to assess for an impact on efficacy. In the sarilumab+DMARD long-term safety population, one patient on sarilumab+DMARD with persistent antibody response, and no patients with NAb, discontinued due to lack or loss of efficacy

Reviewer comments

These data show that ADA formation clearly reduces sarilumab exposure. I defer to the Clinical and Clinical Pharmacology review teams as to whether this reduced exposure has an impact on sarilumab therapy. However, I would note that these data extend for one year, and with at least one other chronic biologic therapy (Betaseron for MS) immune mediated loss of efficacy becomes more pronounced after a year of treatment.

Hypersensitivity in Sarilumab-treated patients

Overall, there was an ~ two fold increase in reported for hypersensitivity in sarilumab-treated patients versus those treated with placebo; i.e.

200 mg q2w	7.3% of 661 patients
150 mg q2w	6.8% of 660 patients
placebo	3.9% of 661 patients.

Only 4 hypersensitive SAEs were reported-one in a 200 mg q2w patient and three in 150 mg q2w patients. Reassuringly, the Sponsor found that there were no reported cases of anaphylaxis.

In the placebo-controlled population, the incidence of hypersensitivity leading to permanent discontinuation was <1% with a numerically higher incidence observed in sarilumab (0.9% in 200 mg q2w and 0.5% in 150 mg q2w) compared to placebo (0.2%) with similar incidence

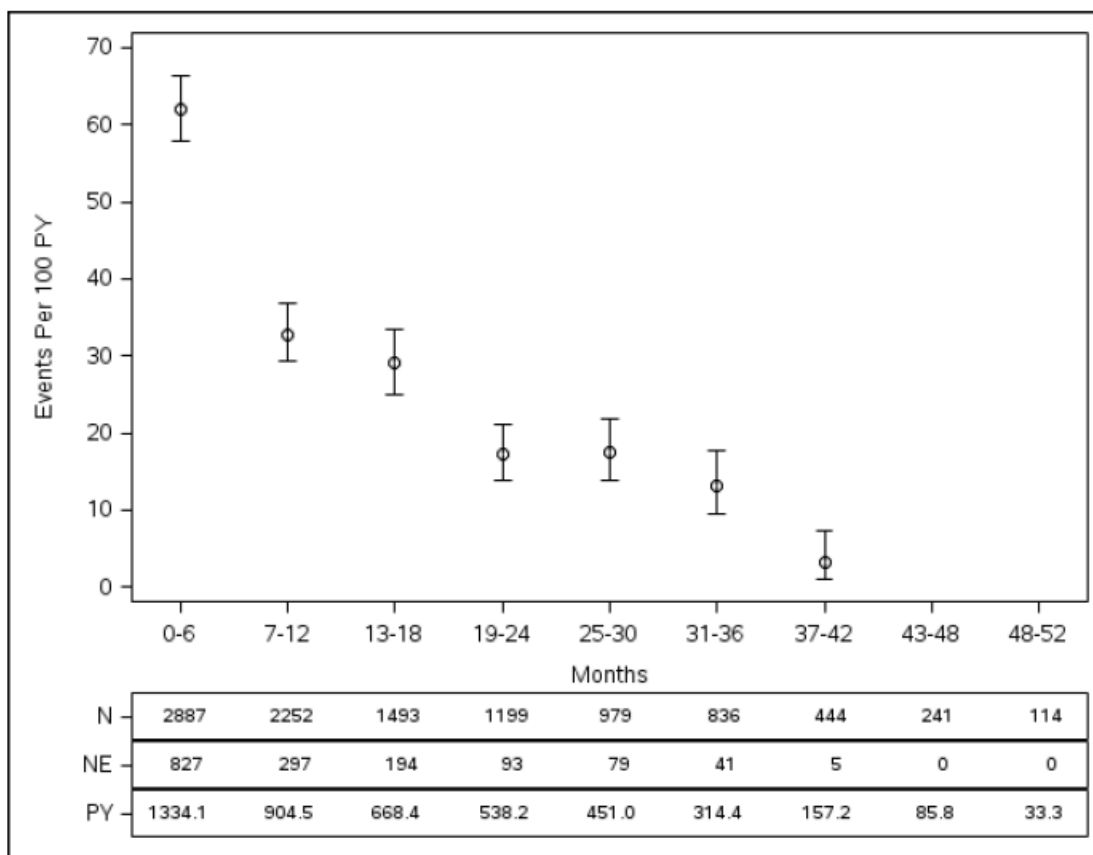
observed between the 2 doses of sarilumab. This translated into 27 patients discontinuing. Of these patients 25 were ADA negative.

Reviewer comments

The lack of observed ADA in hypersensitive patients is not necessarily surprising-particularly in the case of IgE mediated hypersensitivity, serum antibody levels may not correlate with hypersensitive reactions, which are often local rather than systemic.

Injection site reactions showed the clearest hypersensitive signal above the placebo background, being observed in 9.5% of 200 mg q2w patients and 8% of 150 q2w patients versus only 1.4% of placebo patients. However, there was an apparent beneficial adaptation to dosing resulting in a decline in injection site reactions, as shown in the following figure:

Figure 25 - Exposure-adjusted rate of injection site reaction (95% CI) by 6-month intervals during the entire TEAE period - Any sarilumab dose group in the sarilumab+DMARD long-term safety population (Pool 2)



N: sample size. NE: number of events in a 6-month period. PY: patient-years.

The 95% confidence interval was calculated using the exact method.

PGM=PRODOPS/SAR153191/OVERALL/CSS/REPORT/PGM/ae_expo_adju_s_g.sas OUT=REPORT/OUTPUT/ae_expo_adju_injec_s_g_i.rtf (29JUN2015 - 18:33)

Reviewer comments

The incidence of hypersensitivity with sarilumab, including injection sites reactions, is consistent with actemra, the licensed anti-IL6R α therapy for rheumatoid arthritis. According to the actemra package insert,

“Anaphylaxis and other hypersensitivity reactions that required treatment discontinuation were reported in 0.1% (3 out of 2644) of patients in the 6-month controlled trials of intravenous ACTEMRA, 0.2% (8 out of 4009) of patients in the intravenous all-exposure RA population, 0.7% (8 out of 1068) in the subcutaneous 6-month controlled RA trials, and in 0.7% (10 out of 1465) of patients in the subcutaneous all-exposure population.”

For infusion reactions

“ In the 24 week, controlled clinical studies, adverse events associated with the infusion (occurring during or within 24 hours of the start of infusion) were reported in 8% and 7% of patients in the 4 mg per kg and 8 mg per kg ACTEMRA-IV plus DMARD group, respectively, compared to 5% of patients in the placebo plus DMARD group.”

Moreover, for embrel, which is a widely prescribed RA therapeutic, the package insert describes allergic reactions <2%, but a high infusion site reaction rate of 37%.

Therefore, it appears that from a hypersensitivity standpoint, sarilumab is a relatively safe therapeutic, although I defer to the clinical review team for final assessment from this perspective.

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ADA assay validation

Summary table

Validation Parameters and Acceptance Criteria	Results
Minimum Required Dilution (MRD)	1:30 (3.3% Serum)
Concentration of Bridging Antibodies (Bio-REGN88 and Ru-REGN88)	2 µg/mL
Positive Control	Mouse anti-REGN88 monoclonal Ab (REGN589)
Positive Control – Quality Controls (neat serum concentration) HQC MQC LQC	24 µg/mL 2.4 µg/mL 0.12 µg/mL
Cut Point (CP) – RF⁺ Naïve Individual Serum Samples Screening/Titer Confirmation (Specificity)	2.76 34%
Cut Point (CP) – Baseline Samples from Individuals with Rheumatoid Arthritis Screening Confirmation (Specificity) Titer	3.09 26% 5.69
Specificity %Drop PQC's > Confirmation Assay Cut Point (34%)	75 – 93%
Sensitivity (in neat serum) Positive Control (mouse anti-REGN88 monoclonal antibody – REGN589):	63.5 ng/mL
Recalculated Sensitivity (in neat serum) – using CP from Rheumatoid Arthritis Individuals Positive Control (mouse anti-REGN88 monoclonal antibody – REGN589):	75.6 ng/mL
Dilution Linearity Mean R ² ≥ 0.95	0.998
Drug Tolerance Limit (DTL) Positive Control (mouse anti-REGN88 monoclonal antibody – REGN589): 120 ng/mL (30X LQC) 500 ng/mL Polyclonal Antibody Control (rabbit anti-REGN88 antibody – REGN2186): 500 ng/mL	71.5 µg/mL 536.0 µg/mL 555.8 µg/mL
Recalculated Drug Tolerance Limit (DTL) - using CP from Rheumatoid Arthritis Individuals Positive Control (mouse anti-REGN88 monoclonal antibody – REGN589): 500 ng/mL Polyclonal Antibody Control (rabbit anti-REGN88 antibody – REGN2186): 500 ng/mL	471.1 µg/mL 510.0 µg/mL
Ligand Tolerance Limit (LTL) IL-6Rα (REGN78):	1979.4 ng/mL

Precision (Screening Assay) LQC Error rate (false negative responses) LQC CV% Counts $\leq$ 25%	0% 0-7%
NQC Error rate (false positive responses)	0%
Precision (Titer Assay) (75% of the HQC titer values must fall within 2 dilution factors of the Median Titer) HQC Median Titer HQC Titer Range % of HQC Titers within 2 dilution factors of the Median Titer	 7680 7680 100%
Recovery At least 80% of LQC-spiked samples with Mean Counts > cut point	100% (20 out of 20 samples)
Analyte Stability (Short- and Long-Term Stability) PQCs %AR $\geq$ 75% (CV% Counts $\leq$ 25) 4°C Overnight 4 hours Room Temperature 10X Freeze/Thaw Cycles Long-term storage in a -20°C freezer (up to 24 months) Long-term storage in a -80°C freezer (up to 24 months)	 101 – 107% (1 – 3%) 94 – 102% (0 – 6%) 111 – 116% (2 – 5%) 75 – 170%, 24 months (0 – 11%) 75 – 157%, 24 months (1 – 8%)
Robustness (HQC Titer) (HQC titer must fall within 2 dilution factors of the Median Titer) Different lots of non-critical reagents (Lot A; Lot B) Different lots of MSD plates (Lot A; Lot B) Different MSD instruments (Instrument A; Instrument B)	 7680; 7680 7680; 3840 3840; 3840
Robustness (Intra-plate Variability) LQC CV% Counts $\leq$ 25% At least 90% of LQC values with Counts > cut point	7% 100%
Ruggedness (HQC Titer - Different Analysts) (HQC titer must fall within 2 dilution factors of the Median Titer) MQC Titer – Analyst 1 MQC Titer – Analyst 2	 7680 7680

Minimal Required Dilution (MRD)

Development exercises were performed to assess the minimum required dilution (MRD) for the assay. Serum samples from RF-positive, drug-naïve human individuals were tested to examine the variability in the assay signal across different sample dilutions. The effect of different dilutions on drug tolerance and sensitivity was also assessed; using serum samples spiked with the monoclonal antibody positive control (REGN589) or a rabbit anti-REGN88 polyclonal antibody (REGN2186), in the absence and presence of drug (100 µg/mL REGN88 in neat serum).

