

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125496Orig1s000

OTHER REVIEW(S)

Therapeutic Biological Establishment Evaluation Request (TB-EER) Form

Instructions:

The review team should email this form to the email account "CDER-TB-EER" to submit:

- 1) an initial TB-EER within 10 business days of the application filing date
- 2) a final TB-EER 15-30 days prior to the action date

Note: All manufacturing¹ locations named in the pending submission, whether contract facilities or facilities owned by the applicant, should be listed on this form. For bundled supplements, one TB-EER to include all STNs should be submitted.

APPLICATION INFORMATION

PDUFA Action Date: Action anticipated April 7-12
PDUFA = April 30, 2014

Applicant Name: Janssen Biotech, Inc.
U.S. License #: 1864
STN(s): 125496/0
Product(s): Siltuximab (Sylvant)

Short summary of application: BLA for the treatment of patients with multicentric Castleman's disease (MCD) who are human immunodeficiency virus negative and human herpesvirus-8 negative

FACILITY INFORMATION (DRUG SUBSTANCE)

Manufacturing Location: Leiden, The Netherlands
Firm Name: Janssen Biologics B.V.
Address: Einsteinweg 101
Leiden, The Netherlands CB-2333
FEI: 3002806632

Short summary of manufacturing activities performed: Drug Substance Manufacturing (b) (4)
analytical testing of process intermediates and bulk drug substance; Testing of Final Lyophilized Product

¹ The regulations at 21 C.F.R. § 207.3(a)(8) defines "manufacturing or processing" as "the manufacture, preparation, propagation, compounding, or processing of a drug or drugs as used in section 510 of the act [21 U.S.C. § 360] and is the making by chemical, physical, biological, or other procedures of any articles that meet the definition of drugs in section 201(g) of the act. The term includes manipulation, sampling, testing, or control procedures applied to the final product or to any part of the process. The term also includes repackaging or otherwise changing the container, wrapper, or labeling of any drug package to further the distribution of the drug from the original place of manufacture to the person who makes final delivery or sale to the ultimate consumer."

This site was inspected by CDER-OMPQ from 12/16/2013 – 12/20/2013 and classified VAI. This was a Pre-License Inspection for Siltuximab covering (b) (4) drug substance manufacturing operations. The TRP profile was updated and is acceptable.

Manufacturing Location: Co. Cork, Ireland
Firm Name: Janssen Biologics (Ireland)
Address: Barnahely
Ringaskiddy, Co. Cork, Ireland
FEI: 3007029098

Short summary of manufacturing activities performed: Drug Substance Manufacturing (b) (4) analytical testing of process intermediates and bulk drug substance; Testing of Final Lyophilized Product

This site was inspected by IOG from 3/3/2014 – 3/7/2014 and classified VAI. This was a routine CGMP surveillance inspection covering (b) (4) drug substance and drug product manufacturing operations. The (b) (4) and TRP profiles were updated and are acceptable.

Manufacturing Location: (b) (4)
Firm Name: (b) (4)
Address: (b) (4)
FEI: (b) (4)

Short summary of manufacturing activities performed: (b) (4)

This site was inspected by (b) (4) on (b) (4) and classified NAI. This was a routine CGMP surveillance inspection covering (b) (4) The (b) (4) profile was updated and is acceptable.

Manufacturing Location: Switzerland
Firm Name: Cilag AG
Address: Hochstrasse 201
Schaffhausen, Switzerland CH-8200
FEI: 3002806695

Short summary of manufacturing activities performed: Manufacture, (b) (4) Final Lyophilized Product

This site was inspected by IOG from 2/17/2014 – 2/18/2014 and classified NAI. This was a routine CGMP surveillance inspection covering (b) (4) drug product manufacturing operations. The (b) (4) profile was updated and is acceptable.

OVERALL RECOMMENDATIONS:

There are no pending or ongoing compliance actions that prevent approval of this original BLA.

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/s/

CHRISTINA A CAPACCI-DANIEL
04/23/2014

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

BLA # 125496/0
Product Name: SYLVANT (siltuximab)

PMR 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:	<u>completed</u>
	Trial Completion:	<u>03/31/2017</u>
	Final Report Submission:	<u>08/31/2017</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

This is an ongoing study collecting long term safety information on patients with Multicentric Castleman’s Disease benefiting from continued therapy with siltuximab enrolled in the clinical trial for licensure.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The goal of the study is to evaluate the safety associated with long term chronic therapy with siltuximab.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Collect long term safety information on patients with multicentric Castleman's disease receiving chronic therapy with siltuximab.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
The BLA include an interim report of this study. The PMC is to submit a final study report for the trial.
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 Immunogenicity as a marker of safety
 Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 Dose-response study or clinical trial performed for effectiveness
 Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
 Are the objectives clear from the description of the PMR/PMC?
 Has the applicant adequately justified the choice of schedule milestone dates?
 Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
 There is not enough existing information to assess these risks
 Information cannot be gained through a different kind of investigation
 The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
 The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

R Kane
(Signature line for BLAs)

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
04/16/2014

ROBERT C KANE
04/16/2014

Product Quality (CMC) PMR/PMC Development Template
TO BE USED FOR PMCS NOT REPORTABLE UNDER 506(B)

This template should be completed by the review chemist (ONDQA) or review biologist (OBP) and included for each type of CMC PMR/PMC in the Action Package. See #4 below for list of CMC PMR/PMC types

125496/siltuximab

PMC #1 Description: Reassessment of release and shelf-life specifications for the 100 mg/vial Drug Product after manufacture of a sufficient number of commercial lots to allow for better statistical analysis.

PMC wording: "To re-evaluate siltuximab 100 mg/vial final lyophilized product lot release and stability specifications using the commercial manufacturing process 5 years from the PDUFA date of April 2014 or after the manufacture of 30 lots, whichever occurs first. The 30 lots will include the 9 lots which were included in the analysis of specifications submitted in the BLA and any subsequent FLP lots manufactured. The corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications

(b) (4)

(b) (4)

PMC Schedule Milestones:

Study Completion Date:

04/2019

Final Report Submission Date:

07/2019

PMC #2 Description: Reassessment of release and shelf-life specifications for the 400 mg/vial Drug Product after manufacture of a sufficient number of commercial lots to allow for better statistical analysis.

PMC wording: "To re-evaluate siltuximab 400 mg/vial final lyophilized product lot release and stability specifications using the commercial manufacturing process 5 years from the PDUFA date of April 2014 or after the manufacture of 30 lots, whichever occurs first. The 30 lots will include the 7 lots which were included in the analysis of specifications submitted in the BLA and any subsequent FLP lots manufactured. The corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications

(b) (4)

(b) (4)

PMC Schedule Milestones:

Study Completion Date:

04/2019

Final Report Submission Date:

07/2019

PMC #3 Description:

Reassessment of release and shelf-life specifications for the formulated bulk drug substance after manufacture of a sufficient number of commercial lots to allow for better statistical analysis.

PMC wording: "To re-evaluate siltuximab formulated bulk lot release and stability specifications using the commercial manufacturing process 5 years from April 2014 or after the manufacture of 30 lots, whichever occurs first. The 30 lots will include the 13 lots which were included in the analysis of specifications submitted in the BLA and any subsequent FB lots manufactured. The corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications (b) (4)

(b) (4)

PMC Schedule Milestones:

Study Completion Date:

04/2019

Final Report Submission Date:

07/2019

PMC #4 Description:

Reassessment of release and shelf-life specifications for (b) (4) intermediate after manufacture of a sufficient number of commercial lots to allow for better statistical analysis.

PMC wording: "To re-evaluate siltuximab (b) (4) intermediate lot release and stability specifications using the commercial manufacturing process 2 years from April 2014 or after the manufacture of 30 lots, whichever occurs first. The 30 lots will include the 7 lots which were included in the analysis of cIEF specifications submitted in the BLA and any subsequent (b) (4) lots manufactured. The cIEF and SE-HPLC data from all lots manufactured using the commercial manufacturing process will 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 (b) (4)

(b) (4)

PMC Schedule Milestones:

Study Completion Date:	04/2016
Final Report Submission Date:	07/2016

PMC # 7 Description: Reassessment of the (b) (4) reference material (b) (4) requalification acceptance criterion for potency after a sufficient data are collected to allow an appropriate statistical evaluation.

PMC wording: "To tighten the (b) (4) reference material requalification acceptance criteria based on appropriate statistical evaluation and a sufficient amount of data points required for such an evaluation. The updated acceptance criterion and supporting data will be submitted as a CBE0 by November 2014."

PMC Schedule Milestones:

Final Report Submission Date:	11/2014
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- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC/OBP NON-REPORTABLE PMCS FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL. USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**
- **DO NOT USE THIS FORM IF ANY STUDIES WILL BE REQUIRED UNDER FDAIA OR WILL BE PUBLICLY REPORTABLE**

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check the reason below and describe.

- Need for drug (Unmet need/ Life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

The current release and shelf-life specifications approved under BLA for FB and FLP, and the current potency specification for requalification of (b) (4) are sufficient to ensure adequate quality and safety of siltuximab for the initial marketed product. Increased manufacturing and testing experience gained post licensure can facilitate improved specifications.

2. Describe the particular review issue and the goal of the study.

Siltuximab release and shelf-life specifications are based on clinical and manufacturing experience during the BLA review; This is also true of the potency specification for (b) (4) requalification. However, the number of lots or datapoints to date do not allow for a robust statistical analysis of the data. Some specifications have a statistical component that should be re-assessed when a sufficient number of marketed product lots or datapoints have been tested.

3. [OMIT—for PMRs only]

4. What type of study is agreed upon (describe and check the type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the Agreed upon study:

Statistical analysis of release data acquired following manufacture of additional commercial lots.

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs only)

Product Quality (CMC) PMR/PMC Development Template
TO BE USED FOR PMCS NOT REPORTABLE UNDER 506(B)

This template should be completed by the review chemist (ONDQA) or review biologist (OBP) and included for each type of CMC PMR/PMC in the Action Package. See #4 below for list of CMC PMR/PMC types

PMC #5 Description: Confirmation of (b) (4) using a validated reduced scale model.

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

PMC Schedule Milestones:

Final Report Submission Date: 12/2014

PMC #6 Description: Confirmation of (b) (4) using a validated reduced scale model.

PMC wording: "To confirm the anticipated amount of (b) (4) The results of this study will be submitted by December 2014."

PMC Schedule Milestones:

Final Report Submission Date: 12/2014

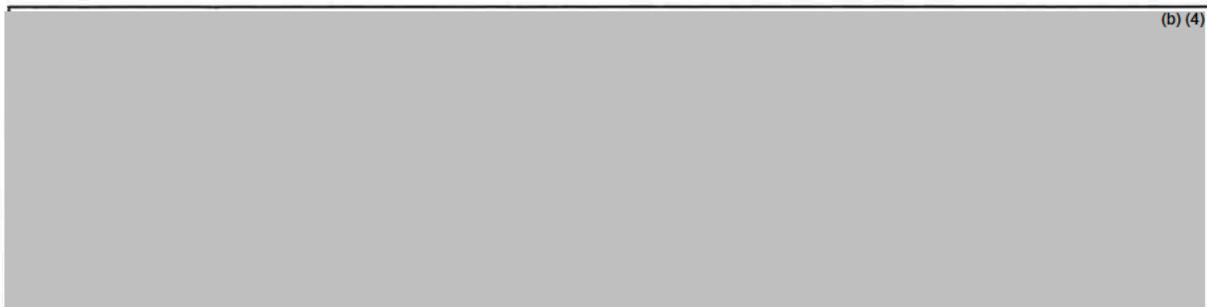
- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC/OBP NON-REPORTABLE PMCS FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL. USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**
- **DO NOT USE THIS FORM IF ANY STUDIES WILL BE REQUIRED UNDER FDAAA OR WILL BE PUBLICLY REPORTABLE**

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check the reason below and describe.

- Need for drug (Unmet need/ Life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval

- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

(b) (4)



2. Describe the particular review issue and the goal of the study.

(b) (4)



3. [OMIT—for PMRs only]

4. What type of study is agreed upon (describe and check the type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the Agreed upon study:

(b) (4)



5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs only)

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check the reason below and describe.

- Need for drug (Unmet need/ Life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

The sponsor provided adequate data to support the stability of MCB, WCB and the consistency of the levels of (b) (4) in their process. In addition, the sponsor provided characterization data to support using (b) (4) (b) (4) These data provided are sufficient to ensure adequate quality and safety of siltuximab for the initial marketed products. Additional control strategies are needed to ensure the long term and comprehensive control for the parameters identified.

2. Describe the particular review issue and the goal of the study.

There were insufficient programs and strategies to ensure the long term monitoring of the points identified. (8) there was an insufficient stability program to identify continued stability of the MCB and WCB.(9) there was an insufficient monitoring strategy to identify continued control of the (b) (4) that may impact product quality, even though the levels do not appear to significantly change for the lots in the BLA . (10) there was insufficient monitoring strategy to identify continued control of the levels of (b) (4) Development of control and monitoring strategies requested would ensure that these do not change during the product lifecycle.

3. [OMIT—for PMRs only]

4. What type of study is agreed upon (describe and check the type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the Agreed upon study:

Additional control strategies are required to ensure control over the product lifecycle.

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs only)

Product Quality (CMC) PMR/PMC Development Template
TO BE USED FOR PMCS NOT REPORTABLE UNDER 506(B)

This template should be completed by the review chemist (ONDQA) or review biologist (OBP) and included for each type of CMC PMR/PMC in the Action Package. See #4 below for list of CMC PMR/PMC types

PMC #11 Description: To confirm the stability of the 100 mg/vial FLP by executing additional lyophilization runs with specific Process Parameters of the lyophilization process, and monitoring the drug product stability.

PMC wording: "To provide confirmatory data by executing manufacturing run of the 100 mg/vial FLP batch at (b) (4) (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."

PMC Schedule Milestones:	Final protocol Submission Date:	Completed
	Study Completion Date:	09/2017
	Final Report Submission Date:	12/2017

PMC #12 Description: To confirm the stability of the 400 mg/vial FLP by executing additional lyophilization runs with specific Process Parameters of the lyophilization process, and monitoring the drug product stability.

PMC wording: "To provide confirmatory data by executing manufacturing run of the 400 mg/vial FLP batch at (b) (4) (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."

PMC Schedule Milestones:	Final protocol Submission Date:	Completed
	Study Completion Date:	09/2017
	Final Report Submission Date:	12/2017

PMC #13 Description: To confirm the stability of the 100 mg/vial FLP by executing additional runs with specific Process Parameters of the lyophilization process, and monitoring the drug product stability.

PMC wording: "To provide confirmatory data by executing a manufacturing run of the 100 mg/vial FLP batch at (b) (4) (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."

PMC Schedule Milestones:	Final protocol Submission Date:	<u>Completed</u>
	Study Completion Date:	<u>09/2017</u>
	Final Report Submission Date:	<u>12/2017</u>

PMC #14 Description: To confirm the stability of the 400 mg/vial FLP by executing additional runs with specific Process Parameters of the lyophilization process, and monitoring the drug product stability.

PMC wording: "To provide confirmatory data by executing a manufacturing run of the 400 mg/vial FLP batch (b) (4) (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."

PMC Schedule Milestones:	Final protocol Submission Date:	<u>Completed</u>
	Study Completion Date:	<u>09/2017</u>
	Final Report Submission Date:	<u>12/2017</u>

- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC/OBP NON-REPORTABLE PMCS FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL. USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**
- **DO NOT USE THIS FORM IF ANY STUDIES WILL BE REQUIRED UNDER FDAAA OR WILL BE PUBLICLY REPORTABLE**

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check the reason below and describe.

- Need for drug (Unmet need/ Life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

The validation of all target Critical Process Parameters (CPP) of the drug product manufacturing process approved under BLA are sufficient to ensure adequate quality and safety of siltuximab for the initial marketed product. In the BLA, few CPP ranges of the lyophilization process were supported by developmental process data, which need to be confirmed in manufacturing scale and monitored for long term stability.

2. Describe the particular review issue and the goal of the study.

Although the target CPPs were adequately validated to assure drug product manufacturing process, the selected developmental manufacturing runs to support the described CPP ranges were executed by developmental manufacturing process or did not provide sufficient long term product stability data. The proposed PMC studies employ the full scale commercial manufacturing and will provide long term stability data for drug product manufactured by the CPPs identified.

3. [OMIT—for PMRs only]

4. What type of study is agreed upon (describe and check the type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the Agreed upon study:

Manufacture drug product batches with the specified lyophilization process parameters and perform long term stability studies on the manufactured batches.

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs only)

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/s/

YUNHUA JIA
04/15/2014

BAZARRAGCHAA DAMDINSUREN
04/15/2014

MARJORIE A SHAPIRO on behalf of CHANA FUCHS
04/15/2014



Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Division of Monoclonal Antibodies
Office of Biotechnology Products

FINAL LABEL AND LABELING REVIEW

Date: March 17, 2014

Reviewer: Bazarragchaa Damdinsuren, M.D., Ph.D.
Division of Monoclonal Antibodies

Through: Chana Fuchs, Ph.D., Team Leader
Division of Monoclonal Antibodies

Application: BLA 125496/0

Product: Sylvant (siltuximab)

Applicant: Janssen Biotech, Inc.

Submission Date(s): August 29, 2013

Executive Summary

The carton and container labels for SYLVANT (siltuximab) were reviewed and found to comply with the following regulations: 21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57, 21 CFR 200.100 and United States Pharmacopeia, 36. Labeling deficiencies initially identified were communicated to the sponsor on 2/21/2014 and are listed in the end of the review. The sponsor revised the labels according to the recommendations discussed below and provided the revised carton and container labels to the BLA on 3/7/2014. The draft carton and container labels submitted on 3/7/2014 are acceptable.

Background and Summary Description

STN 125496/0 for siltuximab is an original Biologic License Application (BLA) indicated for the treatment of patients with multicentric Castleman's disease (MCD) who are HIV and HHV-8 negative, as a single-agent. The product is supplied as a 100 mg/vial and 400 mg/vial lyophilized ^{(b) (4)} in a single-use vial.

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

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/s/

BAZARRAGCHAA DAMDINSUREN
03/31/2014

CHANA FUCHS
04/11/2014

Product Quality (CMC) PMR/PMC Development Template
TO BE USED FOR PMCS NOT REPORTABLE UNDER 506(B)

This template should be completed by the review chemist (ONDQA) or review biologist (OBP) and included for **each** type of CMC PMR/PMC in the Action Package. See #4 below for list of CMC PMR/PMC types

125496/siltuximab

PMC #1 Description: Reassessment of release and shelf-life specifications for the 100 mg/vial Drug Product after manufacture of a sufficient number of commercial lots to allow for better statistical analysis.

PMC wording: "To re-evaluate siltuximab 100 mg/vial final lyophilized product lot release and stability specifications using the commercial manufacturing process 5 years from the PDUFA date of April 2014 or after the manufacture of 30 lots, whichever occurs first. The 30 lots will include the 9 lots which were included in the analysis of specifications submitted in the BLA and any subsequent FLP lots manufactured. The corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications

(b) (4)

(b) (4)

PMC Schedule Milestones:	Final protocol Submission Date:	<u>MM/YYYY</u>
	Study Completion Date:	<u>04/2019</u>
	Final Report Submission Date:	<u>07/2019</u>
	Other: _____	<u>MM/YYYY</u>

PMC #2 Description: Reassessment of release and shelf-life specifications for the 400 mg/vial Drug Product after manufacture of a sufficient number of commercial lots to allow for better statistical analysis.

