CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125496Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 125496/0 Supplement Number: _____ NDA Supplement Type (e.g. SE5): ____

Division Name: Division of Hematology Products PDUFA Goal Date: 4/30/2014 Stamp Date: 8/30/2013

Proprietary Name: SYLVANT

Established/Generic Name: siltuximab

Dosage Form: lyophilized powder in a single-use vial

Applicant/Sponsor: Janssen Biotech, Inc.

Indication(s) *previously approved* (please complete this question for supplements and Type 6 NDAs only):
(1) _____
(2) _____
(3) _____
(4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1
(Attach a completed Pediatric Page for each indication in current application.)

Indication: SYLVANT is indicated for the treatment of patients with multicentric Castleman's disease (MCD) who are human immunodeficiency virus (HIV)-negative and human herpesvirus-8 (HHV-8)-negative.

Q1: Is this application in response to a PREA PMR? Yes ☐ Continue
No ☒ Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #:_____ PMR #:_____

Does the division agree that this is a complete response to the PMR?

☐ Yes. Please proceed to Section D.

☐ No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW ☒ active ingredient(s) (includes new combination); ☒ indication(s); ☒ dosage form; ☒ dosing regimen; or ☒ route of administration?*

(b) ☐ No. PREA does not apply. **Skip to signature block.**

**** Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.***

Q3: Does this indication have orphan designation?

☒ Yes. PREA does not apply. **Skip to signature block.**

☐ No. Please proceed to the next question.

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmhs@fda hhs.gov) OR AT 301-796-0700.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

- ☐ Yes: (Complete Section A.)
- ☐ No: Please check all that apply:
  - ☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)
  - ☐ Deferred for some or all pediatric subpopulations (Complete Sections C)
  - ☐ Completed for some or all pediatric subpopulations (Complete Sections D)
  - ☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
  - ☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

  (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____
- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible#	Not meaningful therapeutic benefit*	Ineffective or unsafe†	Formulation failed∆
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____

***** Not meaningful therapeutic benefit:

- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

∆ Formulation failed:

- ☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4)

additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification †**
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____						

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as

pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:					
Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

_____

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

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

/s/

PATRICIA N GARVEY
03/17/2014

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

BLA # 125496	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: **SYLVANT** Established/Proper Name: **siltuximab** Dosage Form: **lyophilized powder in single-use vial**		Applicant: **Janssen Biotech, Inc.** Agent for Applicant: **Janssen Research & Development, LLC**
RPM: **Patricia Garvey, RPh**		Division: **Division of Hematology Products**

NDA Application Type: ☐ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

BLA Application Type: ☐ 351(k) ☒ 351(a)
Efficacy Supplement: ☐ 351(k) ☐ 351(a)

For ALL 505(b)(2) applications, two months prior to EVERY action:

- **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

☐ No changes
☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check:

Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is April 30, 2014	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain	☐ Received

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.
[2] For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

❖ Application Characteristics [3]	
Review priority: ☐ Standard ☒ Priority Chemical classification (new NDAs only): N/A ***(confirm chemical classification at time of approval)*** ☐ Fast Track ☐ Rolling Review ☒ Orphan drug designation ☐ Breakthrough Therapy designation ☐ Rx-to-OTC full switch ☐ Rx-to-OTC partial switch ☐ Direct-to-OTC NDAs: Subpart H ☐ Accelerated approval (21 CFR 314.510) ☐ Restricted distribution (21 CFR 314.520) Subpart I ☐ Approval based on animal studies BLAs: Subpart E ☐ Accelerated approval (21 CFR 601.41) ☐ Restricted distribution (21 CFR 601.42) Subpart H ☐ Approval based on animal studies ☐ Submitted in response to a PMR ☐ Submitted in response to a PMC ☐ Submitted in response to a Pediatric Written Request REMS: ☐ MedGuide ☐ Communication Plan ☐ ETASU ☐ MedGuide w/o REMS ☒ REMS not required Comments:	
❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☒ Yes, **04/23/2014**
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☒ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Indicate what types (if any) of information were issued	☐ None ☒ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☒ Other – OHOP Burst
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☐ Verified ☐ Not applicable because drug is an old antibiotic.

[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Reference ID: 3494828

CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	**Approval 4/23/2014**
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☐ Included
• Original applicant-proposed labeling	☒ Included **8/29/2013**
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☒ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☐ Included
• Original applicant-proposed labeling	☒ Included **8/29/2013**
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☒ Included **8/29/2013**
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	**Acceptability letter 11/8/2013** **Review 11/5/2013**
❖ Labeling reviews *(indicate dates of reviews)*	**RPM: 10/29/2013** **DMEPA: 11/6/2013** **DMPP/PLT: 3/12/2014** **OPDP: 1/24/2014** SEALD: None CSS: None **Other: OBP 4/11/2014**
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)* ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Committee	**RPM Filing Review (including Memo of Filing Meeting) 10/29/2013** ☒ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☐ Included

[4] Filing reviews for scientific disciplines should be filed with the respective discipline.

Reference ID: 3494828

❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP ○ If yes, Center Director's Exception for Review memo *(indicate date)* ○ If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC **N/A** If PeRC review not necessary, explain: **orphan drug designation**	**Pediatric Page 3/17/2014**
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters) *(do not include previous action letters, as these are located elsewhere in package)*	**4/22/2014; 4/15/2014; 4/10/2014; 4/2/2014; 4/1/2014; 3/28/2014; 3/21/2014; 3/20/2014 (2); 3/19/2014; 3/17/2014; 3/14/2014; 3/11/2014; 3/6/2014; 3/3/2014; 2/27/2014; 2/21/2014; 2/18/2014; 2/14/2014; 2/7/2014; 2/4/2014; 1/29/2014; 1/27/2014; 1/17/2014 (2); 1/7/2014; 12/20/2013; 12/11/2013; 12/6/2013 (2); 12/3/2013; 11/14/2013; 10/29/2013; 10/21/2013; 10/9/2013; 10/8/2013; 9/24/2013; 9/18/2013; 9/12/2013; 9/11/2013**
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	**4/8/2014 and 3/20/2014**
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A
• Pre-NDA/BLA meeting *(indicate date of mtg)*	**12/18/2012**
• EOP2 meeting *(indicate date of mtg)*	
• Mid-cycle Communication *(indicate date of mtg)*	**12/13/2013**
• Late-cycle Meeting *(indicate date of mtg)*	**2/25/2014**
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	**4/23/2014**
Division Director Summary Review *(indicate date for each review)*	**4/23/2014**
Cross-Discipline Team Leader Review *(indicate date for each review)*	**4/3/2014**
PMR/PMC Development Templates *(indicate total number)*	**4**

Reference ID: 3494828

Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	**2/26/2014 and 2/3/2014**
• Clinical Review(s) *(indicate date for each review)*	**Review 1/29/2014** **Filing Checklist 10/22/2013**
• Social Scientist Review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	**See 1/29/2014 Clinical Review – page 16**
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	**SEALD Review 2/6/2014**
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ N/A
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	**Review 1/30/2014**
❖ OSI Clinical Inspection Review Summary(ies) (include copies of OSI letters to investigators)	**Review 3/7/2014** **Letter 5/21/2013**
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ No separate review **Co-signed 1/22/2014 review**
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review **Co-signed 1/22/2014 review**
Statistical Review(s) *(indicate date for each review)*	**Review 1/22/2014** **Filing Checklist 10/22/2013**
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review **Co-signed 2/5/2014 review**
Clinical Pharmacology review(s) *(indicate date for each review)*	**Review 2/5/2014 (includes Pharmacometrics Review)** **IRT-QT Review 12/6/2013** **Filing & Review Form 10/26/2013**
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None requested

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Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	**3/4/2014**
• Supervisory Review(s) *(indicate date for each review)*	**1/24/2014**
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	**Reviews 3/4/2014 and 1/23/2014** **Filing Checklist 10/16/2013**
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☒ No separate review **Co-signed 4/11/2014 TL review**
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	**4/11/2014**
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	**Review 4/11/2014** **Filing Review 10/22/2013**
❖ Microbiology Reviews ☐ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☒ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) *(indicate date of each review)*	**Drug Substance Review** **3/18/2014 and 2/10/2014** **Drug Product Review** **4/7/2014 and 2/3/2014** **Filing Review 10/28/2013**
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	**See 2/10/2014 Microbiology Drug Substance review, page 34** **See 2/3/2014 Microbiology Drug Product review, page 35**
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	

Reference ID: 3494828

❖ Facilities Review/Inspection	
☐ NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report; date completed must be within **2 years** of action date) *(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[5])*	Date completed: ☐ Acceptable ☐ Withhold recommendation ☒ Not applicable
☒ BLAs: TB-EER (date of most recent TB-EER must be within **30 days** of action date) *(original and supplemental BLAs)*	Date completed: **4/23/2014** ☒ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☐ Completed ☐ Requested ☐ Not yet requested ☐ Not needed (per review)
Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☐ No changes ☐ New patent/exclusivity *(Notify CDER OND IO)*
• Finalize 505(b)(2) assessment	☐ Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☒ Done
❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* section of DARRTS, and that the proprietary name is identified as the "preferred" name	☒ Done
❖ Ensure Pediatric Record is accurate	☒ Done
❖ Send approval email within one business day to CDER-APPROVALS	☒ Done

[5] i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Reference ID: 3494828

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/s/

PATRICIA N GARVEY
04/23/2014

Garvey, Patricia

From: Garvey, Patricia
Sent: Tuesday, April 22, 2014 8:26 PM
To: Maloney, Brian [JRDUS]
Cc: Rothschild, Melanie [JRDUS]
Subject: BLA 125496 siltuximab - FDA Agreed Upon USPI 4/22/2014
Attachments: Siltuximab JBI proposed USPI 03252014_FDA Agreed with minor change CLEAN 04-22-2014.doc

Dear Brian,

Please refer to your Biologics License Application (BLA) 125496 SYLVANT (siltuximab) submitted under section 351(a) of the Public Health Service Act (PHS Act).

We also refer your email communication on April 22, 2014 regarding editorial changes to the Indications and Usage section under Highlights and the FPI. The following corrections have been made.

Highlights

SYLVANT is an interleukin-6 (IL-6) antagonist indicated for the treatment of patients with multicentric Castleman's disease (MCD) who are human immunodeficiency virus (HIV-)-negative and human herpes virus -8 (HHV-8) -negative. (1)

Limitation of Use
SYLVANT was not studied in patients with MCD who are HIV - positive or HHV-8 - positive because SYLVANT did not bind to virally produced IL-6 in a nonclinical study.

> **Change to**: SYLVANT is an interleukin-6 (IL-6) antagonist indicated for the treatment of adult patients with multicentric Castleman's disease (MCD) who are human immunodeficiency virus (HIV) negative and human herpesvirus-8 (HHV-8) negative.
>
> Limitation of Use
> SYLVANT was not studied in patients with MCD who are HIV positive or HHV-8 positive because SYLVANT did not bind to virally produced IL-6 in a nonclinical study.

FPI

SYLVANT is indicated for the treatment of patients with multicentric Castleman's disease (MCD) who are human immunodeficiency virus (HIV-)-negative and human herpes virus -8 (HHV-8) -negative.

Limitation of Use
SYLVANT was not studied in patients with MCD who are HIV - positive or HHV-8 - postive because SYLVANT did not bind to virally produced IL-6 in a nonclinical study.

> **Change to:** SYLVANT is indicated for the treatment of adult patients with multicentric Castleman's disease (MCD) who are human immunodeficiency virus (HIV) negative and human herpesvirus-8 (HHV-8) negative.
>
> Limitation of Use
> SYLVANT was not studied in patients with MCD who are HIV positive or HHV-8 positive because SYLVANT did not bind to virally produced IL-6 in a nonclinical study.

Reference ID: 3493975

The attached clean copy of the revised USPI is now considered the FDA agreed upon USPI, therefore please confirm that edits are correct.

Please contact me if you have any questions.

Kind Regards,
Patty

Patty Garvey, R.Ph.
CAPT, U.S. Public Health Service
Senior Regulatory Project Manager
Division of Hematology Products | Office of Hematology and Oncology Products
Center for Drug Evaluation and Research | Food and Drug Administration
10903 New Hampshire Avenue, WO22 - Room 2329
Silver Spring, MD 20993
Phone: 301-796-8493 | Fax: 301-796-9849 | ✉ patricia.garvey@fda.hhs.gov

---

From: Maloney, Brian [JRDUS] [mailto:BMalone1@ITS.JNJ.COM]
Sent: Tuesday, April 22, 2014 9:41 AM
To: Garvey, Patricia
Cc: Rothschild, Melanie [JRDUS]
Subject: RE: BLA 125496 siltuximab - FDA Agreed Upon USPI

Hi Patty,

We checked with an editor and determined the following to be the correct reference to the phrases. Note that this also affects the "Limitation of Use" section as well.

The correct text is as noted below, no hyphen after the "(HIV)" inside the bracket, no hyphens before the text "negative", "herpesvirus" is one word:
"SYLVANT is indicated for the treatment of adult patients with multicentric Castleman's disease (MCD) who are human immunodeficiency virus (HIV) negative and human herpesvirus-8 (HHV-8) negative."

Similarly we should delete hyphens before the text "positive" under "Limitations of Use" both in the Highlights and FPI as shown highlighted in red.
"Limitation of Use
SYLVANT was not studied in patients with MCD who are HIV - positive or HHV-8 - positive because SYLVANT did not bind to virally produced IL-6 in a nonclinical study."

So the text should read
"Limitation of Use
SYLVANT was not studied in patients with MCD who are HIV positive or HHV-8 positive because SYLVANT did not bind to virally produced IL-6 in a nonclinical study."

Let me know if you have any questions or concerns
Kind regards
Brian

From: Garvey, Patricia [mailto:Patricia.Garvey@fda.hhs.gov]
Sent: Tuesday, April 22, 2014 7:15 AM
To: Maloney, Brian [JRDUS]
Cc: Rothschild, Melanie [JRDUS]
Subject: FW: BLA 125496 siltuximab - FDA Agreed Upon USPI
Importance: High

Reference ID: 3493975

Hello Brian,

The Highlight Indications and Usage vs FPI Indications and Usage have a minor differences – see yellow highlighted text.

Highlight
SYLVANT is an interleukin-6 (IL-6) antagonist indicated for the treatment of patients with multicentric Castleman's disease (MCD) who are human immunodeficiency virus (HIV-)-negative and human herpes virus -8 (HHV-8) -negative. (1)

FPI
SYLVANT is indicated for the treatment of patients with multicentric Castleman's disease (MCD) who are human immunodeficiency virus (HIV)-negative and human herpesvirus-8 (HHV-8)-negative.

Please let me know if this should be corrected ASAP.

Best,
Patty

Patty Garvey, R.Ph.
CAPT, U.S. Public Health Service
Senior Regulatory Project Manager
Division of Hematology Products | Office of Hematology and Oncology Products
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10903 New Hampshire Avenue, WO22 - Room 2329
Silver Spring, MD 20993
Phone: 301-796-8493 | Fax: 301-796-9849 | ✉ patricia.garvey@fda.hhs.gov

---

From: Garvey, Patricia
Sent: Tuesday, April 15, 2014 11:21 AM
To: 'Maloney, Brian [JRDUS]'
Cc: 'Rothschild, Melanie [JRDUS]'
Subject: BLA 125496 siltuximab - FDA Agreed Upon USPI

Dear Brian,

Please refer to your Biologics License Application (BLA) 125496 SYLVANT (siltuximab) submitted under section 351(a) of the Public Health Service Act (PHS Act).

We also refer your communication on April 14, 2014, stating that there is a typo in the USPI Section 8.6 Patients with Renal Impairment and Table 5. The following corrections have been made.

1. Section 8.6 - abbreviating CLcr corrected to CLCr
2. Table 5 – Heading "P-value" corrected to "p-value[a]"

The attached clean copy of the revised USPI is now considered the FDA agreed upon USPI.

Reference ID: 3493975

Please contact me if you have any questions.

Kind Regards,
Patty

Patty Garvey, R.Ph.
CAPT, U.S. Public Health Service
Senior Regulatory Project Manager
Division of Hematology Products | Office of Hematology and Oncology Products
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Reference ID: 3493975

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/s/

PATRICIA N GARVEY
04/22/2014

MEMORANDUM OF TELECONFERENCE

Teleconference Date: April 8, 2014

Application Number: BLA 125496
Product Name: SYLVANT (siltuximab)
Applicant Name: Janssen Biotech, Inc.

Subject: OBP CMC PMCs

FDA Participants
Chana Fuchs, PhD – Team Leader, Division of Monoclonal Antibodies (DMA), Office of Biotechnology Products (OBP)
Bazarragchaa Damdinsuren, MD, PhD – Product Quality Reviewer, DMA, OBP
Audrey Jia, MD, PhD – Product Quality Reviewer, DMA, OBP
Patricia Garvey, RPh – Sr. Regulatory Project Manager, Division of Hematology Products, Office of Hematology and Oncology Products

Applicant Participants
Tom Hogan, PhD - Scientific Director, CMC Regulatory Affairs
Milad Khan, MS – Manager, Regulatory Affairs
Manny Lopez – Scientific Director, Portfolio Management
Brian Maloney, RPh, MS – Director, Regulatory Affairs
Willemijn Neher-van Minnen – Associate Director, Regulatory Affairs
Melanie Rothschild – Manager, Regulatory Affairs

1.0 BACKGROUND:

On April 1, 2014, FDA provided OBP PMCs to the Applicant. On April 3, 2014, the Applicant provided a response to the PMCs. The purpose of this teleconference was to discuss the Applicant's response to the PMCs.

2.0 DISCUSSION:

PMC #1 and #2: FDA requested clarification regarding the Applicant's rewording of the PMC to ensure that both FDA and Janssen understand the same thing. The Applicant identified their manufacturing forecast (b) (4) batches will be manufactured) and the intent t (b) (4) after approval. FDA clarified that the request is for the reanalysis to be done once a total of 30 lots manufactured by commercial manufacturing process are available. This includes those lots already manufactured and in the BLA.

PMC #3: For the re-evaluate siltuximab formulated bulk lot (FB) release and stability specifications, FDA stated that this is the same consideration as discussed for PMC # 1 and 2.