Sera from 11 RF-positive individuals were tested in the ADA assay at a 25%, 12.5%, 6.25%, and 3.13 %. The ECL signals from these untreated patient samples were very low, but variability between samples was reduced at lower serum concentrations.

The effects of serum dilutions on assay sensitivity were also assessed using serum spiked with the mouse monoclonal positive control antibody (REGN589), or the rabbit polyclonal positive control antibody (REGN2186). For the monoclonal PC, there was a modest (twofold) improvement in the signal going from 25% serum down to 3.13%. For the polyclonal PC, the sensitivity is approximately 5 fold better at 25% serum versus 3.13%, but at 3.13% serum a high sensitivity (6.54 ng/ ml) was still maintained.

Finally, signal as a function of serum dilution was evaluated in the presence of on board REGN88 at a concentration of 100 μ g/ ml. In going from 25% to 3.13% serum, the signal improved approximately twofold for the monoclonal PC, and two to fourfold for the polyclonal PC. Similar results were obtained at 250 ng/ ml monoclonal or polyclonal PC, with a range of on-board REGN88 concentrations; i.e., as expected for an on-board product effect, the signal was improved by serum dilution, because this also dilutes the on-board product.

Reviewer comments

Overall, I agree with the Sponsor's decision to use an MRD of 1/32 (3.13% patient serum concentration, because this reduces variability, maintains sensitivity, and also reduces on-board product interference. The MRD is consistent with the 2016 FDA immunogenicity guidance, which recommends MRDs no greater than 1/100.

Screening Cut Point

The Screen Cut Point is calculated for each assay run by multiplying the Mean Counts of the negative control of each plate (NQC) by a cut point factor (CF), an experimentally established value obtained from the analysis of naïve samples. The CF was determined by analyzing seventy-two commercially available, RF-positive naïve human serum samples (male and female). Each sample was analyzed by two analysts on three separate days. A statistical evaluation of the results from all RF-positive naïve samples was performed. All data was normalized to their respective plate negative controls (NQC), with normalized values calculated as sample value/plate NQC. As part of the statistical analysis, the data were analyzed using normal or lognormal distributions and the estimated and observed percentiles were compared. Based on this analysis, a total of 27 individual results, from six samples, were considered to be outliers. Excluding these 27 outlier results, the most appropriate CF appeared to be the observed 95th percentile based on quantiles. Observed quantiles are shown in Table 4.

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Table 4: Screening Cut Point Factor Calculation - Observed Quantiles

Data Distribution – Observed Quantiles ^a	
Percent	
1.0	0.91667
5.0	1.00000
10.0	1.04918
25.0	1.19444
50.0	1.39474
75.0	1.86111
90.0	2.36111
95.0	<u>2.75610</u> ^b
99.0	3.27500
99.5	3.39474
99.9	3.64706

a - All values were calculated using the UNIVARIATE procedure in SAS.

b - Bold underlined number = Cut Point Factor.

Based on this approach, a CF of 2.76 was selected and used to calculate the plate-specific cut points for all additional validation exercises (excluding specificity cut point exercises).

Reviewer comments

The assay validation is generally consistent with FDA guidance (Guidance for Industry: Assay Development and Validation for Immunogenicity Testing of Therapeutic Protein Products 2016) Excluding outliers, the CF determination is based on results from 45 samples. These samples were RF factor positive, which is important given the likelihood of immune-mediated background in RF patients. Therefore I find the CF to appropriately determined.

Specificity/Confirmation Cut Point

In the assay, samples that are positive in the screening assay are re-analyzed, in duplicate, using a Master Mix prepared with or without excess of unlabeled REGN88. Excess unlabeled drug in the solution competes with Bio-REGN88 and/or Ru-REGN88 for binding to anti-REGN88-specific antibodies, resulting in a signal reduction (%Drop or %Inhibition) compared to the sample tested without the excess unlabeled drug. Samples that are positive in the screening assay are confirmed as ADA positive if the signal reduction is greater than the confirmation cut point. The confirmation cut point is defined as a threshold value (%Drop/%Inhibition) used to distinguish a drug-specific versus a non-specific antibody response.

The confirmation cut point was originally determined by analyzing thirty-two commercially available, RF-positive naive human serum samples (male and female), selected randomly from those samples analyzed for the CF determination. Each sample was analyzed in duplicate, by two analysts, with one replicate run in the absence of REGN88 and the other replicate run in the presence of 20 µg/mL of REGN88. In addition to the RF-positive naive serum samples, one set of QCs was also analyzed in duplicate, in every plate used for the determination of the confirmation cut point (for a total of six sets). The confirmation cut point (corresponding to a 0.1% false positive , or Type 1 error rate) was calculated as:

Confirmation cut point = Mean %Inhibition + Stdev %Inhibition x 3.09

The Mean % Inhibition of all samples was 5% with a Stdev % Inhibition of 9%, generating a confirmation cut point of 34%.

The confirmation cut point was subsequently re-calculated using baseline serum samples from rheumatoid arthritis patients participating in a Phase 3 REGN88 clinical study. Based on the statistical analysis of the data obtained from the analysis of these baseline samples, a confirmation cut point of 26.0% was determined for this population.

Reviewer comments

Examination of Sponsor's tabulated data for inhibition of positive controls by 20 µg/ ml REGN88 (Table 6-data not shown) is reassuring in indicating little variability between runs and analysts. The Sponsor appears to have appropriately excluded outliers in the naïve serum sample measurements (Table 7)

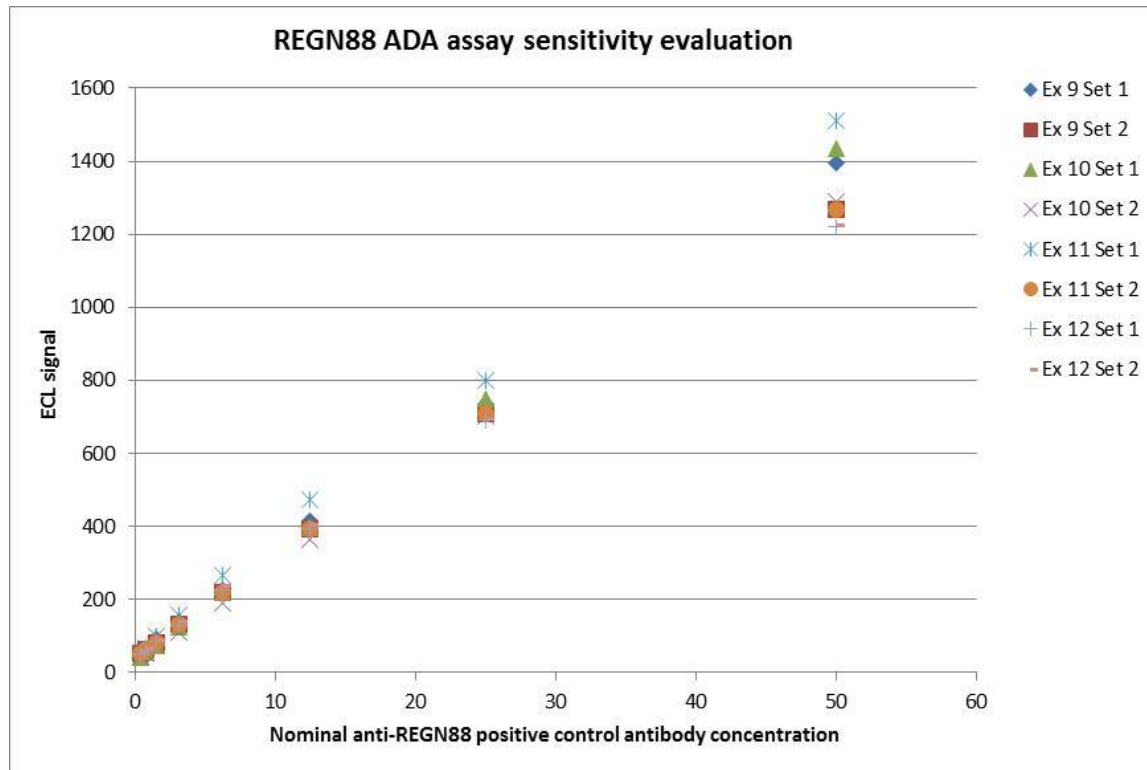
Because this is a confirmatory assay for which a high degree of certainty is required, using the formula:

Confirmation cut point = Mean %Inhibition + Stdev %Inhibition x 3.09 is acceptable.

This formula results in a Confirmatory CP value of 34% for commercially available RF sera, and a 26% inhibition Confirmatory CP for patient pre-treatment samples. These results are within the range used for Confirmatory CPs for other biologics, and satisfy the technical requirement for a readily detectable amount of inhibition. If the Sponsor can provide a satisfactory explanation for the apparent difference in between analysts for naïve serum values, I would agree that the Confirmatory assay is appropriately validated and suitable for confirming screening ADA positive samples as true positives.

Sensitivity

Sensitivity was determined for the positive control (REGN589), by comparing eight sets of dilutions of 30X HQC (24 µg/mL) performed by two analysts (two independent observations per plate, two plates per analyst, over two different days). Two-fold dilutions of the 30X HQC ranged from 1:16 (1500 ng/mL) to 1:2048 (11.7 ng/mL), resulting in a final assay concentration range from 50 ng/mL to 0.39 ng/mL of REGN589 (Exercises 9 to 12). Mean Counts for each HQC dilution were plotted against their nominal concentrations and the curve was fitted using the 5 PLV equation (). The Lower Limit of Detection (LLOD), defined as the concentration of REGN589 giving a signal equal to the plate cut point, was then interpolated from each regression curve using the plate Negative Quality Control (NQC) to calculate the plate cut point.

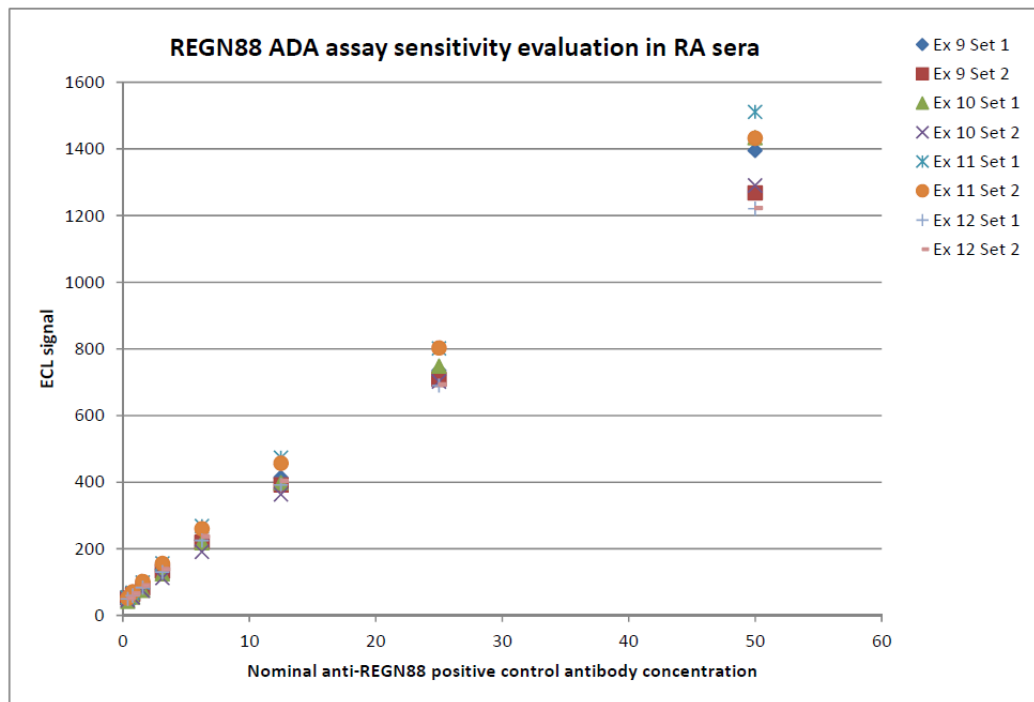


Reviewer comments

Graphing the data shows a high degree of linearity and reproducibility, supporting the accuracy of the sensitivity determination. The extrapolated values are in a relatively narrow range of 1.78-2.43 ng / ml, with a mean of 2.12 ng/ ml and a %CV of 10%. Given the 33.3 fold dilution factor, this corresponds to 63.5 ng/ ml in neat serum, well within the recommended sensitivity from guidance. Therefore the ADA assay sensitivity determination is adequate.