PMC wording: "Tto re-evaluate siltuximab 400 mg/vial final lyophilized product lot release and stability specifications using the commercial manufacturing process 5 years from the PDUFA date of April 2014 or after the manufacture of 30 lots, whichever occurs first. The 30 lots will include the 7 lots which were included in the analysis of specifications submitted in the BLA and any subsequent FLP lots manufactured. The corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications

(b) (4)

(b) (4)

PMC Schedule Milestones:	Final protocol Submission Date:	<u>MM/YYYY</u>
	Study Completion Date:	<u>04/2019</u>

Final Report Submission Date: 07/2019
Other: _____ MM/YYYY

PMC #3 Description: Reassessment of release and shelf-life specifications for the formulated bulk drug substance after manufacture of a sufficient number of commercial lots to allow for better statistical analysis.

PMC wording: "To re-evaluate siltuximab formulated bulk lot release and stability specifications using the commercial manufacturing process 5 years from April 2014 or after the manufacture of 30 lots, whichever occurs first. The 30 lots will include the 13 lots which were included in the analysis of specifications submitted in the BLA and any subsequent FB lots manufactured. The corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications _____ (b) (4)

_____ (b) (4)

PMC Schedule Milestones: Final protocol Submission Date: MM/YYYY
Study Completion Date: 04/2019
Final Report Submission Date: 07/2019
Other: _____ MM/YYYY

PMC #4 Description: Reassessment of release and shelf-life specifications for _____ (b) (4) intermediate after manufacture of a sufficient number of commercial lots to allow for better statistical analysis.

PMC wording: "To re-evaluate siltuximab _____ (b) (4) intermediate lot release and stability specifications using the commercial manufacturing process 2 years from April 2014 or after the manufacture of 30 lots, whichever occurs first. The 30 lots will include the 7 lots which were included in the analysis of cIEF specifications submitted in the BLA and any subsequent _____ (b) (4) lots manufactured. The cIEF and SE-HPLC data from all lots manufactured using the commercial manufacturing process will 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 _____ (b) (4)

_____ (b) (4)

PMC Schedule Milestones:	Final protocol Submission Date:	<u>MM/YYYY</u>
	Study Completion Date:	<u>04/2016</u>
	Final Report Submission Date:	<u>07/2016</u>
	Other:	<u>MM/YYYY</u>

PMC # 7 Description: Reassessment of the (b)(4) reference material (b)(4) requalification acceptance criterion for potency after a sufficient data are collected to allow an appropriate statistical evaluation.

PMC wording: “To tighten the (b)(4) reference material requalification acceptance criteria based on appropriate statistical evaluation and a sufficient amount of data points required for such an evaluation. The updated acceptance criterion and supporting data will be submitted as a CBE0 by November 2014.”

PMC Schedule Milestones:	Final protocol Submission Date:	<u>MM/YYYY</u>
	Study Completion Date:	<u>MM/YYYY</u>
	Final Report Submission Date:	<u>11/2014</u>
	Other:	<u>MM/YYYY</u>

- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC/OBP NON-REPORTABLE PMCS FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL. USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**
- **DO NOT USE THIS FORM IF ANY STUDIES WILL BE REQUIRED UNDER FDAAA OR WILL BE PUBLICLY REPORTABLE**

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check the reason below and describe.

- Need for drug (Unmet need/ Life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

The current release and shelf-life specifications approved under BLA for FB and FLP, and the current potency specification for requalification of (b)(4) are sufficient to ensure adequate quality and safety of siltuximab for the initial marketed product. Increased manufacturing and testing experience gained post licensure can facilitate improved specifications.

2. Describe the particular review issue and the goal of the study.

Siltuximab release and shelf-life specifications are based on clinical and manufacturing experience during the BLA review; This is also true of the potency specification for (b) (4) requalification. However, the number of lots or datapoints to date do not allow for a robust statistical analysis of the data. Some specifications have a statistical component that should be re-assessed when a sufficient number of marketed product lots or datapoints have been tested.

3. [OMIT—for PMRs only]

4. What type of study is agreed upon (describe and check the type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the Agreed upon study:

Statistical analysis of release data acquired following manufacture of additional commercial lots.

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs only)

Product Quality (CMC) PMR/PMC Development Template
TO BE USED FOR PMCS NOT REPORTABLE UNDER 506(B)

This template should be completed by the review chemist (ONDQA) or review biologist (OBP) and included for each type of CMC PMR/PMC in the Action Package. See #4 below for list of CMC PMR/PMC types

PMC #5 Description: Confirmation of (b) (4) using a validated reduced scale model.

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

PMC Schedule Milestones:	Final protocol Submission Date:	<u>MM/YYYY</u>
	Study Completion Date:	<u>MM/YYYY</u>
	Final Report Submission Date:	<u>12/2014</u>
	Other:	<u>MM/YYYY</u>

PMC #6 Description: Confirmation of clearance of (b) (4) using a validated reduced scale model.

PMC wording: "To confirm the anticipated amount of (b) (4) using a validated reduced scale model. The results of this study will be submitted by December 2014.

PMC Schedule Milestones:	Final protocol Submission Date:	<u>MM/YYYY</u>
	Study Completion Date:	<u>MM/YYYY</u>
	Final Report Submission Date:	<u>12/2014</u>
	Other:	<u>MM/YYYY</u>

- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC/OBP NON-REPORTABLE PMCS FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL. USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**
- **DO NOT USE THIS FORM IF ANY STUDIES WILL BE REQUIRED UNDER FDAAA OR WILL BE PUBLICLY REPORTABLE**

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check the reason below and describe.

- Need for drug (Unmet need/ Life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval

- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

(b) (4)

2. Describe the particular review issue and the goal of the study.

(b) (4)

3. [OMIT—for PMRs only]

4. What type of study is agreed upon (describe and check the type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the Agreed upon study:

(b) (4)

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs only)

Product Quality (CMC) PMR/PMC Development Template
TO BE USED FOR PMCS NOT REPORTABLE UNDER 506(B)

This template should be completed by the review chemist (ONDQA) or review biologist (OBP) and included for each type of CMC PMR/PMC in the Action Package. See #4 below for list of CMC PMR/PMC types

PMC #8 Description: Establishment of stability programs for master cell bank (MCB) and working cell bank (WCB).

PMC wording : “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.

PMC Schedule Milestones:	Final protocol Submission Date:	<u>MM/YYYY</u>
	Study Completion Date:	<u>MM/YYYY</u>
	Final Report Submission Date:	<u>08/2014</u>
	Other: _____	<u>MM/YYYY</u>

PMC #9 Description: Establishment of a control strategy for using the (b) (4)

(b) (4)

PMC wording : “ To establish a control strategy for the (b) (4)

(b) (4) The updated control strategy and supporting data will be submitted as a CBE0 in August 2014.

PMC Schedule Milestones:	Final protocol Submission Date:	<u>MM/YYYY</u>
	Study Completion Date:	<u>MM/YYYY</u>
	Final Report Submission Date:	<u>08/2014</u>
	Other: _____	<u>MM/YYYY</u>

PMC #10 Description: Establishment of a quantitative acceptance criterion for (b) (4) monitoring and trending.

PMC wording: “To re-evaluate the (b) (4) using data from drug substance batches manufactured up to October 2016. The analysis and supporting data will be submitted as a CBE30 by December 2016.”

PMC Schedule Milestones:	Final protocol Submission Date:	<u>MM/YYYY</u>
	Study Completion Date:	<u>10/2016</u>
	Final Report Submission Date:	<u>12/2016</u>
	Other: _____	<u>MM/YYYY</u>

- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC/OBP NON-REPORTABLE PMCS FOR WHICH THE FOLLOWING ANSWERS WILL BE**

IDENTICAL. USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.

- **DO NOT USE THIS FORM IF ANY STUDIES WILL BE REQUIRED UNDER FDA 2013 OR WILL BE PUBLICLY REPORTABLE**

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check the reason below and describe.

- Need for drug (Unmet need/ Life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

The sponsor provided adequate data to support the stability of MCB, WCB and the consistency of the levels of (b)(4) in their process. In addition, the sponsor provided characterization data to support (b)(4). These data provided are sufficient to ensure adequate quality and safety of siltuximab for the initial marketed products. Additional control strategies are needed to ensure the long term and comprehensive control for the parameters identified.

2. Describe the particular review issue and the goal of the study.

There were insufficient programs and strategies to ensure the long term monitoring of the points identified. (8) there was an insufficient stability program to identify continued stability of the MCB and WCB.(9) there was an insufficient monitoring strategy to identify continued control of the (b)(4) that may impact product quality, even though the levels do not appear to significantly change for the lots in the BLA . (10) there was insufficient monitoring strategy to identify continued control of the levels of (b)(4) Development of control and monitoring strategies requested would ensure that these do not change during the product lifecycle.

3. [OMIT—for PMRs only]

4. What type of study is agreed upon (describe and check the type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues

Other

Describe the Agreed upon study:

Additional control strategies are required to ensure control over the product lifecycle.
--

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs only)

Product Quality (CMC) PMR/PMC Development Template
TO BE USED FOR PMCS NOT REPORTABLE UNDER 506(B)

This template should be completed by the review chemist (ONDQA) or review biologist (OBP) and included for each type of CMC PMR/PMC in the Action Package. See #4 below for list of CMC PMR/PMC types

PMC #11 Description: To confirm the stability of the 100 mg/vial FLP by executing additional lyophilization runs with specific Process Parameters of the lyophilization process, and monitoring the drug product stability.

PMC wording: "To provide confirmatory data by executing manufacturing run of the 100 mg/vial FLP batch at (b) (4) (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."

PMC Schedule Milestones:	Final protocol Submission Date:	<u>MM/YYYY</u>
	Study Completion Date:	<u>09/2017</u>
	Final Report Submission Date:	<u>12/2017</u>
	Other: _____	<u>MM/YYYY</u>

PMC #12 Description: To confirm the stability of the 400 mg/vial FLP by executing additional lyophilization runs with specific Process Parameters of the lyophilization process, and monitoring the drug product stability.

PMC wording: "To provide confirmatory data by executing manufacturing run of the 400 mg/vial FLP batch at (b) (4) (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."

PMC Schedule Milestones:	Final protocol Submission Date:	<u>MM/YYYY</u>
	Study Completion Date:	<u>09/2017</u>
	Final Report Submission Date:	<u>12/2017</u>
	Other: _____	<u>MM/YYYY</u>

PMC #13 Description: To confirm the stability of the 100 mg/vial FLP by executing additional runs with specific Process Parameters of the lyophilization process, and monitoring the drug product stability.

PMC wording: "To provide confirmatory data by executing a manufacturing run of the 100 mg/vial FLP batch (b) (4) (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."

PMC Schedule Milestones:	Final protocol Submission Date:	<u>MM/YYYY</u>
	Study Completion Date:	<u>09/2017</u>
	Final Report Submission Date:	<u>12/2017</u>
	Other:	<u>MM/YYYY</u>

PMC #14 Description: To confirm the stability of the 400 mg/vial FLP by executing additional runs with specific Process Parameters of the lyophilization process, and monitoring the drug product stability.

PMC wording: "To provide confirmatory data by executing a manufacturing run of the 400 mg/vial FLP batch (b) (4) (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."

PMC Schedule Milestones:	Final protocol Submission Date:	<u>MM/YYYY</u>
	Study Completion Date:	<u>09/2017</u>
	Final Report Submission Date:	<u>12/2017</u>
	Other:	<u>MM/YYYY</u>

- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC/OBP NON-REPORTABLE PMCS FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL. USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**
- **DO NOT USE THIS FORM IF ANY STUDIES WILL BE REQUIRED UNDER FDA 2012 OR WILL BE PUBLICLY REPORTABLE**

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check the reason below and describe.

- Need for drug (Unmet need/ Life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

The validation of all target Critical Process Parameters (CPP) of the drug product manufacturing process approved under BLA are sufficient to ensure adequate quality and safety of siltuximab for the initial marketed product. In the BLA, few CPP ranges of the lyophilization process were supported by developmental process data, which need to be confirmed in manufacturing scale and monitored for long term stability.

2. Describe the particular review issue and the goal of the study.

Although the target CPPs were adequately validated to assure drug product manufacturing process, the selected developmental manufacturing runs to support the described CPP ranges were executed by developmental manufacturing process or did not provide sufficient long term product stability data. The proposed PMC studies employ the full scale commercial manufacturing and will provide long term stability data for drug product manufactured by the CPPs identified.

3. [OMIT—for PMRs only]

4. What type of study is agreed upon (describe and check the type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the Agreed upon study:

Manufacture drug product batches with the specified lyophilization process parameters and perform long term stability studies on the manufactured batches.

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs only)

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

/s/

YUNHUA JIA
04/11/2014

BAZARRAGCHAA DAMDINSUREN
04/11/2014

CHANA FUCHS
04/11/2014

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

BLA # 125496/0
Product Name: SYLVANT (siltuximab)

PMR 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:	<u>completed</u>
	Trial Completion:	<u>03/31/2017</u>
	Final Report Submission:	<u>08/31/2017</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

This is an ongoing study collecting long term safety information on patients with Multicentric Castleman’s Disease benefiting from continued therapy with siltuximab enrolled in the clinical trial for licensure.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The goal of the study is to evaluate the safety associated with long term chronic therapy with siltuximab.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Collect long term safety information on patients with multicentric Castleman's disease receiving chronic therapy with siltuximab.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
The BLA include an interim report of this study. The PMC is to submit a final study report for the trial.
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 Immunogenicity as a marker of safety
 Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 Dose-response study or clinical trial performed for effectiveness
 Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
 Are the objectives clear from the description of the PMR/PMC?
 Has the applicant adequately justified the choice of schedule milestone dates?
 Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
 There is not enough existing information to assess these risks
 Information cannot be gained through a different kind of investigation
 The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
 The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

R Kane
(Signature line for BLAs)

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
03/28/2014

ROBERT C KANE
03/28/2014

Product Quality (CMC) PMR/PMC Development Template
TO BE USED FOR PMCS NOT REPORTABLE UNDER 506(B)

This template should be completed by the review chemist (ONDQA) or review biologist (OBP) and included for each type of CMC PMR/PMC in the Action Package. See #4 below for list of CMC PMR/PMC types

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 August 2014.

PMC Schedule Milestones:	Final protocol Submission Date:	<u>MM/YYYY</u>
	Study Completion Date:	<u>MM/YYYY</u>
	Final Report Submission Date:	<u>08/2014</u>
	Other:	<u>MM/YYYY</u>

- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC/OBP NON-REPORTABLE PMCS FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL. USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**
- **DO NOT USE THIS FORM IF ANY STUDIES WILL BE REQUIRED UNDER FDA 201 OR WILL BE PUBLICLY REPORTABLE**

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check the reason below and describe.

- Need for drug (Unmet need/ Life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

The (b) (4) were tested for (b) (4) using the (b) (4) test and passed. In addition, microbial retention studies demonstrated that exposure with this product does not alter the (b) (4). Therefore, the (b) (4) were shown to be adequate for their intended purpose, therefore this is not an approvability issue. For these reasons, it is acceptable for the sponsor to submit the results from the study after the review cycle.

2. Describe the particular review issue and the goal of the study.

(b) (4)

3. [OMIT—for PMRs only]

4. What type of study is agreed upon (describe and check the type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the Agreed upon study:

The sponsor will determine the volume of the (b) (4) necessary to achieve consistent (b) (4) test conditions, provide supportive data, and use the determined volume in the (b) (4) test.

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs only)

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/s/

CANDACE GOMEZ-BROUGHTON
03/24/2014

PATRICIA F HUGHES TROOST
03/25/2014

Product Quality (CMC) PMR/PMC Development Template
TO BE USED FOR PMCS NOT REPORTABLE UNDER 506(B)

This template should be completed by the review chemist (ONDQA) or review biologist (OBP) and included for each type of CMC PMR/PMC in the Action Package. See #4 below for list of CMC PMR/PMC types

PMC #1 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 protocol Submission Date:	<u>MM/YYYY</u>
	Study Completion Date:	<u>MM/YYYY</u>
	Final Report Submission Date:	<u>07/2014</u>
	Other: _____	<u>MM/YYYY</u>

PMC #2 Description: _____

PMC Schedule Milestones:	Final protocol Submission Date:	<u>MM/YYYY</u>
	Study Completion Date:	<u>MM/YYYY</u>
	Final Report Submission Date:	<u>MM/YYYY</u>
	Other: _____	<u>MM/YYYY</u>

- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC/OBP NON-REPORTABLE PMCS FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL. USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**
- **DO NOT USE THIS FORM IF ANY STUDIES WILL BE REQUIRED UNDER FDAAA OR WILL BE PUBLICLY REPORTABLE**

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check the reason below and describe.

- Need for drug (Unmet need/ Life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

Previous study conducted using one batch of formulated drug substance suggests no impact on endotoxin recovery after holding the formulated bulk in routine production conditions. The applicant plans to confirm those results with additional batches of formulated drug substance. Since the provisional results suggest no impact of formulated drug substance on endotoxin recovery, the risk for false endotoxin negatives in the finished product is deemed low.

2. Describe the particular review issue and the goal of the study.

The study will confirm preliminary data suggesting no impact of formulated drug substance in endotoxin recovery.

3. [OMIT—for PMRs only]

4. What type of study is agreed upon (describe and check the type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the Agreed upon study:

To assess endotoxin recovery in formulated drug substance held under production conditions

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs only)

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/s/

REYES CANDAU-CHACON
03/24/2014

PATRICIA F HUGHES TROOST
03/25/2014

Therapeutic Biological Establishment Evaluation Request (TB-EER) Form

Instructions:

The review team should email this form to the email account "CDER-TB-EER" to submit:

- 1) an initial TB-EER within 10 business days of the application filing date
- 2) a final TB-EER 15-30 days prior to the action date

Note: All manufacturing locations named in the pending submission, whether contract facilities or facilities owned by the applicant, should be listed on this form. For bundled supplements, one TB-EER to include all STNs should be submitted.

APPLICATION INFORMATION

PDUFA Action Date: TBD

Applicant Name: Janssen Biotech, Inc.
U.S. License #: 1864
STN(s): 125496/0
Product(s): Siltuximab (Sylvant)

Short summary of application: BLA for the treatment of patients with multicentric Castleman's disease (MCD) who are human immunodeficiency virus negative and human herpesvirus-8 negative

FACILITY INFORMATION (DRUG SUBSTANCE)

Manufacturing Location: Leiden, The Netherlands
Firm Name: Janssen Biologics B.V.
Address: Einsteinweg 101, Leiden, The Netherlands CB-2333
FEI: 3002806632

Short summary of manufacturing activities performed: Drug Substance Manufacturing (b) (4), analytical testing of process intermediates and bulk drug substance; Testing of Final Lyophilized Product

Manufacturing Location: Co. Cork, Ireland
Firm Name: Janssen Biologics (Ireland)
Address: Barnahely, Ringaskiddy, Co. Cork, Ireland
FEI: 3007029098

Short summary of manufacturing activities performed: Drug Substance Manufacturing (b) (4), analytical testing of process intermediates and bulk drug substance; Testing of Final Lyophilized Product

Manufacturing Location: (b) (4)
Firm Name: (b) (4)
Address: (b) (4)
FEI: 1 (b) (4)

Short summary of manufacturing activities performed: (b) (4) (b) (4) testing

FACILITY INFORMATION (DRUG PRODUCT)

Manufacturing Location: Switzerland

Firm Name: Cilag AG

Address: Hochstrasse 201, Schaffhausen, Switzerland CH-8200

FEI: 3002806695

Short summary of manufacturing activities performed: Manufacture, (b) (4)
Final Lyophilized Product

³

The regulations at 21 C.F.R. § 207.3(a)(8) defines “manufacturing or processing” as “the manufacture, preparation, propagation, compounding, or processing of a drug or drugs as used in section 510 of the act [21 U.S.C. § 360] and is the making by chemical, physical, biological, or other procedures of any articles that meet the definition of drugs in section 201(g) of the act. The term includes manipulation, sampling, testing, or control procedures applied to the final product or to any part of the process. The term also includes repackaging or otherwise changing the container, wrapper, or labeling of any drug package to further the distribution of the drug from the original place of manufacture to the person who makes final delivery or sale to the ultimate consumer.”