PMC#4: FDA linked discussion of this PMC with the discussion regarding the controls for (b) (4) (PMC #10). FDA noted that siltuximab generated from different phases (b) (4) have different quality attributes such as (b) (4) For PMC #4, FDA crafted the original wording and number of lots as it did specifically because it was noted that a footnote to the updated table on (b) (4) release specifications identified that the Applicant will discontinue testing charge profile by cIEF after 30 batches of (b) (4) are released. Since measurement of the (b) (4) occurs at the (b) (4) and acceptance criterion is set relatively wide (see PMC #10), (b) (4) (b) (4) FDA does not understand how the Applicant's control strategy would ensure that (b) (4) derived from the (b) (4) would result in products that still represent the validated state throughout the product lifecycle. The wording originally proposed by FDA would allow a reassessment of the cIEF control strategy prior to Janssen's proposed change in testing. The Applicant concurred with the concern and proposed to continue the cIEF testing for (b) (4) release.

PMC#7: FDA clarified that our wording of the PMC is correct and intended for requalification of (b) (4) The Applicant acknowledged FDA's clarification, and agreed to update the PMC.

PMC#10: FDA reiterated that the (b) (4) limit for (b) (4) at FB (b) (4) is set very wide based on the limited data available. The intent of this PMC was to assess the control strategy action limit once data from additional lots are available to enable a more robust analysis of this action limit. The Applicant agreed to re-evaluate the (b) (4) limit after sufficient numbers of FB are generated.

PMCs #11-14: FDA verified with the Applicant that until completion of validation of the manufacturing process parameters covered in these PMCs, sponsor will market only FLP lots manufactured using the validated process parameters of the lyophilization. The Applicant confirmed that the manufacturing will be executed only at (b) (4) until the validations of the ranges specified in the PMC are completed.

Other issue: FDA notified the Applicant that the current control strategy for stability of FLP lots released at (b) (4) by cIEF is only valid for a 24 months shelf life, and would not support a longer shelf-life. Therefore, the annual stability protocol for the FLP cannot be approved for the purpose of extending the expiration dating period under 21 CFR 601.12. Extension of expiration dating for the FLP with supporting data and control strategy will have to be conducted under Prior Approval Supplement.

3.0 ACTION ITEM:

The Applicant will submit the revised PMCs by April 10, 2014.

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/s/

PATRICIA N GARVEY
04/15/2014

Garvey, Patricia

From: Garvey, Patricia
Sent: Tuesday, April 15, 2014 11:21 AM
To: 'Maloney, Brian [JRDUS]'
Cc: 'Rothschild, Melanie [JRDUS]'
Subject: BLA 125496 siltuximab - FDA Agreed Upon USPI
Attachments: Siltuximab JBI proposed USPI 03252014_FDA Agreed with minor change CLEAN 04-15-2014.pdf

Dear Brian,

Please refer to your Biologics License Application (BLA) 125496 SYLVANT (siltuximab) submitted under section 351(a) of the Public Health Service Act (PHS Act).

We also refer your communication on April 14, 2014, stating that there is a typo in the USPI Section 8.6 Patients with Renal Impairment and Table 5. The following corrections have been made.

1. Section 8.6 - abbreviating CLcr corrected to CLCr
2. Table 5 – Heading "P-value" corrected to "p-value[a]"

The attached clean copy of the revised USPI is now considered the FDA agreed upon USPI.

Please contact me if you have any questions.

Kind Regards,
Patty

Patty Garvey, R.Ph.
CAPT, U.S. Public Health Service
Senior Regulatory Project Manager
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Reference ID: 3489780

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/s/

PATRICIA N GARVEY
04/15/2014

Garvey, Patricia

From: Garvey, Patricia
Sent: Thursday, April 10, 2014 6:22 PM
To: 'Maloney, Brian [JRDUS]'
Cc: 'Rothschild, Melanie [JRDUS]'
Subject: RE: BLA 125496 siltuximab - FDA Agreed Upon USPI and PPI
Attachments: Siltuximab JBI proposed USPI 03252014_FDA Agreed with minor change 04-10-2014.doc

Dear Brian,

Please refer to your Biologics License Application (BLA) 125496 SYLVANT (siltuximab) submitted under section 351(a) of the Public Health Service Act (PHS Act).

We also refer to your email correspondence dated April 9, 2014, which stated that there is a typo in the USPI Table 3 heading.

We have corrected the Table 3 heading and made two additional changes – delete comma in Long Term Exposure information paragraph and added a comma after Janssen Biotech at the end of the USPI. The attached revised USPI is now considered the FDA agreed upon USPI.

Please contact me if you have any questions.

Kind Regards,
Patty

Patty Garvey, R.Ph.
CAPT, U.S. Public Health Service
Senior Regulatory Project Manager
Division of Hematology Products | Office of Hematology and Oncology Products
Center for Drug Evaluation and Research | Food and Drug Administration
10903 New Hampshire Avenue, WO22 - Room 2329
Silver Spring, MD 20993
Phone: 301-796-8493 | Fax: 301-796-9849 | ✉ patricia.garvey@fda.hhs.gov

---

From: Maloney, Brian [JRDUS] [mailto:BMalone1@ITS.JNJ.COM]
Sent: Wednesday, April 09, 2014 8:13 AM
To: Garvey, Patricia
Cc: Rothschild, Melanie [JRDUS]
Subject: RE: BLA 125496 siltuximab - FDA Agreed Upon USPI and PPI

Hi Patty,

Our labeling group was performing a QC of the label and noticed a minor typo in Table 3 of the USPI. In the yellow highlight below, it should be “N=26”. Is this something we can/should fix now or should we change after an action? Not sure if you can make the change on your end and we will accept it on our end as final labeling.

Happy to discuss if needed.
Kind regards
Brian

Reference ID: 3487832

	SYLVANT+BSC[a] N=53		Placebo+BSC N+26	
	All Grades	Grades 3-4	All Grades	Grades 3-4
Skin disorders				
Rash (rash, rash generalized, rash maculo-papular, rash popular and rash pruritic)	15 (28%)	1 (2%)	3 (12%)	0

From: Garvey, Patricia [mailto:Patricia.Garvey@fda.hhs.gov]
Sent: Friday, March 28, 2014 4:06 PM
To: Maloney, Brian [JRDUS]
Cc: Rothschild, Melanie [JRDUS]
Subject: BLA 125496 siltuximab - FDA Agreed Upon USPI and PPI

Dear Brian,

Please refer to your Biologics License Application (BLA) 125496 SYLVANT (siltuximab) submitted under section 351(a) of the Public Health Service Act (PHS Act). We also refer to your submissions dated March 24 and 25, 2014, containing revisions to proposed patient package insert (PPI) and package insert (USPI) respectively.

We have completed the review of the Patient Package Insert (PPI) and have accepted the revisions. In addition, we added a comma in the second sentence of "Infusion and allergic reactions" paragraph and moved the issued date at the end of the PPI to a separate line.

We have also completed the review of the USPI and have accepted the revisions. In addition, we added a period to the end of Section 17 Contraception sentence.

In our discussion on March 27, 2014, you agreed to these revisions, therefore the FDA agreed upon USPI and PPI in tracked changes are attached.

Please contact me if you have any questions.

Kind Regards,
Patty

Patty Garvey, R.Ph.
CAPT, U.S. Public Health Service
Senior Regulatory Project Manager
Division of Hematology Products | Office of Hematology and Oncology Products
Center for Drug Evaluation and Research | Food and Drug Administration
10903 New Hampshire Avenue, WO22 - Room 2329
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Phone: 301-796-8493 | Fax: 301-796-9849 | patricia.garvey@fda.hhs.gov

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Reference ID: 3487832

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/s/

PATRICIA N GARVEY
04/10/2014

Garvey, Patricia

From: Garvey, Patricia
Sent: Tuesday, April 01, 2014 7:04 PM
To: Maloney, Brian [JRDUS] (BMalone1@ITS.JNJ.COM)
Cc: Rothschild, Melanie [JRDUS] (MRothsch@ITS.JNJ.COM)
Subject: BLA 125496 siltuximab - FDA Product Quality PMCs

Dear Brian,

Please refer to your Biologics License Application (BLA) 125496 SYLVANT (siltuximab) submitted under section 351(a) of the Public Health Service Act (PHS Act).

We have determined following are post-marketing commitments based on the data available to date. The brief description of the necessary study is intended to describe the main objective and study characteristics of interest. Please provide edits and comments in clarifying mutually acceptable description of the key study elements. For the yellow highlight "MM/YYYY", please provide a date. For a yellow highlight with an actual month/year (i.e. December 2014), please provide agreement. If you disagree with the date, please provide a proposed date.

Note – these are not all the commitments that were made in the BLA. The following are a subset of commitments that require data to be submitted within a specific timeline.

1. Description: To re-evaluate siltuximab 100 mg/vial final lyophilized product lot release and stability specifications after (b) (4) lots have been manufactured using the commercial manufacturing process. The corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be submitted by MM/YYYY.

2. Description: To re-evaluate siltuximab 400 mg/vial final lyophilized product lot release and stability specifications after (b) (4) lots have been manufactured using the commercial manufacturing process. The corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be submitted by MM/YYYY.

3. Description: To re-evaluate siltuximab formulated bulk lot release and stability specifications after (b) (4) lots have been manufactured using the commercial manufacturing process. The corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be submitted by MM/YYYY.

4. Description: To re-evaluate siltuximab (b) (4) intermediate lot release and stability specifications for lots manufactured using the commercial manufacturing process, once cIEF data from (b) (4) (b) (4) lots are available. The SE-HPLC data from all lots manufactured using the commercial manufacturing process should be included in this evaluation. The corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be submitted by MM/YYYY.

5. Description: To confirm the anticipated amount of (b) (4) using a validated reduced scale model. Results of the study will be submitted by December 2014.

Reference ID: 3481872

6. Description: To confirm the anticipated amount of [redacted] (b) (4) using a validated reduced scale model [redacted] (b) (4) The results of this study will be submitted by December 2014.

7. Description: To tighten the [redacted] (b) (4) reference material requalification acceptance criteria of [redacted] (b) (4) for potency. This analysis will be based on appropriate statistical evaluation and a sufficient amount of datapoints required for such an evaluation. The updated acceptance criterion and supporting data will be submitted as a CBE0 by MM/YYYY.

8. Description: To implement specific siltuximab master cell bank (MCB) and working cell bank (WCB) stability programs. The protocols (SOP) for the MCB and WCB stability programs and supporting data for the protocols will be submitted as a CBE0 by August 2014.

9. Description: To establish a control strategy for the [redacted] (b) (4) The updated control strategy and supporting data will be submitted as a CBE0 in August 2014.

10. Description: To develop and submit a control strategy for monitoring and trending of the [redacted] (b) (4) The control strategy will be submitted as a CBE0 by MM/YYYY.

11. Description: To provide confirmatory data by executing manufacturing run of the 100 mg/vial FLP batch at [redacted] (b) (4) The drug product from this run will be placed on a stability protocol. The study report, release and stability data will be submitted in Annual Reports.
    Study Completion Date: MM/YYYY
    Final Report Submission Date: MM/YYYY

12. Description: To provide confirmatory data by executing manufacturing run of the 400 mg/vial FLP batch at [redacted] (b) (4). The drug product from this run will be placed on a stability protocol. The study report, release and stability data will be submitted in Annual Reports.
    Study Completion Date: MM/YYYY
    Final Report Submission Date: MM/YYYY

13. Description: To provide confirmatory data by executing a manufacturing run of the 100 mg/vial FLP batch at [redacted] (b) (4) The drug product from this run will be placed on a stability protocol. The study report, release and stability data will be submitted in Annual Reports.
    Study Completion Date: MM/YYYY
    Final Report Submission Date: MM/YYYY

14. Description: To provide confirmatory data by executing a manufacturing run of the 400 mg/vial FLP batch at [redacted] (b) (4) The drug product from this run will be placed on a stability protocol. The study report, release and stability data will be submitted in Annual Reports.
    Study Completion Date: MM/YYYY
    Final Report Submission Date: MM/YYYY

Reference ID: 3481872

Upon mutual agreement on the PMC description and timeline, we ask you to submit both by email and officially a copy of the PMC with a statement that you agree to PMC as described and within the timelines that you specify. Note that milestone dates only need month and year. Final PMR/PMC designation numbers will be assigned later.

Please provide a response by COB, Thursday, April 3, 2014. Please contact me if you have any questions.

Kind Regards,
Patty

Patty Garvey, R.Ph.
CAPT, U.S. Public Health Service
Senior Regulatory Project Manager
Division of Hematology Products | Office of Hematology and Oncology Products
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Reference ID: 3481872

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/s/

PATRICIA N GARVEY
04/02/2014

Garvey, Patricia

From: Garvey, Patricia
Sent: Wednesday, April 02, 2014 7:26 AM
To: 'Maloney, Brian [JRDUS] (BMalone1@ITS.JNJ.COM)'
Cc: 'Rothschild, Melanie [JRDUS] (MRothsch@ITS.JNJ.COM)'
Subject: BLA 125496 siltuximab - FDA Agreed Upon Carton and Immediate Container Labels

Good Morning Brian,

Please refer to your Biologics License Application (BLA) 125496 SYLVANT (siltuximab) submitted under section 351(a) of the Public Health Service Act (PHS Act). We also refer to your submission dated March 7, 2014, containing revisions to the proposed carton and immediate container labels.

We have completed the review of the carton and immediate container labels and have accepted the revisions. The FDA agreed upon carton and immediate container labels are attached.

Please contact me if you have any questions.

Kind Regards,
Patty

Carton and Container l ....

Patty Garvey, R.Ph.
CAPT, U.S. Public Health Service
Senior Regulatory Project Manager
Division of Hematology Products | Office of Hematology and Oncology Products
Center for Drug Evaluation and Research | Food and Drug Administration
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Phone: 301-796-8493 | Fax: 301-796-9849 | patricia.garvey@fda.hhs.gov

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Reference ID: 3481913

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/s/

PATRICIA N GARVEY
04/02/2014

Garvey, Patricia

From: Garvey, Patricia
Sent: Friday, March 28, 2014 4:06 PM
To: 'Maloney, Brian [JRDUS] (BMalone1@ITS.JNJ.COM)'
Cc: 'Rothschild, Melanie [JRDUS] (MRothsch@ITS.JNJ.COM)'
Subject: BLA 125496 siltuximab - FDA Agreed Upon USPI and PPI

Dear Brian,

Please refer to your Biologics License Application (BLA) 125496 SYLVANT (siltuximab) submitted under section 351(a) of the Public Health Service Act (PHS Act). We also refer to your submissions dated March 24 and 25, 2014, containing revisions to proposed patient package insert (PPI) and package insert (USPI) respectively.

We have completed the review of the Patient Package Insert (PPI) and have accepted the revisions. In addition, we added a comma in the second sentence of **"Infusion** and allergic **reactions"** paragraph and moved the issued date at the end of the PPI to a separate line.

We have also completed the review of the USPI and have accepted the revisions. In addition, we added a period to the end of Section 17 Contraception sentence.

In our discussion on March 27, 2014, you agreed to these revisions, therefore the FDA agreed upon USPI and PPI in tracked changes are attached.

Please contact me if you have any questions.

Kind Regards,
Patty

Patty Garvey, R.Ph.
CAPT, U.S. Public Health Service
Senior Regulatory Project Manager
Division of Hematology Products | Office of Hematology and Oncology Products
Center for Drug Evaluation and Research | Food and Drug Administration
10903 New Hampshire Avenue, WO22 - Room 2329
Silver Spring, MD 20993
Phone: 301-796-8493 | Fax: 301-796-9849 | patricia.garvey@fda.hhs.gov

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/s/

PATRICIA N GARVEY
04/03/2014
Email to Applicant on March 28, 2014

Garvey, Patricia

From: Garvey, Patricia
Sent: Friday, March 21, 2014 7:16 PM
To: 'Rothschild, Melanie [JRDUS] (MRothsch@ITS.JNJ.COM)'
Cc: 'Maloney, Brian [JRDUS] (BMalone1@ITS.JNJ.COM)'; Hennessey, Lyndsay; 'Islam, Naushad [JRDUS] (NIslam@ITS.JNJ.COM)'
Subject: RE: BLA 125496 siltuximab - BMAB information request

Please note that this info request is from the Office Biotechnology Products product quality team not BMAB as written in the subject line.

Patty Garvey, R.Ph.
CAPT, U.S. Public Health Service
Senior Regulatory Project Manager
Division of Hematology Products | Office of Hematology and Oncology Products
Center for Drug Evaluation and Research | Food and Drug Administration
10903 New Hampshire Avenue, WO22 - Room 2329
Silver Spring, MD 20993
Phone: 301-796-8493 | Fax: 301-796-9849 | patricia.garvey@fda.hhs.gov

---

From: Garvey, Patricia
Sent: Friday, March 21, 2014 7:15 PM
To: Rothschild, Melanie [JRDUS] (MRothsch@ITS.JNJ.COM)
Cc: 'Maloney, Brian [JRDUS] (BMalone1@ITS.JNJ.COM)'; Hennessey, Lyndsay; Islam, Naushad [JRDUS] (NIslam@ITS.JNJ.COM)
Subject: RE: BLA 125496 siltuximab - BMAB information request

Dear Melanie,

Please refer to your Biologics License Application (BLA) submitted under section 351 of the Public Health Service Act for BLA 125496 SYLVANT (siltuximab).

We have following product quality information request:

1. We note in your response to question iii.1 that Janssen is proposing to reevaluate the proposed drug product concentration stability limits following execution of additional FLP batches. As discussed in the late-cycle meeting on February 25, 2014, as Janssen implements a tighter [redacted] (b) (4) process control for the production of the new drug substance batches, the specification for concentration of the subsequent drug product batches manufactured, both for release and for stability, should be within target range of [redacted] (b) (4) mg/mL.

2. Submit to the BLA the protocol DS-TMD-4091 which is to be used for Particulate Matter [redacted] (b) (4)) testing for siltuximab 400 mg/vial FLP at release and stability.

3. The [redacted] (b) (4) time ranges of [redacted] (b) (4) for lyophilization process parameters, respectively for 100 mg/ vial FLP and for 400 mg/vial FLP as currently

Reference ID: 3475638

identified in Tables 2 of section 3.2.P.3.3, appear outside of the validated (b) (4) rates. These (b) (4) time ranges appear to apply to the (b) (4). Update the BLA with the corrected Tables or provide an explanation if this is the intended process.