The sensitivity of the assay, based on the original assay cut point and the calculated LLOD values, was re-evaluated after the determination of the CF using baseline serum samples from rheumatoid arthritis patients. This was done by re-analyzing the sensitivity data obtained during the validation using the updated CF. These results are presented in [Appendix M](#). In the 3.3% assay matrix, the sensitivity of the assay, using the population-based cut point, is 2.52 ng/mL, or approximately 75.6 ng/mL in the neat serum sample.

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Reviewer comments

As is also seen for dilutions in normal sera, graphing the data shows a high degree of linearity and reproducibility, supporting the accuracy of the sensitivity determination. 2.15-2.89.

Multiplying by the 33.3 fold dilution factor, this corresponds to 75.6 ng/ml in neat serum, well within the recommended sensitivity from guidance. Therefore, the Sponsor has appropriately validated assay sensitivity for measurement of ADA levels in RA patients.

Dilution Linearity

Dilution linearity was determined by comparing four independent observations of eight two-fold dilutions. Dilutions ranged from 1:2 (12 µg/mL) to 1:256 (93.8 ng/mL), resulting in a final assay concentration range from 400 ng/mL to 3.13 ng/mL of the REGN589 control antibody.

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Table 9: Dilution Linearity

			Exercise 13				Exercise 14			
			Analyst #1				Analyst #2			
HQC Dilution	HQC Final Dilution	REGN589 Nominal Concentration (ng/mL)	Set 1		Set 2		Set 1		Set 2	
			Mean Counts ^a	CV% Counts	Mean Counts	CV% Counts	Mean Counts	CV% Counts	Mean Counts	CV% Counts
2	1:60	400.00	15810	4	15656	2	15377	1	14152	3
4	1:120	200.00	6919	3	6848	2	6919	2	6442	4
8	1:240	100.00	3279	1	3267	4	3251	4	3005	3
16	1:480	50.00	1619	1	1546	4	1571	2	1477	3
32	1:960	25.00	855	3	827	7	869	2	773	8
64	1:1920	12.50	468	2	442	5	481	2	440	4
128	1:3840	6.25	253	2	257	10	271	5	241	8
256	1:7680	3.13	145	5	152	3	168	1	157	4
Plate Cut Point			124				142			
R ²			0.999		0.998		0.997		0.998	
Mean R ^{2b}			0.998							

Reviewer comments

The dilution linearity runs all show very close fits to a straight line (R^2 values ≥ 0.998) with little difference between two runs each that were performed by two different operators. The linearity of 8 sensitivity curves is also shown above, providing supporting data. Thus the Sponsor has demonstrated adequate linearity of the ADA assay.

Hook effect

A development exercise was performed to assess the dose response curve of the positive controls and to determine whether hook effects were observed. The anti-REGN88 monoclonal antibody positive control (REGN589) and the rabbit polyclonal antibody (REGN2186) were serially diluted in NQC (1:2 dilution) and analyzed. Concentrations tested ranged from 300 $\mu\text{g/mL}$ to 2.34 $\mu\text{g/mL}$ in neat serum, resulting in final assay concentrations from 10,000 ng/mL to 78.13 ng/mL. For both antibodies, no hook effects were observed with concentrations up to 75 $\mu\text{g/mL}$, with a decrease and/or plateau in signal observed at the higher concentrations (150 and 300 $\mu\text{g/mL}$) tested.

Reviewer comments

A Hook effect is demonstrated at very high concentrations (150 and 300 $\mu\text{g/mL}$) of antibody positive controls. Positive patient responses will be assessed with titer determinations in which high signals will be diluted to a cutpoint, so a Hook effect/ plateau at low serum dilutions would not be expected to affect the evaluation of patient antibody responses in terms of assigning antibody positivity and titer.

Drug Tolerance

The drug tolerance limit (DTL) was originally defined as the concentration of drug that will reduce the signal of the anti-REGN88 monoclonal antibody positive control (at the LQC level) to the plate cut point value, as interpolated from a regression curve fit. The DTL was first determined by eight independent observations (two independent observations per plate, two

plates per analyst, two analysts, over two different days) of a sample containing the positive control (REGN589) at 120 ng/mL, resulting in a DTL of 71.5 µg/mL.

Additional development exercises were later performed using the original assay cut point to determine the DTL of the assay in the presence of 500 ng/mL of either the monoclonal antibody, positive control (REGN589), or a rabbit anti-REGN88 polyclonal antibody (REGN2186). These studies were performed by two analysts, with three independent observations per analyst. In the presence of 500 ng/mL of the monoclonal antibody positive control the DTL was found to be 536 µg/mL of REGN88, while for 500 ng/mL of the rabbit polyclonal antibody was approximately 556 µg/mL.

After the determination of the CF (Cutpoint Factor) using baseline serum samples from rheumatoid arthritis patients, data obtained from these developmental exercises were re-analyzed using the updated CF (results below in Table 38). Using the population-based cut point, the re-calculated Mean DTL in neat serum, for the monoclonal antibody positive control (REGN589) is approximately 471 µg/mL of REGN88, while for the rabbit polyclonal antibody, the Mean DTL is approximately 510 µg/mL in neat sera.

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**Table 38: Drug Tolerance – Monoclonal Antibody (REGN589 at 500 ng/mL)
Point for Rheumatoid Arthritis Population**

	Analyst 1 - Set 1		Analyst 1 - Set 2		Analyst 1 - Set 3	
REGN88 (µg/mL)	Mean Counts ^a	CV% Counts	Mean Counts	CV% Counts	Mean Counts	CV% Counts
4000.0	33	14	32	3	33	2
2000.0	37	8	40	6	41	3
1000.0	55	5	57	6	54	9
500.0	89	2	97	7	93	5
250.0	171	1	187	2	178	3
125.0	287	1	306	1	315	5
62.5	416	3	461	2	443	2
0	628	7	717	2	655	4
Plate Cut Point ^b	104				89	
DTL (µg/mL)	429.7		481.8		548.7	
	Analyst 2 - Set 1		Analyst 2 - Set 2		Analyst 2 - Set 3	
REGN88 (µg/mL)	Mean Counts	CV% Counts	Mean Counts	CV% Counts	Mean Counts	CV% Counts
4000.0	37	4	35	9	34	20
2000.0	44	15	43	4	47	1
1000.0	55	6	54	7	61	7
500.0	94	8	105	7	113	5
250.0	175	6	183	1	212	3
125.0	295	8	315	1	358	2
62.5	404	4	446	4	504	2
0	604	2	665	5	696	1
Plate Cut Point	109				112	
DTL (µg/mL)	424.2		443.4		498.5	
Mean DTL (µg/mL) ^c	471.1					
Stdev DTL	48.1					
CV% DTL	10					

Reviewer comments

The drug tolerance values of 336 µg/mL and 409 µg/mL are well above expected sarilumab serum concentrations of 6.63-16.5 µg/ml.

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**Table 39: Drug Tolerance – Polyclonal Antibody (REGN2186 at 500 ng/mL)
Cut Point for Rheumatoid Arthritis Population**

	Analyst 1 - Set 1		Analyst 1 - Set 2		Analyst 1 - Set 3	
REGN88 (µg/mL)	Mean Counts ^a	CV% Counts	Mean Counts	CV% Counts	Mean Counts	CV% Counts
4000.0	28	5	30	6	35	11
2000.0	34	3	32	8	33	9
1000.0	46	9	46	14	46	5
500.0	95	2	94	3	103	10
250.0	263	2	256	3	265	6
125.0	621	3	579	4	659	4
62.5	1275	4	1155	2	1390	4
0	4751	4	4290	3	4640	3
Plate Cut Point ^b	104		89			
DTL (µg/mL)	469.7		524.3		534.6	
	Analyst 2 - Set 1		Analyst 2 - Set 2		Analyst 2 - Set 3	
REGN88 (µg/mL)	Mean Counts	CV% Counts	Mean Counts	CV% Counts	Mean Counts	CV% Counts
4000.0	34	6	32	19	29	7
2000.0	35	6	38	17	37	11
1000.0	52	4	50	10	55	2
500.0	108	3	105	3	133	1
250.0	267	4	268	3	376	1
125.0	660	4	630	7	883	1
62.5	1353	4	1227	5	1816	1
0	4855	3	4545	3	5042	3
Plate Cut Point	109		112			
DTL (µg/mL)	491.7		473.7		566.0	
Mean DTL (µg/mL) ^c	510.0					
Stdev DTL	38.0					
CV% DTL	7					

Ligand Tolerance

The ligand tolerance limit (LTL) is the maximum concentration of free ligand that can be present in a serum sample without generating a false positive signal, as interpolated from a regression curve fit. LTL was determined by four independent observations (two independent observations per plate, two plates, over two different days) of an NQC sample, spiked with increasing concentrations of IL-6Rα, ranging from 156.3 ng/mL to 10,000 ng/mL

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Table 11: Ligand Tolerance

	Exercise 21-R				Exercise 22			
IL-6Ra Concentration (ng/mL)	Set 1		Set 2		Set 1		Set 2	
	Mean Counts ^a	CV% Counts	Mean Counts	CV% Counts	Mean Counts	CV% Counts	Mean Counts	CV% Counts
10000.0	488	3	429	6	398	1	375	5
5000.0	252	2	233	4	209	3	209	4
2500.0	149	2	136	4	124	4	119	2
1250.0	98	2	91	2	72	7	71	6
625.0	71	7	73	2	55	9	52	12
312.5	62	2	59	7	43	2	34	17
156.3	51	11	51	9	32	5	32	13
0.0	43	13	47	8	24	14	29	10
LTL (ng/mL)	2102.7		2376.1		1644.7		1794.1	
Plate Cut Point	132				92			
Mean LTL in neat serum (ng/mL) ^b	1979.4							
Stdev (LTL)	326.1							
CV% (LTL)	16							

Precision

Precision for the screening assay was assessed by examining the frequency of false negative and false positive results from four independent LQCs and NQCs, respectively, run on each of eight plates, by two analysts.