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/s/

REYES CANDAU-CHACON
03/20/2014

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: March 12, 2014

To: Ann Farrell, MD
Director
Division of Hematology Products (DHP)
Robert Kane, MD
Deputy Director for Safety
Division of Hematology Products (DHP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)
Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Karen Dowdy, RN, BSN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)
Nisha Patel, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): SYLVANT (siltuximab)

Dosage Form and Route: for Injection, for Intravenous infusion

Application Type/Number: BLA 125496

Applicant: Janssen Biotech, Inc. c/o Janssen Research & Development, LLC

1 INTRODUCTION

On August 30, 2013, Janssen Research and Development, LLC, on behalf of Janssen Biotech, Inc. submitted for the Agency's review an original Biologics License Application (BLA) 125496 for SYLVANT (siltuximab) for Injection with the proposed indication for the treatment of patients with multicentric Castleman's disease (MCD) who are human immunodeficiency virus negative and human herpesvirus-8 negative.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to the requests by the Division of Hematology Products (DHP) on September, 23, 2013 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for SYLVANT (siltuximab) for Injection.

2 MATERIAL REVIEWED

- Draft SYLVANT (siltuximab) for Injection PPI received on August 30, 2013 and received by DMPP and OPDP on March 3, 2014.
- Draft SYLVANT (siltuximab) for Injection Prescribing Information (PI) received on August 30, 2013, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on March 3, 2014.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Verdana font, size 10.

In our collaborative review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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

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/s/

KAREN M DOWDY
03/12/2014

NISHA PATEL
03/12/2014

LASHAWN M GRIFFITHS
03/12/2014

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: March 7, 2014

TO: Patricia Garvey, Regulatory Project Manager
Pat Dinndorf, M.D., Medical Officer
Albert Deisseroth, M.D., Ph.D. Cross Discipline Team Leader
Division of Hematology Products (DHP)

FROM: Anthony Orenca, M.D., F.A.C.P.
Medical Officer, GCP Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Janice Pohlman, M.D., M.P.H.
Team Leader, GCP Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

Kassa Ayalew, M.D., M.P.H.
Acting Branch Chief, GCP Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections
BLA#: 125496
APPLICANT: Janssen Biotech
DRUG: siltuximab
NME: Yes

THERAPEUTIC CLASSIFICATION/REVIEW: Priority

INDICATION: Treatment of multicentric Castleman's Disease

CONSULTATION REQUEST DATE: September 24, 2013
INSPECTION SUMMARY GOAL DATE (original): February 28, 2014
INSPECTION SUMMARY (DHP-extended) DATE: March 7, 2014
DIVISION ACTION GOAL DATE: April 29, 2014
PDUFA DATE: April 29, 2014

I. BACKGROUND:

Multicentric Castleman's disease (MCD) is a rare lymphoproliferative disease in patients with or without HIV. MCD is characterized by variable clinical features with systemic manifestations, particularly in patients with the plasma cell or mixed-type variants of the disease. Lymph node, liver and spleen enlargements, anemia, hypoalbuminemia, and hypocholesterolemia are frequent. Manifestations of the POEMS syndrome (that is, polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes) may also be seen.

Multicentric Castleman's disease is thought to be due to a dysregulated production of IL-6. Siltuximab (CNTO 328) is a potent inhibitor of human IL-6. Tocilizumab (Actemra), a humanized anti-IL-6 receptor monoclonal antibody (mAb), is approved in Japan for its demonstrated benefit in improving symptoms and laboratory findings in Castleman's disease.

A single domestic clinical site participating in Study CNTO328MCD2001 was selected for inspection because the site had enrollment of a large number of study subjects and treatment responders. This clinical study site inspection was cancelled. The same study protocol, study subjects conducted by the same principal investigators was previously inspected by CDER OSI Good Clinical Practice Enforcement Branch (GCPEB). The sponsor was audited at its headquarters in New Jersey.

Protocol CNTO328MCD2001:

The study was a Phase 2 randomized, double-blind, placebo-controlled, multicenter study performed to determine the safety and efficacy of siltuximab with Best Supportive Care (BSC) compared with BSC, in subjects with symptomatic MCD. The primary objective of this study was to demonstrate siltuximab in combination with BSC was superior to BSC in terms of durable tumor and symptomatic response among subjects with MCD. Subjects received siltuximab (11 mg/kg) or placebo by a 1-hour IV infusion every three weeks. Dose modification (increase or decrease) was not permitted. Subjects were randomly assigned to two treatment groups: (1) Treatment Group A: Placebo + BSC and (2) Treatment Group B: drug product + BSC. The primary efficacy endpoint was complete or partial durable tumor and symptomatic response, based on independent review.

II. RESULTS:

Name of CI City, State	Protocol/Study Site/Number of Subjects Enrolled (n)	Inspection Date	Classification*
Janssen Biotech (U.S. Agent: Janssen Research & Development, LLC) Titusville, New Jersey	CNTO328MCD2001 Sponsor	December 3 to 12, 2013	Preliminary NAI (No Action Indicated)
Saad Usmani, M.D. and Frits van Rhee, M.D. (For Cause Inspection) Little Rock, AR	CNTO328MCD2001/ Site #0102	September 17 to 28, 2012	NAI

*Key to Classifications

NAI = No deviation from regulations. Data acceptable.

VAI-No Response Requested = Deviations(s) from regulations. Data acceptable.

OAI = Significant deviations from regulations. Data unreliable/Critical findings may affect data integrity.

Preliminary= The Establishment Inspection Report (EIR) has not been received, findings are based on preliminary communication with the field at the Office of Regulatory Affairs (ORA), or final review of the EIR is pending. Once a final letter is issued by CDER to the inspected entity and the case file is closed, the preliminary designation is converted to a final regulatory classification.

SPONSOR SITE AUDIT

1. Janssen Biotech/ Protocol CNTO328MCD2001

Titusville, NJ

a. What was inspected:

The inspection was conducted in accordance with Compliance Program 7348.810, from December 3 to 12, 2013.

The inspection evaluated the following: documents related to study monitoring visits and correspondence, Institutional Review Board (IRB) approvals, completed Form FDA 1572s, monitoring reports, financial disclosures, drug accountability, and training of staff and site monitors.

b. General observations/commentary:

The sponsor maintained adequate oversight of the clinical trial. There were no noncompliant sites, and monitoring of the investigator sites was considered adequate. No salient issues were identified. There was no evidence of under-reporting of adverse events.

No discrepancies were noted. This clinical site appeared to be in compliance with Good Clinical Practices. No Form FDA 483 was issued at the end of the sponsor inspection.

c. Assessment of data integrity:

The study appears to have been conducted adequately. Data submitted by this sponsor appear acceptable in support of the respective indication.

PREVIOUS CLINICAL STUDY SITE INVESTIGATOR FOR CAUSE INSPECTION:

**1.Saad Usmani, M.D. and Frits van Rhee, M.D. (Co-PIs), /Protocol CNTO328MCD2001/
Site #0102**

Little Rock, AR

a. What was inspected:

The inspection was conducted from September 17 to 28, 2012 in response to a complaint (Complaint #3769). On February 10, 2012, the Office of Scientific Investigations received a report from the University of Arkansas for Medical Sciences Institutional Review Board (IRB) sent a report stating that Janssen Research and Development suspended enrollment of new subjects in the study due to serious non-compliance at the principal investigator's (Dr. Usmani) site. Specifically, the IRB reported the following about Site #0102:

- (1) performance of laboratory tests that potentially unblinded subjects' treatment allocation
- (2) failure to perform required laboratory tests and study procedures
- (3) delayed reporting of these unblinding issues and protocol deviations
- (4) delayed reporting of adverse events and serious adverse events, and
- (5) incomplete and inconsistent documentation of study records.

There were eight subjects screened, and five subjects were enrolled. One of the enrolled subjects failed treatment and was terminated early from the study. There were a total of eight SAEs, including two deaths. An audit of four subjects' records was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

b. General observations/commentary:

In general, this clinical site appeared to be in compliance with Good Clinical Practices. However, a Form FDA 483 (List of Inspectional Observations) was issued at the end of the inspection for not conducting the investigation according to plan.

Specifically, laboratory tests that could potentially unblind the subject's treatment were performed.

a. For subject #0102-207, the following locally prohibited tests were performed:

- (1) ESR test was performed at study visit Cycle 1/Day 1 (12/1/2010) and Cycle 1/Day 8 (12/10/2010)
- (2) IL-6 tests were performed at study visit Cycle 1/Day 8 (12/10/2010), Cycle 1/Day 15 (12/17/2010) and Cycle 2/Day 1 (12/22/2010)
- (3) IgG, IgA and IgM quantitative assays were assessed at study visit Cycle 2/Day 1 (12/22/2010) and Cycle 3/Day 1 (1/14/2011), and
- (4) CRP levels were assessed at study visit Cycle 1/Day 8 (12/10/2010), Cycle 4/Day 1 (2/4/2011), Cycle 18/Day 1 (12/5/2011) and Cycle 19/Day 1(12/27/2011).

- b. For subject #0102-003, a locally prohibited test, CRP, was performed at Cycle 31/Day 1 [REDACTED] ^{(b) (6)} when the patient was admitted to the ER for a serious adverse event. Additionally, CRP was performed during various cycle dates in April, November, and December 2010. Additionally, other locally prohibited tests including ESR at Cycle 11/Day 1 (11/1/2010), IL-6 at Cycle 2 (4/28/2010), and Cycle 4 (6/7/2010) were performed.

The Myeloma Institute for Research and Therapy (MIRT) at the University of Arkansas for Medical Sciences staff consisting of Saad Usmani, M.D. (Director of Developmental Therapeutics) and Frits van Rhee, M.D. (Director of Developmental and Translational Medicine), and Nathan M. Petty (Director of Clinical Trials and Regulatory Affairs) responded adequately to the FDA Form 483 in a signed letter on October 15, 2012.

Although the FDA ORA field investigator issued a Form FDA 483 to Dr. Usmani and preliminarily classified the inspection as Voluntary Action Indicated (VAI), the final CDER classification of the inspection was No Action Indicated (NAI) since Dr. Usmani was not responsible for the study at the time the regulatory violations occurred. Dr. van Rhee was actively involved during the time the regulatory deficiencies occurred; however the IRB complaint was related specifically to Dr. Usmani.

Medical Officer's comment:

The Division of Hematology Products (DHP) notes that although the above are regulatory deficiencies, their impact on study outcome is a clinical review issue. During initial conversations with DHP, the Medical Team acknowledged that the study's blinding procedures may not be guaranteed in the course of standard medical care. DHP would take these observations under consideration in its assessment of the BLA, however given the study protocol's stringent criteria, the data for Patient #0102-027 and Patient #0102-003 could be used despite the above observations.

c. Assessment of data integrity:

Despite the above regulatory deficiencies, data submitted by this clinical site and as discussed with DHP, appear acceptable in support of this specific indication.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

A sponsor audit was conducted for this BLA covering Protocol CNTO0328MCD2001. The CDER OSI preliminary classification for this inspection is NAI. Based on the results of the clinical inspection, data submitted by this sponsor appear acceptable in support of the respective indication.

A previous OSI for cause inspection of Dr. Usmani's site (Site 0102) had been conducted for Protocol CNTO0328MCD2001. While a Form FDA 483 had been issued for

regulatory violations, specifically for conducting laboratory studies with potential for unblinding the study, the final classification of the inspection was NAI as described above. The regulatory violations observed have been discussed with the review division, DHP, who will make the final determination of impact of these violations on study assessments and outcome.

{See appended electronic signature page}

Anthony Orenca, M.D.
Medical Officer
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Janice Pohlman, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Kassa Ayalew, M.D., M.P.H.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

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/s/

ANTHONY J ORENCIA
03/07/2014

JANICE K POHLMAN
03/07/2014

KASSA AYALEW
03/07/2014

STUDY ENDPOINT CONSULT REVIEW

SEALD TRACKING NUMBER	AT2013-136
IND/NDA/BLA NUMBER	BLA 125496
LETTER DATE/SUBMISSION NUMBER	August 29, 2013
PDUFA GOAL DATE	April 29, 2014
DATE OF CONSULT REQUEST	September 27, 2013
REVIEW DIVISION	DHP
MEDICAL REVIEWER	Patricia Dinndorf
REVIEW DIVISION PM	Patty Garvey
SEALD REVIEWER(S)	Ashley Slagle
SEALD ENDPOINTS TEAM LEADER	Elektra Papadopoulos (acting)
SEALD DIRECTOR	Sandy Kweder (acting)
REVIEW COMPLETION DATE	February 4, 2014
ESTABLISHED NAME	Siltuximab
TRADE NAME	Sylvant
SPONSOR/APPLICANT	Janssen Biotech, Inc
CLINICAL OUTCOME ASSESSMENT TYPE	PRO
ENDPOINT(S) CONCEPT(S)	Multicentric Castleman's Disease Signs and Symptoms
MEASURE(S)	Multicentric Castleman's Disease Signs and Symptoms (MSC-SS)
INDICATION	Multicentric Castleman's Disease
INTENDED POPULATION(S)	Men and women with symptomatic MCD at least 18 years and human immunodeficiency virus (HIV) negative and human herpes virus (HHV)-8 negative

SEALD Review

Ashley Slagle

BLA 125496

Siltuximab / Sylvant

Multicentric Castleman's Disease Signs and Symptoms

A. EXECUTIVE SUMMARY

This Study Endpoints and Labeling Development (SEALD) review is provided as a response to a request for consultation by the Division of Hematology Products (DHP) regarding BLA 125496. The sponsor has investigated the safety and efficacy of Siltuximab in a confirmatory clinical trial in symptomatic patients with Multicentric Castleman's Disease (MCD) who are at least 18 years of age and are HIV negative and HHV-8 negative. The sponsor used the Multicentric Castleman's Disease Signs and Symptoms (MCD-SS) assessment for the measurement of symptoms of MCD as a secondary endpoint in this trial.

The review concludes that the evidence submitted by the sponsor suggests that the MCD-SS overall score is an acceptable and comprehensive measure of MCD symptoms and patient-reported signs in the context in which it was used, (b) (4)

However, given the low baseline scores among the population in study CNTO 328 and the large proportion of patients who do not experience certain individual symptoms (i.e., symptom variability across patients), it may be difficult to detect symptom improvement using the total score of this instrument (i.e., this instrument may not be sensitive enough to detect improvement among this patient population). For future studies, we would recommend sponsors consider identifying the key symptoms most often experienced by the majority of the target population to assess as the basis for primary or secondary endpoints. Limiting outcome assessments to the most prevalent symptoms across all patients in the study will improve the likelihood of being able to detect a treatment difference. This may be particularly important in rare diseases, such as MCD, where sample sizes are necessarily small. Other symptoms, infrequently experienced across patients, may be assessed to ensure there is no deterioration, but might not be included in the primary or secondary efficacy endpoint assessments. In addition, future patient selection criteria should include a minimum score level at baseline on the assessment that will be the basis for outcome assessment to ensure the patient population is sufficiently symptomatic to detect improvements in symptoms.

In general, the instrument development process was in line with the good instrument development principles as described in the recommendations of the FDA PRO Guidance. There is some evidence of adequate content validity (for English speaking patients), construct validity (known groups and convergent), reliability (test-retest and internal consistency), and ability to detect change. In addition to the recommendations above, there are some specific concerns and considerations for instrument improvement (b) (4)

These
considerations include:

- existence of double barreled items (e.g., sores or rash);

SEALD Review

Ashley Slagle

BLA 125496

Siltuximab / Sylvant

Multicentric Castleman's Disease Signs and Symptoms

- one item (fever) was removed from the instrument after instrument testing was complete;
- the instructions ask patients to attribute symptoms to the condition, which is generally advised against;
- the evidence to support what is a meaningful amount of change to identify responders is lacking;
- the cognitive debriefing interviews were completed in very educated patients, therefore it would be useful to confirm that patients with lower levels of reading ability are able to comprehend and respond appropriately to the MCD-SS;
- no documentation of the process used for translation and cultural validation was submitted;
- based on the evaluation of measurement properties (test-retest reliability, internal consistency reliability, known-groups validity, and convergent validity), the fatigue domain seems to perform much better than the other domains. (b) (4)

However, for future use of this instrument in other clinical trials, it is recommended that further evaluation of the items, domains, and total score be considered prior to engaging in a confirmatory registration trial using the MCD-SS in order to improve the likelihood of the MCD-SS being able to detect a meaningful and interpretable treatment benefit.

B. COMMENTS TO SPONSOR/APPLICANT

There are no specific questions from or comments to the Sponsor. The comments provided here address the division's request for SEALD's review:

"This application includes a PRO as a secondary endpoint, using MCD-SS. The primary endpoint is a composite response endpoint comprised of reduction and disappearance of lymph nodal masses by CT and disappearance of all baseline MCD symptoms (as measure by a composite score (presumably the PCD-SS)). The application includes a Validation Report for the MCD-SS instrument for Multicentric Castleman's Disease [5.3.5.1 MCD-SS - Validation Report]. Please review the adequacy of this report (b) (4)

The MCD-SS was used to support a secondary endpoint, and was not part of the primary composite endpoint. The Validation Report describes the development of the MCD-SS (b) (4)

In general, the instrument development process was in line with the good instrument development principles as described in the recommendations of the FDA PRO Guidance. There is some evidence of adequate content validity (for English speaking patients), construct validity (known groups and convergent), reliability (test-retest and internal consistency), and ability to

SEALD Review

Ashley Slagle

BLA 125496

Siltuximab / Sylvant

Multicentric Castleman's Disease Signs and Symptoms

detect change. However, given the low baseline scores among the population in study CNTO 328 and the large proportion of patients who do not experience certain individual symptoms (i.e., symptom variability across patients), it may be difficult to detect symptom improvement using the total score of this instrument (i.e., this instrument may not be sensitive enough to detect improvement among this patient population). For future studies, we would recommend identifying the key symptoms most often experienced by the majority of the target population to assess as the basis for primary or secondary endpoints. Limiting outcome assessments to the most prevalent symptoms across all patients in the study will improve the likelihood of being able to detect a treatment difference. This may be particularly important in rare diseases, such as MCD, where sample sizes are necessarily small. Other symptoms, infrequently experienced across patients, may be assessed to ensure there is no deterioration, but might not be included in the primary or secondary efficacy endpoint assessments. In addition, future patient selection criteria should include a minimum score level at baseline on the assessment that will be the basis for outcome assessment to ensure the patient population is sufficiently symptomatic to detect improvements in symptoms.

In addition to the recommendations above, there are some specific concerns and considerations for instrument improvement. (b) (4)

. However, these considerations are described in the spirit of instrument improvement that may benefit future assessment of MCD patients using the MCD-SS, or a modified version:

- Considerations for future improvement in the content validity of the instrument include: removing or modifying double barreled items (e.g., “sores or rash”); revising the instructions to avoid asking patients to attribute symptoms to the condition; and performing cognitive debriefing interviews among patients with limited education to ensure comprehension by patients with lower level of reading ability. Response thresholds for each item were not described and it is unclear if the response thresholds are appropriately ordered.*
- It is not clear whether the removal of the fever item following psychometric testing has a significant impact on the overall instrument. While this is unlikely a critical flaw, it may be useful to repeat psychometric testing when the final instrument is used again within a clinical trial to provide further evidence of measurement properties of the final instrument.*
- The fatigue domain of the MCD-SS has measurement properties that appear superior to the other domains.*

SEALD Review

Ashley Slagle

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- *The rash/itching domain has low test-retest reliability. This may be attributable in part to the large numbers of patients who do not experience this symptom, or it may be due to the study design where patients completed the instrument before and after treatment. This low reliability finding should be considered and may make it more difficult to detect treatment benefit using this assessment. In addition, the rash/itching domain does not perform optimally when evaluating known-groups validity. The rash/itch domain did not show change in the expected direction with improvements in tumor response. Additional evaluation of these concerns may be warranted for future use or potential modifications of this instrument.*
- *The sweats domain does not appear to detect deterioration in symptoms as compared to changes on the SF-36 PCS or MCS. Additional evaluation of this may be warranted for future use or potential modifications of this instrument.*
- *It is not clear that the meaningful amount of change of 0.75 on the total score is appropriate for determining responders. While the ½ standard deviation approach is one piece of information that may be useful to ensure large enough change is considered, additional methods (e.g., anchoring methods) may be useful to aid in determining the amount of change that is clinically meaningful. For example, when looking at the score change of the MCD-SS for those patients with at least an increase of 5 or more points on the SF-36 PCS compared to no change on the SF-36 PCS (defined as score change between >-5 and <5), there is some initial evidence supporting a clinically meaningful change on the MCD-SS as being approximately 1.38. Other anchoring approaches may be used to further support a meaningful change on the MCD-SS.*

The sponsor's cut off point for responders is not fully supported, and a change of 0.75 may not be sufficiently large change to be clinically meaningful. (b) (4)

Future development of the instrument should include additional evaluation of what is clinically meaningful change in order to establish a responder definition.