4. From 3.2.S.2.6 Manufacturing Process Development- (b) (4) it is noted that (b) (4) This parameter was not included as one of PARs in 3.2.S.2.2 at the relevant stage of the manufacturing process. Update to include this PAR in section 3.2.S.2.2.

5. In the concurrent validation of (b) (4) Table 1 in 3.2.S.2.5 Manufacturing Scale Protocol, (b) (4) listed the tests to be performed for the verification study. HCP was not included in the test performed to verify the lifetime of the (b) (4) even though this is one of the main steps that are used (b) (4). Include (b) (4) with acceptance criteria in your concurrent verification study protocol for (b) (4)

6. In the concurrent validation of (b) (4), Table 1 in 3.2.S.2.5 Manufacturing Scale Protocol, (b) (4) listed the tests to be performed for the verification study.

   a.

   b.

   (b) (4)

7. It is noted that you commit to place one FB batch for each of the (b) (4) on stability per the non-annual stability protocol. In the Information Request response submitted on March 7, 2014, the post-approval non-annual stability protocol for FB was removed from the BLA submission. Identify the protocol that will be used to monitor the stability of the reprocessed FB batches, including the testing schedule and specifications.

8. In the updated requalification acceptance criteria for (b) (4) shown in 3.2.S.5 Table 1, the acceptance criteria for cSDS (reduced), cIEF and DW-SE-HPLC include “report results.” In Janssen’s response to FDA’s item 18b from 17 Jan 2014, Janssen identified that quantitative acceptance criteria for DW SE-HPLC (b) (4) These acceptance criteria are not reflected in the updated requalification protocol submitted. Additionally, “report results”

Reference ID: 3475638

does not provide sufficient control of requalification of RM. Provide quantitative acceptance criteria for these quality attributes.

9. In response Q1c submitted on February 21, 2014, Janssen identifies that polysorbate 80 (b) (4) This is not acceptable. PS80 is a critical excipient that (b) (4) should be controlled for each lot manufactured. Revise your control strategy to incorporate this as part of lot release testing

We request a response by **March 26, 2014, 4:00 PM (EDT)** in order to continue our evaluation of your BLA.

Please contact me if you have any questions.

Kind Regards,
Patty

Patty Garvey, R.Ph.
CAPT, U.S. Public Health Service
Senior Regulatory Project Manager
Division of Hematology Products | Office of Hematology and Oncology Products
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Phone: 301-796-8493 | Fax: 301-796-9849 | ✉ patricia.garvey@fda.hhs.gov

Reference ID: 3475638

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/s/

PATRICIA N GARVEY
03/21/2014

Garvey, Patricia

From: Garvey, Patricia
Sent: Thursday, March 20, 2014 5:47 PM
To: Rothschild, Melanie [JRDUS] (MRothsch@ITS.JNJ.COM)
Cc: Maloney, Brian [JRDUS] (BMalone1@ITS.JNJ.COM)
Subject: BLA 125496 siltuximab - FDA proposed PPI

Dear Melanie,

Please refer to your Biologics License Application (BLA) 125496 SYLVANT (siltuximab) submitted under section 351(a) of the Public Health Service Act (PHS Act). We also refer to your email correspondence dated March 20, 2014, which contains a revision to Table 3 in the USPI and revisions to the Patient Package Insert (PPI).

Please review and provide revisions/comments to the attached FDA proposed PPI. Using the same draft, please provide your comments in the following manner:
· Where you agree with the labeling revisions, "accept" the tracked changes.
· Where you disagree with the labeling revisions, provide your comments and proposed language (shown in tracked changes). If necessary, edit but do not "reject" the FDA-proposed changes.

We will get back with you regarding the percentage of thrombocytopenia revision in Table 3 in the USPI. Please provide a response to FDA proposed PPI by COB, Monday, March 24th, 2014.

Please contact me if you have any questions.

Kind Regards,
Patty

Siltuximab PPI 03-20 ....

Patty Garvey, R.Ph.
CAPT, U.S. Public Health Service
Senior Regulatory Project Manager
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Center for Drug Evaluation and Research | Food and Drug Administration
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2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Reference ID: 3474807

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/s/

PATRICIA N GARVEY
03/20/2014

Garvey, Patricia

From: Garvey, Patricia
Sent: Thursday, March 20, 2014 2:49 PM
To: Rothschild, Melanie [JRDUS] (MRothsch@ITS.JNJ.COM)
Cc: Maloney, Brian [JRDUS] (BMalone1@ITS.JNJ.COM)
Subject: BLA 125496 siltuximab - FDA Clinical PMR

Dear Melanie,

Please refer to your Biologics License Application (BLA) 125496 SYLVANT (siltuximab) submitted under section 351(1) of the Public Health Service Act (PHS Act).

We have determined that the following clinical trial is necessary as post-marketing requirements (PMRs) based on the data available to date. The brief description of the necessary study/trial is intended to describe the main objective and trial characteristics of interest. Please provide edits and comments in clarifying mutually acceptable description of the key trial elements. For any new studies/trials, submit the protocol for FDA review and concurrence prior to initiating. Note that the "Final Protocol Submission" date is the date by which you HAVE submitted a complete protocol AND have already received full concurrence by the Division, that the protocol is considered acceptable to address the PMR/PMC.

PMC #1 Description: Complete the trial and submit the final study report of CNTO328MCD2002 "An Open-label, Multicenter Study to Evaluate the Safety of Long-term Treatment with Siltuximab in Subjects with Multicentric Castleman's Disease."

PMR Schedule Milestones:	Final Protocol Submission:	completed
	Trial Completion:	03/31/2017
	Final Report Submission:	08/31/2017

Upon mutual agreement on the PMR description and timeline, we ask you to submit both by email and officially a copy of the PMR studies/trials to us with a statement that you agree to perform the trials as described and within the timelines that you specify for the trial. Note that milestone dates only need month and year. For milestone calculation purposes only, assume that an approval occurs on the PDUFA date. Final PMR designation numbers will be assigned later.

Please note that we will have additional PMCs from the Office of Biotechnology Product Quality team. Please provide a response by COB, Monday, March 24, 2014. Please contact me if you have any questions.

Kind Regards,
Patty

Patty Garvey, R.Ph.
CAPT, U.S. Public Health Service
Senior Regulatory Project Manager
Division of Hematology Products | Office of Hematology and Oncology Products
Center for Drug Evaluation and Research | Food and Drug Administration
10903 New Hampshire Avenue, WO22 - Room 2329
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Phone: 301-796-8493 | Fax: 301-796-9849 | patricia.garvey@fda.hhs.gov

Reference ID: 3474601

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/s/

PATRICIA N GARVEY
03/20/2014

MEMORANDUM OF TELECONFERENCE

Teleconference Date: March 20, 2014

Application Number: BLA 125496
Product Name: SYLVANT (siltuximab)
Applicant Name: Janssen Biotech, Inc.

Subject: OBP CMC Stability

FDA Participants
Chana Fuchs, PhD – Team Leader, Division of Monoclonal Antibodies (DMA), Office of Biotechnology Products (OBP)
Bazarragchaa Damdinsuren, MD, PhD – Product Quality Reviewer, DMA, OBP
Audrey Jia, MD, PhD – Product Quality Reviewer, DMA, OBP
Lyndsay Hennessey – Regulatory Health Project Manager, OBP
Patricia Garvey, RPh – Sr. Regulatory Project Manager, Division of Hematology Products, Office of Hematology and Oncology Products

Applicant Participants
Debra Daly – Nonclinical, Sr. Scientist, Tech Support
Kundan Doshi, PhD – Associate Director, Global Labeling
Mary Guilfoyle, MS – Compound Development Team Leader
Naushad Islam, RPh, MS – Director, Global Regulatory Leader
Milad Khan, MPh, MS – Manager, Regulatory Affairs
Brian Maloney, RPh, MS – Director Regulatory Affairs
Pauline Martin, PhD – Sr. Scientific Director, Toxicology
Tom Puchalski, PharmD – Scientific Director, Pharmacokinetics
Melanie Rothschild, MBA - Manager, Regulatory Affairs

1.0 BACKGROUND:

Based on the degradation patterns/rates seen for some individual lots, e.g. lots ACS3H02, BBS0N01 and BCS2U02 for the 100 mg lots, and lots CIS1302 and CIS3Q00 for the 400 mg lots (though the few time points for this presentation may impact the data), it is not clear that lots released around the release acceptance criterion of (b) (4) by cIEF would not fail stability at the proposed expiration timelines.

OBP would like the applicant to discuss and address this issue to make sure OBP and the applicant are all seeing the same data, specifically because the applicant did sufficiently address this point.

2.0 DISCUSSION:

a. FDA presented the observation of significant downward trending (b) (4) by cIEF in several of the 100 mg/vial FLP batches, including batch ACS3H0, BBS0N01, and

BCS2U02, that were released at around [redacted] (b) (4) and questioned whether lots released close to the release acceptance criterion of [redacted] (b) (4) would not fail stability at the proposed expiration timelines. In the post-approval situation, with only a single lot placed on stability, such lots would not be monitored so one would not know that they had failed to meet the stability specification.

The Applicant agreed with the observation, and stated that other lots showed a much more shallow downward trend. The Applicant understood FDA's concern and suggested implementing control with alert investigation/action limit at release and stability monitoring, if the limit is reached. FDA agreed that some paradigm of an action limit with placement of the lots on stability may be acceptable, and asked the sponsor to submit a robust and comprehensive proposal of the control strategy. The Applicant proposed that this will be submitted early next week.

b. FDA stated that the applicant's proposal submitted on March 7, 2014 (response to question iii.1) appears to be for reevaluation of the proposed drug product concentration stability limits rather than implementing the [redacted] (b) (4) mg/mL acceptance criteria on stability. FDA understood from the discussion in the late-cycle meeting on February 25, 2014 that Janssen will implement a tighter [redacted] (b) (4) process control for the manufacturing of the new drug substance batches starting in August, and that the stability limits for concentration of the new drug product batches manufactured will be set at [redacted] (b) (4) mg/mL. FDA identified that the proposed stability limit submitted is not acceptable and that the acceptance criteria will have to be set at [redacted] (b) (4) mg/mL. This will also be communicated in the next information request.

c. Janssen provided an update on the status of the commitment to provide additional information on the control strategy for oxidation of siltuximab. They have repeated the photostability study for [redacted] (b) (4) siltuximab (item 2c in the Late-Cycle Meeting minutes) at different timelines and data support the single photostability conditions in the IND. The Applicant will submit the study results earlier than March 31, 2014.

3.0 ACTION ITEMS:

Action Item/Description	Owner	Due Date
Information request that stability limit acceptance criteria will have to be set at [redacted] (b) (4) mg/mL.	FDA	March 21, 2014
Proposed control strategy	Applicant	March 24-28, 2014
[redacted] (b) (4) study results	Applicant	March 31, 2014

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/s/

PATRICIA N GARVEY
04/15/2014

Garvey, Patricia

From: Garvey, Patricia
Sent: Wednesday, March 19, 2014 1:14 PM
To: 'Rothschild, Melanie [JRDUS]'
Cc: Maloney, Brian [JRDUS]
Subject: RE: BLA 125496 siltuximab - FDA proposed labeling #4 with PPI
Attachments: Siltuximab PPI_Tracked FDA 03142014.doc; Siltuximab PPI_Clean FDA 03142014.doc

Hello Melanie,

The team is requesting that you make revisions to the PPI separate from the USPI in order to maintain its formatting. In addition, to the PPI tracked change version, attached is a clean version, sent to you on March 14, 2014 as a reference.

Please contact me if you have any questions.

Kind Regards,
Patty

Patty Garvey, R.Ph.
CAPT, U.S. Public Health Service
Senior Regulatory Project Manager
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Phone: 301-796-8493 | Fax: 301-796-9849 | patricia.garvey@fda.hhs.gov

---

From: Rothschild, Melanie [JRDUS] [mailto:MRothsch@ITS.JNJ.COM]
Sent: Tuesday, March 18, 2014 1:22 PM
To: Garvey, Patricia
Cc: Maloney, Brian [JRDUS]
Subject: RE: BLA 125496 siltuximab - FDA proposed labeling #4 with PPI

Dear Patty,

Attached please find the marked and clean versions of the revised USPI including the PPI, as one document. All previous comments in the main portion of the USPI have been accepted.

In the marked version any changes we made or text we would like to delete is highlighted in yellow with comments except the two editorial changes on PPI page 15 under “What should I tell my healthcare provider before receiving SYLVANT?” (bullets 2 and 3 do not have comments, just marked text).

Please let me know if you have any questions or concerns.

Kind regards, Melanie

From: Garvey, Patricia [mailto:Patricia.Garvey@fda.hhs.gov]
Sent: Friday, March 14, 2014 10:00 PM
To: Maloney, Brian [JRDUS]

Reference ID: 3473836

Cc: Rothschild, Melanie [JRDUS]
Subject: BLA 125496 siltuximab - FDA proposed labeling #4 with PPI

Dear Brian,

Please refer to your Biologics License Application (BLA) 125496 SYLVANT (siltuximab) submitted under section 351(a) of the Public Health Service Act (PHS Act). We also refer to your submission dated March 7, 2014 and email correspondence dated March 13, 2014, which is a response to FDA proposed labeling request dated March 11, 2014.

We accept your minor revision to Table 5. We have also made revisions to HL/Contraindications and FPI/Section 8.1.

We have completed the review of the Patient Package Insert (PPI). In addition to content, we often make significant revisions to the format in review of patient labeling. Therefore, we have a separate patient labeling that we have attached as the base document for making subsequent changes. Using the attached patient labeling will ensure specifically that the formatting changes are preserved.

Please review and provide revisions/comments to the attached FDA proposed labeling and PPI. Using the same draft, please provide your comments in the following manner:
· Where you agree with the labeling revisions, "accept" the tracked changes.
· Where you disagree with the labeling revisions, provide your comments and proposed language (shown in tracked changes). If necessary, edit but do not "reject" the FDA-proposed changes.

We are still reviewing the carton and container labels.

Please provide your labeling revisions/comments by NLT, March 19, 2014. In addition, please follow up with a formal submission of your label to the BLA. Please contact me if you have any questions.

Kind Regards,
Patty

Patty Garvey, R.Ph.
CAPT, U.S. Public Health Service
Senior Regulatory Project Manager
Division of Hematology Products | Office of Hematology and Oncology Products
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/s/

PATRICIA N GARVEY
03/19/2014

Garvey, Patricia

From: Garvey, Patricia
Sent: Monday, March 17, 2014 5:02 PM
To: Rothschild, Melanie [JRDUS] (MRothsch@ITS.JNJ.COM)
Cc: Maloney, Brian [JRDUS] (BMalone1@ITS.JNJ.COM)
Subject: BLA 125496 siltuximab - FDA BMAB Product Quality PMCs

Dear Melanie,

Please refer to your Biologics License Application (BLA) 125496 SYLVANT (siltuximab) submitted under section 351(a) of the Public Health Service Act (PHS Act).

We have determine that the following PMCs are necessary based on the data available to date. The brief description of the necessary studies/trials is intended to describe the main objective and trial characteristics of interest. Please review and provide edits/comments in clarifying mutually acceptable descriptions of the key trial elements. The "Final Protocol Submission" date is the date by which you HAVE submitted a complete protocol that has already received full concurrence by FDA.

PMC #1 Description: *To determine the volume of the* (b) (4) *necessary to achieve consistent* (b) (4) *test conditions, provide the supportive data, and use the determined volume in the* (b) (4) *test of the drug product* (b) (4) *by May 2014.*

PMC Schedule Milestones: Final Report Submission Date: 05/2014

PMC #2 Description: *To conduct study for endotoxin recovery from formulated drug substance held in* (b) (4) *at process conditions and submit summary report to the Agency per 21CFR601.12 by July 30, 2014.*

PMC Schedule Milestones: Final Report Submission Date: 07/2014

Upon mutual agreement, please submit both by email and officially a copy of the PMC studies/trials to us with a statement that you agree to perform the trials as described and within the timelines that you specify for the trial. Note that milestone dates only need month and year. For milestone calculation purposes only, assume that an approval occurs on the PDUFA date. Final PMR or PMC designation numbers will be assigned later.

Please note that we will have additional PMRs/PMCs from the Clinical and Office of Biotechnology Product Quality teams. Please provide a response by COB, March 20, 2014. Please contact me if you have any questions.

Kind Regards,
Patty

Patty Garvey, R.Ph.
CAPT, U.S. Public Health Service
Senior Regulatory Project Manager
Division of Hematology Products | Office of Hematology and Oncology Products
Center for Drug Evaluation and Research | Food and Drug Administration
10903 New Hampshire Avenue, WO22 - Room 2329

Reference ID: 3472135

Silver Spring, MD 20993
Phone: 301-796-8493 | Fax: 301-796-9849 | ✉ patricia.garvey@fda.hhs.gov

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/s/

PATRICIA N GARVEY
03/18/2014

Garvey, Patricia

From: Garvey, Patricia
Sent: Friday, March 14, 2014 10:00 PM
To: 'Maloney, Brian [JRDUS] (BMalone1@ITS.JNJ.COM)'
Cc: 'Rothschild, Melanie [JRDUS] (MRothsch@ITS.JNJ.COM)'
Subject: BLA 125496 siltuximab - FDA proposed labeling #4 with PPI

Dear Brian,

Please refer to your Biologics License Application (BLA) 125496 SYLVANT (siltuximab) submitted under section 351(a) of the Public Health Service Act (PHS Act). We also refer to your submission dated March 7, 2014 and email correspondence dated March 13, 2014, which is a response to FDA proposed labeling request dated March 11, 2014.

We accept your minor revision to Table 5. We have also made revisions to HL/Contraindications and FPI/Section 8.1.

We have completed the review of the Patient Package Insert (PPI). In addition to content, we often make significant revisions to the format in review of patient labeling. Therefore, we have a separate patient labeling that we have attached as the base document for making subsequent changes. Using the attached patient labeling will ensure specifically that the formatting changes are preserved.