Table 12: Precision – Screening Assay (LQC)

Observation # (Exercise #)	LQC ID	Mean Counts ^a	CV% Counts	Plate Cut Point	Outcome	Observation # (Exercise #)	LQC ID	Mean Counts	CV% Counts	Plate Cut Point	Outcome
1 (Ex. 9)	01-LQC	228	1	111	POS. ^b	17 (Ex. 13)	01-LQC	238	3	124	POS.
2 (Ex. 9)	02-LQC	228	4	111	POS.	18 (Ex. 13)	02-LQC	233	3	124	POS.
3 (Ex. 9)	03-LQC	231	2	111	POS.	19 (Ex. 13)	03-LQC	222	3	124	POS.
4 (Ex. 9)	04-LQC	225	1	111	POS.	20 (Ex. 13)	04-LQC	223	2	124	POS.
5 (Ex. 10)	01-LQC	169	3	143	POS.	21 (Ex. 14)	01-LQC	242	2	142	POS.
6 (Ex. 10)	02-LQC	179	2	143	POS.	22 (Ex. 14)	02-LQC	246	4	142	POS.
7 (Ex. 10)	03-LQC	173	4	143	POS.	23 (Ex. 14)	03-LQC	241	2	142	POS.
8 (Ex. 10)	04-LQC	177	3	143	POS.	24 (Ex. 14)	04-LQC	245	4	142	POS.
9 (Ex. 11)	01-LQC	227	3	120	POS.	25 (Ex. 15)	01-LQC	195	2	103	POS.
10 (Ex. 11)	02-LQC	224	1	120	POS.	26 (Ex. 15)	02-LQC	196	2	103	POS.
11 (Ex. 11)	03-LQC	213	7	120	POS.	27 (Ex. 15)	03-LQC	191	3	103	POS.
12 (Ex. 11)	04-LQC	216	1	120	POS.	28 (Ex. 15)	04-LQC	192	2	103	POS.
13 (Ex. 12)	01-LQC	196	1	98	POS.	29 (Ex. 16)	01-LQC	215	1	114	POS.
14 (Ex. 12)	02-LQC	210	2	98	POS.	30 (Ex. 16)	02-LQC	219	1	114	POS.
15 (Ex. 12)	03-LQC	207	2	98	POS.	31 (Ex. 16)	03-LQC	215	2	114	POS.
16 (Ex. 12)	04-LQC	215	2	98	POS.	32 (Ex. 16)	04-LQC	226	0	114	POS.
% Positive Samples ^c								100			
%Error								0			
Mean LQC Counts								214			
Stdev LQC Counts								21			
CV% LQC Counts								10			

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Table 13: Precision – Screening Assay (NQC)

Observation # (Exercise #)	NQC ID	Mean Counts ^a	Plate Cut Point	Outcome	Observation # (Exercise #)	NQC ID	Mean Counts	Plate Cut Point	Outcome
1 (Ex. 9)	01-NQC	39	111	NEG. ^b	17 (Ex. 13)	01-NQC	37	124	NEG.
2 (Ex. 9)	02-NQC	42	111	NEG.	18 (Ex. 13)	02-NQC	43	124	NEG.
3 (Ex. 9)	03-NQC	40	111	NEG.	19 (Ex. 13)	03-NQC	42	124	NEG.
4 (Ex. 9)	04-NQC	38	111	NEG.	20 (Ex. 13)	04-NQC	39	124	NEG.
5 (Ex. 10)	01-NQC	46	143	NEG.	21 (Ex. 14)	01-NQC	48	142	NEG.
6 (Ex. 10)	02-NQC	48	143	NEG.	22 (Ex. 14)	02-NQC	45	142	NEG.
7 (Ex. 10)	03-NQC	48	143	NEG.	23 (Ex. 14)	03-NQC	51	142	NEG.
8 (Ex. 10)	04-NQC	56	143	NEG.	24 (Ex. 14)	04-NQC	50	142	NEG.
9 (Ex. 11)	01-NQC	40	120	NEG.	25 (Ex. 15)	01-NQC	37	103	NEG.
10 (Ex. 11)	02-NQC	41	120	NEG.	26 (Ex. 15)	02-NQC	42	103	NEG.
11 (Ex. 11)	03-NQC	41	120	NEG.	27 (Ex. 15)	03-NQC	40	103	NEG.
12 (Ex. 11)	04-NQC	42	120	NEG.	28 (Ex. 15)	04-NQC	45	103	NEG.
13 (Ex. 12)	01-NQC	37	98	NEG.	29 (Ex. 16)	01-NQC	39	114	NEG.
14 (Ex. 12)	02-NQC	38	98	NEG.	30 (Ex. 16)	02-NQC	36	114	NEG.
15 (Ex. 12)	03-NQC	39	98	NEG.	31 (Ex. 16)	03-NQC	39	114	NEG.
16 (Ex. 12)	04-NQC	41	98	NEG.	32 (Ex. 16)	04-NQC	44	114	NEG.
% Negative Samples ^c							100		
% Error							0		

Reviewer comments

The CV% Counts for all LQCs ranged from 0 to 7% and were all well above the plate cutpoints, showing a high degree of reproducibility, even in the low signal range of the assay. Similarly, all the negative control values were well below the plate cutpoints, and showed a modest range of variability in this low signal range. Together, these data mean that the screening assay is well controlled in terms of its precision.

Precision for the titer assay was assessed by determining the variability of the titer of a HQC sample in eight independent observations of eight, two-fold dilutions (two observation per plate, two plates per analyst, two analysts, over two different days). This was done by analyzing eight dilutions of the 30X HQC from the sensitivity parameter. Dilutions analyzed ranged from 1:16 to 1:2048; which translated into final titers of 480 to 61440. The titer of the sample (HQC) was determined as the highest reciprocal dilution with a signal above the assay cut point.

Table 14: Precision – Titer Assay

	Analyst #1		Analyst #2	
Observation Number	Exercise Number	Titer ^a	Exercise Number	Titer
1	9 - Set 1	7680	10-R - Set 1	7680
2	9 - Set 2	7680	10-R - Set 2	7680
3	11 - Set 1	7680	12 - Set 1	7680
4	11 - Set 2	7680	12 - Set 2	7680
Observed Titer Range	7680		7680	
Median Titer	7680			
Titer Range around the Median Titer	7680			
% Titer values within two dilutions of the Median Titer Value	100%			

Reviewer comments

The assay is capable of high reproducible determination of titer, with the same value over a range of operational scenarios; i.e. two different operators on different days, with different plates. Thus assay titer determination is adequately validated.

Recovery

Recovery was evaluated by analyzing twenty RF-positive naïve individual human serum samples spiked with REGN589 control antibody at a nominal concentration of 4 ng/ml the same as the LQC, and above the reported sensitivity for RA patients of 2.12 ng/ml. All values were above the cutpoint (84 ECL units) in the range 92-155 ECL units, except for one sample with a value of 288.

These data indicate that low antibody levels can be detected in RA patient sera. However, the LQC values in other phases of validation were uniformly > 200 ECL units, suggesting there is some assay inhibition in patient sera at low antibody levels. The Sponsor should explain how this potential inhibition may affect assignment of antibody positive patients.

Analyte Stability

The short-term stability of the monoclonal antibody positive control (REGN589) in human serum was examined by exposing QCs (HQC, MQC, LQC, NQC and SNQC) to either ten freeze-thaw cycles, room temperature storage for at least four hours (4 hours and 36 minutes), or storage in a 4°C refrigerator overnight (23 hours and 27 minutes). Analyte recovery (%AR) was calculated as:

$\%AR = 100 \times (\text{Mean Counts of stability QC} \div \text{Mean Counts of reference QC})$

%AR Results were:

Refrigerator storage 101-107%

RT storage 94-102 %

10 freeze-thaw cycles 111-116%

Thus there no /or minimal changes demonstrating adequate analyst stability under these conditions

The Sponsor also assessed analyte storage in a -80 °C freezer. At 21 months the QCs still showed % AR values in the range 97%. The Sponsor proposed an acceptable storage time of $\geq$ 24 months, at which time the %AR values were HQC 98%, MQC 75% , LQC 105%. These values met the Sponsor 75% acceptance criteria, and I agree that adequate 24 month stability appears to be demonstrated. I note that at 16 months, all the ECL values were high—in some cases two fold those of baseline, and the Sponsor should describe the frequency of high ECL readings, and whether or not high reading have an impact on determination of patient ADAs.

Robustness

Robustness is a measure of the capacity of an analytical method to remain unaffected by deliberate variations in method parameters. Variations tested for this study were: different lots of non-critical reagents and streptavidin-coated MSD plates and instrument variability. Robustness was initially assessed by comparing two observations of eight two-fold dilutions of the 30X HQC (24 µg/mL)

Reviewer comments

The Sponsor has demonstrated in Table 19 (data not shown) that there is a maximum difference of 16% (at the lowest dilution) for data acquired with different sets (lots) of non-critical reagents. Higher dilutions, which produce lower ECL signals, are in closer agreement, so that the same HQC titer is calculated using both sets of reagents. This titer is also in agreement with the HQC titer determined in Precision validation. Thus there is no significant effect of changing non-critical reagents.

As shown in Table 20, the Sponsor assessed the effect of using different assay plates. The ECL values below the lowest dilution/highest ECL signal appear to be in close agreement. However Plate B, shows a higher cutpoint than Plate A, so that a 1:7680 dilution is the last dilution above the cutpoint, and the reported titer, while for Plate B a 1:3840 dilution is the last dilution above the cutpoint, resulting in a reported titer of 3840. This difference in plate cutpoint has created a two fold dilution difference/ one titer step difference, and the validation meets the Sponsor's acceptance criterion of 4 fold dilution / 2 titer steps.

Table 20: Robustness – Plate Variability

Reagents Lot A, Instrument A (Exercise 24A and 24B)						
HQC Dilution	HQC Final Dilution	REGN589 Nominal Concentration (ng/mL)	Plate Lot A		Plate Lot B	
			Mean Counts ^a	CV% Counts	Mean Counts	CV% Counts
16	1:480	50.00	1098	9	1252	1
32	1:960	25.00	601	1	682	2
64	1:1920	12.50	326	3	375	4
128	1:3840	6.25	180	2	204	2
256	1:7680	3.13	110	8	125	4
512	1:15360	1.56	84	4	81	6
1024	1:30720	0.78	59	8	68	11
2048	1:61440	0.39	54	8	54	3
Plate Cut Point			108		132	
HQC Titer ^b			7860		3840	
Median Titer (From Table 14)			7680			

Examination of Table 21 (data not shown) shows that there is little effect of changing the ECL instrument, with mean counts at any dilution differing by < 6.5% between two different instruments.

Thus adequate Robustness relative to use of different ECL instruments is demonstrated.

Intra-plate variability was tested by analyzing a single LQC sample added to an entire plate. All eighty-one wells (100%) have Counts values above the plate cut point (116), with Counts ranging from 157 to 207 and a Mean Counts value of 180. The CV% Counts was 7%.

Reviewer comments

Similar to the Sponsor's precision evaluation, this aspect of the Robustness assessment shows a high degree of reproducibility, adequately supporting the ability of the assay to detect samples with signals slightly above the cutpoint, such as the LPC.