- *No details were provided regarding specific translation and cultural validation procedures, though study report 328 indicates translations were available for all languages required for the study. It is unclear whether the instrument was appropriately translated for use in patients at non-US sites. We recommend the use of translation and cultural validation procedures as described by the ISPOR Task Force (Wild et al., 2005) to ensure PRO assessments are appropriate for non-English speaking trial participants.*

Evidence of comparability in measurement properties between versions should be provided.

SEALD's review focused on the development of the MCD-SS

(b) (4)

SEALD did not review the clinical trial protocol and analysis plan.

C. STUDY ENDPOINT REVIEW

1 CONTEXT OF USE (COU)

1.1 Target Study Population and Clinical Setting

CNT0328 Study Report: "Men and women with symptomatic MCD confirmed by central pathology review who were at least 18 years and were human immunodeficiency virus (HIV) negative and human herpes virus (HHV)-8 negative. Symptomatic disease was defined clinically by the presence of symptoms with National Cancer Institute Common Terminology Criteria Adverse Event (NCI CTCAE) grading ≥ 1 that were attributable to the disease, and for which treatment was indicated. Subjects were required to have measurable disease, which was not to be limited to cutaneous lesions. Laboratory abnormalities (eg, elevations in acute phase proteins [CRP, fibrinogen] and increased erythrocyte sedimentation rate [ESR]) in the absence of clinical symptoms did not qualify as symptomatic disease."

1.2 Clinical Trial Design

CNT0328 Study Report: "This was a randomized, double-blind, placebo-controlled, multicenter, Phase 2 study to determine the safety and efficacy of siltuximab + BSC compared with BSC, in subjects with symptomatic MCD. Subjects were stratified according to corticosteroid use (yes vs no). Subjects were randomized in a 2:1 ratio to siltuximab + BSC or placebo + BSC, and were to receive siltuximab (11 mg/kg) or placebo by a 1-hour intravenous (IV) infusion every 3 weeks. The study consisted of a Screening Period (from initial screening visit until double-blind randomization), blinded Treatment Period (starting from the first dose of study agent), unblinded Treatment Period (subjects who did not respond to placebo + BSC were provided the opportunity to be treated with siltuximab every 3 weeks), an End-of-Treatment Visit, and a Follow-up Period."

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1.3 Endpoint Positioning

The MCD-SS total score was used to support a secondary endpoint of median time to improvement. All endpoints are provided below:

Primary Endpoint: “durable tumor and symptomatic response rate, based on independent review, defined as complete response (CR): complete disappearance of all measurable and evaluable disease (eg, pleural effusion) and resolution of baseline symptoms attributed to MCD, sustained for at least 18 weeks + partial response (PR): a $\geq 50\%$ decrease in sum of the product of the diameters (SPD) of index lesion(s), with at least SD in all other evaluable disease in the absence of treatment failure, sustained for at least 18 weeks.”

Secondary Endpoints (listed only if in prespecified hierarchy):

1. tumor response rate;
2. time to treatment failure;
3. proportion of subjects with an increase in hemoglobin at Week 13 of 15 g/L or more;
4. Time to \Rightarrow 1pt improvement (from baseline) on the MCD Symptom Scale (MCD-SS).
5. Time to \Rightarrow 3pts improvement (from baseline) on the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F);
6. proportion of subjects who discontinued corticosteroids;

Other endpoints (not prespecified in the hierarchy):

- duration of tumor and symptomatic response;
- duration of tumor response;
- treatment failure rate;
- maximum change from baseline in hemoglobin in the absence of transfusion
- proportion of subjects with an increase in hemoglobin at Week 13 of 20 g/L or more;
- improvement in MCD-related symptom improvement [based on the clinician's reported outcome assessment];
- overall survival
- other patient-reported outcome (PRO) endpoints included:
 - Time to \Rightarrow 5pts improvement (from baseline) on the Medical Outcome Study Short-Form-36 (SF-36) Physical Component Summary (PCS)
 - Time to \Rightarrow 5pts improvement (from baseline) on the Mental Component Score (MCS);

1.4 Labeling or promotional claim(s) based on the COA

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No specific labeling claims related to the MCD-SS have been proposed.

(b) (4)

2 CONCEPT OF INTEREST (COI) AND CONCEPTUAL FRAMEWORK

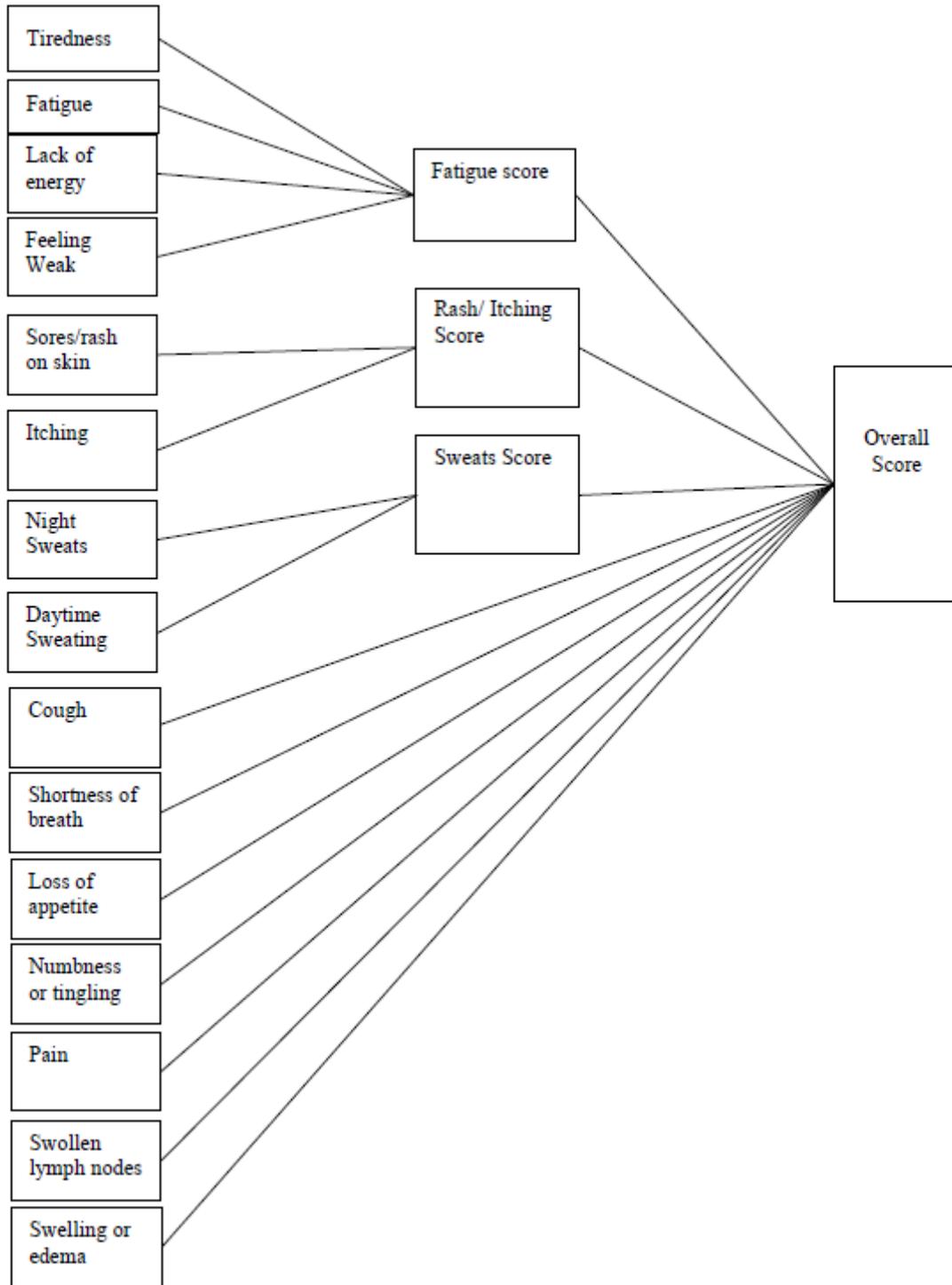
The MCD-SS is intended to assess the severity of symptoms of MCD. A diagram of the conceptual framework is provided below. It consists of three domains (fatigue, sweats and rash/itching) plus individual items that are not part of the domains, but comprised part of the total score.

The conceptual framework was developed using information from both a literature review and quantitative data generated in the CNTO 328 study, using item correlations and exploratory factor analysis (EFA). "Five factors were extracted from the [EFA]. Rotated factor loadings (Varimax) and final communality estimates [were provided]... An additional exploratory factor analysis was conducted on the MCD-SS after removing the 4 items related to fatigue. Rotated factor loadings (Varimax) and final communality estimates [were] provided... and are similar to factor loadings obtained using oblique rotations (Promax). ...the rotated factor loadings with item Q12 (fever) removed [were provided] since it was determined that fever was best evaluated through use of a thermometer rather than patient evaluation.

The rotated factor structure including all items indicated the first factor was comprised primarily of fatigue related items plus pain... Fatigue items clearly form the strongest subscale. These items were removed and the factor structure reanalyzed to better understand the pattern of the remaining items. The results of this analysis...indicated a general common first factor (variance explained = 2.208). The three remaining factors relate to scores/itching, pain/fever, and night and day sweating. The factor loadings with fever removed [were provided]. While removal of this item does not improve the clarity of the factor structure, it makes more sense from an assessment perspective.

Examination of both the inter-item correlations...and factor analysis results...indicated strong association among items related to fatigue (4 items), rash/itching (2 items) and sweating (2 items). Each of these sets of items was combined into a domain. Among the item scores not contributing to a domain, greater than 50% of subjects indicated at least some pain, swollen lymph nodes, numbness, tingling and shortness of breath. With the exception of fever (Q12), which was reported by only 18 of the 78 subjects, all items were retained in the final instrument to maintain comprehensiveness.

Figure 2: Conceptual Framework



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3 CLINICAL OUTCOME ASSESSMENT (COA) MEASURE(S)

- Multicentric Castleman's Disease – Symptom Scale (MCD-SS) Instrument (see Appendix 1)
 - 15 item scale including common and important MCD symptoms
 - Cough
 - Shortness of breath
 - Loss of appetite
 - Fatigue (4 items: tiredness; fatigue; lack of Energy; feeling weak))
 - Rash/Itching (2 items: sores or rash on skin; itching)
 - Numbness or tingling
 - Pain
 - Swollen lymph nodes
 - Swelling or edema
 - Sweats (2 items: night sweats; excessive daytime sweating)
 - Response options: did not experience, very mild, mild, moderate, severe, very severe
 - 24 hour recall
- This was a newly developed instrument, so no prior versions exist. However, as the instrument was developed, drafts were updated based on new findings. For example, the version of the instrument used for psychometric testing is slightly different than the final version, as a fever item was removed after testing.
- No user manual was submitted for review.
- The MCD-SS was completed by patients during clinic visits using the following assessment schedule: Day 1 of each cycle, on Day 8 and Day 15 of Cycle 1, and at the End of Treatment Visit. Each Cycle was based on the administration of siltuximab or placebo, and was 3 weeks in duration.

CNTO 328: Clinical Protocol CNTO328MCD2001 - Amendment 5

	Screening Day -28 to -1 ^a	Cycle 1 Day 1	Cycle 1 Day 8	Cycle 1 Day 15	Cycle 2+ Day 1	End-of-Treatment 30 days (± 7 days) after last dose	Follow-up Period
Patient-reported outcome measurements		X ^b	X	X	X ^c	X	

^a The MCD Symptom Scale and FACIT-F will be collected on Day 1 of each Cycle, on Day 8 and Day 15 of Cycle 1, and at the End-of-Treatment Visit. SF-36 will be collected at Cycles 1, 3, 6, and every third cycle thereafter; and at the End-of-Treatment Visit.

- Available scores include: a total score (0-10), fatigue domain score (0-10), rash/itching domain score (0-10), and a sweats domain score (0-10). Lower scores represent less symptom severity.
- Training method/materials (patient, investigator and other study site personnel) have not been provided.

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Reviewer's comments: It is not clear whether the removal of the fever item following psychometric testing has a significant impact on the overall instrument. While this is unlikely a critical flaw, it may be useful to repeat psychometric testing when the final instrument is used again within a clinical trial to provide further evidence of measurement properties of the final instrument.

4 CONTENT VALIDITY

Concept elicitation interviews were performed among 12 patients with MCD from 2 centers in the US during a 1 hour telephone interview. Open ended questions were used to elicit information about disease experiences, including symptom experiences and impacts of symptoms on their patient's daily lives. Transcripts were coded for themes using Atlas.ti. Findings indicate that symptom experiences are variable from patient to patient, from day to day and in some cases within a day. Transcripts were not provided, however, patient quotes were organized by concept theme for review.

Cognitive debriefing interviews were performed to evaluate the MCD-SS. Ten participants from one site were interviewed. The first part of the interview included open ended concept elicitation interviews to confirm the findings from the first round of CE interviews. Then the patients were asked to complete the MCD-SS and were asked questions about the instructions, items, and response options. An item tracking matrix was included for review, and shows the evolution of items as they were reviewed with patients, discussed with experts (clinical and translation experts). No changes to the items were made as a result of the patient interviews, and patients seemed to generally understand the items as intended.

Literature review, patient interviews and expert input was used in the development of the instrument. Qualitative study protocols and interview guides for individual patient telephone interviews were provided and appear adequate. The chronology of events for item generation, modification and finalization appear appropriate. The qualitative study summary was reviewed and justification for recall period (24-hours) and evidence of saturation appear adequate.

The quantitative study summary describes that floor and ceiling effects were evaluated for each item. Items are scored from 0 (did not experience) to 5 (very severe), and none of the 16 items show mean scores at baseline of greater than 2.5 (range: 0.5-2.5). A high percentage of patients (12%-55%) did not experience most of the items. Given the low baseline scores among this population and the large proportion of patients who do not experience individual symptoms, it will likely be difficult to detect treatment benefit with this instrument (i.e., this instrument may not be sensitive enough to detect improvement among this patient population).

Justification for scoring was provided, and was based on examination of inter-item correlations and factor analysis results. Each symptom contributes the same amount of weight to the score (e.g., the fatigue domain and the cough item are contributing equally to the total score).

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Cognitive debriefing of the near-final instrument was submitted, reviewed, and appears adequate. Fever was removed from the instrument after cognitive debriefing and pilot testing.

Methods used to develop the items are adequate to ensure that items and domains are appropriate to the concept, clinically important and important to patients. Content validity was confirmed with cognitive debriefing interviews to sufficiently demonstrate that patients understand the questions and response options in the way intended. While not considered critical flaws, considerations for improvement in the measure include:

- Double barreled items included (e.g., “sores or rash”)
- Instructions ask patients to attribute symptoms to condition
- Patients included in cognitive debriefing were very educated; additional evidence supporting comprehension in patients with low reading level would be useful

Methods used to finalize the items are described and appear adequate. Items appear to cover the full range of experience in the targeted population, with the exception of “fever”, which was removed as it was determined it was better assessed using other methods. Response thresholds for each item were not provided, so it is unclear if they are appropriately ordered. Scores represent the measurement concepts reflected in the conceptual framework and are adequate to directly determine the appropriate labeling claims related to total symptoms or specific domains (fatigue, rash/itching, and sweats).

Reviewer's comments: In general, the methods used to develop and support the content validity of the instrument are acceptable. While none of the concerns with the content validity are considered critical flaws, some considerations for future improvement in the content validity of the instrument include: removing or modifying double barreled items (e.g., “sores or rash”); revising the instructions to avoid asking patients to attribute symptoms to the condition; and performing cognitive debriefing interviews among patients with limited education to ensure comprehension by patients with lower level of reading ability. Response thresholds for each item were not described and it is unclear if the response thresholds are appropriately ordered.

Given the low baseline scores among this population and the large proportion of patients who do not experience certain individual symptoms (i.e., symptom variability across patients), it will likely be difficult to detect symptom improvement using the total score of this instrument (i.e., this instrument may not be sensitive enough to detect improvement among this patient population).

5 OTHER MEASUREMENT PROPERTIES (RELIABILITY, CONSTRUCT VALIDITY, ABILITY TO DETECT CHANGE)

Using data from the CNTO 328 study, unblinded data from cycle 1 day 1 were used to conduct an item level analysis in order to examine response option endorsement and floor and ceiling

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effects. In addition, exploratory factor analysis (EFA) was used on the same data to define a preliminary scoring algorithm.

The sponsor provides evidence of construct validity (known groups validity and convergent validity), reliability (test-retest and internal consistency), ability to detect change, and discussion of what is meaningful amount of change.

Internal consistency exceeded 0.7 for all domains and the total score, except for the rash/itching domain, perhaps because over 50% of the subjects indicated no presence of this symptom.

Test-retest findings

The measurement properties were evaluated in the context of the phase 3 clinical trial, therefore the patient population and testing situation is relevant and appropriate for the evaluation of measurement properties.

- Reliability:
 - Test-retest reliability was assessed using intraclass correlation coefficients using data from the first two assessments at cycle 1 day 1 and cycle 1 day 8. Treatment was administered at cycle 1 day 1, so these two time points for assessment do not represent identical testing situations. However, the test-rest ICCs exceeded 0.70 for the total score and the fatigue and sweats domains. The rash/itching ICC was 0.65.
 - Internal consistency was adequate. All item-total and domain-total correlations were 0.70 or higher.
- Known-groups validity was evaluated using the ECOG performance status scale. It was hypothesized that worse MCD-SS symptoms scores would be observed for the higher grades of ECOG score. The expected pattern of increasing MCD-SS scores with increasing levels of ECOG status for fatigue, sweats, and the total scores. There was little difference in the rash/itching domain between ECOG status of 0 and 1.
- Construct validity hypotheses were specified a priori, and cross-sectional convergent validity was assessed at cycle 1 day 1, using the FACIT-F and investigator toxicity grades for multiple symptoms were assessed and summed (general MCD score).
 - The MCD-SS total score and FACIT-F score showed acceptable correlation ($r=0.70$)
 - The MCD-SS total score was moderately correlated with the general MCD score (clinician rating of symptoms), $r=0.48$.
- No evidence of discriminant validity was provided for review.

Ability to detect change was assessed by comparing the change on the MCD-SS against various levels of response on the SF-36 PCS and MCS scores (using change from baseline to cycle 3 day 1) and tumor response (using change from baseline to cycle 4 day 1).

 - Change on the MCD-SS (total score and domain scores, except for the sweats domain) showed an expected pattern across the varying levels of change on the

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SF-36 PCS and MCS. As patients improved on the SF-36, they also showed improvements on the MCD-SS. Likewise, as patients showed deterioration on the SF-36, they showed deterioration on the MCD-SS.

- Scores for the MCD-SS fatigue domain appear to be moderately associated with tumor response. The association between other domains and tumor response are less robust and unclear.