Please review and provide revisions/comments to the attached FDA proposed labeling and PPI. Using the same draft, please provide your comments in the following manner:
· Where you agree with the labeling revisions, "accept" the tracked changes.
· Where you disagree with the labeling revisions, provide your comments and proposed language (shown in tracked changes). If necessary, edit but do not "reject" the FDA-proposed changes.

We are still reviewing the carton and container labels.

Please provide your labeling revisions/comments by NLT, March 19, 2014. In addition, please follow up with a formal submission of your label to the BLA. Please contact me if you have any questions.

Kind Regards,
Patty

ximab USPI Siltuximab (Manuscri.... PPI FDA O....

Patty Garvey, R.Ph.
CAPT, U.S. Public Health Service
Senior Regulatory Project Manager
Division of Hematology Products | Office of Hematology and Oncology Products
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/s/

PATRICIA N GARVEY
03/14/2014

Garvey, Patricia

From: Garvey, Patricia
Sent: Tuesday, March 11, 2014 5:02 PM
To: 'Maloney, Brian [JRDUS] (BMalone1@ITS.JNJ.COM)'
Cc: 'Rothschild, Melanie [JRDUS] (MRothsch@ITS.JNJ.COM)'
Subject: BLA 125496 siltuximab - FDA proposed labeling #3

Dear Brian,

Please refer to your Biologics License Application (BLA) 125496 SYLVANT (siltuximab) submitted under section 351(a) of the Public Health Service Act (PHS Act). We also refer to your submission dated March 7, 2014.

We accept your proposed Limitation of Use statement, revised Highlights/Warnings & Precautions/GI Perforation information, and made minor editorial/format changes.

Please review and provide revisions/comments to the attached FDA proposed labeling. Using the same draft, please provide your comments in the following manner:
· Where you agree with the labeling revisions, "accept" the tracked changes.
· Where you disagree with the labeling revisions, provide your comments and proposed language (shown in tracked changes). If necessary, edit but do not "reject" the FDA-proposed changes.

We are still reviewing the USPI Patient Information page and carton & container labels.

Please provide your labeling revisions/comments by NLT, March 13, 2014. In addition, please follow up with a formal submission of your label to the BLA. Please contact me if you have any questions.

Kind Regards,
Patty

siltuximab 100 mg Vial 40....

Patty Garvey, R.Ph.
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/s/

PATRICIA N GARVEY
03/11/2014

Garvey, Patricia

From: Garvey, Patricia
Sent: Thursday, March 06, 2014 6:56 PM
To: 'Maloney, Brian [JRDUS]'; Hennessey, Lyndsay
Cc: Rothschild, Melanie [JRDUS]
Subject: RE: BLA 125496 siltuximab - CMC Follow-up Information Request

Importance: High

Hello Brian,

The team has reviewed your February 28, 2014 email correspondence and attachments (below). There are number of documents (e.g. protocols, procedures etc.) that are missing. The "link" is there, so we assume that you plan to submit them in the formal electronic submission, however, it was not the attachments to the email.

Please let me know when you will formally submit this information. If you do not plan to formally submit them tomorrow, please provide the information via email for the team to review. We are requesting all the documents that should have been attached in the email to be provided as soon as possible.

Please contact me if you have any questions.

Kind Regards,
Patty

Patty Garvey, R.Ph.
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Phone: 301-796-8493 | Fax: 301-796-9849 | patricia.garvey@fda.hhs.gov

---

From: Maloney, Brian [JRDUS] [mailto:BMalone1@ITS.JNJ.COM]
Sent: Friday, February 28, 2014 4:04 PM
To: Garvey, Patricia; Hennessey, Lyndsay
Cc: Rothschild, Melanie [JRDUS]
Subject: RE: BLA 125496 siltuximab

Hi Patty and Lyndsay,

Attached please find Janssen's responses to the CMC issues identified in the FDA's Late Cycle meeting briefing document and as discussed in the meeting on 25 February.

In addition, our team was hoping to receive FDA feedback on the issue regarding [redacted] (b) (4), identified as item "iii) 1 Regarding FLP lot release and stability specifications, (page 8) at your earliest convenience.

Should the FDA wish to discuss any further issues or have additional questions, we would be happy to schedule a teleconference if needed.

Reference ID: 3466496

Thanks and kind regards
Brian

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/s/

PATRICIA N GARVEY
03/06/2014

Garvey, Patricia

From: Garvey, Patricia
Sent: Monday, March 03, 2014 11:02 AM
To: Maloney, Brian [JRDUS] (BMalone1@ITS.JNJ.COM)
Cc: Rothschild, Melanie [JRDUS] (MRothsch@ITS.JNJ.COM)
Subject: BLA 125496 siltuximab - FDA proposed labeling #2

Dear Brian,

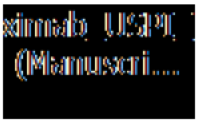
Please refer to your Biologics License Application (BLA) 125496 SYLVANT (siltuximab) submitted under section 351(a) of the Public Health Service Act (PHS Act). We also refer to your submission dated August 29 and November 1, 2013 and e-mail correspondence February 14, 2014.

Please review and provide revisions/comments to the attached FDA proposed labeling. Using the same draft, please provide your comments in the following manner:
· Where you agree with the labeling revisions, "accept" the tracked changes.
· Where you disagree with the labeling revisions, provide your comments and proposed language (shown in tracked changes). If necessary, edit but do not "reject" the FDA-proposed changes.

Due to revisions being made, please review the document for formatting and correct where appropriate. Note that we have not completed the review of the Patient Information page.

Please provide your labeling revisions and comments by COB, March 5, 2014. Please contact me if you have any questions.

Kind Regards,
Patty



Patty Garvey, R.Ph.
CAPT, U.S. Public Health Service
Senior Regulatory Project Manager
Division of Hematology Products | Office of Hematology and Oncology Products
Center for Drug Evaluation and Research | Food and Drug Administration
10903 New Hampshire Avenue, WO22 - Room 2329
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Phone: 301-796-8493 | Fax: 301-796-9849 | patricia.garvey@fda.hhs.gov

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

Reference ID: 3464037

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/s/

PATRICIA N GARVEY
03/03/2014

Garvey, Patricia

From: Garvey, Patricia
Sent: Thursday, February 27, 2014 11:13 AM
To: 'Maloney, Brian [JRDUS] (BMalone1@ITS.JNJ.COM)'
Cc: 'Rothschild, Melanie [JRDUS] (MRothsch@ITS.JNJ.COM)'
Subject: BLA 125496 Siltuximab - FDA BMAB Drug Substance Information Request

Dear Brian,

Please refer to your Biologics License Application (BLA) dated August 29, 2013, received August 30, 2013, submitted under section 351(a) of the Public Health Service Act for SYLVANT (siltuximab).

We also refer to your e-mail correspondence dated February 24, 2014, in which Janssen committed to conduct a study spiking standard endotoxin in formulated drug substance held in (b) (4) at process conditions followed by a recovery study for a minimum of 48 hours; the study will be conducted in parallel with the production of the next three available batches of Siltuximab formulated drug substance.

We have the following questions:

1. Indicate when the study will be completed and when the report will be submitted to the Agency
2. Indicate which actions will be taken if the proposed study determines low endotoxin recovery in the formulated drug substance after hold

Please provide a response by COB, March 11, 2014. Please contact me if you have any questions.

Kind Regards,
Patty

Patty Garvey, R.Ph.
CAPT, U.S. Public Health Service
Senior Regulatory Project Manager
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Center for Drug Evaluation and Research | Food and Drug Administration
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Reference ID: 3464036

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/s/

PATRICIA N GARVEY
03/03/2014

Garvey, Patricia

From: Garvey, Patricia
Sent: Friday, February 21, 2014 7:13 PM
To: 'Maloney, Brian [JRDUS] (BMalone1@ITS.JNJ.COM)'
Cc: 'Rothschild, Melanie [JRDUS] (MRothsch@ITS.JNJ.COM)'
Subject: BLA 125496 Siltuximab - FDA Comments on Container and Carton Labeling

Dear Brian,

Please refer to your Biologics License Application (BLA) 125496 Siltuximab submitted under section 351(a) of the Public Health Service Act (PHS Act).

We also refer to your submission dated August 29, 2013. We have completed the review of the container and carton labeling. Please find attached FDA comments on the container and carton labeling.

Please provide revised container and carton labeling by COB, March 4, 2014.

Kind Regards,
Patty

Patty Garvey, R.Ph.
CAPT, U.S. Public Health Service
Senior Regulatory Project Manager
Division of Hematology Products | Office of Hematology and Oncology Products
Center for Drug Evaluation and Research | Food and Drug Administration
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Reference ID: 3459126

BLA 125496 SYLVANT (siltuximab)
FDA Comments on Container and Carton Labeling
February 21, 2014

Container Label for 100 mg/vial and 400 mg/vial products:

1. Move the manufacturer information to the side panel as it clutters the principal display panel and takes readers' attention away from important information such as proprietary and proper names and strength.

2. Consider re-orientating the barcode to a vertical position to improve the scannability of the barcode. Barcodes placed in a horizontal position may not scan due to vial curvature.

3. Add the statement "Protect from light" in the side panel.

Carton Labeling for 100 mg and 400 mg Products:

1. Revise the statement [redacted] (b) (4) to read

   Reconstitution: Reconstitute with XX mL Sterile Water for Injection, USP. DO NOT shake reconstituted solution. Each mL will contain XX mg of siltuximab."
   Dilution: Must be further diluted with 5% Dextrose Injection, USP. This will improve readability for reconstitution instructions for both 100 mg/vial and 400 mg/vial products.

2. Separate the statement "Once reconstituted, each mL contains 20 mg siltuximab, L-Histindine (from L-Histidine and L-histidine monohydrochloride monohydrate) (0.7 mg), Polysorbate 80 (0.16 mg), and Sucrose (34 mg)." to a second paragraph to reduce information crowding and visual clutter.

3. Include instructions on post-reconstitution expiration date and storage if space permits.

Container and Carton Labels for 100 mg and 400 mg Products:

1. Remove the [redacted] (b) (4) next to the trade name and proper name to minimize risk of "sylvant" being misread as [redacted] (b) (4)

2. Revise the statement [redacted] (b) (4) to "For intravenous infusion only." We recommend this revision to minimize the risk of administering the drug too fast based on our post marketing experiences.

3. Debold the statement "Rx Only" as this information completes for prominent information such as established name on the principal display panel.

4. There is insufficient differentiation between the different strengths. The only difference between the two strengths is the font color of the strength placement, which may be inadequate in preventing selection of the wrong strength error. Thus, please provide sufficient differentiation between the two strengths of the product through the use of colors, boxing, or other means for the background to highlight the different strengths.

5. Revise the dosage form from [redacted] (b) (4) to "*For Injection*" on all carton and container labels to comply with the USP 36/NF 31, General Chapter <1> Injections, Nomenclature and Definitions.

6. Identify whether the label is affixed to the vial so that there is a visual area of inspection per 21 CFR 610.60 (e). Provide a sample of a labeled vial.

7. Revise carton and container labels to have the proper/established name in parenthesis - *(siltuximab)*.

8. Revise [redacted] (b) (4) statements on the carton label to comply with 21 CFR 610.64 as follows:

   Manufactured by: Janssen Biotech Inc.,
   Horsham, PA 19044
   U.S. License No. 1864
   At Cilag AG,
   Schaffhausen, Switzerland".

9. Remove the statement "Product of the Netherlands" from the carton label.

10. Revise the statement "*Usual Dosage: See package insert for full prescribing, reconstitution and product information*" on the carton labels to "*Dosage: See package insert for full prescribing, reconstitution, administration and product information*."

11. Revise the statement [redacted] (b) (4) on the container labels to "*Dosage: See prescribing information*".

12. Provide any proposed printed information that is to be found on the vial Ferrules and Cap Overseals for 100 mg and 400 mg siltuximab vials. This information should comply with USP 36/NF 31, General Chapter <1> Injections, Packaging.

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/s/

PATRICIA N GARVEY
02/21/2014

Baird, Amy

From: Baird, Amy
Sent: Tuesday, February 18, 2014 10:28 AM
To: Maloney, Brian [JRDUS] (BMalone1@ITS.JNJ.COM)
Cc: Garvey, Patricia
Subject: BLA 125496 Siltuximab - FDA Microbiology Request

Brian,

Please refer to your Biologics License Application (BLA) 125496 SYLVANT (siltuximab) submitted under section 351(a) of the Public Health Service Act (PHS Act).

Per the request of the FDA Drug Product Quality Microbiology review team, please provide a response to the following request by 12:00pm, Monday, February 25, 2014.

Drug Product Quality Microbiology

The information request submitted by the Agency on November 14, 2013, stated:

"The effect of hold time on endotoxin recovery should be assessed by spiking a known amount of endotoxin into undiluted drug substance and drug product and then testing for recoverable endotoxin over time. The studies should be conducted using containers of similar composition as those used for drug substance and drug product during hold."

Your proposed study appears to be addressing the hold time of samples [redacted] (b) (4). Although the proposed study appears to be adequate for that purpose, it does not address our concern of low endotoxin recovery during maximum hold of formulated drug substance and drug product. Please conduct studies to demonstrate effects of hold on undiluted drug product or drug substance samples spiked with endotoxin; the study should cover the maximum hold times and should be conducted in containers of similar composition as those used for drug substance and drug product during hold. We recommend using standard endotoxin for the study to facilitate quantification (using standard curve with standard endotoxin) and for comparison with results from the previous study.

Please do not hesitate to contact me should you have any questions.

Regards,

Amy Baird
Regulatory Project Manager
Division of Hematology Products, CDER, FDA
10903 New Hampshire Ave
WO #22, Room 2122
Silver Spring, MD 20993
Telephone: 301-796-4969
Facsimile: 301-796-9845
Email: amy.baird@fda.hhs.gov

Reference ID: 3455466

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/s/

AMY C BAIRD
02/18/2014

Baird, Amy

From: Baird, Amy
Sent: Friday, February 07, 2014 4:21 PM
To: 'Maloney, Brian [JRDUS]'; Garvey, Patricia
Cc: Rothschild, Melanie [JRDUS]
Subject: RE: Labeling Clarification Request

Brian,

The FDA team reviewed your email and have the following response regarding the ADR table. Please review and contact me should you have further questions.

(b) (4)

Regarding Table 3. This table was constructed from dataset adae. Column “AEPERIOD” selected “TREATMENT”; Column “DOSENUM” selected “1” through “8.” Generally preferred terms were used but for rash, edema, hypotension more than one preferred term was used to evaluate the category. In the SOC Infection high level terms rather than preferred terms were used.

Reference ID: 3450774

Note: The verbatim term "creatine kinase higher than normal" was incorrectly mapped to the preferred term renal impairment.

Regards,

Amy Baird
Regulatory Project Manager
Division of Hematology Products, CDER, FDA
10903 New Hampshire Ave
WO #22, Room 2122
Silver Spring, MD 20993
Telephone: 301-796-4969
Facsimile: 301-796-9845
Email: amy.baird@fda.hhs.gov

From: Maloney, Brian [JRDUS] [mailto:BMalone1@ITS.JNJ.COM]
Sent: Friday, February 07, 2014 1:47 PM
To: Baird, Amy; Garvey, Patricia
Cc: Rothschild, Melanie [JRDUS]
Subject: Labeling Clarification Request

Hi Amy,

Janssen is currently reviewing the FDA comments and proposed revisions on the draft labeling for Sylvant. To help Janssen understand the FDA proposed ADR table, would the FDA be able to share the algorithm/criteria and the customized AE groupings created, specifically listing the included Preferred Term per AE group?

This would help reconcile the ADR table

Thanks and please let me know if you have any questions.

Thanks and kind regards
Brian

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/s/

AMY C BAIRD
02/07/2014

Garvey, Patricia

From: Garvey, Patricia
Sent: Tuesday, February 04, 2014 8:13 PM
To: Maloney, Brian [JRDUS] (BMalone1@ITS.JNJ.COM)
Cc: Rothschild, Melanie [JRDUS] (MRothsch@ITS.JNJ.COM)
Subject: BLA 125496 Siltuximab - FDA proposed labeling

Dear Brian,

Please refer to your Biologics License Application (BLA) 125496 SYLVANT (siltuximab) submitted under section 351(a) of the Public Health Service Act (PHS Act). We also refer to your submission dated August 29 and November 1, 2013.

Please review and provide revisions/comments to the attached FDA proposed labeling. Please address the yellow highlighted comment bubbles. The "Note to Sponsor" attachment provides an explanation for (b) (4)

We have not completed the review of the Patient Information page and carton and container labels. We will provide comments to these documents once it is completed.

Please provide your labeling revisions and comments by NLT February 14, 2014. Please contact me if you have any questions.

Kind Regards,
Patty

Siltuximab JBI propos.... Siltuximab label FDA ....

Patty Garvey, R.Ph.
CAPT, U.S. Public Health Service
Senior Regulatory Project Manager
Division of Hematology Products | Office of Hematology and Oncology Products
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/s/

PATRICIA N GARVEY
02/04/2014

Garvey, Patricia

From: Garvey, Patricia
Sent: Wednesday, January 29, 2014 6:49 AM
To: 'Maloney, Brian [JRDUS]'
Cc: 'Rothschild, Melanie [JRDUS]'
Subject: BLA 125496 Siltuximab - BMAB Drug Substance Microbial Quality Info Request

Dear Brian,

Please refer to your Biologics License Application (BLA) 125496 Siltuximab submitted under section 351(a) of the Public Health Service Act (PHS Act). We also refer to your submission dated January 24, 2014 and have the following information request:

FDA Information Request (III) for STN 125496/0 (drug substance microbial quality)

FDA Comment to Response to Information Request 3g submitted on January 24, 2014
Include action limits for the new endotoxin monitoring at (b) (4) in section 3.2.S.2.4.

FDA Comment to Response to Information Request 8b submitted on January 24, 2014
Submit bioburden suitability study report for in-process intermediates and formulated bulk from the next two commercial production campaigns in the next Annual Report.

Please provide a response by COB, February 4, 2014 and officially submit the response to the BLA.