Ruggedness

Ruggedness was assessed by determining the variability of the titer of a sample (30X HQC; 24 µg/mL), in four independent observations (two observations per plate, one plate per analyst, two analysts). This was done by analyzing eight two-fold dilutions of the 30X HQC (24 µg/mL), ranging from 1:16 (1500 ng/mL) to 1:2048 (11.7 ng/mL), which translated into final titers of 480 to 61440. The HQC titers obtained for both analysts were 7680, equal to the Median Titer value. The results meet the acceptance criteria of the validation protocol that the HQC titers must fall within two dilution factors of the Median Titer (7680), with CV% Counts less than or equal to 25% for all samples with Mean Counts greater than the plate cut point.

Table 23: Ruggedness

HQC Dilution			Analyst #1				Analyst #2			
			Exercise 15				Exercise 16			
			Set 1		Set 2		Set 1		Set 2	
HQC Final Dilution	REGN589 Nominal Concentration (ng/mL)	Mean Counts ^a	CV% Counts	Mean Counts	CV% Counts	Mean Counts	CV% Counts	Mean Counts	CV% Counts	
16	1:480	50.00	1250	3	1213	2	1480	2	1381	2
32	1:960	25.00	632	2	633	1	778	2	726	3
64	1:1920	12.50	350	1	349	2	426	4	380	3
128	1:3840	6.25	192	1	192	1	239	3	213	1
256	1:7680	3.13	119	3	113	4	135	1	121	7
512	1:15360	1.56	79	3	75	3	87	2	79	4
1024	1:30720	0.78	57	3	57	9	62	11	53	7
2048	1:61440	0.39	45	6	48	3	52	8	46	8
Plate Cut Point			103				114			
HQC Titer ^b			7680		7680		7680		7680	
Median Titer (From Table 14)			7680							

a - All values listed under Mean Counts, CV% Counts and Plate Cut Point were calculated by SoftMax Pro software.

b - All values listed under HQC Titer and Median Titer were generated manually.

Reviewer comments

The acceptance criteria for Ruggedness are rather broad, only requiring that the HQC titers fall within two dilution factors (4 fold) of the Median Titer(determined in the Precision Exercise), and CV% counts > 25% for samples above the CutPoint. However, the actual values of Mean Counts are in good agreement between the analysts, with the median Mean Counts for Analyst # 1 differing from the median Mean Count for Analyst# 2 by < 19%, % CV values are < 11%, and HQC titer determined in both runs by both analysts being in exact agreement with the Median Titer determined in the Precision Exercise. Therefore a high degree of Ruggedness is demonstrated, and this aspect of the validation is acceptable.

Neutralizing Antibody Assay

A competitive ligand binding (CLB) assay has been developed to detect anti-REGN88 neutralizing antibodies (NAb) in human serum samples using electrochemiluminescence. Samples and controls were diluted in acetic acid and then neutralized using a Tris-base solution containing Bio-REGN88 (biotinylated REGN88) and REGN17 (an anti-IL6R monoclonal antibody). Acid treatment dissociates NAb:drug and drug:target complexes present in serum samples, reducing drug interference in the assay. In order to mitigate target interference, an anti-IL6R monoclonal antibody (REGN17) is used to bind free target released by the acid treatment. Upon incubation, the positive control (REGN575) or any Ab present in the sample binds to the Bio-REGN88. The acid treated samples are then added to avidin-coated microplate, where the avidin captures the Bio-REGN88 along with any NAb that is bound to it. After a wash step, Ru-REGN78 (Detection reagent) is added to the microplate to bind to captured Bio-REGN88. In the absence of NAb in the sample, the Bio-REGN88 binds the Ru-REGN78 forming a Bio-REGN88:Ru-REGN78 complex which generates a signal when the tripropylamine (TPA) based read buffer is added to the microplate and the microplate is read by a Meso Scale Discovery (MSD) electrochemiluminescence reader. However, in the presence of NAb, the NAb binds to Bio-REGN88, preventing formation of the Bio-REGN88:Ru-REGN78 complex, which in turn reduces the electrochemiluminescent signal in the well. Therefore, the measured electrochemiluminescence signal (ECL counts) is inversely proportional to the amount of positive control/NAb antibodies in the sample.

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Summary Table

3. VALIDATION SUMMARY

Parameter	Result
Cut point (%Inhibition):	40% (0.1% False positive rate)
Limit of Detection (LOD): • REGN575 (monoclonal Ab) • REGN2186 (polyclonal Ab)	Approximately 150 ng/mL in neat serum Approximately 257 ng/mL in neat serum
Dilution Linearity (R^2): • Mean $R^2 \geq 0.95$ of REGN575 • Mean $R^2 \geq 0.95$ of REGN2186	0.997, No hook effect observed in the conc. range tested 0.996, No hook effect observed in the conc. range tested
Drug Tolerance Limit (DTL): • At 500 ng/mL of REGN575 • At 500 ng/mL of REGN2186	Approximately 509 ng/mL of REGN88 in neat serum Approximately 224 ng/mL of REGN88 in neat serum
Inter-plate Precision: • CV% of %Inhibition LQC • CV% of Mean Counts NQC • Mean %Inhibition NQC < Mean %Inhibition LQC	8% 6% (NQC) -3 < (LQC) 49
Intra-plate Precision: • CV% of %Inhibition (HQC, MQC and LQC) • CV% of Counts NQC • Mean %Inhibition NQC < Mean %Inhibition LQC < Mean %Inhibition MQC < Mean %Inhibition HQC	(HQC) 0%, (MQC) 1% and (LQC) 7% 4% (NQC) 0 < (LQC) 44 < (MQC) 70 < (HQC) 93
Recovery:	No assay interference from RF, hemoglobin, or high LDL
Analyte Stability: • Freeze-Thaws • Room Temperature Storage • 4°C Refrigerator • -20°C Freezer • -80°C Freezer	10 Stable up to 4 hours and 32 minutes Stable up to 23 hours and 20 minutes 24 months 24 months
Robustness and Ruggedness:	Assay remained unaffected by changes in analysts, lots of non-critical reagents and avidin coated plates, or by changes in incubation times

Cut point (% inhibition)

The cut point is the threshold value (i.e., % Inhibition) above which a sample is defined to be NAb positive. The cut point is an experimentally established value obtained from the analysis of drug-naïve (diseased) samples. The cut point is then used to determine whether controls and patient samples are NAb positive or negative in the assay. The cut point was determined by the analysis of eighty drug-naïve (diseased) serum samples. Each sample was analyzed by two analysts on three separate days. This study resulted in a total of 480 inhibition data points from the percent inhibition cut point. These data were analyzed by statistical consultants (b) (4) with this analysis identifying outliers and assessing cutpoints at a 1% confidence (false positive) level, as well as a 0.1 confidence level, as summarized below in Table 5

Table 5 presents a summary of inhibition cut point calculations for a 1% false-positive error rate. Cut point values are also listed in the following table.

False Positive Error Rate	Inhibition Cutpoint (%)	
	Parametric Estimate	Non Parametric Estimate
1%	36	36
0.1%	40	38

The Sponsor is using a cutpoint at the 0.1% false positive level.

Reviewer comments

There is little difference in the actual cuptoint values at the 1% and 0.1% false positive rate (36% vs. 40% inhibition) so there is expected to be little “loss” of Nab positive patients, as well as a corresponding increase in certainty in going to a 0.1% false positive level. Therefore I find the Sponsor’s Nab positive cutpoint to be acceptable.

Sensitivity

Assay sensitivity (LOD) is defined as the minimal concentration of NAb needed to produce a %Inhibition equal to the cut point determined for the assay. Sensitivity was determined for the mouse monoclonal positive control (REGN575) by comparing eight independent observation sets (two independent observations per plate, two plates per analyst, two analysts, over two different days) of eight dilutions for REGN575. Two-fold dilutions of the 20X HQC (REGN575) ranged from 1:4 (1000 ng/mL) to 1:512 (7.8 ng/mL), resulting in a final assay concentration range from 50 ng/mL to 0.39 ng/mL of REGN575. All eight LOD values from each HQC dilution set were used to determine the Mean LOD and ranged from 7.19 ng/mL to 7.97 ng/mL of REGN575. The CV% Counts (ranging from 0% to 11%) for all dilution sets meet the acceptance criteria of less than or equal to 20% for samples with a %Inhibition greater than the cut point (Table 1-below). In the 5% assay matrix, the Mean LOD for REGN575 is 7.50 ng/mL corresponding to a LOD of 150 ng/mL in the neat serum sample.

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Table 1: Sensitivity

		Analyst #1						Analyst #2					
		Ex. 7 Set 1			Ex. 7 Set 2			Ex. 8 Set 1			Ex. 8 Set 2		
REGN575 Dilution	Nominal (ng/mL)	Mean Counts ^a	CV% Counts	%Inhibition	Mean Counts	CV% Counts	%Inhibition	Mean Counts	CV% Counts	%Inhibition	Mean Counts	CV% Counts	%Inhibition
1:4	50.00	514	4	91	514	3	91	479	4	91	467	4	91
1:8	25.00	1093	2	81	1121	2	80	1028	1	80	943	2	82
1:16	12.50	2355	4	58	2469	4	56	2287	2	55	2136	2	58
1:32	6.25	3706	1	35	3755	1	34	3452	0	33	3354	5	34
1:64	3.13	4698	1	17	4810	2	15	4198	1	18	4111	1	20
1:128	1.56	5255	1	7	5133	2	9	4862	0	5	4736	4	7
1:256	0.78	5414	3	5	5456	2	4	5011	1	2	4824	3	6
1:512	0.39	5433	3	4	5582	2	2	5007	3	2	5032	5	2
NQC Mean Counts		5671						5119					
LOD (ng/mL)		7.38			7.65			7.77			7.19		
		Ex. 9 Set 1			Ex. 9 Set 2			Ex. 10 Set 1			Ex. 10 Set 2		
REGN575 Dilution	Nominal (ng/mL)	Mean Counts	CV% Counts	%Inhibition	Mean Counts	CV% Counts	%Inhibition	Mean Counts	CV% Counts	%Inhibition	Mean Counts	CV% Counts	%Inhibition
1:4	50.00	481	3	91	482	2	91	480	2	90	489	1	90
1:8	25.00	983	1	81	1010	1	81	991	1	79	958	1	80
1:16	12.50	2138	3	59	2190	0	58	2221	0	54	2090	5	56
1:32	6.25	3468	5	34	3480	2	34	3219	3	33	3214	2	33
1:64	3.13	4407	1	16	4350	0	17	3897	6	19	3676	11	23
1:128	1.56	4801	2	8	4854	1	7	4173	1	13	4369	2	9
1:256	0.78	4975	1	5	5265	1	0	4272	3	11	4563	2	5
1:512	0.39	4973	2	5	5188	1	1	4532	8	5	4725	2	1
NQC Mean Counts		5243						4787					
LOD (ng/mL)		7.49			7.37			7.97			7.20		
Cut point		40											
Mean LOD (ng/mL) ^b		7.50											
LOD in neat serum (ng/mL)		150											