Reviewer's comments: The fatigue domain of the MCD-SS has measurement properties that are superior to the other domains.

The rash/itching domain has low test-retest reliability. This may be attributable in part to the large numbers of patients who do not experience this symptom, or it may be due to the study design where patients completed the instrument before and after treatment. This low reliability finding should be considered and may make it more difficult to detect treatment benefit using this assessment.

Additionally, the rash/itching domain does not perform optimally when evaluating known-groups validity. The rash/itch domain did not show change in the expected direction with improvements in tumor response. Additional evaluation of these concerns may be warranted for future use or potential modifications of this instrument.

The sweats domain does not appear to detect deterioration in symptoms as compared to changes on the SF-36 PCS or MCS. Additional evaluation of this may be warranted for future use or potential modifications of this instrument.

6 INTERPRETATION OF SCORES

- The sponsor defines meaningful amount of change that is based on $\frac{1}{2}$ the standard deviation of the baseline scores, and proposed by the sponsor to be 0.75. The sponsor also included cumulative distribution functions (CDF) showing the percent of patients with various levels of MCD-SS total score change from baseline (see figure below with threshold for change scores ranging from 0 to 2.5).

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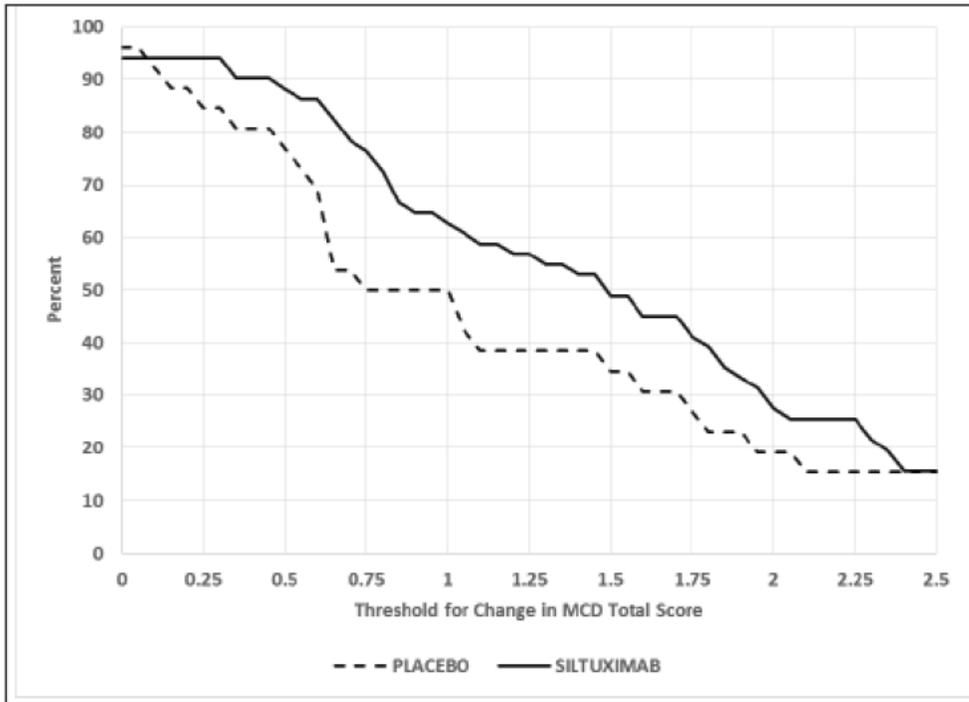
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Figure 6: Proportion of Patients Achieving a Specified Level or Change or Greater in MCD Total Score during Double-Blind Treatment Period



Reviewer's comments: It is not clear that the meaningful amount of change of 0.75 on the total score is appropriate for determining responders. While the $\frac{1}{2}$ standard deviation approach is one piece of information that may be useful to ensure large enough change is considered, additional methods (e.g., anchoring methods) may be useful to aid in determining the amount of change that is clinically meaningful. For example, when looking at the score change of the MCD-SS for those patients with at least an increase of 5 or more points on the SF-36 PCS compared to no change on the SF-36 PCS (defined as score change between >-5 and <5), there is some initial evidence supporting a clinically meaningful change on the MCD-SS as being approximately 1.38. Other anchoring approaches may be used to further support a meaningful change on the MCD-SS.

The sponsor's cut off point for responders is not fully supported, and a change of 0.75 may not be sufficiently large change to be clinically meaningful. (b) (4)

Future development of the instrument should include additional evaluation of what is clinically meaningful change in order to establish a responder definition.

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7 LANGUAGE TRANSLATION AND CULTURAL ADAPTATION

The ITM notes that items were edited during development by a translational expert, however, no details related to translation and cultural validation were provided in either the MCD-SS validation report or the Study Report (CNTO 328). Patients from China and Hong Kong were included in the clinical trial population, and study report CNTO 328 notes that "Translations are available in all languages required for the study."

Reviewer's comments: No details were provided regarding specific translation and cultural validation procedures, though study report 328 indicates translations were available for all languages required for the study. It is unclear whether the instrument was appropriately translated for use in patients at non-US sites. We recommend the use of translation and cultural validation procedures as described by the ISPOR Task Force (Wild et al., 2005) to ensure PRO assessments are appropriate for non-English speaking trial participants. Evidence of comparability in measurement properties between versions should be provided.

8 REFORMATTING FOR NEW METHOD OR MODE OF ADMINISTRATION

The MCD-SS is a newly developed assessment, and no reformatting for new method or mode of administration has been described

9 REVIEW USER MANUAL

- No user manual has been submitted for review.

10 PROTOCOL AND ANALYSIS PLAN

- This was not reviewed.

Reviewer's comments: SEALD's review focused on the development of the MCD-SS (b) (4) collaboration with the review division and the statistical reviewers, (b) (4)

SEALD did not review the clinical trial protocol and analysis plan.

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11 REFERENCES

Wild D, Grove A, Martin M, et al. Principles of good practice for the translation and cultural adaptation process for patient-reported outcomes (PRO) measures: report of the ISPOR task force for translation and cultural adaptation. *Value in Health*; 8(2): 2005.

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D. APPENDIX 1

Note: the instrument was developed and tested with the 16 items below. The fever item was not included in the final version of the instrument.

Multicentric Castleman's Disease Symptom Scale

When filling out this questionnaire, please consider your experiences with Castleman's Disease symptoms during the past 24 hours. Choose the response that best describes your experiences with Castleman's Disease symptoms by marking the corresponding box (☐).

Please rate the severity of the following symptoms during the past 24 hours.	Did not experience	Very Mild	Mild	Moderate	Severe	Very Severe
1. Cough	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
2. Shortness of breath	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
3. Loss of appetite	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
4. Tiredness	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
5. Fatigue	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
6. Lack of Energy	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
7. Feeling Weak	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
8. Sores or rash on your skin (skin lesions)	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
9. Itching	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
10. Numbness or Tingling	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
11. Pain	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
12. Fever	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
13. Swollen lymph nodes (swollen lumps in neck area, under arms, or groin area)	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
14. Swelling or edema in other body areas (face, chest, abdomen, arms, hands, legs, or feet)	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
15. Night Sweats	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
16. Excessive daytime sweating	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

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/s/

ASHLEY F SLAGLE
02/06/2014

ELEKTRA J PAPADOPOULOS
02/06/2014

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

******Pre-decisional Agency Information******

Memorandum

Date: January 24, 2014

To: Patricia Garvey, Senior Regulatory Project Manager
Division of Hematology Products (DHP)

From: Nisha Patel, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Karen Rulli, Team II Leader, OPDP

Subject: Comments on draft labeling (Package Insert) for
Sylvant (siltuximab) for Injection, for Intravenous infusion
BLA 125496

In response to your consult dated September 23, 2013, we have reviewed the draft Package Insert (PI) for Sylvant (siltuximab) for Injection, for Intravenous infusion (Sylvant) and offer the following comments. OPDP has made these comments using the version updated by the FDA on 1/16/14.

Section	Statement from draft	Comment
Highlights, Warnings and Precautions	<ul style="list-style-type: none"> • (b) (4) ○ Do not administer SYLVANT to patients with severe infections until the infection resolves. ○ Monitor patients receiving SYLVANT closely for infections. Institute prompt anti-infective therapy and do not administer Sylvant until the infection resolves. 	<p>We note that the bolded information regarding (b) (4) does not appear in the Warnings and Precautions section of the full PI.</p> <p>We also note that the order of the Warnings and Precautions listed in the Highlights section differs from the order of the Warnings and Precautions listed in section 5 of the full PI (b) (4).</p> <p>Finally, the headers listed in the Highlights, Warnings and Precautions section (i.e., (b) (4)) are inconsistent with the headers listed in sections 5 and 6 of the full PI (i.e., concurrent active severe infections and concurrent active serious infections).</p>

Section	Statement from draft	Comment
	<p style="text-align: right;">(b) (4)</p> <ul style="list-style-type: none"> • <u>Infusion related reactions</u> (6.1): Administer SYLVANT in a setting that provides resuscitation equipment, medication, and personnel trained to provide resuscitation (bolded and underlined emphasis added) 	<p>We recommend revising the Highlights, Warnings and Precautions section to ensure consistency with the <i>content and order</i> of the information listed in sections 5 and 6 of the full PI.</p>
<p>Highlights, Adverse Reactions</p> <p>6 Adverse Reactions</p>	<p>The most common adverse reactions (>10% compared to placebo) during treatment with SYLVANT in the MCD clinical trial were pruritus, increased weight, rash, hyperuricemia, and upper respiratory tract infection.</p>	<p>According to Table 2 from the full PI, “Edema (general and localized)” was reported in 26% of patients during treatment with Sylvant. We recommend revising the list of the most commonly occurring adverse reactions in the Highlights, Adverse Reactions section and section 6 to ensure consistency with Table 2 from the full PI.</p>
<p>6 Adverse Reactions</p>	<p>Study 2 was an international, multicenter, randomized phase 2 study of every 4 week infusions comparing Sylvant and BSC to placebo and BSC. There were 50 patients randomized to the SYLVANT arm at a dose of 15 mg/kg and 26 patients randomized to the placebo arm. (emphasis added)</p>	<p>The bolded information could be used promotionally to imply or suggest a dose for Sylvant beyond the approved dose. Please consider deleting this information or clearly indicating that this section contains information regarding an unapproved dose for Sylvant.</p>
<p>6 Adverse Reactions</p>	<p>Long Term Exposure</p> <p>The safety of long term administration of SYLVANT to patients with MCD was evaluated in Study 3. Study 3 enrolled patients from Study 1 or the initial dose finding study of Sylvant with MCD who were benefiting from chronic SYLVANT therapy. SYLVANT was administered at a dose of 11 mg/kg every 3 to 6 weeks. At the time of data cut off 19 patients were enrolled. The median age was 44 years (range 18 - 76), 63% male, 84% Caucasian, 11% Asian, and 5% Black. The median exposure to Sylvant 5.1 years (range 3.4 to 7.2). No patient was removed from therapy for any reason. There were no deaths. There were no cumulative toxicities identified with prolonged treatment with SYLVANT. (emphasis added)</p>	<p>“Long term exposure” information in the labeling has promotional implications since this could be used to imply that long term administration of Sylvant is both safe and effective. Does data from Study 3, which enrolled patients from Study 1 or the initial dose finding study, constitute substantial evidence to support long term administration of Sylvant? Is it essential to include this information in the PI? If not, please consider deleting.</p> <p>Additionally, the “dose of 11 mg/kg every 3 to 6 weeks” could be used promotionally to imply or suggest a dose for Sylvant beyond the approved dose (emphasis added). If Study 3 must be included in the PI, please consider deleting this information or clearly indicating that this section contains information regarding an unapproved dose for Sylvant.</p> <p>Finally, the bolded information could be used promotionally to overstate the efficacy or minimize the risks associated with Sylvant. If</p>

Section	Statement from draft	Comment
		Study 3 must be included in the PI, please consider including quantitative safety information from Study 3, if available.
6 Adverse Reactions	(b) (4) 750 patients have been treated with Sylvant. Of these, one patient experienced an anaphylactic reaction.	Please consider changing (b) (4) 750” to “approximately 750” or providing an exact number to clearly communicate the patient population evaluated.
6 Adverse Reactions	(b) (4)	The phrase (b) (4),” is vague, (b) (4) We recommend deleting this phrase.
14 Clinical Studies	<p>“Other analyses included tumor response, time to treatment failure and a increase in hemoglobin of 1.5 g/dL, in patients who were anemic at time of study entry, at week 13” and corresponding results from Table (b) (4) in the full PI</p> <p>A consistent treatment effect was confirmed on subgroup analysis for all parameters evaluated with the exception of the hyaline vascular histological subtype. There were no patients with hyaline vascular histology who demonstrated a durable tumor and symptomatic response. However, activity was suggested in this subtype based on change in hemoglobin and median time to treatment failure.</p> <p>One year survival rate was 100% in the SYLVANT arm and 92% in the placebo arm.</p>	<p>These statements have promotional implications since results from secondary endpoints and subgroup analyses often has the potential to be misleading when presented in the context of promotional materials. Were the secondary efficacy variables and subgroup analyses pre-specified and are they supported by substantial evidence? If not, please consider deleting these statements. Additionally, we note that the Clinical Study Report states that, “At the time of the analysis, overall survival data were not mature.”</p>
17 Patient Counseling Information		This section should contain information that a prescriber should discuss with the patient (e.g., most important safety issues from the main safety sections of the label, and/or any important info on proper dosing, etc.). We recommend revising this section to incorporate these concepts.

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/s/

NISHA PATEL
01/24/2014

**Interdisciplinary Review Team for QT Studies Consultation:
Thorough QT Study Review**

BLA	125496
Generic Name	Siltuximab
Sponsor	Janssen Biotech, Inc.
Indication	Treatment of Multicentric Cavity Disease (MCD) in Patients who are immunodeficiency virus negative (HIV-), and human herpes virus – 8 negative (HHV-8-)
Dosage Form	IV Infusion
Drug Class	Chimeric antibody against IL-6
Therapeutic Dosing Regimen	11 mg/kg
Duration of Therapeutic Use	Acute
Maximum Tolerated Dose	Not identified
Submission Number and Date	SDN 001/29 Aug 2013
Review Division	DHP

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

No large change (i.e., > 20 ms) in the QTc interval was detected when siltuximab 15 mg/kg administered every 3 weeks by a 1-hour IV infusion for 4 cycles. Using Fridericia corrected QT (QTcF) interval, the largest upper bound of the 2-sided 90% CI mean change from baseline in QTcF was 6.6 ms. There are no placebo or positive control arms.

In this Phase 1, open-label, single-arm, multicenter study, twenty-five subjects received siltuximab 15 mg/kg every 3 weeks for 4 cycles. An overall summary of findings is presented in Table 1.

Table 1: Analysis Results of Δ QTcF for Siltuximab 15 mg/kg

Cycle	Δ QTcF (ms)	90% CI (ms) for Mean
CYCLE 1 DAY 1- 3 hours after infusion	3.1	(-0.4, 6.5)

The suprathreshold dose (15 mg/kg) produces mean C_{max} values approximately 40% higher than the mean C_{max} for the therapeutic dose (11 mg/kg). At these concentrations there are no detectable prolongations of the QT-interval.

1.2 RESPONSES TO QUESTIONS POSED BY REVIEW DIVISION

Question 10: Does the Division agree with the proposed presentation for QTc and electrocardiograph (ECG) data in the BLA?

QT-IRT Response: Yes. 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.

2 PROPOSED LABEL

Our proposed language is a recommendation only. We defer final labeling language to the Division.

12.2 Pharmacodynamics

Cardiac Electrophysiology

The effect of multiple doses of DRUGNAME (15 mg/kg every 3 weeks for 4 cycles) on the QTc interval was evaluated in an open label, single arm study in 30 patients with Monoclonal Gammopathy of Undetermined Significance, Smoldering Multiple Myeloma, or Indolent Multiple Myeloma. No large changes in the mean QTc interval (i.e., > 20 ms) were detected in the study.

3 BACKGROUND

3.1 PRODUCT INFORMATION

Siltuximab (CNTO 328) is a chimeric (murine-human) immunoglobulin G (IgG1k) mAb that specifically binds to and neutralizes human IL-6 with high affinity. Siltuximab has an approximate molecular weight of ^{(b) (4)} kDa.

3.2 MARKET APPROVAL STATUS

Siltuximab is not approved for marketing in any country.

3.3 PRECLINICAL INFORMATION

Studies as per S7B guidance were not conducted.

3.4 PREVIOUS CLINICAL EXPERIENCE

No sudden deaths were reported linked to siltuximab. No ventricular arrhythmias, Torsade de pointes or other ECG abnormalities linked to repolarization disturbances were reported.

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of Siltuximab's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting this study under IND 11461. The sponsor submitted the study report CNTO328SMM1001 for the study drug, including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

A Study of Siltuximab (Anti-IL-6 Monoclonal Antibody) Effects on the QT Interval in Subjects with Monoclonal Gammopathy of Undetermined Significance (MGUS), Smoldering Multiple Myeloma (SMM), or Indolent Multiple Myeloma (IMM)

4.2.2 Protocol Number

CNTO328SMM1001

4.2.3 Study Dates

First subject consented data: 25 Oct 2010

Last subject visit for the primary analysis date: 22 May 2012

Data cutoff date: 22 May 2012

4.2.4 Objectives

Primary objective: The primary objective was to determine if siltuximab would have an effect on the QT interval in subjects with monoclonal gammopathy of undetermined significance (MGUS), smoldering multiple myeloma (SMM), or indolent multiple myeloma (IMM).

Secondary objectives: to evaluate the safety, preliminary activity (monoclonal protein [M-protein] response), pharmacokinetics, pharmacodynamics, pharmacokinetic/pharmacodynamic relationships, and immunogenicity of siltuximab in subjects with MGUS, SMM, or IMM.

4.2.5 Study Description

4.2.5.1 Design

This was a Phase 1, open-label, single-arm, multicenter study of 25 evaluable subjects with MGUS, SMM, or IMM to evaluate the effect of siltuximab on the QT interval.

During the Treatment Period, subjects were to receive siltuximab at a dose of 15 mg/kg every 3 weeks for 4 cycles. At the end of the Treatment Period, subjects who achieved a response (defined as a $\geq 50\%$ reduction in M-protein) were eligible to receive extended treatment with siltuximab at a dose of 15 mg/kg every 4 weeks for a maximum of 2 years. Subjects who did not complete electrocardiogram (ECG) assessments at each prespecified timepoint (must have had at least duplicate ECG measurements at each timepoint in Cycle 1 and Cycle 4) or did not receive 4 full doses of siltuximab in the Treatment Period were to

be replaced until 25 subjects were considered evaluable. Subjects in the Extended Treatment Period were not to be replaced.

4.2.5.2 Controls

This study do not provide placebo and positive (moxifloxacin) control arms.

4.2.5.3 Blinding

This is an open-label single-arm study.

4.2.6 Treatment Regimen

Subjects receive siltuximab at a dose of 15 mg/kg every 3 weeks for 4 cycles. At the end of the Treatment Period, subjects who achieved a response (defined as a $\geq 50\%$ reduction in M-protein) were eligible to receive extended treatment with siltuximab at a dose of 15 mg/kg every 4 weeks for a maximum of 2 years.

4.2.6.1 Sponsor's Justification for Doses

The dose for the Treatment Period was selected based on International Conference on Harmonisation (ICH) guidance that QT assessment should be conducted using a suprathereapeutic dose. The highest dose intensity of siltuximab in the current registration studies is 11 mg/kg every 3 weeks. The dose of siltuximab for the Treatment Period of the current study was 15 mg/kg administered every 3 weeks by a 1-hour IV infusion.

Reviewer's Comment: The dose is acceptable.

4.2.6.2 Instructions with Regard to Meals

The protocol apparently did not specify the timing of meals.

Reviewer's Comment: Acceptable. Siltuximab is administered via i.v. infusion.