Kind Regards,
Patty

Patty Garvey, R.Ph.
CAPT, U.S. Public Health Service
Senior Regulatory Project Manager
Division of Hematology Products | Office of Hematology and Oncology Products
Center for Drug Evaluation and Research | Food and Drug Administration
10903 New Hampshire Avenue, WO22 - Room 2329
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Phone: 301-796-8493 | Fax: 301-796-9849 | patricia.garvey@fda.hhs.gov

Reference ID: 3443930

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/s/

PATRICIA N GARVEY
01/29/2014

Hennessey, Lyndsay

From: Hennessey, Lyndsay
Sent: Monday, January 27, 2014 9:02 AM
To: Maloney, Brian [JRDUS] (BMalone1@ITS.JNJ.COM)
Cc: Garvey, Patricia; Hennessey, Lyndsay
Subject: BLA 125496 Siltuximab - CMC Information Request - January 27, 2014

Follow Up Flag: Follow up
Due By: Friday, January 31, 2014 2:00 PM
Flag Status: Flagged

Dear Dr. Maloney,

Please refer to your Biologics License Application (BLA) 125496 Siltuximab dated August 29, 2013, received August 30, 2013, submitted under 351(a) of the Public Health Service Act. We have the following CMC information request:

1. We do not agree with the proposed acceptance criteria for the specifications indicated below The data and justification provided for formulated bulk drug substance (FB) and final lyophilized drug product (FLP) lots do not support the proposed acceptance criteria for select release and stability specifications. Submit a revised BF specification, FLP specification and post-approval stability protocols to the BLA.
    a. Color (b) (4): the proposed acceptance criteria are currently (b) (4) For DS it is noted that all the released batches of FB are tested (b) (4) and the 24 and 36 months stability results of FB indicated that color of the samples (b) (4) and for FLP, color ranges from (b) (4)
    b. Particulate Matter (b) (4)) – the proposed specification relates to (b) (4) particles but should be to (b) (4) (b) (4)
    c. (b) (4) is a critical component of formulation that impacts the quality of FDS and DP. Implement release testing and a quantitative acceptance criteria for (b) (4) in the siltuximab FDS release testing
    d. Quantity (b) (4) The proposed specifications are (b) (4) mg/mL for both the 100 and 400 mg/vial presentations with a target of (b) (4) mg/mL. Justification provided was based on statistical modeling for release and stability, but did not include consideration related to the dose a patient would receive based on these limits. The upper limit of (b) (4) mg/mL is higher than identified as used in clinical trials and should be justified with the appropriate information or the upper limit should be narrowed to (b) (4) mg/mL which is (b) (4) from the target dose.

2. Multiple testing sites were listed in 3.2.S.2.1 and 3.2.P.3.1 for the testing of (b) (4) bulk, FB and FLP. Identify the specific tests that are executed at each site for cell banks, (b) (4) bulk, (b) (4) formulated bulk/drug substance and final lyophilized drug product. For each assay, specify what the test is used for (e.g. FB release, FLP stability, etc.).

3. 21 CFR 610.14 requires that identity testing be performed on each filled lot after all labeling operations have been completed. The manufacturing step from which the samples used for identity testing of siltuximab are obtained was not clearly identified in Section 3.2.P.3.3 or Section 3.2.P.5.1. Clarify your current process and amend the process, if necessary, to conform to the regulation. Update the relevant section(s) of the BLA accordingly.

Reference ID: 3442227

4. It appears that (b) (4) does not have any post approval stability requirements based on the lack of a post-approval stability protocol in the BLA. You propose to store (b) (4) for up to (b) (4) months, therefore stability monitoring throughout the product's lifecycle is required. Submit plans for stability monitoring, including protocol with proposed testing timelines and specifications.

5. Reconstitution time for validation batch BDS4D00 at 24 months point in recommended storage condition was reported as (b) (4). This result would fail the proposed commercial acceptance criterion. Please provide results of your investigation of this event and reason of potential failure.

6. In Section 3.2.P.2.2.1.5.3, stability trending comparison graphs, is unclear how the trend lines were calculated. (b) (4) please provide this information.

7. In section 3.2.P.5.6 Justification of Specifications: 18. UNIFORMITY OF DOSAGE UNITS the Uniformity of Dosage test was described as the procedure is performed (b) (4), which does not match with protocol provided (Uniformity of Dosage Units: DS-TMD-3942) and referenced compendia. Additionally, the specification for the Uniformity of Dosage is with those specifications done for (b) (4) Verify that the release testing is done per protocol DS-TMD-3942 and update the BLA accordingly.

8. The representative drawing of the closure ((b) (4) screw cap) shown in Figure 2 of 3.2.S.6 Container Closure System indicated that the cap for the (b) (4) container is from (b) (4). However, the cross-reference authorization letter provided to the BLA for DMF (b) (4) indicated that (b) (4) are the manufacturer of the cap. Clarify the manufacturer of the (b) (4) screw cap and provide the correct cross-reference letter, if necessary.

9. (b) (4) is a compendial raw material that is in the formulation of the drug product. In 3.2.S.2.6, Process Control Strategy Development, Table 26 indicates that material attributes associated with (b) (4) are (b) (4) However, no detailed control strategy information for (b) (4) was provided. (b) (4) may contain impurities which have been known to increase during long term storage under certain conditions. Some impurities such as (b) (4) can interact with siltuximab as well as with other formulation components e.g. (b) (4). Provide the control strategy used to assure that the (b) (4) used in the formulation is of appropriate quality at time of use.

10. It is described in 3.1.5. (b) (4) for 100 mg/vial and for 400 mg/vial formulations in Section 3.2.P.2.3 "Manufacturing Process Development" that the samples will be monitored for 6 months and for 12 months at different storage conditions. We note that the stability results at 0 months and 3 months for 100 mg/vial and only 0 months for 400 mg/vial formulations are provided in the BLA submission. Provide all available data up to date.

11. In 3.2.S.2.4 Control of Critical Steps and Intermediates, validation of SE-HPLC, section 1.3.8 stated that the LOD was estimated by (b) (4). The acceptance criterion for LOD is (b) (4) The rationale behind the estimation of LOD was not provided. Provide the reason for the LOD estimated as (b) (4)

12. (b) (4)

Reference ID: 3442227

13. (b) (4)

14. (b) (4) is no longer monitored based on release specifications proposed for the to-be-marketed product and has been identified as a nCQA in section 3.2.S.2.6 Process Control Strategy Development. During product development this species was monitored for stability of FB and data do not identify trending of (b) (4) on stability. (b) (4) . Therefore, the levels of (b) (4) should be monitored and trended in the siltuximab annual report (Janssen's quality system AR for siltuximab, not the Annual report of minor changes that is to be submitted annually to the FDA).

15. In 3.2.S.2.5 Process Validation and/or Evaluation, Validation of Quantitative (b) (4) Determination by HPLC. You stated that the validation was performed according to the protocol. Provide the protocols for quantitative (b) (4) determination by HPLC respectively.

We request a written response to the items enumerated above by January 31, 2014. Please email a PDF copy of the official submission.

If you have any questions, please contact me.

Kind regards,

Lyndsay Hennessey
Regulatory Health Project Manager
FDA/CDER/OPS/OBP-IO
10903 New Hampshire Ave.
WO Building 21 Room 1523
Silver Spring, Maryland 20993-0002
Lyndsay.Hennessey@fda.hhs.gov
240-402-3746

Reference ID: 3442227

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/s/

LYNDSAY J HENNESSEY
01/27/2014

Hennessey, Lyndsay

From: Hennessey, Lyndsay
Sent: Friday, January 17, 2014 4:07 PM
To: Maloney, Brian [JRDUS] (BMalone1@ITS.JNJ.COM)
Cc: Garvey, Patricia; Hennessey, Lyndsay
Subject: BLA 125496 Siltuximab - CMC Information Request - January 17, 2014

Follow Up Flag: Follow up
Flag Status: Flagged

Dear Dr. Maloney,

Please refer to your Biologics License Application (BLA) 125496 Siltuximab submitted under 351(a) of the Public Health Service Act. We also refer to your submission dated August 29, 2013 and have the following CMC information request:

(b) (4)

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

Reference ID: 3439175

(b) (4)

[redacted]

We request a written response to the items enumerated above by January 22, 2014. Please email a PDF copy of the official submission.

If you have any questions, please contact me.

Kind regards,

Lyndsay Hennessey

Regulatory Health Project Manager
FDA/CDER/OPS/OBP-IO
10903 New Hampshire Ave.
WO Building 21 Room 1523
Silver Spring, Maryland 20993-0002
Lyndsay.Hennessey@fda.hhs.gov
240-402-3746

Reference ID: 3439175

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/s/

LYNDSAY J HENNESSEY
01/20/2014

Garvey, Patricia

From: Garvey, Patricia
Sent: Friday, January 17, 2014 6:53 AM
To: Maloney, Brian [JRDUS] (BMalone1@ITS.JNJ.COM)
Cc: Rothschild, Melanie [JRDUS] (MRothsch@ITS.JNJ.COM)
Subject: BLA 125496 Siltuximab - BMAB Drug Substance Microbial Quality Info Request

Dear Brian,

Please refer to your Biologics License Application (BLA) 125496 Siltuximab submitted under section 351(a) of the Public Health Service Act (PHS Act). We also refer to your submission dated December 5, 2013 and have the following information request:

FDA Information Request (II) for STN 125496/0 (drug substance microbial quality)

FDA Comment to Response to Information Request 3g submitted in Amendment 0015
Revise section 3.2.S.2.4 of the BLA to include new endotoxin monitoring at [redacted] (b) (4).

FDA Information Request 3j
Submit limits for the additional bioburden monitoring step after [redacted] (b) (4) into [redacted] (b) (4); revise section 3.2.S.2.4 of the BLA to include the new monitoring step and limits.

FDA Comment to Response to Information Request 8b submitted in Amendment 0015
Conduct bioburden suitability test in two additional batches of in-process intermediates and formulated bulk.

Please provide a response by COB, January 24, 2014 and official submit the response to the BLA.

Kind Regards,
Patty

Patty Garvey, R.Ph.
CAPT, U.S. Public Health Service
Senior Regulatory Project Manager
Division of Hematology Products | Office of Hematology and Oncology Products
Center for Drug Evaluation and Research | Food and Drug Administration
10903 New Hampshire Avenue, WO22 - Room 2329
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Reference ID: 3438085

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/s/

PATRICIA N GARVEY
01/17/2014

Garvey, Patricia

From: Garvey, Patricia
Sent: Tuesday, January 07, 2014 1:58 PM
To: 'Maloney, Brian [JRDUS]'
Cc: 'Rothschild, Melanie [JRDUS]'
Subject: BLA 125496 Siltuximab - Statistical Information Request

Dear Brian,

Please refer to your Biologics License Application (BLA) 125496 Siltuximab submitted under section 351(a) of the Public Health Service Act (PHS Act). We also refer to your submission dated January 2, 2014 and have the following information request.

Statistical

Please provide the reason(s) for the quick decrease in number of patients taking the questionnaire over time. Please provide, for each treatment group, the number of patients with missing assessments (i.e. patients who should have but did not take the questionnaire) by visit. In addition, please clarify how your analysis handled the patients who did not have an end of treatment assessment.

Please provide a response as soon as possible and contact me if you have any questions.

Best Regards,
Patty

Patty Garvey, R.Ph.
CAPT, U.S. Public Health Service
Senior Regulatory Project Manager
Division of Hematology Products | Office of Hematology and Oncology Products
Center for Drug Evaluation and Research | Food and Drug Administration
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Phone: 301-796-8493 | Fax: 301-796-9849 | ✉ patricia.garvey@fda.hhs.gov

Reference ID: 3432732

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/s/

PATRICIA N GARVEY
01/07/2014

Garvey, Patricia

From: Garvey, Patricia
Sent: Friday, December 20, 2013 3:47 PM
To: 'Maloney, Brian [JRDUS]'
Cc: 'Rothschild, Melanie [JRDUS]'
Subject: BLA 125496 Siltuximab - Statistical Information Request

Importance: High

Dear Brian,

Please refer to your Biologics License Application (BLA) 125496 Siltuximab submitted under section 351(a) of the Public Health Service Act (PHS Act). We also refer to your submission dated August 29, 2013 and have the following information request.

Statistical

For the MCD-SS PRO instrument data collected during study MCD2001 blinded treatment period, please provide summary of missing data by items over time.

Please provide a response by Friday, January 3, 2014, 12:00 PM (EST) and contact me if you have any questions.

Best Regards,
Patty

Patty Garvey, R.Ph.
CAPT, U.S. Public Health Service
Senior Regulatory Project Manager
Division of Hematology Products | Office of Hematology and Oncology Products
Center for Drug Evaluation and Research | Food and Drug Administration
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Reference ID: 3426488

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/s/

PATRICIA N GARVEY
12/20/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA125496/0

MID-CYCLE COMMUNICATION

Janssen Biotech, Inc.
c/o Janssen Research & Development, LLC
Attention: Brian Maloney, R.Ph., M.S.
Director, Regulatory Affairs
920 Route 202
P.O. Box 300
Raritan, NJ 08869

Dear Mr. Maloney:

Please refer to your Biologic License Application (BLA) submitted under section 351(a) of the Public Health Service Act for Sylvant (siltuximab).

We also refer to the teleconference between representatives of your firm and the FDA on December 13, 2013. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, please contact Patricia Garvey, Senior Regulatory Project Manager at (301) 796-8493.

Sincerely,

{See appended electronic signature page}

Ann Farrell, M.D.
Director
Division of Hematology and Oncology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Mid-Cycle Communication

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MID-CYCLE COMMUNICATION

Meeting Date and Time: December 13, 2013 at 9:00 AM (EST)

Application Number: BLA 125496
Product Name: Sylvant (siltuximab)
Indication: Treatment of multicentric Castleman's Disease (MCD) in patients who are immunodeficiency virus negative (HIV-), and human herpes virus -8 negative (HHV-8-)
Applicant Name: Janssen Biotech, Inc.

Meeting Chair: Albert Deisseroth, M.D., Ph.D.
Meeting Recorder: Patricia Garvey, R.Ph.

FDA ATTENDEES

OFFICE OF HEMATOLOGY AND ONCOLOGY PRODUCTS (OHOP)/DIVISION OF HEMATOLOGY PRODUCTS
Ann Farrell, M.D. – Director
Al Deisseroth, M.D., Ph.D. – Clinical Team Leader
Patricia Dinndorf, M.D. – Clinical Reviewer
Patricia Garvey, R.Ph. – Senior Regulatory Project Manager

OHOP/DIVISION OF HEMATOLOGY, ONCOLOGY, TOXICOLOGY
Pedro Del Valle, Ph.D. – Pharmacologist
Brenda Gehrke, Ph.D. – Pharmacologist

OFFICE OF BIOSTATISTICS/ DIVISION OF BIOMETRICS V
Lei Nie, Ph.D. – Acting Biostatistics Team Leader
Chia-Wen Ko, Ph.D. – Biostatistics Reviewer

OFFICE OF COMPLIANCE/OFFICE OF MANUFACTURING AND PRODUCT QUALITY/DIVISION OF GOOD MANUFACTURING PRACTICE ASSESSMENT/BIOTECH MANUFACTURING ASSESSMENT BRANCH
Patricia Hughes, Ph.D. – Team Leader
Maria Candau-Chacon, Ph.D. – Product Quality Microbiology Reviewer (Drug Substance)
Candace Gomez-Broughton, Ph.D. – Product Quality Microbiology Reviewer (Drug Product)

OFFICE OF PHARMACEUTICAL SCIENCE/OFFICE OF BIOTECHNOLOGY PRODUCTS/DIVISION OF MONOCLONAL ANTIBODIES
Audrey Jia, M.D., Ph.D. – Product Quality Reviewer (Drug Substance)
Bazarragchaa Damdinsuren, M.D., Ph.D. – Product Quality Reviewer (Drug Product)

OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY/OFFICE OF PHARMACOVIGILANCE AND EPIDEMIOLOGY/DIVISION OF PHARMACOVIGILANCE II
Tracy Salaam, Pharm.D. – Team Leader

OFFICE OF STRATEGIC PROGRAMS/OFFICE OF PROGRAM & STRATEGIC ANALYSIS/PROGRAM EVALUATION AND IMPLEMENTATION STAFF
Kimberly Taylor – Operations Research Analyst

EASTERN RESEARCH GROUP ATTENDEE
Patrick Zhou – Independent Associate

APPLICANT ATTENDEES
Rajesh Bandekar – Associate Director, Biostatistics
Shalini Chaturvedi – Principal Scientist
Kindan Doshi – Global Labeling Product Leader
Mary Guilfoyle – Senior Director, CDTL
Naushah Islam – Director, Regulatory Affairs
Milad Khan – Manager, Regulatory Affairs
Barbara Kolb – Senior Directory, Regulatory Affairs
Manny Lopez – Scientific Director
Pauline Martin – Senior Scientific Director
Jeffrey Nemeth – Associate Scientific Director
Willemijn Neher-van Minnen – Associate Director, CMC Regulatory Affairs
Thomas Puchalski – Director, Biologics Clinical Pharmacology
Ming Qi, M.D., Ph.D. – Director, Clinical Development
Sandra Rattray – Vice President, Regulatory Affairs
Melanie Rothschild – Manager, Regulatory Affairs
Helgi van de Velde, M.D., Ph.D. – Senior Director, Clinical Development
Jessica Vermeulen, M.D., Ph.D. – Director, Clinical Development

1.0 INTRODUCTION

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

2.0 SIGNIFICANT ISSUES

Product Quality Microbiology
Description and summary data for the rabbit pyrogen test for siltuximab in conformance with 21 CFR 610.13 (b) on three lots of finished drug product was not included in the BLA. This information was requested in an information request submitted on December 6, 2013.

Reference ID: 3426371

3.0 INFORMATION REQUESTS

Product Quality Microbiology

We are currently awaiting response to an information request sent on December 6, 2013. In addition, we will send you an official information request for the protocol for the low endotoxin recovery study planned for early 2014. The data for the previous study was included in amendment 0015 as a response to an information request sent on November 14, 2013. FDA stated that it is unclear if the test was done using undiluted drug product. The Applicant indicated that they understood FDA concerns.

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

There are no major safety concerns identified at this time and there is currently no need for a Risk Evaluation and Mitigation Strategy (REMS).