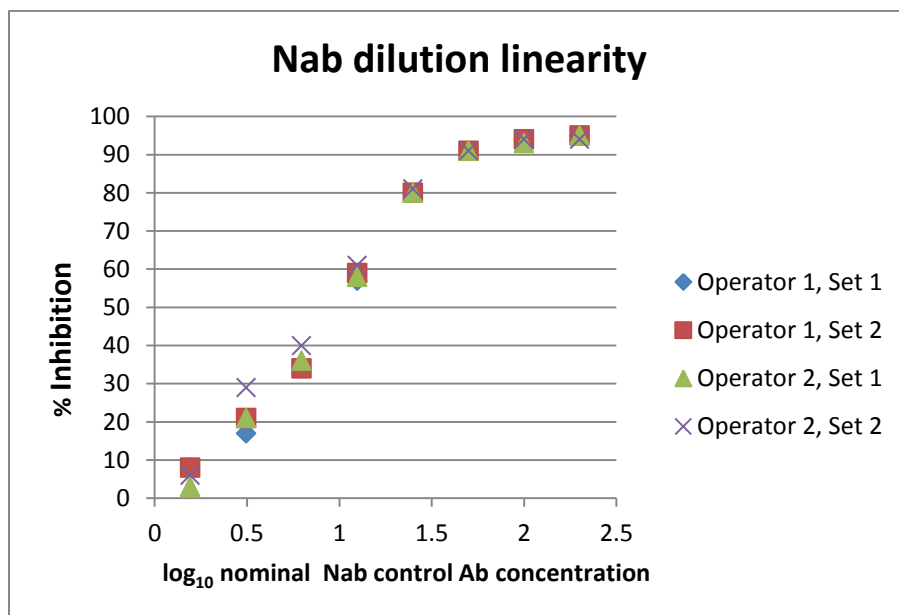
Reviewer comments

Examination of the 8 datasets shows that in every case % inhibition drops below the 40% cutpoint in going from 12.5 ng/ml to 6.25 ng/ml. This is consistent with the Sponsor's calculated sensitivity of 7.5 ng/ml in 5% serum, which translates into 150 ng/ml in undiluted serum. A Nab assay sensitivity of 150 ng/ml is consistent with guidance and well within the ranges seen for the Nab assay for other biologics. Therefore I find the sensitivity of the Nab assay to be appropriately validated and suitable for its intended purpose.

Dilution Linearity

Dilution linearity is defined as the ability (within a given range of concentration) to demonstrate that the signal (%Inhibition) increases with increasing concentrations of the analyte in the sample. Dilution linearity was determined for the mouse monoclonal positive control (REGN575) by comparing four independent observation sets (two independent observations per plate, one plate per analyst, two analysts) of eight dilutions for REGN575. The R₂ values of each dilution set varied between 0.991 and 1, with a Mean R₂ value of 0.997. The CV% Counts for all samples with % Inhibition greater than the cut point ranged from 0% to 9%.

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These data were fitted to a 4-parameter logistic (4-PL) equation; i.e.

$$y = (A-D) / (1+(x/C)^B) + D$$

where A is the y-value corresponding to the bottom asymptote, D is the y-value corresponding to the top asymptote, C is the x-value corresponding to the inflection point or estimated mid-range of the curve, and B is the slope.

Reviewer comments

As seen above, I have graphed the Sponsor's data for % Inhibition vs. Log10 of the nominal REGN575 control antibody concentration, which shows a high degree of reproducibility for the four data sets. I also have analyzed the Sponsor's tabulated dilution data using an online curve fitting resource (www.mycurvefit.com) and found that the R2 values for the four data sets are very high in the range 0.991-0.998, with similar C values for the inflection points (6.53-10.07), well as similar B values for slopes at the inflection points (96.4-98.6). Therefore I find the Nab assay dilutions have a high degree of reproducibility and linearity.

Drug Tolerance Limit (DTL)

The drug tolerance limit (DTL) is defined as the concentration of drug that will reduce the %Inhibition of a sample containing 500 ng/mL of the positive control (REGN575) to the cut point. The DTL of the assay was determined by eight independent observations (two independent observations per plate, two plates per analyst, two analysts, over two different days) of a sample containing the mouse monoclonal positive control (REGN575) at 500 ng/mL, spiked with increasing concentrations of REGN88, ranging from 156 ng/mL to 10000 ng/mL. The %Inhibition for each set of drug-spiked REGN575 samples were plotted against their REGN88 concentrations and the curve was fitted using the 4-PL equation. The DTL was then interpolated from each regression curve at the cut point. The Mean Counts, CV% Counts, and %Inhibition for

each spiked REGN575 sample, NQC Mean Counts, cut point, and DTL. All eight DTL values from each spiked sample set were used to determine the Mean DTL and ranged from 369 ng/mL to 645 ng/mL of REGN88, with a mean of 509 ng/ ml REGN88.

Reviewer comments

I have independently analyzed the Sponsor's % inhibition vs. REGN88 data, again using the 4-PL curve fitting tool from www.mycurvefit.com, where

$$y = (A-D) / (1+(x/C)^B) + D$$

with y=% inhibition and x=REGN88 concentration.

Fits to all eight inhibition data sets were of high quality with R^2 values ≥ 99 . Using the inverse function for 4-PL as

$$x = C*((A-D)/(y-D)-1)^{1/B}$$

with the y value set at the 40% cutpoint, I obtain DTL values in close agreement with those calculated by the Sponsor. Therefore I agree with the Sponsor's determination of the Drug Tolerance Limit.

However, because the Sponsor's antibody sampling plan specifies that samples will be taken immediately before a given REGN88 dosing, or 14 days after the last dose, I asked Dr. Jianmeng Chen, Clinical PharmTox reviewer for this BLA, to provide information on expected serum concentrations of REGN88. In his response 5/16/16, Dr. Chen stated:

"For the 150-mg every two weeks dose regimen, the estimated mean ($\pm$ SD) steady-state Cmin of sarilumab was 6.35 ± 7.54 mg/L, and this should be the concentration at 14 days after last sarilumab administration. For the 200-mg every two weeks dose regimen, the estimated mean ($\pm$ SD) steady-state Cmin of sarilumab was 16.5 ± 14.1 mg/L, and this should be the concentration at 14 days after last sarilumab administration. After the last steady state dose of 150 mg and 200 mg sarilumab, the median times to non-detectable concentration are 28 and 43 days, respectively".

These serum concentrations convert to a range of 6.63-16.5 μ g/ ml, well above the Sponsor's validated 509 ng/ ml REGN88 DTL. Therefore the Sponsor should modify the Nab assay so as to obtain accurate data patient sera with the expected ranges of on-board REGN88.

Precision

Inter-plate precision was assessed by examining the variability of NAb-negative and Nab positive results from four independent LQCs and NQCs, respectively, run on each of eight plates, by two analysts. Intra-plate precision was assessed by examining the variability of QC samples (prepared in bulk) added across ten wells of a single microplate. The intra-plate precision data is summarized in following section of Table 6.

Sample	Statistical Profile					
	Mean Counts	Stdev Counts	CV% Counts	Mean %Inhibition	Stdev %Inhibition	CV% of %Inhibition
HQC	343	9	3	93	0	0
MQC	1452	44	3	70	1	1
LQC	2717	147	5	44	3	7
NQC	4894	190	4	0	N/A ^b	N/A
SNQC	4742	209	4	3	N/A	N/A

Reviewer comments

The Sponsor's data in Table 4 for Inter-Plate Precision data shows a good degree of precision, with % inhibition for 32 LGC determinations ranging from 40-54%, with a mean of 49% and an 8% CV. For 32 NQC determinations the % inhibition ranges from 7% to -11%, with a mean of -3% inhibition, and a 6% CV. The Intraplate Precision data, as expected, shows a higher degree of reproducibility, with the SDs for all the controls being less than 5% of the raw counts. Therefore, the Sponsor has demonstrated the ability to perform the assay within limited variability within a plate and between runs, and the variability observed is unlikely to affect the analysis of patient serum samples.

Recovery

Recovery is defined as the specific detection of the analyte in the presence of known and unknown matrix components. To evaluate matrix interference, two sets of individual human serum samples (serum from RF+ individuals and serum from individuals with high low-density lipoprotein (LDL) level (>130 mg/dL)) were identified and tested with and without 2mg/mL hemoglobin and/or 200 ng/mL Nab control antibody REGN575.

Reviewer comments

Adding hemoglobin to the samples produced only modest changes in inhibition values; i.e. samples alone without Hb gave 17% mean inhibition vs. 22.9% mean inhibition, in both cases well below the 40% inhibition cutpoint. Similarly, samples + 200 ng/ ml REGN575 control antibody gave 55.7% mean inhibition without Hb, and 58.9% inhibition with Hb, with all samples well above the 40% cutpoint.

For 5 male and 5 female high LDL samples alone gave a mean inhibition of 17% inhibition (well below the 40% cutpoint and similar to the RF+, REGN88 naïve sample discussed above), while samples with +200 ng/ ml REGN575 gave a mean inhibition of 54.3%, well above the 40% cutpoint and similar to the values seen above for the Hb matrix effect study.

Therefore, I agree that the Sponsor has shown little or no matrix effect resulting from the common expected confounders of RBC lysis (hemoglobin) or high LDL samples.

Analyte Stability

Analyte stability was determined by the effect of accelerated stress conditions and long-term and short-term storage of QCs on assay performance. The stability of the positive control (mouse anti-REGN88 monoclonal antibody; REGN575) in human serum was examined by exposing at different dilutions (HQC, MQC, LQC) as well as the negative control (NQC) and the negative control spiked with anti-IL6R α control antibody (SNQC) to either ten freeze-thaw cycles, room temperature storage for at least four hours (4 hours and 32 minutes), or storage in a 4°C refrigerator overnight (23 hours and 20 minutes).

Reviewer comments

I have examined the Sponsor's tabulated analyte stability data in Tables 9-11, and find that the Nab assay inhibition produced by the QCs is essentially unchanged under any of the storage or freeze thaw conditions. Thus stability for the QCs is adequately validated.

Robustness

Robustness is a measure of the capacity of an analytical method to remain unaffected by deliberate variations in method parameters. Robustness was assessed by comparing independent sets of QCs on two different lots of avidin-coated plates (Plate Lots A and B) using two different lots of non-critical reagents (Reagent Lots A and B). The non-critical reagents that were composed in each of these Reagent lots A or B were 5% BSA Blocking Buffer, 1.5 M Trizma Base, and 4X Read Buffer.

Table 13: Robustness – Plate Lots

Sample	Nominal (ng/mL)	Reagents Lot A					
		Plate Lot A					
		Ex. 15A QC Set 1			Ex. 15A QC Set 2		
		Mean Counts ^a	CV% Counts	%Inhibition	Mean Counts	CV% Counts	%Inhibition
HQC	200	310	1	95	315	4	94
MQC	20	1251	1	78	1334	2	77
LQC	10	2729	2	52	2670	0	53
NQC	0	5684	2	0	5592	2	2
SNQC	0	5199	1	9	5408	0	5
NQC Mean Counts		5684					
Sample	Nominal (ng/mL)	Plate Lot B					
		Ex. 15B QC Set 1			Ex. 15B QC Set 2		
		Mean Counts	CV% Counts	%Inhibition	Mean Counts	CV% Counts	%Inhibition
		Mean Counts	CV% Counts	%Inhibition	Mean Counts	CV% Counts	%Inhibition
HQC	200	329	1	95	341	3	94
MQC	20	1245	2	79	1354	1	78
LQC	10	2747	1	55	2820	0	54
NQC	0	6066	2	0	6054	1	0
SNQC	0	5705	2	6	5869	0	3
NQC Mean Counts		6066					
Cut point		40					

Reviewer comments

The Sponsor's data provided in Table 13 shows very little difference between different sets of QCs or lots of assay plates, both of which would be expected to be critical for assay performance. These data indicate that within the range of changes explored, samples can be assayed with different QCs and plates without an effect on results.