4.2.6.3 ECG and PK Assessments

ECGs and Blood samples for pharmacokinetic analysis were collected on Cycle 1 pre-dose, end of infusion, and 1, 3 and 24 hours post-infusion and on Cycle 4 pre-dose, end of infusion and 1 hour post-infusion.

Reviewer's Comment: The timing of ECGs is adequate.

4.2.6.4 Baseline

The sponsor used both the time-matched and the average of the individual QTc values on Day -1 as baselines.

4.2.7 ECG Collection

Standard 12-Lead ECGs were obtained in triplicates while subjects are recumbent using ECG machines provided by the central ECG laboratory.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

Thirty participants, the median age was 59.5 years (range 24 to 79 years). Twice as many female subjects (20 subjects; 66.7%) were enrolled in the study compared with male subjects (10 subjects; 33.3%). All subjects were White, with only 1 subject (3.3%) of Hispanic or Latino ethnicity. The median weight was 69.30 kg (range 52.1 to 135.5 kg). Of the 30 treated subjects, 28 subjects (93.3%) completed the Treatment Period and 2 subjects (6.7%) discontinued study treatment during the Treatment Period, both due to an AE. Two subjects (6.7%) entered the Extended Treatment Period.

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

The primary endpoint was mean differences between baseline to Cycle 1 Day 1 (predose, end of infusion, 1 hour after infusion, 3 hours after infusion, and 24 hours after infusion) and Cycle 4 Day 1 (predose, end of infusion, and 1 hour after infusion) in QTcF. The sponsor used a mixed-effects analysis of variance (ANOVA) and the results are presented in Table 2. The model included time and treatment as fixed effects and subject as a random effect. The upper bound of the 90% confidence interval for siltuximab was less than 20 ms.

Table 2: Sponsor's Analysis of Least Square Mean and 90% CI in QTcF from Baseline to Cycle 4 Day 1 – Mixed Model

QTcF interval (ms)	LSMean	SE	90% CI of LSMean
Cycle 1 Day 1- End of infusion	0.9	1.53	(-1.67, 3.55)
Cycle 1 Day 1- 1 hour after infusion	0.1	1.63	(-2.72, 2.85)
Cycle 1 Day 1- 3 hours after infusion	3.2	1.89	(-0.01, 6.45)
Cycle 1 Day 1- 24 hours after infusion	-3.3	2.40	(-7.36, 0.82)
Cycle 4 Day 1- Predose	-0.2	2.20	(-3.93, 3.58)
Cycle 4 Day 1- End of infusion	1.0	1.94	(-2.29, 4.31)
Cycle 4 Day 1- 1 hour after infusion	1.5	2.12	(-2.16, 5.07)

Source: Clinical Study Report, Table 15, pg 51/161

Reviewer's Comments: We will provide our independent analysis results in Section 5.2.

4.2.8.2.2 Assay Sensitivity

There is no assay sensitivity established in this study because no positive control arm was included.

4.2.8.2.3 Categorical Analysis

Categorical analysis was used to summarize in the categories of QTc \leq 450 ms, between 450 ms and 480 ms, between 480 ms and 500 ms, and $>$ 500 ms, and changes from baseline QTc \leq 30 ms, between 30 and 60 ms, and $>$ 60 ms. No subject's absolute QTc $>$ 480 ms and Δ QTc $>$ 30 ms.

4.2.8.3 Safety Analysis

Of the 30 treated subjects, 20 subjects (66.7%) had AEs, 8 subjects (26.7%) had AEs grade 3 or higher (including neutropenia in 3 subjects), 3 subjects (10%) had SAEs, 2 subjects (6.7%) had AEs leading to discontinuation of siltuximab, and no subject had an AE leading to death. The most frequently occurring treatment-emergent adverse events (TEAEs) by preferred term were fatigue and nausea (6 subjects each; 20.0%); thrombocytopenia and headache (4 subjects each; 13.3%); and upper respiratory tract infection, leukopenia, neutropenia, paresthesia, dyspnea, and abnormal hepatic function (3 subjects each; 10.0%). Three subjects (10%) had SAEs: Grade 3 cellulitis and Grade 3 peripheral edema, Grade 1 peripheral neuropathy, and Grade 2 atrial fibrillation.

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

The PK results are presented in Table 3. The C_{max} on Cycle 4 was roughly 40% higher than the $C_{max,ss}$ reported in Study C0328T03 following the therapeutic dose of 11 mg/kg.

Table 3: Summary of Siltuximab Concentrations (ug/mL)

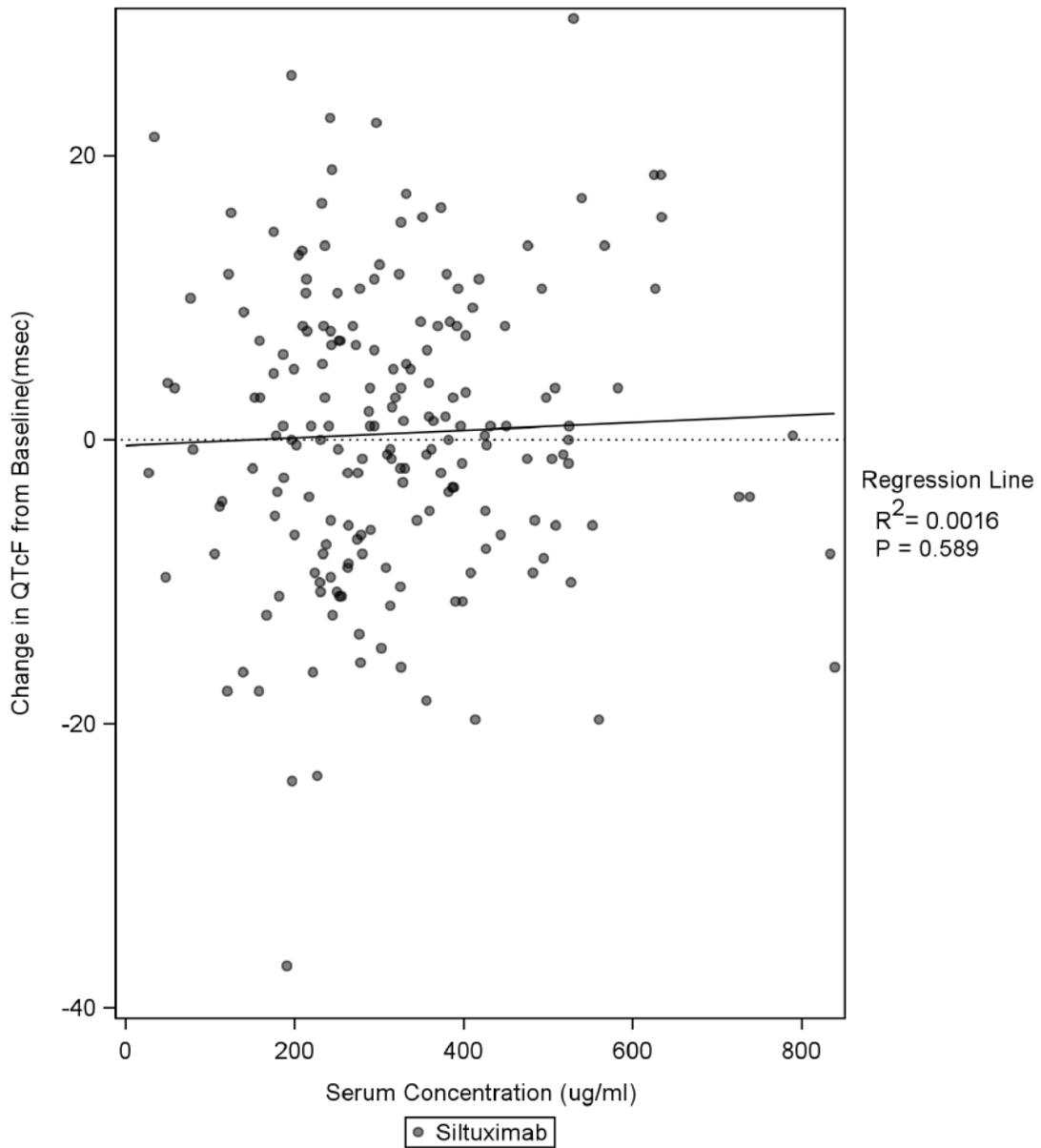
	Siltuximab
Subjects treated	30
Cycle 1 Day 1, predose	
N	30
Mean (SD)	0.00 (0.010)
Median	0.00
IQ range	(0.00; 0.00)
Range	(0.0; 0.1)
Cycle 1 Day 1, end of infusion	
N	30
Mean (SD)	343.63 (108.533)
Median	325.57
IQ range	(263.25; 391.82)
Range	(177.7; 625.0)
Cycle 1 Day 1, 1 hour after end of infusion	
N	30
Mean (SD)	315.92 (90.896)
Median	304.95
IQ range	(242.18; 378.24)
Range	(179.2; 524.8)
Cycle 1 Day 1, 3 hours after end of infusion	
N	30
Mean (SD)	310.52 (74.446)
Median	297.26
IQ range	(253.99; 369.18)
Range	(185.9; 483.9)
Cycle 1 Day 1, 24 hours after end of infusion	
N	30
Mean (SD)	240.20 (60.853)
Median	233.10
IQ range	(195.77; 276.68)
Range	(139.6; 382.0)
Cycle 4 Day 1, predose	
N	28
Mean (SD)	147.37 (79.273)
Median	144.85
IQ range	(92.39; 195.73)
Range	(27.4; 390.1)
Cycle 4 Day 1, end of infusion	
N	28
Mean (SD)	460.00 (154.859)
Median	457.58
IQ range	(346.37; 517.31)
Range	(208.6; 839.2)
Cycle 4 Day 1, 1 hour after end of infusion	
N	28
Mean (SD)	447.51 (144.017)
Median	415.75
IQ range	(359.23; 541.00)
Range	(214.5; 833.4)

Source: Clinical Study Report, Table 11, Page 47.

4.2.8.4.2 Exposure-Response Analysis

The Sponsor explored the relationship between $\Delta QTcB$ and $\Delta QTcF$ and serum concentrations of siltuximab using least-squares regression analysis and did not find a relationship (Figure 1).

Figure 1: Relationship between $\Delta QTcF$ and Siltuximab Concentration



Source: Clinical Study Report, Figure 1, Page 56.

Reviewer's Analysis: A plot of $\Delta QTcF$ vs. siltuximab concentrations is presented in Figure 3.

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

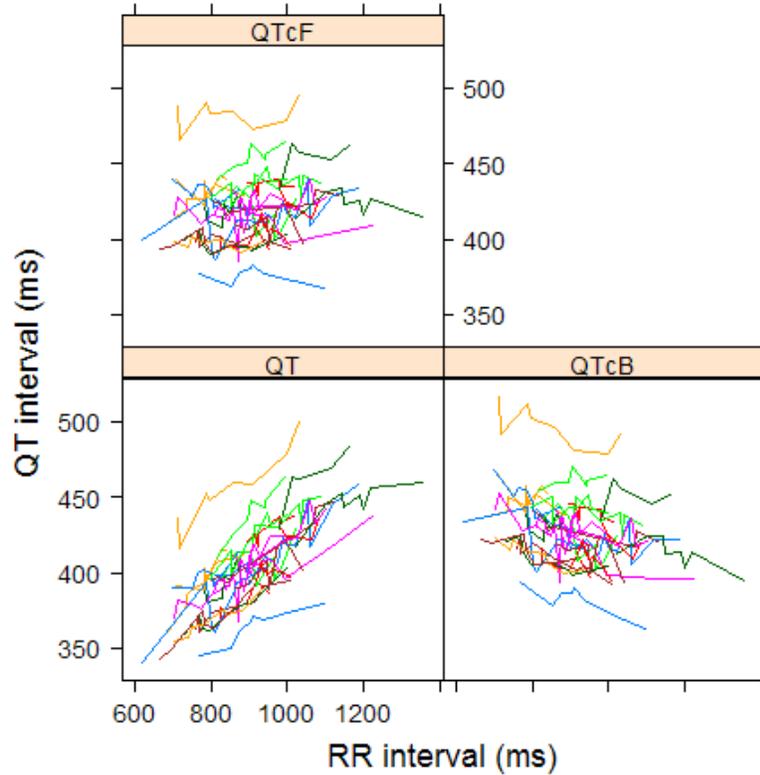
We used the criterion of Mean Sum of Squared Slopes (MSSS) from individual regressions of QTc versus RR. The smaller this value is, the better the correction. Based on the results listed in Table 4, it appears that QTcF is better than QTcB. To be consistent with the sponsor's analyses, we choose to present QTcF results.

Table 4: Average of Sum of Squared Slopes for Different QT-RR Correction Methods

Treatment Group	Correction Method			
	QTcB		QTcF	
	N	MSSS	N	MSSS
Siltuximab	30	0.0120	30	0.0063
All	30	0.0120	30	0.0063

The QT-RR interval relationship is presented in Figure 2 together with the Bazett's (QTcB) and Fridericia (QTcF) corrections.

Figure 2: QT, QTcB, and QTcF vs. RR (Each Subject's Data Points are Connected with a Line)



5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for the Study Drug

The statistical reviewer used mixed model to analyze the Δ QTcF effect. The model includes treatment as fixed effect and baseline values as a covariate. The analysis results are listed in Table 5. The sponsor provided the following time points: Cycle 1 Day 1 (predose, end of infusion, 1 hour after infusion, 3 hours after infusion, and 24 hours after infusion) and Cycle 4 Day 1 (predose, end of infusion, and 1 hour after infusion). The largest upper bound of the 2-sided 90% CI for the mean differences between baseline to Cycle 1 Day 1 and Cycle 4 Day 1 is 6.5 ms.

Table 5: Analysis Results of Δ QTcF for Siltuximab

Cycle	N	LS		90% CI
		Mean	Std	
CYCLE 1 DAY 1- End of infusion	30	1.2	1.8	(-1.9, 4.2)
CYCLE 1 DAY 1 - 1 hour after infusion	30	0.4	1.7	(-2.6, 3.4)
CYCLE 1 DAY 1- 3 hours after infusion	30	3.1	2.0	(-0.4, 6.5)
CYCLE 1 DAY 1- 24 hours after infusion	30	-2.7	2.3	(-6.6, 1.2)
CYCLE 4 DAY 1- Predose	28	-0.2	2.1	(-3.8, 3.5)
CYCLE 4 DAY 1 - End of infusion	28	1.2	1.9	(-2.1, 4.4)
CYCLE 4 DAY 1- End of infusion	27	1.5	2.2	(-2.2, 5.1)

5.2.1.2 Categorical Analysis

Table 6 lists the number of subjects as well as the number of observations whose QTcNi values are ≤ 450 ms, between 450 ms and 480 ms, and between 480 ms and 500 ms, and changes from baseline QTc ≤ 30 ms, between 30 and 60 ms, and >60 ms. No subject's QTcF is above 500 ms (see Table 6). No subject's change from baseline is above 30 ms.

Table 6: Categorical Analysis for QTcF

Treatment Group	Total N	Value \leq 450 ms	450 ms<Value \leq 480 ms	480 ms<Value \leq 500 ms
Siltuximab	30	27 (90.0%)	2 (6.7%)	1 (3.3%)

5.2.2 HR Analysis

The statistical reviewer used mixed model to analyze the Δ HR effect. The model includes treatment as fixed effect and baseline values as a covariate. The analysis results are listed in Table 7. The largest upper bound of the 2-sided 90% CI for the mean differences between baseline to Cycle 1 Day 1 and Cycle 4 Day 1 is 3.6 bpm. Table 8 presents the categorical analysis of HR. No subject who experienced HR interval greater than 100 bpm is in the siltuximab group.

Table 7: Analysis Results of Δ HR for Siltuximab

Cycle	N	LS		90% CI
		Mean	Std	
CYCLE 1 DAY 1- End of infusion	30	-0.8	0.9	(-2.3, 0.7)
CYCLE 1 DAY 1 - 1 hour after infusion	30	-1.9	1.1	(-3.8, 0.0)
CYCLE 1 DAY 1- 3 hours after infusion	30	-1.2	1.1	(-3.2, 0.7)
CYCLE 1 DAY 1- 24 hours after infusion	30	0.4	1.8	(-2.7, 3.6)
CYCLE 4 DAY 1- Pre-dose	28	-2.5	1.4	(-4.8, -0.2)
CYCLE 4 DAY 1 - End of infusion	28	-3.1	1.6	(-5.8, -0.5)
CYCLE 4 DAY 1- End of infusion	27	-3.0	1.4	(-5.4, -0.5)

Table 8: Categorical Analysis for HR

Treatment Group	Total N	HR < 100 bpm	HR >=100 bpm
Siltuximab	30	30 (100%)	0 (0.0%)

5.2.3 PR Analysis

The statistical reviewer used mixed model to analyze the Δ PR effect. The model includes treatment as fixed effect and baseline values as a covariate. The analysis results are listed in Table 9. The largest upper bound of the 2-sided 90% CI for the mean differences between baseline to Cycle 1 Day 1 and Cycle 4 Day 1 is 11.9 ms. Table 10 presents the categorical analysis of PR. Six subjects who experienced PR interval greater than 200 ms are in the siltuximab group.

Table 9: Analysis Results of Δ PR

Cycle	N	LS Mean	Std	90% CI
CYCLE 1 DAY 1- End of infusion	30	4.3	1.9	(1.1, 7.5)
CYCLE 1 DAY 1 - 1 hour after infusion	30	0.7	1.5	(-1.9, 3.3)
CYCLE 1 DAY 1- 3 hours after infusion	30	0.6	2.2	(-3.1, 4.3)
CYCLE 1 DAY 1- 24 hours after infusion	30	-1.4	1.6	(-4.1, 1.3)
CYCLE 4 DAY 1- Pre-dose	28	0.9	1.6	(-1.9, 3.7)
CYCLE 4 DAY 1 - End of infusion	28	7.4	2.6	(2.9, 11.9)
CYCLE 4 DAY 1- End of infusion	27	3.3	2.0	(-0.1, 6.7)

Table 10: Categorical Analysis for PR

Treatment Group	Total N	PR < 200 ms	PR >=200 ms
Siltuximab	30	24 (80.0%)	6 (20.0%)

5.2.4 QRS Analysis

The statistical reviewer used mixed model to analyze the Δ QRS effect. The model includes treatment as fixed effect and baseline values as a covariate. The analysis results are listed in Table 11. The largest upper bound of the 2-sided 90% CI for the mean differences between baseline to Cycle 1 Day 1 and Cycle 4 Day 1 is 3.2 ms. Table 12 presents the categorical analysis of QRS. No subject who experienced QRS interval greater than 110 ms is in siltuximab group.