5.0 ADVISORY COMMITTEE MEETING

Currently, there are no plans for an advisory committee meeting.

6.0 LATE-CYCLE MEETING/OTHER PROJECTED MILESTONES

The late-cycle meeting is scheduled for February 25, 2014 at 10:00 AM (EST). We plan to communicate proposed labeling and, if necessary, any post-marketing requirement/commitment requests by February 6, 2014.

Reference ID: 3426371

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/s/

ANN T FARRELL
12/20/2013

Garvey, Patricia

From: Garvey, Patricia
Sent: Wednesday, December 11, 2013 2:15 PM
To: Rothschild, Melanie [JRDUS] (MRothsch@ITS.JNJ.COM)
Cc: 'Maloney, Brian [JRDUS] (BMalone1@ITS.JNJ.COM)'
Subject: BLA 125496 siltuximab - Clinical Information Request (label)

Dear Melanie,

Please refer to your biologics license application (BLA) dated August 29, 2013, received August 30, 2013, submitted under section 351 of the Public Health Service Act for Sylvant (siltuximab).

We also refer to your proposed label submitted on November 1, 2013.

We have the following information request regarding the end of Section 6.1 of the proposed labeling:

(b) (4)

(b) (4)

We request a response by NLT Friday, December 13, 2013, 12:00 pm (EST) in order to continue our evaluation of your BLA.

Please contact me if you have any questions.

Kind Regards,
Patty

Patty Garvey, R.Ph.
CAPT, U.S. Public Health Service
Senior Regulatory Project Manager
Division of Hematology Products | Office of Hematology and Oncology Products
Center for Drug Evaluation and Research | Food and Drug Administration
10903 New Hampshire Avenue, WO22 - Room 2329
Silver Spring, MD 20993
Phone: 301-796-8493 | Fax: 301-796-9849 | patricia.garvey@fda.hhs.gov

Reference ID: 3420598

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/s/

PATRICIA N GARVEY
12/11/2013

Garvey, Patricia

From: Garvey, Patricia
Sent: Friday, December 06, 2013 12:12 PM
To: 'Maloney, Brian [JRDUS]'
Subject: BLA 125496 Siltuximab - Clinical Pharmacology Information Request

Dear Brian,

Please refer to your Biologics License Application (BLA) 125496 Siltuximab submitted under section 351(a) of the Public Health Service Act (PHS Act). We also refer to your submission dated August 29, 2013 and have the following information request.

Clinical Pharmacology

Please provide the location in the submission where the bioanalytical method validation report is for measurement of the C-reactive protein (CRP) concentrations in the pop PK/PD model.

Please provide a response as soon as possible and contact me if you have any questions.

Best Regards,
Patty

Patty Garvey, R.Ph.
CAPT, U.S. Public Health Service
Senior Regulatory Project Manager
Division of Hematology Products | Office of Hematology and Oncology Products
Center for Drug Evaluation and Research | Food and Drug Administration
10903 New Hampshire Avenue, WO22 - Room 2329
Silver Spring, MD 20993
Phone: 301-796-8493 | Fax: 301-796-9849 | ✉ patricia.garvey@fda.hhs.gov

Reference ID: 3418890

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/s/

PATRICIA N GARVEY
12/06/2013

Garvey, Patricia

From: Garvey, Patricia
Sent: Friday, December 06, 2013 12:26 PM
To: 'Maloney, Brian [JRDUS] (BMalone1@ITS.JNJ.COM)'
Subject: BLA 125496 siltuximab - BMAB drug product information request

Dear Brian,

Please refer to your biologics license application (BLA) dated August 29, 2013, received August 30, 2013, submitted under section 351 of the Public Health Service Act for Sylvant (siltuximab).

We have following information request regarding the drug product quality microbiology:

1. Information and validation of [redacted] (b) (4) equipment is included in the Appendix section. Amend the BLA to include that information in Section 3.2.P.3.5.
2. With regard to container closure integrity studies, provide the sensitivities of both the dye ingress test and microbial ingress test used to qualify the container closure integrity test for the siltuximab drug product. The sensitivity of the microbial ingress test should be correlated to that of the dye ingress test using the same challenge conditions (pressure/vacuum) and evaluated. Please provide a description of how the positive and negative controls were prepared for both the dye ingress and microbial ingress tests. Provide information on the breach sizes detected. Indicate if the worst-case speeds and forces for the crimping machine were simulated in the container closure studies.
3. Submit the [redacted] (b) (4) microbial retention study from [redacted] (b) (4). The report should include the following information:
   a. Positive and negative controls
   b. Acceptance criteria

   [redacted] (b) (4)
4. Submit the [redacted] (b) (4) integrity test, please include the following information:

   [redacted] (b) (4)
5. Indicate actions taken in the event of a media fill failure.
6. Indicate actions taken when environmental monitoring action limits are exceeded.
7. Describe the media fill growth promotion test.
8. Indicate if refiltration at any step of the manufacturing process is allowed.
9. Provide a description and summary data for the rabbit pyrogen test for siltuximab in conformance with 21 CFR 610.13 (b) on three lots of finished drug product. Include container closure integrity in lieu of sterility as part of your stability program. Container closure should be assessed annually and at expiry.

Reference ID: 3418432

We request a response by **NLT Friday, December 20, 2013, 12:00 pm (EST)** in order to continue our evaluation of your BLA.

Please contact me if you have any questions.

Best Regards,
Patty

Patty Garvey, R.Ph.
CAPT, U.S. Public Health Service
Senior Regulatory Project Manager
Division of Hematology Products | Office of Hematology and Oncology Products
Center for Drug Evaluation and Research | Food and Drug Administration
10903 New Hampshire Avenue, WO22 - Room 2329
Silver Spring, MD 20993
Phone: 301-796-8493 | Fax: 301-796-9849 | ✉ patricia.garvey@fda.hhs.gov

Reference ID: 3418432

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/s/

PATRICIA N GARVEY
12/06/2013

Garvey, Patricia

From: Garvey, Patricia
Sent: Tuesday, December 03, 2013 6:29 AM
To: Maloney, Brian [JRDUS] (BMalone1@ITS.JNJ.COM)
Subject: BLA 125496 siltuximab - OSE information request

Dear Brian,

Please refer to your biologics license application (BLA) dated August 29, 2013, received August 30, 2013, submitted under section 351 of the Public Health Service Act for Sylvant (siltuximab).

We have following information request from the Office of Surveillance and Epidemiology, Office of Pharmacovigilance and Epidemiology:

FDA encourages sponsors to submit a Pharmacovigilance Plan designed to detect new safety risks and to further evaluate identified safety risks with **Siltuximab BLA 125496** following market approval. Guidance for pharmacovigilance planning is included in the FDA Guidance for Industry on Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (2005), and the FDA Guidance for Industry on E2E Pharmacovigilance Planning (2005). If the plan is available, please include it in the **BLA** application in the appropriate module so it can be reviewed accordingly.

We request a response by COB, Wednesday, December 11, 2013, 4:00 pm (EST) in order to continue our evaluation of your BLA.

Please contact me if you have any questions.

Best Regards,
Patty

Patty Garvey, R.Ph.
CAPT, U.S. Public Health Service
Senior Regulatory Project Manager
Division of Hematology Products | Office of Hematology and Oncology Products
Center for Drug Evaluation and Research | Food and Drug Administration
10903 New Hampshire Avenue, WO22 - Room 2329
Silver Spring, MD 20993
Phone: 301-796-8493 | Fax: 301-796-9849 | patricia.garvey@fda.hhs.gov

Reference ID: 3415916

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/s/

PATRICIA N GARVEY
12/03/2013

Garvey, Patricia

From: Garvey, Patricia
Sent: Thursday, November 14, 2013 5:28 PM
To: Maloney, Brian [JRDUS] (BMalone1@ITS.JNJ.COM)
Subject: BLA 125496 siltuximab - BMAB information request

Dear Brian,

Please refer to your biologics license application (BLA) dated August 29, 2013, received August 30, 2013, submitted under section 351 of the Public Health Service Act for Sylvant (siltuximab).

We have following information request regarding the microbial quality of drug substance:

S.2.2 Description of the Manufacturing Process and Process Controls

Information Request 1

Provide a list of all products manufactured in each of the drug substance manufacturing facilities. Provide a list of the shared equipment indicating the products that share the equipment with siltuximab.

Information Request 2

a. Indicate at which temperatures each manufacturing process step is conducted; b. describe routine shipping conditions of frozen [redacted] (b) (4) and of formulated drug substance [redacted] (b) (4); include minimum and maximum routine loads and maximum travel duration; c. indicate if frozen [redacted] (b) (4) can be refrozen; d. indicate if [redacted] (b) (4); e. clarify if chromatography steps [redacted] (b) (4); f. indicate if refiltration at any stage may occur in the event of bioburden above action limits; g. maximum in-process hold times for all steps [redacted] (b) (4)

S.2.3 Control of Critical Steps and Intermediates

Information Request 3

[redacted] (b) (4)

S.2.5 Process Validation and/or Evaluation

Information Request 4

Provide a description of the studies conducted to evaluate maximum hold times of [redacted] (b) (4) for microbial quality (endotoxin and bioburden). Qualification of [redacted] (b) (4) for microbial quality should be conducted for all in-process steps at manufacturing scale in triplicates unless a valid justification is provided.

Reference ID: 3407342

FDA Information Request 5
Submit microbial quality specifications (b) (4).

FDA Information Request 6
a. Submit shipping validation report for the (b) (4) containers; b. Describe the vibration and drop testing conducted for the shipping validation studies.

S.4.2 Analytical Procedures
FDA Information Request 7
Describe the bioburden (b) (4) and endotoxin analytical methods for formulated bulk and in-process intermediates.

S.4.3 Validation of Analytical Procedures
FDA Information Request 8
(b) (4)

FDA Information Request 9
(b) (4)

We request a response by NLT Wednesday, November 27, 2013, 12:00 pm (EST) in order to continue our evaluation of your BLA.

Please contact me if you have any questions.

Kind Regards,
Patty

Patty Garvey, R.Ph.
CAPT, U.S. Public Health Service
Senior Regulatory Project Manager
Division of Hematology Products | Office of Hematology and Oncology Products
Center for Drug Evaluation and Research | Food and Drug Administration
10903 New Hampshire Avenue, WO22 - Room 2329
Silver Spring, MD 20993
Phone: 301-796-8493 | Fax: 301-796-9849 | patricia.garvey@fda.hhs.gov

Reference ID: 3407342

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/s/

PATRICIA N GARVEY
11/14/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

BLA 125496/0

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Janssen Biotech, Inc.
c/o Janssen Research & Development, LLC.
920 Route 202
P.O. Box 300
Raritan, NJ 08869

Attention: Brian Maloney, RPh, MS
Director, Regulatory Affairs

Dear Mr. Maloney:

Please refer to your Biologics License Application (BLA) dated August 29, 2013, received August 30, 2013, submitted under section 351(a) of the Public Health Service Act, for Siltuximab, 100 mg/vial and 400 mg/vial.

We also refer to your September 6, 2013, correspondence, received September 6, 2013, requesting review of your proposed proprietary name, Sylvant. We have completed our review of the proposed proprietary name, Sylvant and have concluded that it is acceptable.

If **any** of the proposed product characteristics as stated in your September 6, 2013 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Sonny Saini, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301)796-0532. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Patricia Garvey, at (301) 796-8493.

Sincerely,

{See appended electronic signature page}

Kellie A. Taylor, Pharm.D., MPH
Deputy Director
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

KELLIE A TAYLOR
11/08/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125496/0

FILING COMMUNICATION –
FILING REVIEW ISSUES IDENTIFIED

Janssen Biotech, Inc.
c/o Janssen Research & Development, LLC
Attention: Brian Maloney, R.Ph., M.S.
Director, Regulatory Affairs
920 Route 202
P.O. Box 300
Raritan, NJ 08869

Dear Mr. Maloney:

Please refer to your Biologics License Application (BLA) dated August 29, 2013, received August 30, 2013, submitted under section 351(a) of the Public Health Service Act for SYLVANT (siltuximab).

We also refer to your amendments dated September 6, 17, 23, 26 and October 2, 10, 16 and 24, 2013.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 601.2(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority.** This application is also subject to the provisions of "the Program" under the Prescription Drug User Fee Act (PDUFA) V (refer to: http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm . Therefore, the user fee goal date is April 30, 2014.

We are reviewing your application according to the processes described in the *Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products*. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by February 5, 2014. In addition, the planned date for our internal mid-cycle review meeting is December 3,

2013. We are not currently planning to hold an advisory committee meeting to discuss this application.

During our filing review of your application, we identified the following potential review issues:

1. The "Comments" hyperlinks in the CRFs for trial CNTO328MCD2001 are not functional. Please submit revised CRFs with functional hyperlinks to facilitate review of the comments.

2. For Study MCD2001, neither the protocol nor the statistical analysis plan specified how to determine the primary endpoint in presence of missing data. You indicated in your October 16, 2013, response to information request that you did not impute any values for missing data, implying that the primary endpoint was determined based on available individual data. Please provide an individual data listing supporting the determination of the primary endpoint in all study subjects.

3. For Study MCD2001, please also provide data listings for secondary endpoints included in your proposed product label.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

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

1. Initial U.S. Approval in Highlights (HL) section must be placed immediately beneath the product title, **bolded**, and include the verbatim "**Initial U.S. Approval:**" followed by the **4-digit year**.

2. Bolded revision date (i.e., "Revised" MM/YYYY or Month Year") must be at the end of HL.

3. The section headings and subheadings (including title of the Boxed Warning) in the Table of Content must match the headings and subheadings in the Full Prescribing Information (FPI). The HL 5.1 subsection title (b) (4)" does not match the title for FPI 5.1 subsection.

We request that you resubmit labeling (Microsoft Word format) that addresses these issues by November 12, 2013. The resubmitted labeling will be used for further labeling discussions.

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

PROMOTIONAL MATERIAL

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

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

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

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

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

If you have any questions, please contact Patricia Garvey, Senior Regulatory Project Manager, at (301) 796-8493.

Sincerely,

{See appended electronic signature page}

Ann T. Farrell, M.D.
Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

ANN T FARRELL
10/29/2013

Hennessey, Lyndsay

From: Hennessey, Lyndsay
Sent: Monday, October 21, 2013 2:34 PM
To: Maloney, Brian [JRDUS] (BMalone1@ITS.JNJ.COM)
Cc: Garvey, Patricia; Hennessey, Lyndsay
Subject: BLA 125496 Siltuximab - CMC Information Request

Dear Dr. Maloney,

Please refer to your Biologics License Application (BLA) 125496 Siltuximab submitted under 351(a) of the Public Health Service Act. We also refer to your submission dated August 29, 2013 and have the following CMC information request:

1. [redacted] (b) (4)

2. Submit to the BLA all protocols for the analytical assays used in siltuximab DS and final lyophilized DP release and stability testing.

3. Submit to the BLA protocols for the following analytical assays used in 3.2.S.2.4 Control of critical steps and intermediates: SE-HPLC, [redacted] (b) (4) impurity assay, as well as the protocols for the assays identified in 3.2.S.2.5 for polysorbate 80, [redacted] (b) (4) (b) (4).

4. [redacted] (b) (4)

5. [redacted] (b) (4)

6. [redacted] (b) (4)

Reference ID: 3393675

(b) (4)

We request a written response to the items enumerated above by October 28, 2013. Please email a PDF copy of the official submission.

If you have any questions, please contact me.

Kind regards,

Lyndsay Hennessey
Quality Regulatory Health Project Manager
FDA/CDER/OPS/OBP-IO
10903 New Hampshire Ave.
WO Building 21 Room 1523
Silver Spring, Maryland 20993-0002
Lyndsay.Hennessey@fda.hhs.gov
240-402-3746

Reference ID: 3393675

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/s/

LYNDSAY J HENNESSEY
10/21/2013

Garvey, Patricia

From: Garvey, Patricia
Sent: Wednesday, October 09, 2013 4:09 PM
To: 'Maloney, Brian [JRDUS] (BMalone1@ITS.JNJ.COM)'
Subject: BLA 125496 Siltuximab - Statistical and Clinical Pharmacology Information Request

Hello Brian,

Please refer to your Biologics License Application (BLA) 125496 Siltuximab submitted under section 351(a) of the Public Health Service Act (PHS Act). We also refer to your submission dated August 29, 2013 and have the following information request.

Statistical

For Study CNTO328MCD2001, please clarify how you determined the primary and the major secondary endpoints in presence of missing or incomplete data. Please provide a response by COB, Wednesday, October 16, 2013.

Clinical Pharmacology

- Please provide a response to request # 1 by COB, Friday, October 11, 2013.
- Please provide responses to all other requests by COB, Wednesday, October 16, 2013.

1. We could not locate the datasets/code for the PK/PD report, please submit these.

2. In addition to your submitted population PK analysis, please also conduct a categorical analysis using the classification of Renal Function Based on Estimated GFR (eGFR) and Estimated Creatinine Clearance (CLcr), see the guidance for further information. Please submit the dataset/code used. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM204959.pdf

3. In addition to your submitted population PK analysis, please also conduct a categorical analysis based on hepatic function (i.e. **NCI classification for mild, moderate and severe hepatic impairment**, or the Child-Pugh classification). Please also include this categorical analysis based on hepatic function in the final population PK analysis. Please submit the dataset/code used.

4. In Section 12.3 of the proposed package insert you describe the PK of your drug as follows:

(b) (4)

[redacted]

Reference ID: 3388126

All of the cross-reference hyperlinks in this section only take you to the Summary of Clinical Pharmacology Studies Module 2.7.2. The Sections that the hyperlinks take you to in Module 2.7.2 do not have hyperlinks to the sources of the specific data or PK parameters that are included in the package insert. Please include cross-reference hyperlinks in Module 2.7.2 that allow the reviewer to locate the sources (Study Reports) of the PK parameters referred to in Section 12.3 of the proposed package insert.

5. In your Summary of Clinical Pharmacology Studies Module 2.7.2, please include cross-reference hyperlinks to the sources of data in all sections including the following sections:
   - Summary of Clinical Pharmacology Findings
   - Section 1.6 Pharmacodynamic Biomarker Studies

6. In Section 1.6 of Module 2.7.2 you state the following:

(b) (4)

Please provide hyperlinks to take the reviewer to the sources of data that support these statements.