Ruggedness

Ruggedness is defined as the degree of reproducibility of test results obtained by the analysis of samples by two analysts. It was assessed by analyzing four independent sets of QCs (two observations per plate, one plate per analyst, two analysts).

Table 14: Ruggedness

		Analyst #1					
		Ex. 9 Set 1			Ex. 9 Set 2		
Sample	Nominal (ng/mL)	Mean Counts ^a	CV% Counts	%Inhibition	Mean Counts	CV% Counts	%Inhibition
HQC	200	297	1	94	301	5	94
MQC	20	1268	2	76	1273	4	76
LQC	10	2658	4	49	2537	5	52
NQC	0	5243	1	0	5278	7	-1
SNQC	0	5036	2	4	4744	1	10
NQC Mean Counts		5243					
		Analyst #2					
		Ex. 10 Set 1			Ex. 10 Set 2		
Sample	Nominal (ng/mL)	Mean Counts	CV% Counts	%Inhibition	Mean Counts	CV% Counts	%Inhibition
HQC	200	267	6	94	274	3	94
MQC	20	1185	4	75	1161	4	76
LQC	10	2357	14	51	2387	3	50
NQC	0	4787	3	0	4984	2	-4
SNQC	0	4634	5	3	4887	4	-2
NQC Mean Counts		4787					
Cut point		40					

Reviewer comments

The Sponsor's ruggedness data provided in Table 14 shows very little difference between analysts sets of QCs, providing assurance that the QC inhibition in the Nab assay is not analyst-dependent.

Taken together the Stability, Robustness and Ruggedness data support the expectation that the Nab assay will perform consistently across a long life cycle of use.

APPEARS THIS WAY ON ORIGINAL



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
WO Bldg. 51, 10903 New Hampshire Ave.
Silver Spring, MD 20993

Date: October 13, 2016
To: Administrative File, STN 761037/0
From: Laura Fontan, Consumer Safety Officer, CDER/OPQ/OPF/DIA
Endorsement: Peter Qiu, Ph.D., Branch Chief, CDER/OPQ/OPF/DIA
Subject: New Biologic License Application (BLA)
US License: 1752
Applicant: Sanofi-Aventis U.S. LLC
Mfg Facility: Drug Substance: Regeneron Pharmaceuticals, Rensselaer, NY (FEI 1000514603)
Drug Product: Sanofi Winthrop Industrie, LeTrait, France (FEI 3003259844)
Product: (b) (4) (sarilumumab, SAR153191)
Dosage: Sterile solution supplied in a pre-filled syringe, 150 and 200 mg (b) (4).
Indication: Treatment for adult patients with moderately to severe active rheumatoid arthritis.
Due Date: October 30, 2016

Recommendation: This submission is recommended for withhold of approval from a facility review perspective due to significant deficiencies found at the drug product manufacturing site Sanofi Winthrop Industrie, LeTrait, France (FEI #2977302488) during the last inspection completed 7/19/2016. All other proposed manufacturing and testing sites are found to be acceptable from a facilities assessment standpoint.

SUMMARY

The subject BLA proposes manufacture of Sarilumab Drug Substance and Drug Product at the following facilities.

Regeneron Pharmaceuticals in Rensselaer, NY (FEI #1000514603) is responsible for DS manufacturing and in-process, release, and stability testing of the DS. Regeneron also performs testing (b) (4) for adventitious viral contaminants by a (b) (4) at their 26 Tech Valley Drive facility in East Greenbush NY (also FEI #1000514603). A PLI was conducted on 2/1/2016 to 2/5/2016. No FDA 483 observations were issued with a final recommendation of NAI. The facility is currently in compliance.

The manufacturing of the bulk pre-filled syringe, analytical testing of bulk pre-filled syringe (b) (4) for release testing for Sarilumab DP is performed at Sanofi Winthrop Industrie,

LeTrait, France (FEI #2977302488). The last inspection conducted (b) (4) covered the production and filling of (b) (4) NON RESPONSIVE, formulation and fill of (b) (4) NON RESPONSIVE, and filling of (b) (4) NON RESPONSIVE. At the conclusion of the inspection, a 13 item FDA 483, was issued. The initial recommendation as a result of the observations is OAI for refusals and significant GMP deficiencies.

Sanofi-Aventis U.S. LLC (1000117606) performs secondary packaging, and release for distribution of the DP, and is found to be acceptable. All other facilities performing testing on DS and DP are currently in acceptable compliance status. The facility descriptions submitted in this BLA have been reviewed and found to be adequate to support the manufacture of sarilumab Drug Substance and Drug Product.

ASSESSMENT

DRUG SUBSTANCE

3.2.S.2.1 Manufacturers

The proposed sarilumab DS manufacturing, storage, release testing, and stability testing sites are listed below in Table 1.

Table 1. Sarilumab Drug Substance Facilities.

Site Name	Address	FEI	Responsibilities
Regeneron Pharmaceuticals	• 81 Columbia Turnpike Rensselaer, NY 12144 • 26 TechValley Drive, East Greenbush, NY 12061	1000514603	Manufacturing and (b) (4), release, and stability testing of DS. (b) (4) testing for adventitious viral contaminants (b) (4) (b) (4)

Review comment: The facilities for the manufacturing, storage, release testing, and stability testing for the sarilumab drug substance are adequately described.

—Satisfactory—

Facility Inspection:

Prior Inspection History



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
WO Bldg 22
10903 New Hampshire Ave.
Silver Spring, MD 20993

Date: May 10, 2016
To: Administrative File, STN 761037
From: Candace Gomez-Broughton, Ph.D., Microbiologist CDER/OPQ/OPF/DMA BIV
Endorsed: Reyes Candau-Chacon, Ph.D. Acting Quality Assessment Lead
CDER/OPQ/OPF/DMA BIV
Subject: Original Biologics License Application
US License: 1752
Applicant: Sanofi-Aventis U.S., LLC
Facility: Regeneron Pharmaceuticals, Inc. Rensselaer, NY
FEI #: 1000514603
Product: KEVZARA® (sarilumab)
Dosage: Solution for subcutaneous injection (150 mg and 200 mg)
Indication: Treatment of adult patients with moderately to severely active rheumatoid arthritis
Due date: October 30, 2016

Recommendation for Approvability: The drug substance section of the BLA, as amended, is recommended for approval from a microbiology product quality perspective.

Review Summary

KEVZARA® (sarilumab, REGN88) is a recombinant human antibody (IgG1 isotype) that binds to soluble and membrane bound IL-6 receptors, and has also been shown to inhibit IL-6 mediated signaling through these receptors. Sarilumab is indicated for treatment of adult patients with moderately to severely active rheumatoid arthritis (RA). Sarilumab is produced by Chinese hamster ovary (CHO) cells engineered to express sarilumab heavy and light chains in culture. Sarilumab drug substance is manufactured at Regeneron Pharmaceuticals in Rensselaer, New York.

This BLA was submitted in eCTD format. This assessment covers the drug substance (b) (4) sections of the application. The drug product section of the BLA was reviewed by Lakshmi Narasimhan, Ph.D. and discussed in a separate document. The original submission and amendments are reviewed here.

Assessment

S DRUG SUBSTANCE

S.1 General Information

S.6 Container Closure System

(b) (4)

. Data on leachables and biological reactivity should be reviewed by OBP/DTP.

Conclusion

- I. The BLA, as amended, is recommended for approval from a CMC microbiology product quality perspective.
- II. CMC product specific information and data should be reviewed by the OBP reviewer.
- III. No follow-up inspection issues were identified.

Candace Y. Gomez-
broughton -A

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broughton -A
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=2000640207,
cn=Candace Y. Gomez-broughton -A
Date: 2016.09.13 12:39:32 -04'00'



Reyes
Candau-Chacon

Digitally signed by Reyes Candau-Chacon
Date: 9/14/2016 11:17:14AM
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Food and Drug Administration
Center for Drug Evaluation and Research
10903 New Hampshire Avenue,
Building 22,
Silver Spring, MD 20993

Date: September 9, 2016
To: Administrative File, BLA761037/0
From: Lakshmi Rani Narasimhan, Ph.D., CDER/OPQ/OPF/DMA
Endorsement: Patricia F. Hughes, Ph.D., Acting Branch Chief, CDER/OPQ/OPF/DMA
Subject: Biological License Application (BLA) Review memo
US License: #1752
Applicant: Sanofi-aventis U.S. LLC.
Facility: Sanofi Winthrop Le Trait, Boulevard Industriel 76580 Le Trait, France (FEI # 3003259844) - Pre-filled syringe (PFS)
Product: Kevzara® (Sarilumab)
Dosage: Sterile, preservative-free liquid formulation in a single-use PFS for subcutaneous injection in dose strengths of 150 mg and 200 mg.
Indication: For the treatment of adult patients with moderately to severely active rheumatoid arthritis
Due Date: October 30, 2016.

Recommendation for Approvability: The drug product section of this BLA, as amended, is recommended for approval from a product quality microbiology and sterility assurance perspective.

SUMMARY:

Sanofi-aventis U.S. LLC submitted a new biologics license application, BLA 761037 to license Sarilumab for the treatment of adult patients with moderately to severely active rheumatoid arthritis. Drug substance is manufactured by Regeneron Pharmaceuticals, Inc., and drug product in pre-filled syringe is manufactured at Sanofi Winthrop, Le Trait, France.

The submission was submitted in eCTD format and included Module 1.1.2-FDA form 356h, Module 1.2-Cover letter, and Module 2 and 3. Module 3 includes appendices and a regional section (3.2.R). Letter of authorization (LOA) for (b) (4) Type III DMF (b) (4) to review the (b) (4), and LOAs for (b) (4) Type V DMF (b) (4) to review (b) (4) used for (b) (4) and (b) (4) Type V DMF (b) (4) to review the (b) (4) were provided.

INTRODUCTION

Sarilumab drug product (DP) is manufactured (b) (4) from sarilumab drug substance (DS) at Sanofi Winthrop, Le Trait, France. This review covers the evaluation of the drug product aspects of the application from a product quality microbiology perspective.

Drug Product Quality Microbiology Information Reviewed

Sequence number	Date	Description
0000	October 30, 2015	Original
0002	December 14, 2015	Response to quality micro IR
0012	March 15, 2016	Response to quality micro IR
0018	May 04, 2016	Response to quality micro IR
0019	May 26, 2016	Response to quality micro IR
0033	August 10, 2016	Response to quality micro IR
0036	August 23, 2016	Response to quality micro IR
0038	September 02, 2016	Response to quality micro IR
0039	September 08, 2016	Response to quality micro IR

ASSESSMENTS:**3.2.P DRUG PRODUCT****Solution for Injection in Prefilled Syringe, 150 mg and/or 200 mg****3.2.P.1 Description and Composition of the Drug Product- Pre-Filled Syringe**

The drug product (DP) presented in a prefilled syringe (PFS) is a sterile, clear, and colorless to pale yellow solution, pH 6.0 for subcutaneous injection. DP is supplied in two strengths, 131.6 mg/mL and 175 mg/mL providing doses of 150 mg and 200 mg, respectively. (b) (4)

(b) (4) (Table 1). The finger flange and product label are color coded for differentiating the two dose strengths.