Table 11: Analysis Results of Δ QRS

Cycle	N	LS Mean	Std	90% CI
CYCLE 1 DAY 1- End of infusion	30	1.9	0.8	(0.5, 3.2)
CYCLE 1 DAY 1 - 1 hour after infusion	30	0.9	0.7	(-0.3, 2.0)
CYCLE 1 DAY 1- 3 hours after infusion	30	1.5	0.6	(0.4, 2.5)
CYCLE 1 DAY 1- 24 hours after infusion	30	0.5	0.8	(-0.8, 1.8)
CYCLE 4 DAY 1- Pre-dose	28	1.1	0.9	(-0.5, 2.7)
CYCLE 4 DAY 1 - End of infusion	28	1.0	1.0	(-0.7, 2.6)
CYCLE 4 DAY 1- End of infusion	27	1.3	0.9	(-0.2, 2.7)

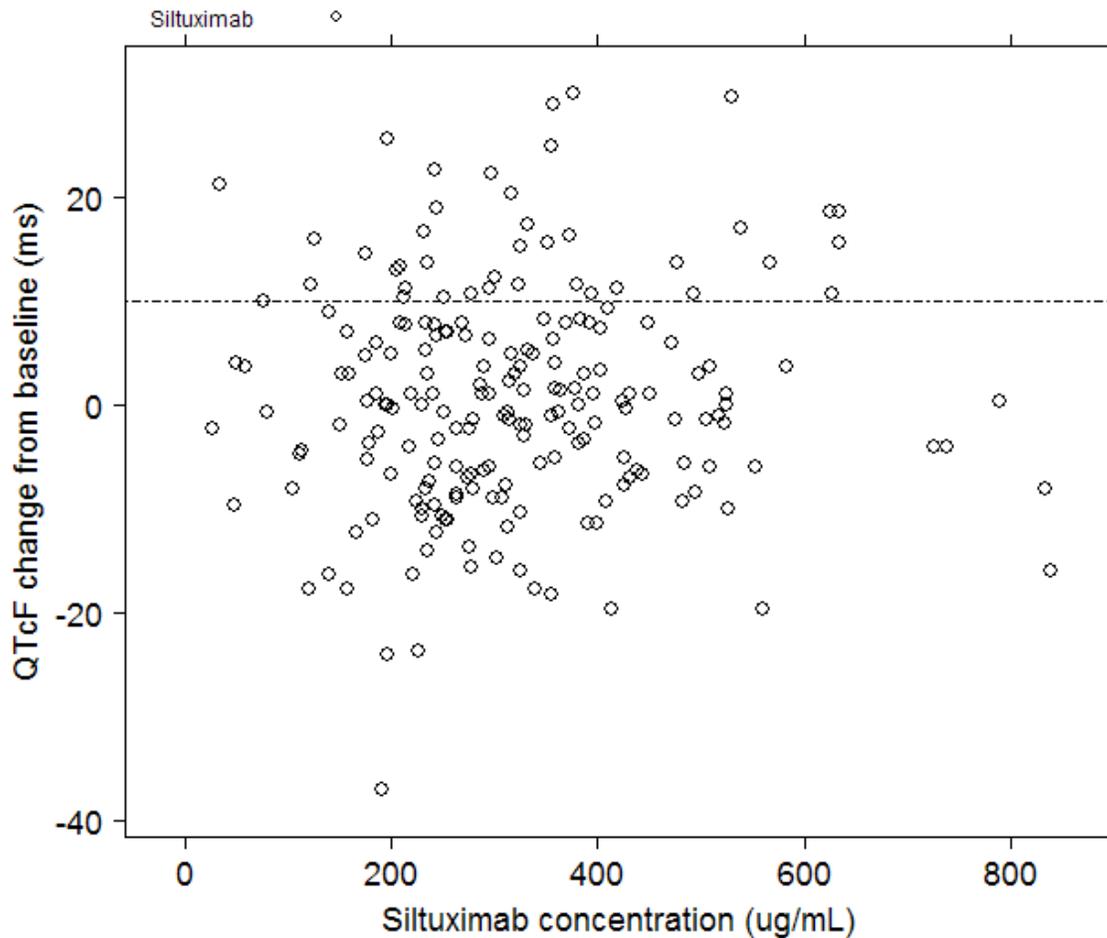
Table 12: Categorical Analysis for QRS

Treatment Group	Total N	QRS < 110 ms	QRS \geq 110 ms
Siltuximab	30	30 (100%)	0 (0.0%)

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The relationship between Δ QTcF and siltuximab concentrations is visualized in Figure 3 with no evident exposure-response relationship.

Figure 3: Δ QTcF vs. Siltuximab concentration



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E 14 guidelines i.e. syncope, seizure, significant ventricular arrhythmias or sudden cardiac death occurred in this study.

5.4.2 ECG assessments

Waveforms from the ECG warehouse were reviewed. According to ECG warehouse statistics 80 % of the ECGs were annotated in the primary lead II, with less than 97% of ECGs reported to have significant QT bias, according to the automated algorithm. Overall ECG acquisition and interpretation in this study appears acceptable.

5.4.3 PR and QRS Interval

Six patients had PR > 200 ms; postbaseline PR valwere < 225 ms and none had a postbaseline increase > 20 %.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose	11 mg/kg every 3 weeks	
Maximum tolerated dose	In clinical studies no MTD has been identified. In cynomolgus monkeys no toxicity has been identified at doses of up to 50 mg/kg/week for up to 6 months.	
Principal adverse events	As per current investigator brochure the following ADRs have been identified: Neutropenia, thrombocytopenia, infusion related reaction (mild to moderate), respiratory tract infection, pneumonia, sepsis, septic shock, bacteraemia, urinary tract infection, cellulitis, and hypertriglyceridemia For more information, see the IB, section 5.2	
Maximum dose tested	Single Dose	15 mg/kg
	Multiple Dose	15 mg/kg every 3 weeks
Exposures Achieved at Maximum Tested Dose	Single Dose	Mean Cmax (CV%) - 340.42 ug/mL (12.3%) and Mean AUC (CV%) - 5680 ug•day /mL (30.4%)
	Multiple Dose ¹	Mean Cmax (CV%) – 558.66 ug/mL (12.3%)
Range of linear PK	0.9 mg/kg to 15 mg/kg following both single and multiple dose	
Accumulation at steady state	Mean accumulation ratio (CV%) - 1.72 (25.2%) for 11 mg/kg every 3 weeks dose	
Metabolites	No metabolites of siltuximab have been identified and none are expected since siltuximab is a IgG-based monoclonal antibody	
Absorption	Absolute/Relative Bioavailability	100% since siltuximab is administered via IV infusion
	Tmax	Occurs at the end of the infusion, the current infusion duration is 60 min
Distribution	Vd/F or Vd	Following the first dose of 11 mg/kg; Mean Vd (%CV) 77.49 ml/kg (24.7%)
	% bound	% bound: 0%; siltuximab is not bound in the systemic circulation
Elimination	Route	Presumably its elimination follows the same catabolic pathway as endogenous IgG
	Terminal t _{1/2}	Following the first dose of siltuximab 11

		mg/kg; Mean Terminal t1/2 (%CV) 16.30 day (26.1%)
	CL/F or CL	Following the first dose of siltuximab 11 mg/kg; Mean CL (%CV) 3.54 mL/day/kg (12.3%)
Intrinsic Factors	Age	Not available
	Sex	Not available
	Race	Not available
	Hepatic & Renal Impairment	Not available
Extrinsic Factors	Drug interactions	No formal drug interaction studies have been performed and no drug interactions affecting siltuximab concentrations are expected
	Food Effects	Not applicable since siltuximab is administered intravenously
Expected High Clinical Exposure Scenario	Highest clinical exposure expected following single agent siltuximab administration. See above for the expected PK parameter values.	

¹ AUC could not be accurately estimated following repeats dose for the Maximum Tested Dose

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/s/

MOH JEE NG
12/06/2013

QIANYU DANG
12/06/2013

KEVIN M KRUDYS
12/06/2013

MONICA L FISZMAN
12/06/2013

NORMAN L STOCKBRIDGE
12/06/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label, Labeling and Packaging Review

Date: November 6, 2013

Reviewer: Tingting Gao, PharmD
Division of Medication Error Prevention and Analysis

Team Leader: Yelena Maslov, PharmD
Division of Medication Error Prevention and Analysis

Drug Name and Strength: Sylvant (siltuximab) for Injection,
100mg/vial, 400mg/vial

Application Type/Number: BLA 125496

Applicant/sponsor: Janssen Biotech, Inc.

OSE RCM #: 2013-2126

*** This document contains proprietary and confidential information that should not be released to the public.***

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1 INTRODUCTION

This review evaluates the proposed container label, carton and insert labeling for Sylvant (siltuximab), BLA 125496, for areas of vulnerability that could lead to medication errors.

1.1 PRODUCT INFORMATION

The following product information is provided in the August 29, 2013 submission.

- Active Ingredient: siltuximab
- Indication of Use: treatment of patients with multicentric Castleman's disease (MCD) who are human immunodeficiency virus (HIV-)-negative and human herpesvirus -8(HHV-8) -negative.
- Route of Administration: continuous intravenous infusion
- Dosage Form: lyophilized powder for reconstitution
- Strength: 100 mg/vial, 400 mg/vial
- Dose and Frequency: 11 mg/kg dose given over 1 hour by intravenous (IV) infusion every 3 weeks until treatment failure
- How Supplied:
 - 100 mg of lyophilized siltuximab in a 8 mL vial
 - 400 mg of lyophilized siltuximab in a 30 mL vial
- Storage: refrigerated at 2°C to 8°C (36°F to 46°F)
- Container and Closure System: Single dose vial individually packed in a carton

2 METHODS AND MATERIALS REVIEWED

DMEPA reviewed Sylvant (siltuximab) vial labels, carton labeling, and package insert labeling submitted by the Applicant on August 29, 2013.

2.1 LABELS AND LABELING

Using the principles of human factors and Failure Mode and Effects Analysis,¹ along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Drug Container Labels submitted August 29, 2013 (Appendix A)
- Carton Labeling submitted August 29, 2013 (Appendix B)
- Insert Labeling submitted August 29, 2013 (no image)

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

3 CONCLUSIONS

DMEPA concludes that the proposed container label, carton labeling can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product to mitigate any confusion. Additionally, the packaging insert can be improved to delete and clarify error prone abbreviations and dose designations as well as simplify reconstitution information. DMEPA provides the following comments for consideration by the review Division prior to the approval of this BLA.

4 RECOMMENDATIONS

4.1 COMMENTS TO THE DIVISION

DMEPA provides the following comments for consideration by the review Division prior to the approval of this BLA:

A. Dosage and Administration Section

1. Dangerous abbreviations, symbols, and dose designations that are included on the Institute of Safe Medication Practice’s List of Error-Prone Abbreviations, Symbols, and Dose Designations appear throughout the package insert. As part of a national campaign to avoid the use of dangerous abbreviations and dose designations, FDA agreed not to approve such error prone abbreviations in the approved labeling of products. Thus, please revise the those abbreviations, symbols, and dose designations as follows:
 - i. Remove the abbreviation “IV” in the statement “...intravenous (IV) infusion...”
 - ii. In Section 2.1, the statement “For 400 mg vials: Each vial must be reconstituted with 20.0 mL of single use sterile water for injection...” contains a trailing zero. Remove the trailing zero (e.g. 20 mL) to avoid a ten-fold misinterpretation.
2. In Section 2.1, we recommend using a table or bulletin points to delineate strength followed by the amount of Sterile Water for Injection required for reconstitution and the post-reconstitution concentration.

For example:

Strength	Amount of Sterile Water for Injection required for reconstitution	Post-reconstitution concentration
100 mg vial	5.2 mL	20 mg/mL
400 mg vial	20 mL	20 mg/mL

OR:

Aseptically reconstitute each TRADEMARK vial as follows:

- 25 mg TRADEMARK vial: Add 5.2 mL of only **Sterile Water for Injection, USP**.
 - 100 mg TRADEMARK vial: Add 20 mL of only **Sterile Water for Injection, USP**.
3. Add the statement “Retain in original package until time of use to protect from light” to this section if applicable.

B. Section 16 How Supplied/Storage and Handling

1. We recommend the Applicant to provide information for Safe Handling and Disposal in Section 16 if indicated.
2. Add the statement “Retain in original package until time of use to protect from light” to this section if applicable.

4.2 COMMENTS TO THE APPLICANT

Based on this review, DMEPA recommends the following be implemented prior to approval of this BLA:

A. Drug container label for 100 mg/vial and 400 mg/vial products:

- a. Remove the (b) (4) next to the trade name and proper name to minimize risk of “sylvant” being misread as (b) (4).
- b. Revise the statement (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.
- c. Debold the statement “Rx Only” as this information completes for prominent information such as established name on the principal display panel.
- d. 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.
- e. 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.
- f. 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.

- g. Add the statement “Protect from light” in the side panel.

B. Carton labeling

- a. Please see sections A.a through A.d.

- b. 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.

- c. Separate the statement “Once reconstituted, each mL contains 20 mg siltuximab, L-Histidine (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.
- d. Include instructions on post-reconstitution expiration date and storage if space permits.

If you have further questions or need clarifications, please contact Sonny Saini, project manager, at 301-796-0532.

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

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

/s/

TINGTING N GAO
11/06/2013

YELENA L MASLOV
11/06/2013

REGULATORY PROJECT MANAGER PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

Application: BLA 125496/0

Application Type: New BLA

Name of Drug: SYLVANT (siltuximab)

Applicant: Janssen Biotech, Inc.

Submission Date: August 29, 2013

Receipt Date: August 30, 2013

1.0 Regulatory History and Applicant's Main Proposals

Janssen Research & Development, LLC submitted this biologic license application (BLA) on behalf of the Janssen Biotech, Inc. Janssen Research & Development, LLC is the sponsor of Investigational New Drug (IND) 011461 for siltuximab.

Siltuximab is a chimeric (human-murine) immunoglobulin Gk (IgGk) monoclonal antibody that binds with high affinity and specificity to human interleukin-6 (IL-6), thereby neutralizing the biological activity of IL-6.

This new BLA provides for the use of siltuximab for the treatment of multicentric Castleman's disease (MCD) in patients who are immunodeficiency virus negative (HIV-) and human herpes virus – 8 negative (HHV-8-).

On May 26, 2006, FDA granted orphan designation to siltuximab for the treatment of Castleman's disease.

2.0 Review of the Prescribing Information (PI)

This review is based on the applicant's submitted Microsoft Word format of the PI. The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3.0 Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SRPI format deficiencies of the PI were conveyed to the applicant in the filing letter. The applicant was asked to correct these deficiencies and resubmit the PI in Word format by November 11, 2013. The resubmitted PI will be used for further labeling review.

4.0 Appendix

Selected Requirements of Prescribing Information (SRPI)

The Selected Requirement of Prescribing Information (SRPI) version 2 is a 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

Highlights (HL)

GENERAL FORMAT

- YES** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

- YES** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

- YES** 4. White space must be present before each major heading in HL.

Comment:

- YES** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Selected Requirements of Prescribing Information (SRPI)

Comment: *WARNINGS AND PRECAUTIONS* section - for Laboratory monitoring bullet change reference (2 and 5.3) to (2, 5.3).

- NO** 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a Boxed Warning is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state “None.”)
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment: *There is no revision date.*

- YES** 7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: “**HIGHLIGHTS OF PRESCRIBING INFORMATION**”.

Comment:

Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”

Comment:

Product Title

- YES** 10. Product title in HL must be **bolded**.

Comment:

Initial U.S. Approval

- NO** 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Selected Requirements of Prescribing Information (SRPI)

Comment: Applicant use hyphen instead of colon after "Initial U.S. Approval"

Boxed Warning

N/A 12. All text must be **bolded**.

Comment:

N/A 13. Must have a centered heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

N/A 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” centered immediately beneath the heading.

Comment:

N/A 15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)

Comment:

N/A 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

N/A 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

N/A 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

N/A 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.

Comment:

N/A 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

YES 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)].”

Comment:

Selected Requirements of Prescribing Information (SRPI)

Dosage Forms and Strengths

- YES** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

- YES** 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

Comment:

- N/A** 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

- YES** 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement

- YES** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**”

Comment:

Revision Date

- NO** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment: *There is not a revised date.*

Contents: Table of Contents (TOC)

GENERAL FORMAT

- YES** 28. A horizontal line must separate TOC from the FPI.

Comment:

- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”.

Comment:

Selected Requirements of Prescribing Information (SRPI)

- NO** 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.
Comment: *WARNINGS AND PRECAUTIONS subsection 5.1 title [REDACTED] ^{(b) (4)} is not the same as the title in FPI "Concurrent active serious infections."*
- N/A** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.
Comment:
- YES** 32. All section headings must be **bolded** and in UPPER CASE.
Comment:
- YES** 33. All subsection headings must be indented, not bolded, and in title case.
Comment:
- YES** 34. When a section or subsection is omitted, the numbering does not change.
Comment:
- YES** 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “**FULL PRESCRIBING INFORMATION: CONTENTS**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”
Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

- YES** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.
Comment:
- YES** 37. All section and subsection headings and numbers must be **bolded**.
Comment:
- YES** 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use

Selected Requirements of Prescribing Information (SRPI)

8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- YES** 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

- YES** 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

Comment:

- N/A** 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

- N/A** 42. All text is **bolded**.

Comment:

- N/A** 43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

- N/A** 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Selected Requirements of Prescribing Information (SRPI)

Contraindications

YES

45. If no Contraindications are known, this section must state “None”.

Comment:

Adverse Reactions

YES

46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”

Comment:

N/A

47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

Patient Counseling Information

YES

48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- “See FDA-approved patient labeling (Medication Guide)”
- “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information)”
- “See FDA-approved patient labeling (Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

Comment:

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/s/

PATRICIA N GARVEY
10/25/2013

AMY C BAIRD
10/29/2013

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # BLA# 125496	NDA Supplement #:S- BLA Supplement # 0	Efficacy Supplement Type SE-
Proprietary Name: SYLVANT Established/Proper Name: Siltuximab Dosage Form: single-use vial lyophilized powder in a vial Strengths: 100 mg vial, 400 mg vial		
Applicant: Janssen Biotech, Inc. Agent for Applicant: Janssen Research & Development, LLC		
Date of Application: August 29, 2013 Date of Receipt: August 30, 2013 Date clock started after UN: N/A		
PDUFA Goal Date: April 30, 2014		Action Goal Date (if different):
Filing Date: October 29, 2013		Date of Filing Meeting: October 22, 2013
Chemical Classification: (1, 2,3 etc.) (original NDAs only) N/A		
Proposed indication(s)/Proposed change(s): Treatment of Multicentric Castleman's Disease (MCD) in Patients who are immunodeficiency virus negative (HIV-) and human herpes virus - 8 negative (HHV-8-)		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 <i>and refer to Appendix A for further information.</i>		
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	

<input type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <input type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product): N/A				
List referenced IND Number: IND 011461				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		Proprietary name will be added to the application tracking system, after the proprietary name approval.
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:	<input type="checkbox"/>	<input type="checkbox"/>		
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

User Fee Status <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>		Payment for this application: <input type="checkbox"/> Paid <input checked="" type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>		Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
505(b)(2) (NDAs/NDA Efficacy Supplements only)		YES	NO	NA	Comment
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].		<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?		<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i>					
Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm		<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
If yes, please list below:					
Application No.	Drug Name	Exclusivity Code		Exclusivity Expiration	
<i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i>					
Exclusivity		YES	NO	NA	Comment
Does another product (same active moiety) have orphan exclusivity for the same indication? Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/ood/index.cfm		<input type="checkbox"/>	<input checked="" type="checkbox"/>		

<p>If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p>If yes, # years requested:</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?</p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<p>If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Format and Content				
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p>				
Overall Format/Content	YES	NO	NA	Comment
<p>If electronic submission, does it follow the eCTD guidance?¹ If not, explain (e.g., waiver granted).</p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<p>Index: Does the submission contain an accurate comprehensive index?</p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<p>Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:</p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

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<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				

Debarment Certification	YES	NO	NA	Comment
<p>Is a correctly worded Debarment Certification included with authorized signature?</p> <p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)²</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		Exempt - Orphan designation

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

If the application triggers PREA , are the required pediatric assessment studies or a full waiver of pediatric studies included?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
If studies or full waiver not included , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Proprietary name in submission dated September 6, 2013.
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input checked="" type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the PI submitted in PLR format? ⁴	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

⁴ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>		
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i> <i>September 23, 2013: DMPP Patient Labeling; IRT/QT Protocol/Study; and OSI Clinical Inspection</i> <i>September 27, 2013: SEALD for PRO instrument</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Meeting Minutes/SPAs	YES	NO	NA	Comment

<p>End-of-Phase 2 meeting(s)? Date(s): November 10, 2009 (cancelled) <i>If yes, distribute minutes before filing meeting</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		<p>Sponsor requested cancellation of EOP2 meeting after receiving FDA draft responses to meeting questions.</p>
<p>Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): July 24, 2013 (CMC only) (cancelled); June 7, 2013 (cancelled); and December 18, 2012 <i>If yes, distribute minutes before filing meeting</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		<p>Sponsor requested cancellation of scheduled July 24, 2013 and June 7, 2013 meetings after receiving FDA draft responses to meeting questions.</p> <p>December 18, 2012 meeting minutes issued January 7, 2013.</p>
<p>Any Special Protocol Assessments (SPAs)? Date(s): July 13, 2009 SPA submission date; October 15, 2009 meeting to discuss SPA no agreement letter <i>If yes, distribute letter and/or relevant minutes before filing meeting</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		<p>No Agreement issued August 27, 2009.</p> <p>October 15, 2009 meeting minutes issued November 10, 2009.</p>

ATTACHMENT

MEMO OF FILING MEETING

DATE: October 25, 2013

BLA/NDA/Supp #: 125496

PROPRIETARY NAME: SYLVANT

ESTABLISHED/PROPER NAME: Siltuximab

DOSAGE FORM/STRENGTH: single-use vial lyophilized powder in a vial/ 100 mg vial, 400 mg vial

APPLICANT: Janssen Biotech, Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Treatment of Multicentric Castleman's Disease (MCD) in Patients who are immunodeficiency virus negative (HIV-) and human herpes virus - 8 negative (HHV-8-)

BACKGROUND: Janssen Research & Development, LLC has submitted a biologic license application (BLA) on behalf of Janssen Biotech, Inc. Janssen Research & Development, LLC is the sponsor of the Investigational New Drug (IND) 011461 for siltuximab. Siltuximab is a chimeric (human-murine) immunoglobulin 1 κ (IgG1 κ) monoclonal antibody that binds with high affinity and specificity to human interleukin-6 (IL-6), thereby neutralizing the biological activity of IL-6.