Please response via email and follow with an official submission to your BLA.

Please contact me if you have any questions.

Best Regards,
Patty

Patty Garvey, R.Ph.
CAPT, U.S. Public Health Service
Senior Regulatory Project Manager
Division of Hematology Products | Office of Hematology and Oncology Products
Center for Drug Evaluation and Research | Food and Drug Administration
10903 New Hampshire Avenue, WO22 - Room 2329
Silver Spring, MD 20993
Phone: 301-796-8493 | Fax: 301-796-9849 | patricia.garvey@fda.hhs.gov

Reference ID: 3388126

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/s/

PATRICIA N GARVEY
10/09/2013

Garvey, Patricia

From: Garvey, Patricia
Sent: Tuesday, October 08, 2013 1:09 PM
To: 'Maloney, Brian [JRDUS] (BMalone1@ITS.JNJ.COM)'
Subject: BLA 125496 Siltuximab - Clinical Information request

Hello Brian,

Please refer to your Biologics License Application (BLA) 125496 Siltuximab submitted under section 351(a) of the Public Health Service Act (PHS Act).

We also refer to your submission dated August 29, 2013. The clinical reviewer has the following information request:

1. Does the application include the detailed reports of the central pathology review of diagnostic tissue beyond the classification in the dataset ADSL in the column HISTYPER?

2. Where can we find the description of MCD-related Signs and Symptom that were classified as "other CSS" in the datasets or CRFs for individual patients? [Table 7 page 62 of 766 of study report]

3. For subject CNTO328MCD2001-4701-00020 what data in the CRFs documents the patient has multicentric disease? I note there was 1 index lesion [abdominal adenopathy 62 x 45], no non- index lesions, no hepatosplenomegally, and no skin lesions.

Please response via email by Monday, October 14, 2013, 4:00pm (EST) and follow with an official submission to your BLA.

Please contact me if you have any questions.

Best Regards,
Patty

Patty Garvey, R.Ph.
CAPT, U.S. Public Health Service
Senior Regulatory Project Manager
Division of Hematology Products | Office of Hematology and Oncology Products
Center for Drug Evaluation and Research | Food and Drug Administration
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Reference ID: 3386763

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/s/

PATRICIA N GARVEY
10/08/2013

Garvey, Patricia

From: Garvey, Patricia
Sent: Tuesday, September 24, 2013 6:16 PM
To: 'Maloney, Brian [JRDUS] (BMalone1@ITS.JNJ.COM)'
Subject: BLA 125496 Siltuximab - Clinical Site Information Request

Importance: High

Hello Brian,

Please refer to your Biologics License Application (BLA) 125496 Siltuximab submitted under 351(a) of the Public Health Service Act. We refer to your submission dated August 29, 2013 and have the following information request:

Please provide the following **subject level patient data listings, by clinical site**, for Site #102 (Dr. Rhee, U.S.A.) and Site #6501 (Dr. Goh, Singapore), respectively:

(a) Study discontinuations (dates and reason for discontinuation)
(b) All adverse events for the ITT population: inclusive dates, resolution, specific adverse event listing, as applicable.
(c) Specific laboratory measurements/results from baseline to end of study: ESR, CRP, fibrinogen and quantitative immunoglobulin levels.
(d) Efficacy endpoint: measurable and evaluable disease for complete or partial responders, or patients with stable disease

Please provide a response via email by **no later than Friday, September 20, 2013, 4:00 PM EST** and follow-up with an official submission to your BLA.

Please contact me if you have any questions.

Kind Regards,
Patty

Patty Garvey, R.Ph.
CAPT, U.S. Public Health Service
Senior Regulatory Project Manager
Division of Hematology Products | Office of Hematology and Oncology Products
Center for Drug Evaluation and Research | Food and Drug Administration
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Reference ID: 3378694

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/s/

PATRICIA N GARVEY
09/24/2013

Garvey, Patricia

From: Garvey, Patricia
Sent: Wednesday, September 18, 2013 1:45 PM
To: Maloney, Brian [JRDUS] (BMalone1@ITS.JNJ.COM)
Subject: BLA 125496 Siltuximab - Manufacturing Information Request

Importance: High

Hello Brian,

Please refer to your Biologics License Application (BLA) 125496 Siltuximab submitted under 351(a) of the Public Health Service Act. We refer to your submission dated August 29, 2013 and have the following information request:

We are attempting to schedule the pre-approval inspections and require the following to facilitate these activities:

1. Provide manufacturing dates for each of the siltuximab batches to be manufactured at Janssen Biologics BV, Leiden and Janssen Biologics, Cork from October 2013 through end of January 2014. (b) (4)

2. We assume that the schedule/date identified in table 8.2 is for the start of each step of the process. In your response to our request under item 1 above please also include your estimate for the duration of each stage of the process identified. (b) (4)

3. During the pre-BLA meeting (June 19, 2013) you presented a schedule for siltuximab manufacturing that included (b) (4) at Janssen Biologics Cork, Ireland on the week of (b) (4). According to your currently proposed timelines, manufacturing in Janssen Biologics, Cork will take place (b) (4) which may further complicate our scheduling of the inspection for that week. We are requesting that you identify additional production schedule dates at Cork (b) (4), and would preferably occur after that timeline, as foreign inspection travel requires us to initiate travel plans more than 2 months prior to the travel date. If possible, it would also be helpful if you identify a manufacturing timeline where (b) (4) at Janssen Biologics BV occurs during a week which is adjacent to manufacturing activities done at Janssen Biologics in Cork, Ireland.

Please provide a response via email by no later than Friday, September 20, 2013, 12:00 PM EST and follow-up with an official submission to your BLA.

Please contact me if you have any questions.

Reference ID: 3375615

Kind Regards,
Patty

Patty Garvey, R.Ph.
CAPT, U.S. Public Health Service
Senior Regulatory Project Manager
Division of Hematology Products | Office of Hematology and Oncology Products
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Reference ID: 3375615

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/s/

PATRICIA N GARVEY
09/18/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125496/0

BLA ACKNOWLEDGEMENT

Janssen Biotech, Inc.
c/o Janssen Research & Development, LLC
Attention: Brian Maloney, R.Ph., M.S.
Director, Regulatory Affairs
920 Route 202
P.O. Box 300
Raritan, NJ 08869

Dear Mr. Maloney:

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

Name of Biological Product: Sylvant (siltuximab)

Date of Application: August 29, 2013

Date of Receipt: August 30, 2013

Our Secondary Tracking Number (STN): BLA 125496/0

Proposed Use: Treatment of multicentric Castleman's Disease (MCD) in patients who are immunodeficiency virus negative (HIV-) and human herpes virus - 8 negative (HHV-8-).

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

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

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

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

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission.

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

If you have any questions, please contact me at (301) 796-8493.

Sincerely,

{See appended electronic signature page}

Patricia Garvey, R.Ph.
Senior Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

PATRICIA N GARVEY
09/12/2013

Garvey, Patricia

From: Garvey, Patricia
Sent: Wednesday, September 11, 2013 7:09 AM
To: Maloney, Brian [JRDUS] (BMalone1@ITS.JNJ.COM)
Subject: BLA 125496 Siltuximab - Information request

Hello Brian,

Please refer to your Biologics License Application (BLA) 125496 Siltuximab submitted under section 351(a) of the Public Health Service Act (PHS Act).

We also refer to your submission dated August 29, 2013. Please decipher the response below from (b) (6) form 3455.

☑	☐	**Significant payments of other sorts, the total of which exceeds USD 25,000, EXCLUDI conducting the trial or other clinical trials.** This could include, for example, payments made to the investigator or the institution to support activities (i.e., a gre research, compensation in the form of equipment, or retainers for ongoing consultation or honoraria). (b) (6) (b) (6) If yes, please describe:

Best,
Patty

Patty Garvey, R.Ph.
CAPT, U.S. Public Health Service
Senior Regulatory Project Manager
Division of Hematology Products | Office of Hematology and Oncology Products
Center for Drug Evaluation and Research | Food and Drug Administration
10903 New Hampshire Avenue, WO22 - Room 2329
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Phone: 301-796-8493 | Fax: 301-796-9849 | patricia.garvey@fda.hhs.gov

Reference ID: 3372095

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/s/

PATRICIA N GARVEY
09/11/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 011461

MEETING MINUTES

Janssen Research & Development, LLC
Attention: Brian Maloney, RPh, MS
Director, Regulatory Affairs
1499 McKean Road
PO Box 776
Spring House, PA 19477

Dear Mr. Maloney:

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

We also refer to the teleconference between representatives of your firm and the FDA on December 18, 2012. The purpose of the meeting was to discuss the proposed content, format and planned efficacy and safety analyses for the BLA targeted for an August 2013 submission in support of the use of siltuximab for the treatment of symptomatic patients with Multicentric Castleman's disease.

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

If you have any questions, call me at (301) 796-9618.

Sincerely,

{See appended electronic signature page}

Kathy Robie-Suh, MD,PhD
Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Pre-BLA
Meeting Date and Time:	December 18, 2012
Meeting Location:	Teleconference
Application Number:	IND 011461
Product Name:	siltuximab
Indication:	Multicentric Castleman's disease in human immunodeficiency virus negative (HIV), human herpesvirus-8 negative (HHV-8) patients
Sponsor/Applicant Name:	Janssen Research & Development, LLC
Meeting Chair:	Kathy Robie-Suh, MD, PhD
Meeting Recorder:	Sherry Stewart, PharmD

FDA ATTENDEES

OFFICE OF NEW DRUGS/OFFICE OF HEMATOLOGY AND ONCOLOGY PRODUCTS/DIVISION OF HEMATOLOGY PRODUCTS
Ann T. Farrell, MD, Director
Kathy Robie-Suh, MD, PhD, Clinical Team Leader
George Shashaty, MD, Clinical Reviewer

OFFICE OF TRANSLATIONAL SCIENCES/OFFICE OF CLINICAL PHARMACOLOGY/ DIVISION OF CLINICAL PHARMACOLOGY 5
Julie Bullock, PharmD, Clinical Pharmacology Team Leader
Joseph Grillo, PharmD, Clinical Pharmacology Reviewer

OFFICE OF TRANSLATIONAL SCIENCES/ OFFICE OF BIOSTATISTICS/ DIVISION OF BIOMETRICS V
Mark D. Rothmann, PhD, Biostatistics Team Leader
Kallapa Koti, PhD, Biostatistics Reviewer

DIVISION OF HEMATOLOGY, ONCOLOGY, TOXICOLOGY
Luan Lee, PhD, Pharmacology/Toxicology Reviewer

Reference ID: 3241174

OFFICE OF PLANNING AND INFORMATICS/OFFICE OF PLANNING AND ANALYSES/PLANNING AND EVALUATION STAFF
Kimberly Taylor, Interdisciplinary Scientist

SPONSOR ATTENDEES

Rajesh Bandekar, PhD, Associate Director, Biostatistics
Leonid Freytor, MS, Director, Regulatory Affairs
Kathleen Frost, Director, Global Regulatory Policy and Intelligence, GRA
Donna Kipphorn, Manager, Regulatory Affairs
Brian Maloney, RPh, MS, Director, Regulatory Affairs
Willemijn Neher-van Minnen Chemistry, Manuf. & Controls
Thomas Puchalski, PharmD, Director, Biologics Clinical Pharmacology
Ming Qi, MD, PhD, Director, Clinical Development
Michael Smith, PhD, Senior Director, Compound Development Team Leader
Helgi van de Velde, MD, PhD, Sr. Director, Clinical Development
Jessica Vermeulen, MD, PhD, Director, Clinical Development

Reference ID: 3241174

1.0 BACKGROUND

Siltuximab is an $IgG_{1\kappa}$ monoclonal antibody (mAb) for the treatment of Castelman's disease in human immunodeficiency virus negative (HIV), human herpes virus-8 negative (hhv-8) patients. The underlying pathophysiology of Castleman's disease is still poorly understood, however IL-6 appears to play a central role. Siltuximab specifically binds to human interleukin-6 (IL-6). Janssen Research and Development, LLC (JRD) received orphan drug status for siltuximab on May 26, 2006. The purpose of this meeting is to discuss JRD's planned BLA for siltuximab.

2.0 DISCUSSION

1. Does the Division agree with the overall organization of the eCTD?

   FDA Response: **Yes.**

   Discussion: ***No discussion occurred.***

2. Does the Division agree that a waiver for pediatric studies is warranted for this indication?

   FDA Response: **The request for the waiver of pediatric studies, along with justification, should be made when the BLA is submitted. The decision for a waiver for pediatric studies will be made after the BLA has been submitted. Drug products for which Orphan Drug Designation has been granted are not subject to requirement for pediatric studies under PREA; however, the Agency encourages studies of drug products for use in pediatric patients where appropriate.**

   Discussion: ***No discussion occurred.***

3. Does the Division agree with the proposed list of studies for submission of financial disclosure information?

   FDA Response: **Yes.**

   Discussion: ***No discussion occurred.***

4. Does the Division agree that our plan for the REMS discussion is acceptable?

   FDA Response: **Yes.**

   Discussion: ***No discussion occurred.***

5. Does the Division agree with the proposed submission of only the SCE and that an ISE is not warranted.

Reference ID: 3241174

FDA Response: **Yes. However, a full study report for each individual study should be provided in the application.**

Discussion: ***No discussion occurred.***

6. Does the Division agree with the proposed organization of the SCS and ISS?

FDA Response: **Yes.**

Discussion: ***No discussion occurred.***

7. Does the Division agree with the proposed data pooling strategy for the integrated safety evaluation of siltuximab in support of the BLA?

FDA Response: **Yes.**

Discussion: ***No discussion occurred.***

8. Does the Division agree with the approach in the statistical analysis plan for the summary of safety shown in Appendix 13.1.3, Attachment 1?

FDA Response: **Yes. If additional analyses are needed, they will be requested during the review.**

Discussion: ***No discussion occurred.***

9. Does the Division agree with the proposed list of adverse events of interest that will be included in the siltuximab BLA?

FDA Response: **In addition to the listed mechanism-related adverse events, you should include other risks identified during development, such as cytokine release syndrome.**

Discussion: ***No discussion occurred.***

10. Does the Division agree with the proposed presentation for QTc and electrocardiographic (ECG) data in the BLA?

FDA Response: **Yes, your proposed presentation is acceptable. Please also refer to the Interdisciplinary Review Team's written advice issued on 10 August 2010 for recommendations regarding the submission of your QT reports. Adequacy of the data is a review issue.**

Reference ID: 3241174

Discussion: ***No discussion occurred.***

11. Does the Division agree that integrated safety analysis to compare the cell lines is not warranted in the BLA?

FDA Response: Yes.

Discussion: ***No discussion occurred.***

12. Does the Division agree with the proposed subgroup analysis in the ISS?

FDA Response: Yes.

Discussion: ***No discussion occurred.***

13. Since the clinical cutoff for the primary analysis of Study CNTO328MCD2001 is scheduled for 31 January 2013, JRD proposes to use the same clinical cutoff date to generate serious adverse event listings from the safety database for ongoing subjects to be included in the BLA. Does the Division agree that this is acceptable?

FDA Response: Yes.

Discussion: ***No discussion occurred.***

14. JRD proposes a cutoff date of 31 July 2013 for the 120-day safety update. Does the Division agree that this is acceptable?

FDA Response: Yes.

Discussion: ***No discussion occurred.***

15. Does the Division agree with our proposal for the biomarker data to be included in the BLA?

FDA Response: Yes, you may include the data in the BLA. Please discuss the difficulties you had developing an IL-6 assay post treatment.

Discussion: ***No discussion occurred.***

16. Does the Division agree with this plan for submission of a stability update not later than 30 days after the initial submission for (b) (4) drug substance FB, 100 mg FLP and 400 mg FLP?

Reference ID: 3241174

FDA Response: Yes, it is acceptable to submit the stability update for (b) (4) drug substance FB, 100 mg FLP and 400 mg FLP within 30 days after the initial submission of the BLA. If the stability data are not available within this time frame, you may receive an information request from the FDA requesting the updated stability data. The data may be submitted upon receipt of this information request.

Discussion: *No discussion occurred.*

17. Does the Division agree that the list of toxicology studies is sufficient to support the proposed indication, as agreed upon at the End of Phase 2 meeting?

FDA Response: The list of toxicology studies appears acceptable to support marketing application of siltuximab for the proposed indication. The adequacy of the studies will be determined after the review of the data in your BLA submission.

Discussion: *No discussion occurred.*

18. Does the Division agree with the proposed criteria for submission of narratives?

FDA Response: The Division does not agree. In addition to the listed, you should also provide narratives for all subjects who experienced serious adverse events whether or not they were adjudged to be related to siltuximab for all three studies (CNTO328MCD2001, C0328T03, and CNTO328MCD2002).

Discussion: *No discussion occurred.*

19. Does the Division agree with the proposal for submission of case report forms?

FDA Response: No. You should include CRFs for all deaths, regardless of cause.

Discussion: *No discussion occurred.*

20. Does the Division agree that our dataset submission plan is acceptable?

FDA Response: We note you plan to submit datasets for trials C0328T01, C0328T03, C0328T04, C0328T05, C0328T06, C0328T07, C0328T08, JPN-C0328-MM-101, CNTO328STM2001, CNTO328SMM1001, CNTO328MMY2001, CNTO328MCD2001, CNTO328MCD2002, and CNTO328MDS2001. Please note the following:

Reference ID: 3241174

- **Provide all concentration-time and derived PK parameter datasets for all studies. In the study reports, present the PK parameter data as geometric mean with coefficient of variation (and mean ± standard deviation) and median with range as appropriate.**
- **Clinical pharmacology and biopharmaceutics related datasets should be complete and not be limited to PK/PD. For example, domains or non-SDTM files related to safety (e.g., ADR's), demographics, non-PK laboratory values, concomitant drug use should be included. All of these are important in identifying patterns of potential clinical pharmacology related causes of clinical safety outcomes.**

- **We encourage you to refer to the following pharmacometric data and models submission guidelines (http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm180482.htm). For any population PK models all datasets used for model development and validation should be submitted as a SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets. Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt). A model development decision tree and/or table which gives an overview of modeling steps. For the population analysis reports we request that you submit, in addition to the standard model diagnostic plots, individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual predication line and the population prediction line. In the report, tables should include model parameter names and units. For example, oral clearance should be presented as CL/F (L/h) and not as THETA(1). Also provide in the summary of the report a description of the clinical application of modeling results.**

  The SAS programs that are used to create the derived datasets for the efficacy endpoints and the SAS programs that are used for efficacy data analysis should be included in the BLA submission.