Table 1: Summary of the PFS Components and Presentations for the 150 mg and 200 mg Dose Forms

(b) (4)

Satisfactory



Lakshmi Rani
Narasimhan

Digitally signed by Lakshmi Rani Narasimhan
Date: 9/14/2016 11:03:47AM
GUID: 508da7160002976791592556d218b997



Patricia
Hughes Troost

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Date: 9/14/2016 11:20:14AM
GUID: 508da717000297bcbfce0919f8c09594
Comments: signed off.



OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

OFFICE of BIOTECHNOLOGY PRODUCTS

Application BLA
761037

Submission Type: 351(a)

Established/Proper Name:

SAR 153191, sarilumab

Applicant: Sanofi

Letter Date: 10/30/15

OND Office: DPARP

Chemical Type:
Biologic

Stamp Date: 10/30/15

Strength: 150 mg & 200 mg

Original BLA

A. FILING CONCLUSION				
	Parameter	Yes	No	Comment
1.	DOES THE OFFICE OF PHARMACEUTICAL QUALITY RECOMMEND THE APPLICATION TO BE FILED?	☒	☐	This BLA can be Filed. Any comments in the sections below specifying the need for additional information do not represent filing issues
2.	If the application is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.			
3.	Are there any potential review issues to be forwarded to the Applicant, not including any filing comments stated above?	☐	☐	

B. NOTEWORTHY ELEMENTS OF THE APPLICATION		Yes	No	Comment
Product Type				
1.	New Molecular Entity ¹	☒	☐	
2.	Botanical ¹	☐	☒	
3.	Naturally-derived Product	☐	☒	
4.	Narrow Therapeutic Index Drug	☐	☒	
5.	PET Drug	☐	☒	
6.	PEPFAR Drug	☐	☒	
7.	Sterile Drug Product	☒	☐	
8.	Transdermal ¹	☐	☒	
9.	Pediatric form/dose ¹	☐	☒	
10.	Locally acting drug ¹	☐	☒	
11.	Lyophilized product ¹	☐	☒	
12.	First generic ¹	☐	☒	
13.	Solid dispersion product ¹	☐	☒	
14.	Oral disintegrating tablet ¹	☐	☒	
15.	Modified release product ¹	☐	☒	

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B. NOTEWORTHY ELEMENTS OF THE APPLICATION		Yes	No	Comment
16.	Liposome product ¹	☐	☒	
17.	Biosimilar product ¹	☐	☒	
18.	Combination Product _____	☐	☒	
19.	Other _____	☒	☐	Humanized monoclonal antibody
Regulatory Considerations				
20.	USAN Name Assigned	☒	☐	sarilumab
21.	End of Phase II/Pre-NDA Agreements	☐	☒	
22.	SPOTS (Special Products On-line Tracking System)	☐	☒	
23.	Citizen Petition and/or Controlled Correspondence Linked to the Application	☐	☒	
24.	Comparability Protocol(s) ²	☐	☒	
25.	Other _____	☐	☒	
Quality Considerations				
26.	Drug Substance Overage	☐	☒	
27.	Design Space	Formulation	☐	☒
28.		Process	☐	☒
29.		Analytical Methods	☐	☒
30.		Other	☐	☒
31.	Real Time Release Testing (RTRT)	☐	☒	
32.	Parametric Release in lieu of Sterility Testing	☐	☒	
33.	Alternative Microbiological Test Methods	☐	☒	
34.	Process Analytical Technology ¹	☐	☒	
35.	Non-compendial Analytical Procedures and/or specifications	Drug Product	☐	☒
36.		Excipients	☐	☒
37.		Microbial	☐	☒
38.	Unique analytical methodology ¹	☐	☒	
39.	Excipients of Human or Animal Origin	☐	☒	
40.	Novel Excipients	☐	☒	
41.	Nanomaterials ¹	☐	☒	
42.	Hold Times Exceeding 30 Days	☐	☒	
43.	Genotoxic Impurities or Structural Alerts	☐	☒	
44.	Continuous Manufacturing	☐	☒	
45.	Other unique manufacturing process ¹	☐	☒	
46.	Use of Models for Release (IVIVC, dissolution models for real time release).	☐	☒	
47.	New delivery system or dosage form ¹	☐	☒	
48.	Novel BE study designs	☐	☒	
49.	New product design ¹	☐	☒	
50.	Other _____	☐	☒	

¹Contact Office of Testing and Research for review team considerations

²Contact Post Marketing Assessment staff for review team considerations

C. FILING CONSIDERATIONS				
Parameter	Yes	No	N/A	Comment
GENERAL/ADMINISTRATIVE				

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

OFFICE of BIOTECHNOLOGY PRODUCTS

C. FILING CONSIDERATIONS					
1.	Has an environmental assessment report or categorical exclusion been provided?	☒	☐	☐	
2.	Is the Quality Overall Summary (QOS) organized adequately and legible? Is there sufficient information in the following sections to conduct a review? ☐ Drug Substance ☐ Drug Product ☐ Appendices ☐ Facilities and Equipment ☐ Adventitious Agents Safety Evaluation ☐ Novel Excipients ☐ Regional Information ☐ Executed Batch Records ☐ Method Validation Package ☐ Comparability Protocols	☒	☐	☐	
FACILITY INFORMATION					
3.	Are drug substance manufacturing sites, drug product manufacturing sites, and additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet? For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? For each site, does the application list: ☐ Name of facility, ☐ Full address of facility including street, city, state, country ☐ FEI number for facility (if previously registered with FDA) ☐ Full name and title, telephone, fax number and email for on-site contact person. ☐ Is the manufacturing responsibility and function identified for each facility, and ☐ DMF number (if applicable)	☒	☐	☐	
4.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission? For BLA: ☐ Is a manufacturing schedule provided? ☐ Is the schedule feasible to conduct an inspection within the review cycle?	☒	☐	☐	
DRUG SUBSTANCE INFORMATION					
5.	For DMF review, are DMF # identified and authorization letter(s), included US Agent Letter of	☒	☐	☐	4 DMF authorization letters are included for container closure system

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OFFICE of BIOTECHNOLOGY PRODUCTS

C. FILING CONSIDERATIONS					
	Authorization provided?				components, as specified on the 356h form.
6.	Is the Drug Substance section [3.2.S] organized adequately and legible? Is there sufficient information in the following sections to conduct a review? ☐ general information ☐ manufacture ○ Includes production data on drug substance manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es) ○ Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots – BLA only ○ Includes complete description of product lots and their uses during development – BLA only ☐ characterization of drug substance ☐ control of drug substance ○ Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred) ○ Includes data to demonstrate process consistency (i.e. data on process validation lots) – BLA only ☐ reference standards or materials ☐ container closure system ☐ stability ○ Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment	☒	☐	☐	
DRUG PRODUCT INFORMATION					
7.	Is the Drug Product section [3.2.P] organized adequately and legible? Is there sufficient information in the following sections to conduct a review? ☐ Description and Composition of the Drug Product ☐ Pharmaceutical Development ○ Includes descriptions of changes in the manufacturing process from material used	☒	☐	☐	

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OFFICE of BIOTECHNOLOGY PRODUCTS

C. FILING CONSIDERATIONS					
	in clinical to commercial production lots ○ Includes complete description of product lots and their uses during development ☐ Manufacture ○ If sterile, are sterilization validation studies submitted? For aseptic processes, are bacterial challenge studies submitted to support the proposed filter? ☐ Control of Excipients ☐ Control of Drug Product ○ Includes production data on drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es) ○ Includes data to demonstrate process consistency (i.e. data on process validation lots) ○ Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred) ○ Analytical validation package for release test procedures, including dissolution ☐ Reference Standards or Materials ☐ Container Closure System ○ Include data outlined in container closure guidance document ☐ Stability ○ Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment ☐ APPENDICES ☐ REGIONAL INFORMATION				
BIOPHARMACEUTICS					
8.	If the Biopharmaceutics team is responsible for reviewing the in vivo BA or BE studies: • Does the application contain the complete BA/BE data? • Are the PK files in the correct format? • Is an inspection request needed for the BE study(ies) and complete clinical site information provided?	☐	☐	☒	
9.	Are there adequate in vitro and/or in vivo data supporting the bridging of formulations throughout	☒	☐	☐	Adequate comparability has been demonstrated throughout product

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C. FILING CONSIDERATIONS					
	the drug product's development and/or manufacturing changes to the clinical product? (Note whether the to-be-marketed product is the same product used in the pivotal clinical studies)				development. Commercial material is same as used in phase III clinical trials.
10.	Does the application include a biowaiver request? If yes, are supportive data provided as per the type of waiver requested under the CFR to support the requested waiver? Note the CFR section cited.	☐	☐	☒	
11.	For a modified release dosage form, does the application include information/data on the in-vitro alcohol dose-dumping potential?	☐	☐	☒	
12.	For an extended release dosage form, is there enough information to assess the extended release designation claim as per the CFR?	☐	☐	☒	
13.	Is there a claim or request for BCS I designation? If yes, is there sufficient permeability, solubility, stability, and dissolution data?	☐	☐	☒	
REGIONAL INFORMATION AND APPENDICES					
14.	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?	☐	☒	☐	
15.	Are Executed Batch Records for drug substance (if applicable) and drug product available?	☒	☐	☐	
16.	Are the following information available in the Appendices for Biotech Products [3.2.A]? ☐ facilities and equipment ○ manufacturing flow; adjacent areas ○ other products in facility ○ equipment dedication, preparation, sterilization and storage ○ procedures and design features to prevent contamination and cross-contamination ☐ adventitious agents safety evaluation (viral and non-viral) e.g.: ○ avoidance and control procedures ○ cell line qualification ○ other materials of biological origin ○ viral testing of unprocessed bulk ○ viral clearance studies ○ testing at appropriate stages of production ☐ novel excipients	☒	☐	☐	
17.	Are the following information available for Biotech Products: ☐ Compliance to 21 CFR 610.9: If not using a test method or process specified by regulation, data are provided to show the alternate is equivalent to that specified by regulation. For example: ○ LAL instead of rabbit pyrogen	☒	☐	☐	

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C. FILING CONSIDERATIONS				
	○ Mycoplasma Compliance to 21 CFR 601.2(a): Identification by lot number and submission upon request, of sample(s) representative of the product to be marketed with summaries of test results for those samples			

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

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OFFICE OF PHARMACEUTICAL QUALITY JOINT FILING REVIEW

Filing reviews were performed by:

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**Michele
Dougherty -S**



Digitally signed by Michele Dougherty -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA,
ou=People, 0.9.2342.19200300.100.1.1=0010556865,
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ATL for BLA 761037

Review Chief, Division of Biotechnology Review and Research IV, Office of Biotechnology Products,
OPQ/CDER/FDA