On May 26, 2006, FDA granted orphan designation to siltuximab for the treatment of Castleman's disease.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Patricia Garvey, RPh	Y
	CPMS/TL:	Amy Baird	Y
Cross-Discipline Team Leader (CDTL)	Al Deisseroth, MD, PhD		Y
Clinical	Reviewer:	Patricia Dimndorf, MD	Y
	TL:	Al Deisseroth, MD, PhD	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:	N/A	
	TL:	N/A	

OTC Labeling Review (<i>for OTC products</i>)	Reviewer:	N/A	
	TL:	N/A	
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:	N/A	
	TL:	N/A	
Clinical Pharmacology	Reviewer:	Jeanne Fourie Zirkelbach, PhD	Y
	TL:	Julie Bullock, PharmD	Y
Biostatistics	Reviewer:	Chia-Wen Ko, PhD	Y
	TL:	Lei Nie, PhD	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Pedro Del Valle, PhD Chris Sheth, PhD Brenda Gehrke, PhD	Y
	TL:	Haleh Saber, PhD	Y
Statistics (carcinogenicity)	Reviewer:	N/A	
	TL:	N/A	
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:	Bazarra Damdinsuren,MD,PhD	Y
	TL:	Chana Fuchs, PhD	Y
Product Quality (CMC)	Reviewer:	Audrey Jia, MD, PhD Bazarra Damdinsuren,MD,PhD	Y Y
	TL:	Chana Fuchs, PhD	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	Reyes Candau-Chacon, PhD Candace Gomez-Broughton, PhD	Y N
	TL:	Patricia Hughes, PhD	N
CMC Labeling Review	Reviewer:	Audrey Jia, MD, PhD Bazarra Damdinsuren,MD,PhD	Y Y
	TL:	Chana Fuchs, PhD	Y
Facility Review/Inspection	Reviewer:	Reyes Candau-Chacon, PhD Audrey Jia, MD, PhD	Y Y
	TL:	Patricia Hughes, PhD Chana Fuchs, PhD	N Y
OSE/DMEPA (proprietary name)	Reviewer:	Tingting Gao, PharmD	Y
	TL:	Yelena Maslov, PharmD	N

OSE/DRISK (REMS)	Reviewer:	Robert Pratt, PharmD	Y
	TL:	Cynthia LaCivita, PharmD	N
OSE/DPV II	Reviewer:	Lynda McCulley, PharmD	Y
	TL:	Tracy Salaam, PharmD	Y
Bioresearch Monitoring (OSI)	Reviewer:	Anthony Orenca, MD	Y
	TL:	Janice Pohlman, MD, MPH	N
Controlled Substance Staff (CSS)	Reviewer:	N/A	
	TL:	N/A	
OMP/OMPI/DMPP	Karen Dowdy, RN		Y
OMP/OPDP	Nisha Patel, PharmD		Y
OND/SEALD	Ashley Slagle, PhD, MS		Y
DHP, Director	Ann Farrell, MD		Y
OSE, PM	Sonny Saini, PharmD		Y

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> • 505(b)(2) filing issues: <ul style="list-style-type: none"> ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., BA/BE studies):</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Electronic Submission comments <p>List comments:</p>	<input checked="" type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA, include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason: The application did not raise significant public health questions on the role of siltuximab in the diagnosis, cure, mitigation, treatment or prevention of a disease.
<ul style="list-style-type: none"> Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments: Review issues conveyed in filing letter, therefore a 74-day letter will not be issued.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter

<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? If no, was a complete EA submitted? If EA submitted, consulted to EA officer (OPS)? <p>Comments:</p>	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>

<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>CMC Labeling Review</u></p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days? 	<input type="checkbox"/> N/A <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • What late submission components, if any, arrived after 30 days? 	<p>N/A</p>
<ul style="list-style-type: none"> • Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

REGULATORY PROJECT MANAGEMENT	
<p>Signatory Authority: Richard Pazdur, MD Director, Office of Hematology and Oncology Products</p> <p>Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): December 3, 2013</p> <p>21st Century Review Milestones (listing review milestones in this document is optional):</p> <p>Comments:</p>	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <i>Comment: The review issues will be conveyed in filing letter, therefore will not issue 74-day letter.</i></p> <p><u>Review Classification:</u></p> <p><input type="checkbox"/> Standard Review</p> <p><input checked="" type="checkbox"/> Priority Review</p>
ACTIONS ITEMS	
<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input checked="" type="checkbox"/>	<p>BLA/BLA supplements: If filed, send 60-day filing letter</p> <p><i>Comment: The review issues will be conveyed in filing letter, therefore will not issue a 74-day letter.</i></p>

<input checked="" type="checkbox"/>	<p>If priority review:</p> <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	<p>Conduct a PLR format labeling review and include labeling issues in the 74-day letter</p> <p><i>Comment: The labeling issues will be conveyed in filing letter, therefore will not issue a 74-day letter.</i></p>
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
<input checked="" type="checkbox"/>	<p>BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at:</p> <p>http://erom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]</p>
<input type="checkbox"/>	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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/s/

PATRICIA N GARVEY
10/25/2013

AMY C BAIRD
10/29/2013

Therapeutic Biological Establishment Evaluation Request (TB-EER) Form

Instructions:

The review team should email this form to the email account “CDER-TB-EER” to submit:

- 1) an initial TB-EER within 10 business days of the application filing date
- 2) a final TB-EER 15-30 days prior to the action date

Note: All manufacturing³ locations named in the pending submission, whether contract facilities or facilities owned by the applicant, should be listed on this form. For bundled supplements, one TB-EER to include all STNs should be submitted.

APPLICATION INFORMATION

PDUFA Action Date: TBD

Applicant Name: Janssen Biotech, Inc.
U.S. License #: 1864
STN(s): 125496/0
Product(s): Siltuximab (Sylvant)

Short summary of application: BLA for the treatment of patients with multicentric Castleman’s disease (MCD) who are human immunodeficiency virus negative and human herpesvirus-8 negative

FACILITY INFORMATION

Manufacturing Location: Leiden, The Netherlands
Firm Name: Janssen Biologics B.V.
Address: Einsteinweg 101
Leiden, the Netherlands CB-2333
FEI: 3002806632

Short summary of manufacturing activities performed: Drug Substance Manufacturing
(b) (4) analytical testing of process intermediates and bulk drug substance; Testing of Final Lyophilized Product

This site was inspected by IOG on September 20 – 28, 2012 and classified VAI. This was a routine CGMP surveillance inspection covering (b) (4) drug substance manufacturing operations. The (b) (4) profile was updated and is acceptable. **BMAB (with the input of OBP) will determine whether this site requires a PLI for this BLA.**

Manufacturing Location: Co. Cork, Ireland

Firm Name: Janssen Biologics (Ireland)
Address: Barnahely, Ringaskiddy
Co. Cork, Ireland
FEI: 3007029098
Short summary of manufacturing activities performed: Drug Substance Manufacturing
(b) (4) analytical testing of process intermediates and bulk drug substance; Testing
of Final Lyophilized Product

This site was inspected by IOG on June 12 – 18, 2012 and classified VAI. This was a routine CGMP surveillance inspection covering biotech drug substance manufacturing operations. The (b) (4) and TRP profiles were updated and are acceptable. **BMAB (with the input of OBP) will determine whether this site requires a PLI for this BLA.**

Manufacturing Location: (b) (4)
Firm Name:
Address:
FEI:
Short summary of manufacturing activities performed: (b) (4)
(b) (4) testing

This site was inspected by (b) (4) on March (b) (4) and classified NAI. This was a routine CGMP surveillance inspection covering biotech drug testing operations. The (b) (4) profile was updated and is acceptable.

Manufacturing Location: Switzerland
Firm Name: Cilag AG
Address: Hochstrasse 201
Schaffhausen, Switzerland CH-8200
FEI: 3002806695
Short summary of manufacturing activities performed: Manufacture (b) (4)
(b) (4) of the Final Lyophilized Product

This site was inspected by IOG on April 20 – 27, 2012 and classified VAI. This was a routine CGMP surveillance inspection covering (b) (4) drug product manufacturing operations. The (b) (4) profile was updated and is acceptable. **BMAB (with the input of OBP) will determine whether this site requires a PLI for this BLA.**

OVERALL RECOMMENDATIONS:

There are no pending or ongoing compliance actions that prevent approval of this supplement. Please resubmit this TB-EER 15-30 days prior to the planned action date for an updated compliance evaluation.

3

The regulations at 21 C.F.R. § 207.3(a)(8) defines “manufacturing or processing” as “the manufacture, preparation, propagation, compounding, or processing of a drug or drugs as used in section 510 of the act [21 U.S.C. § 360] and is the making by chemical, physical, biological, or other procedures of any articles that meet the definition of drugs in section 201(g) of the act. The term includes manipulation, sampling, testing, or control procedures applied to the final product or to any part of the process. The term also includes repackaging or otherwise changing the container, wrapper, or labeling of any drug package to further the distribution of the drug from the original place of manufacture to the person who makes final delivery or sale to the ultimate consumer.”

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/s/

RANJANI PRABHAKARA
10/16/2013

Therapeutic Biological Establishment Evaluation Request (TB-EER) Form

Instructions:

The review team should email this form to the email account "CDER-TB-EER" to submit:

- 1) an initial TB-EER within 10 business days of the application filing date
- 2) a final TB-EER 15-30 days prior to the action date

Note: All manufacturing locations named in the pending submission, whether contract facilities or facilities owned by the applicant, should be listed on this form. For bundled supplements, one TB-EER to include all STNs should be submitted.

APPLICATION INFORMATION

PDUFA Action Date: TBD

Applicant Name: Janssen Biotech, Inc.
U.S. License #: 1864
STN(s): 125496/0
Product(s): Siltuximab (Sylvant)

Short summary of application: BLA for the treatment of patients with multicentric Castleman's disease (MCD) who are human immunodeficiency virus negative and human herpesvirus-8 negative

FACILITY INFORMATION (DRUG SUBSTANCE)

Manufacturing Location: Leiden, The Netherlands
Firm Name: Janssen Biologics B.V.
Address: Einsteinweg 101, Leiden, The Netherlands CB-2333
FEI: 3002806632

Short summary of manufacturing activities performed: Drug Substance Manufacturing (b) (4)
(b) (4) analytical testing of process intermediates and bulk drug substance; Testing of Final Lyophilized Product

Manufacturing Location: Co. Cork, Ireland
Firm Name: Janssen Biologics (Ireland)
Address: Barnahely, Ringaskiddy, Co. Cork, Ireland
FEI: 987061921

Short summary of manufacturing activities performed: Drug Substance Manufacturing (b) (4)
(b) (4), analytical testing of process intermediates and bulk drug substance; Testing of Final Lyophilized Product

Manufacturing Location: (b) (4)
Firm Name: (b) (4)
Address: (b) (4)
FEI: (b) (4)

Short summary of manufacturing activities performed: (b) (4)
(b) (4) testing

FACILITY INFORMATION (DRUG PRODUCT)

Manufacturing Location: Switzerland

Firm Name: Cilag AG

Address: Hochstrasse 201, Schaffhausen, Switzerland CH-8200

FEI: 3002806695

Short summary of manufacturing activities performed: Manufacture. (b) (4)
 of the Final Lyophilized Product

³

The regulations at 21 C.F.R. § 207.3(a)(8) defines “manufacturing or processing” as “the manufacture, preparation, propagation, compounding, or processing of a drug or drugs as used in section 510 of the act [21 U.S.C. § 360] and is the making by chemical, physical, biological, or other procedures of any articles that meet the definition of drugs in section 201(g) of the act. The term includes manipulation, sampling, testing, or control procedures applied to the final product or to any part of the process. The term also includes repackaging or otherwise changing the container, wrapper, or labeling of any drug package to further the distribution of the drug from the original place of manufacture to the person who makes final delivery or sale to the ultimate consumer.”

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/s/

REYES CANDAU-CHACON
09/26/2013

CANDACE GOMEZ-BROUGHTON
09/26/2013

OSI/DGCPC CONSULT: Request for Clinical Inspections

Date: September 23, 2013

To: Ann Meeker-O'Connell, Acting Division Director, DGCPC
Constance Lewin, M.D., M.P.H, Branch Chief, GCPEB*
Susan Thompson, M.D., Acting Branch Chief, GCPAB
Janice Pohlman, M.D., M.P.H., Team Leader GCPAB
Susan Leibenhaut, M.D. Acting Team Leader, GCPAB
CDER OSI PM Track
Name of DSI Primary Reviewer (if known)
Division of Good Clinical Practice Compliance
Office of Scientific Investigations
Office of Compliance/CDER

Through: *Division of Hematology Products (DHP)*
Patricia Dinndorf, M.D./Medical Officer
Albert Deisseroth, M.D., Ph.D./Clinical Team Leader
Ann Farrell, M.D./Division Director

From: *Patricia Garvey, R.Ph., Senior Regulatory Project Manager/DHP*

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: BLA 125496/0

Applicant/ Applicant contact information (to include phone/email):

Janssen Biotech, Inc.

US Agent: Janssen Research & Development, LLC

Brian Maloney, MS, RPh, Director of Regulatory Affairs

920 Route 202

P.O. Box 300

Raritan, NJ 08869

Phone: 908-927-2228

Fax: 908-526-5059

Email: bmalone@its.jnj.com

Drug Proprietary Name: Sylvant

Generic Drug Name: siltuximab

NME or Original BLA (Yes): Yes

Review Priority (Standard or Priority or Not Applicable*): Priority

OSI/DGCPC Consult

version: 09/12/2013

Study Population includes < 17 years of age : No
 Is this for Pediatric Exclusivity: No

Proposed New Indication(s): Treatment of multicentric Castleman’s Disease (MCD) in patients who are immunodeficiency virus negative (HIV) and human herpes virus – 8 negative (HHV – 8 –)

PDUFA: April 29, 2014
 Action Goal Date: April 29, 2014
 Inspection Summary Goal Date: February 29, 2014

II. Protocol/Site Identification

Include the Protocol Title or Protocol Number for all protocols to be audited. Complete the following table (Note: ALL items listed are required, to process inspection request. Failure to provide complete information will result in delay of inspection process).

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication/Primary endpoint and other endpoints for verification
Site #0102 Fritz Van Rhee Myeloma Institute for Research and Therapy 4301 W. Markham Street, Slot 816 Little Rock, AR 72205 Phone: (501) 526-2873 Fax: (501) 526-2273 Email: vanrheefrits@uams.edu	CNTO328 MCD2001	5	

III. Site Selection/Rationale

The major evidence this application relies on is a single trial CNTO328MCD2001 “A Randomized, Double-blind, Placebo controlled Study to Assess the Efficacy and Safety of CNTO 328 (Anti IL-6 Monoclonal Antibody) Plus Best Supportive Care Compared With Best Supportive Care in Subjects With Multicentric Castleman’s Disease” There were 79 subjects randomized 2:1 at 38 sites. Three sites enrolled 5 subjects; 3 sites enrolled 4 subjects; 6 sites enrolled 3 subjects; the remaining 26 sites enrolled 1 or 2 subjects.

There were 3 investigators who submitted Form 3455 indicating they had received Research Funding from Janssen. No other investigators reported receipt of funding.

(b) (6)	Site Site Site	(b) (6)	149,443 US Dollar 200,300 US Dollar 198,000 Euro	(b) (6)
---------	----------------------	---------	--	---------

The primary efficacy endpoint of the study was improvement in independently reviewed durable tumor and symptomatic response rate in the siltuximab group compared with the placebo group (34% vs. 0%, respectively; 95% CI of the difference: 11.1, 54.8; p=0.0012).

All subjects treated with siltuximab at site 0102 (siltuximab n=2; placebo n=3) and site 6501 (siltuximab n=3; placebo n=0) were responders. The single patient enrolled from site 9721 who received siltuximab did not respond. Excluding the 9 subjects from the institutions with investigators who received research funding from Janssen resulted in an independently reviewed durable tumor and symptomatic response rate in the siltuximab group (n=47) of 28% compared to 0% in the placebo group (n=23); the 95% CI for the 28% response rate difference is (3.1%, 50.3%).

Domestic Inspections:

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify):
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify):

International Inspections:

If budget considerations allowed, an inspection of site 6501 in Singapore would be requested. However this site only contributed 3 subjects and if these subjects were excluded from the analysis it would not change the overall conclusion regarding the primary efficacy endpoint.

Reasons for inspections (please check all that apply):

- There are insufficient domestic data
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Other (specify)

IV. Specific Data to be Verified (if applicable)

Site 0102 enrolled 8 patients, 3 were screen failures and 5 were randomized (siltuximab n=2; placebo n=3). The application includes investigator information in section 5.3.5.1. Data sets include discontinuations, adverse events, serious adverse events, prior concomitant or prohibited medications, efficacy endpoints, and protocol deviations.

The primary efficacy endpoint is durable tumor and symptomatic response based on independent review. Durable tumor and symptomatic response is defined as either complete response (CR) or partial response (PR):

- CR: complete disappearance of all measurable and evaluable disease (e.g., pleural effusion) and resolution of baseline symptoms attributed to MCD, sustained for at least 18 weeks

Page 4-Request for Clinical Inspections

- PR: a $\geq 50\%$ decrease in the sum of the product of the diameters (SPD) of index lesion(s), with at least stable disease (SD) in all other evaluable disease in the absence of treatment failure, sustained for at least 18 weeks.

There are 2 items that should be evaluated

- The documentation of data required to make the primary efficacy analysis
- Protocol violations that could potentially lead to unblinding of the treatment arm. The protocol states CRP, fibrinogen, ESR and quantitative immunoglobulin levels may potentially unblind treatment assignment. These laboratory tests were to be obtained in a manner to segregate the data from the clinical team. Evaluate if these laboratory tests were ordered outside the protocol specified manner.

Should you require any additional information, please contact *Patricia Dinndorf, MD* at 301-796-1350.

Concurrence: Patricia Dinndorf, M.D./Clinical Reviewer, DHP
Albert Deisseroth, M.D., Ph.D./Clinical Team Leader, DHP
Ann Farrell, M.D./Director, DHP

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/s/

PATRICIA N GARVEY
09/23/2013

ALBERT B DEISSEROTH
09/24/2013

ANN T FARRELL
09/24/2013