  Please provide the location of the SAS dataset, the names of the variables used and the programs used to get every value that will be appearing in the label.

Reference ID: 3241174

Discussion: ***FDA clarified that all clinical pharmacology studies used to support the indication or labeling claims should include complete data sets as listed in our response. Submission of PK data from the combination therapy studies is not required unless the PK data from these studies will be used to support labeling claims.***

21. JRD proposes to use Medical Dictionary for Regulatory Activities (MedDRA) version 15.1 for all adverse events. Does the Division agree that this is acceptable?

    FDA Response: Yes.

    Discussion: ***No discussion occurred.***

22. JRD proposes to use the WHO Drug Dictionary, September 2012 version for concomitant medications. Does the Division agree that this is acceptable?

    FDA Response: Yes.

    Discussion: ***No discussion occurred.***

Additional Clinical Pharmacology Comments:

- **In the appropriate clinical pharmacology sections of the eCTD include the following:**
  - **An evaluation of the effects of covariates such as age, weight, gender, race, etc. on the PK (pharmacokinetics) of Siltuximab.**
  - **A table listing of patients with renal or hepatic impairment who have received Siltuximab, organized by trial number. Include available renal and hepatic function parameters such as SCr, CLCr calculated by the Cockcroft Gault equation (or eGFR calculated by MDRD), AST/ALT, T.Bili, platelet count, etc for each patient in the listing. Also, provide summaries of the following information for each patient: PK and PD data, safety, and clinical efficacy.**
- **Please see the attached Question Based Review (QBR) format and include this information in section 2.7.2 of your eCTD BLA submission with appropriate links to relevant study reports and analyses used to support your responses.**

  Discussion: ***FDA clarified that for renal and hepatic impairment patients should be classified by either FDA guidance criteria or NCI organ impairment criteria. FDA recommended that the efficacy data does not need to be included in the table.***

Additional Statistics Comments:

- **Please clarify what statistical analysis method was used in the sample size justification for study CNTO328MCD2001 and whether simulations were used.**

Reference ID: 3241174

Discussion: ***The sponsor clarified the statistical analysis method they used in determining sample size. They also assessed the power using a conservative Fishers Exact test and obtained 78% power. The Agency finds this explanation acceptable.***

3.0 DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

The content of a complete application was discussed.

All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. We agreed that the following minor application components may be submitted within 30 calendar days after the submission of the original application:

- Stability data

Prominently identify each submission containing your late component(s) with the following wording in bold capital letters at the top of the first page of the submission:

BLA NUMBER: LATE COMPONENT - QUALITY

4.0 PREA PEDIATRIC STUDY PLAN

The Food and Drug Administration Safety and Innovation Act of 2012 changes the timeline for submission of a PREA Pediatric Study Plan and includes a timeline for the implementation of these changes. You should review this law and assess if your application will be affected by these changes. If you have any questions, please email the Pediatric Team at Pedsdrugs@fda.hhs.gov.

5.0 PRESCRIBING INFORMATION

Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57.

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm. We encourage you to review the information at this website and use it as you draft prescribing information for your application.

6.0 MANUFACTURING FACILITIES

To facilitate our inspectional process, the Office of Manufacturing and Product Quality in CDER's Office of Compliance requests that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

7.0 ISSUES REQUIRING FURTHER DISCUSSION

There are no issues requiring further discussion at this time.

8.0 ATTACHMENTS AND HANDOUTS

No attachments were presented or distributed during this meeting.

Reference ID: 3241174

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/s/

KATHY M ROBIE SUH
01/07/2013

LATE-CYCLE COMMUNICATION DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125496/0

LATE-CYCLE MEETING MINUTES

Janssen Biotech, Inc.
c/o Janssen Research & Development, LLC
Attention: Brian Maloney, RPh, MS
Director, Regulatory Affairs
920 Route 202
P.O. Box 300
Raritan, NJ 08869

Dear Mr. Maloney:

Please refer to your Biologic License Application (BLA) submitted under section 351 of the Public Health Service Act for SYLVANT (siltuximab) for Injection for Intravenous Infusion.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on February 25, 2014.

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

If you have any questions, please contact Patricia Garvey, Senior Regulatory Project Manager at (301) 796-8493.

Sincerely,

{See appended electronic signature page}

Albert Deisseroth, MD, PhD
Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: February 25, 2014 at 10:00 AM (EST)
Meeting Location: Teleconference

Application Number: BLA 125496/0
Product Name: SYLVANT (siltuximab)
Applicant Name: Janssen Biotech, Inc.

Meeting Chair: Albert Deisseroth, MD, PhD
Meeting Recorder: Patricia Garvey, RPh

FDA ATTENDEES

OFFICE OF HEMATOLOGY AND ONCOLOGY PRODUCTS (OHOP)
Richard Pazdur, MD – Director
Jonathan Jarow, MD – Acting Deputy Director

OHOP/DIVISION OF HEMATOLOGY PRODUCTS
Ann Farrell, MD – Director
Albert Deisseroth, MD, PhD – Clinical Team Leader
Patricia Dinndorf, MD – Clinical Reviewer
Robert Kane, MD – Deputy Director for Safety
Diane Leaman – Safety Regulatory Project Manager
Lara Akinsanya, MS – Senior Regulatory Project Manager
Patricia Garvey, RPh – Senior Regulatory Project Manager

OHOP/DIVISION OF HEMATOLOGY, ONCOLOGY, TOXICOLOGY
Pedro Del Valle, PhD – Pharmacologist
Brenda Gehrke, PhD – Pharmacologist

OFFICE OF PHARMACEUTICAL SCIENCE /OFFICE OF BIOTECHNOLOGY PRODUCTS/DIVISION OF MONOCLONAL ANTIBODIES
Chana Fuchs, PhD – Product Quality Team Leader
Audrey Jia, MD, PhD – Product Quality Reviewer (Drug Substance)
Bazarragchaa Damdinsuren, MD, PhD – Product Quality Reviewer (Drug Product)

OFFICE OF COMPLIANCE/OFFICE OF MANUFACTURING AND PRODUCTS QUALITY /DIVISION OF GOOD MANUFACTURING PRACTICE ASSESSMENT/BIOTECHNOLOGY MANUFACTURING ASSESSMENT BRANCH
Patricia Hughes, PhD – Product Quality Microbiology Team Leader
Maria Candau-Chacon, PhD – Product Quality Microbiology Reviewer (Drug Substance)

EASTERN RESEARCH GROUP ATTENDEES
Peter Zhou, Independent Assessor
Uche Chimeh, Independent Assessor

APPLICANT ATTENDEES
Rajesh Bandekar, PhD – Associate Director, Biostatistics
Sudhir Burman, PhD – Associate Director, Product LCM Specs
Shalini Chaturvedi, PhD – Principal Scientist Biomarkers
Kundan Doshi, PhD – Associate Director, Global Labeling
Rada Dubashinsky – Senior Management Product Quality Management
Todd Gibson – Associate Director, Technical Integration
(b) (4)
Cindy Grant – Senior Scientist, Large Molecule Development
Mary Guilfoyle, MS – Compound Development Team Leader
Tom Hogan, PhD – Scientific Director, CMC Regulatory Affairs
Ronald Imhoff – Director, CMC Regulatory Affairs
Naushad Islam, RPh, MS – Director, Global Regulatory Leader
Milad Khan, MPh, MS – Manager, Regulatory Affairs
Barbara Kolb – Senior Director, Regulatory Affairs
Michael Lewis – Director, Large Molecule Development
(b) (4)
Chaomei Lin – Associate Director, Large Molecule Development
Manny Lopez – Scientific Director, Portfolio Management
Brian Maloney, RPh, MS – Director, Regulatory Affairs
(b) (4)
Willemijn Neher-van Minnen – Associate Director, CMC Regulatory Affairs
Jeffrey Nemeth, PhD – Associate Scientific Director
Ming Qi, MD, PhD –Director, Clinical Development
Tom Puchalski, PharmD – Scientific Director, Pharmacokinetics
Sandra Rattray, PhD – Vice President, Regulatory Affairs
Melanie Rothschild, MBA – Manager, Regulatory Affairs
Helgi van de Velde, MD, PhD – Senior Director, Clinical Development
Jessica Vermeulen, MD, PhD – Director, Clinical Development

1.0 BACKGROUND

BLA 125496/0 was submitted on August 29, 2013 for SYLVANT (siltuximab) and is currently under review by FDA. The application has been granted priority review.

Proposed indication: Treatment of multicentric Castleman's Disease (MCD) in patients who are immunodeficiency virus negative (HIV-), and human herpes virus -8 negative (HHV-8-).

PDUFA goal date: April 30, 2014

FDA issued a Background Package in preparation for this meeting on February 14, 2014.

Reference ID: 3468315

2.0 DISCUSSION

1. Introductory Comments

   FDA stated that the purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

2. Discussion of Substantive Review Issues

   In a February 21, 2014 e-mail correspondence , the Sponsor provided CMC comments (attachment at the end of LCM minutes) to FDA substantive CMC review issues included in the February 14, 2014 late-cycle meeting background package.

   For the purpose of this meeting, only the following CMC issues were discussed:

   a. FDA Comment: Regarding FLP lot release and stability specifications: We do not agree with the proposed acceptance criterion for quantity [(b) (4)] mg/mL). The acceptance criterion should be based on the labeled concentration of 20 mg/mL. Revise the acceptance criterion accordingly.

   Discussion: The Sponsor agrees to the acceptance criterion of [(b) (4)] mg/mL. The Sponsor proposes an initial increase in the upper limit of the stability acceptance criterion, with the upper limit of [(b) (4)] mg/mL, explaining that due to assay variability they were concerned about failures of current drug product lots which were released at the higher end of the [(b) (4)] acceptance criterion. The sponsor also explained that they plan to implement [(b) (4)] . These controls should be in place for the new launch batches planned for [(b) (4)] FDA agreed that the higher stability acceptance criterion may be acceptable for the current lots but that the stability specification will need to be adjusted post approval for those FLP lots manufactured from FB that are filled to the target [(b) (4)], and requested that the Sponsor provide the rationale for their proposal to the BLA.

   The Sponsor will provide a response and information on this issue on February 28, 2014.

   b. FDA Comment: There appear to be changes in product quality attributes (e.g., size and charge variants) observed in the [(b) (4)] and FB real time stability studies. While these changes are small, the allowed limits per the stability specifications and the FLP release specifications require limited changes during the shelf-life of each material. In addition, there are no data available to support the stability when [(b) (4)] and FB are used at the end of their expiry periods; the effects of long term storage on quality attributes might be greater than the additive effects, since degradation of biological products is often not linear. Therefore, if additional data to support a combined expiry period of [(b) (4)] for [(b) (4)] and [(b) (4)] for FB cannot be provided, an

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alternative mechanism to control for the overall expiry period for the [redacted] (b) (4) /FB combination will need to be implemented (e.g., individual expiry periods for [redacted] (b) (4) and FB and an combined expiry period of less than the additive time, which would be controlled by Janssen's quality system).

Discussion: ***The Sponsor described their plan of limiting [redacted] (b) (4) and FB to a combined expiration dating of [redacted] (b) (4) with [redacted] (b) (4) not exceeding [redacted] (b) (4) expiration dating and FB not exceeding [redacted] (b) (4) expiration dating. The Agency requested that the Sponsor provide the cumulative shelf lives of [redacted] (b) (4), FB and FLP and rationale to support the requested shelf life taking into consideration the cumulative [redacted] (b) (4) FB, and FLP data as well as the proposed specifications. The Agency stated that it will need to review the complete data in order to make the decision on the shelf life.***

c. FDA Comment: Regarding your assessment of CQAs: [redacted] (b) (4) is linked to increased [redacted] (b) (4) as well as reduced potency by bioassay. Although the reduced potency was within the acceptance criterion of [redacted] (b) (4) of reference (Table 15 of Section 3.2.S.3.2.1.8), it is clearly much reduced when compared to results of control and other forced degradation samples, [redacted] (b) (4) The potency result is also much lower than all potency results reported for FLP on release and stability. Therefore, we do not agree that [redacted] (b) (4) is a minimal severity attribute and do not agree that [redacted] (b) (4) is an nCQA. Adjust your control strategies accordingly and submit the relevant information to the BLA.

Discussion: [redacted] (b) (4)

3. Postmarketing Requirements/Postmarketing Commitments

   a. The final study report of CNTO328MCD2002 "An Open-label, Multicenter Study to Evaluate the Safety of Long-term Treatment with Siltuximab in Subjects with Multicentric Castleman's Disease."

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***Discussion*: The study will be completed March 2017. The final study report will be submitted August 2017.**

b. OBP list (additional PMCs might be necessary, depending on the responses to the current requests for information):
   i. To re-evaluate siltuximab Formulated Bulk lot release and stability specifications and (b) (4) stability specifications after 30 lots have been manufactured using the commercial manufacturing process. The corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be provided by Month/Year (Janssen to provide date).

   ii. To re-evaluate siltuximab Drug Product lot release and stability specifications after 30 lots have been manufactured using the commercial manufacturing process. The corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be provided by Month/Year (Janssen to provide date).

***Discussion*: The Sponsor will provide CMC PMC/PMRs dates at a later date since it will be revised based on Agency review of the CMC February 28, 2014 submission.**

4. Major Labeling Issues

***Discussion*: FDA will provide the next FDA proposed labeling on or after February 28, 2014. Janssen will provide comments to FDA proposed container and carton labels on February 28, 2014.**

5. Review Plans

***Discussion*: The Agency will review the Sponsor's CMC response once it is received on February 28, 2014. The Agency will provide questions/comments if necessary.**

6. Wrap-up and Action Items

***Discussion*: This application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, this meeting did not address the final regulatory decision for the application.**

3.0 ATTACHMENT

The Sponsor's February 21, 2014 responses to FDA comments in February 14, 2014 Late-Cycle Meeting Background Package.

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Reference ID: 3468315

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/s/

ALBERT B DEISSEROTH
03/11/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125496/0

LATE CYCLE MEETING
BACKGROUND PACKAGE

Janssen Biotech, Inc.
c/o Janssen Research & Development, LLC
Attention: Brian Maloney, R.Ph., M.S.
Director, Regulatory Affairs
920 Route 202
P.O. Box 300
Raritan, NJ 08869

Dear Mr. Maloney:

Please refer to your Biologic License Application (BLA) submitted under the Public Health Service Act for SYLVANT (siltuximab) for Injection for Intravenous Infusion.

We also refer to the Late-Cycle Meeting (LCM) scheduled for February 25, 2014. Attached is our background package, including our agenda, for this meeting.

If you have any questions, please contact Patricia Garvey, Senior Regulatory Project Manager, at (301) 796-8493.

Sincerely,

{See appended electronic signature page}

Albert Deisseroth, M.D., Ph.D.
Clinical Team Lead
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:
Late-Cycle Meeting Background Package

LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time:	February 25, 2014 at 10:00 AM to 11:00 AM
Meeting Location:	Teleconference
Application Number:	BLA 125496
Product Name:	SYLVANT (siltuximab)
Indication:	Treatment of multicentric Castleman's Disease (MCD) in patients who are immunodeficiency virus negative (HIV-), and human herpes virus -8 negative (HHV-8-)
Sponsor/Applicant Name:	Janssen Biotech, Inc.

INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

I. BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

1. Discipline Review Letters

No Discipline Review letters have been issued to date.

2. Substantive Review Issues

At this time there are substantive CMC review issues that are delineated below and need to be addressed.

Reference ID: 3454502

II. ADVISORY COMMITTEE MEETING

An Advisory Committee meeting is not planned.

III. REMS OR OTHER RISK MANAGEMENT ACTIONS

No issues related to risk management have been identified to date.

IV. LCM AGENDA

1. Introductory Comments – 5 minutes (RPM/CDTL)
   Welcome, Introductions, Ground rules, Objectives of the meeting

2. Information Requests – 40 minutes

(b) (4)

[redacted]

Reference ID: 3454502

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(b) (4)

3. Postmarketing Requirements/Postmarketing Commitments – 5 minutes

   a. Submit the final study report of CNTO328MCD2002 "An Open-label, Multicenter Study to Evaluate the Safety of Long-term Treatment with Siltuximab in Subjects with Multicentric Castleman's Disease." The study will be completed xx/xx/xxxx. The final study report will be submitted xx/xx/xxxx.

      Please be prepared to provide a proposed timeline for study completion and final study report submission at the February 25 meeting.

OBP list (additional PMCs might be necessary, depending on the responses to the current requests for information):

   b. To re-evaluate siltuximab Formulated Bulk lot release and stability specifications and (b) (4) stability specifications after 30 lots have been manufactured using the commercial manufacturing process. The corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be provided by Month/Year (Janssen to provide date).

      [Note to Janssen: Please note that some of the statistical analysis methods as identified in the justifications sections for DS (3.2.S.4.5) and DP (3.2.P.5.6) were not found acceptable in the initial review. For example, for evaluation of the acceptance criteria of cIEF basic peak for FB, your justification of the proposed specification ignores those release results less than LOQ, which is not appropriate because these are actual results obtained from DS and DP release and stability testing.]

   c. To re-evaluate siltuximab Drug Product lot release and stability specifications after 30 lots have been manufactured using the commercial manufacturing process. The corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be provided by Month/Year (Janssen to provide date).

Drug Product Quality Microbiology:

   d. To determine the volume of the (b) (4) necessary to achieve consistent (b) (4) test conditions, provide the supportive data, and use the determined volume in the (b) (4) test of the drug product (b) (4) by May 2014.

Reference ID: 3454502

4. Review Plans – 5 minutes

   Proposed labeling and, if necessary, any post-marketing requirement/commitment requests will be communicated by October 25, 2013.

5. Wrap-up and Action Items – 5 minutes

Reference ID: 3454502

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/s/

ALBERT B DEISSEROTH
02/14/2014