DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125496/0

BLA APPROVAL

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

Dear Mr. Maloney:

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

We acknowledge receipt of your amendments dated September 6, 17, 23, and 26; October 2, 10, 16, 24, 29, and 30; November 1, 4, 5, and 15; December 5, 10, 13, 18, 20, and 31, 2013; January 2, 13, and 28, February 5 (2), 7, and 21; March 7 (3), 10, 14 (2), 19, 21 (2), 24 (2), 25, 28, and 31; and April 3, and 10, 2014.

LICENSING

We have approved your BLA for SYLVANT™ (siltuximab) effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, SYLVANT™ (siltuximab) under your existing Department of Health and Human Services U.S. License No. 1864. SYLVANT™ (siltuximab) is indicated for the treatment of patients with multicentric Castleman's disease (MCD) who are human immunodeficiency virus (HIV) negative and human herpesvirus-8 (HHV-8) negative.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture siltuximab (b) (4) intermediate at Janssen Biologics B.V. in Leiden, The Netherlands. You are approved to manufacture siltuximab formulated bulk drug substance at Janssen Biologics, Cork, Ireland. The final lyophilized drug product will be manufactured at Cilag AG, Schaffhausen, Switzerland. You may label your product with the proprietary name, SYLVANT™, and will market it as an 8 mL single use vial containing 100 mg siltuximab lyophilized powder for injection and as a 30 mL single use vial containing 400 mg siltuximab lyophilized powder for injection.

DATING PERIOD

The dating period for SYLVANT™ (siltuximab) 100 mg vial shall be 24 months from the date of manufacture when stored at 2-8°C. The dating period for SYLVANT™ (siltuximab) 400 mg vial shall be 24 months from the date of manufacture when stored at 2-8°C. The date of manufacture shall be defined as [redacted]. The dating period for siltuximab [redacted] intermediate shall be [redacted]. The dating period for siltuximab formulated bulk drug substance shall be [redacted]. The dating period for siltuximab formulated bulk drug substance [redacted].

Results of ongoing stability should be submitted to the annual report.

We have approved the annual stability protocols in your license application for the purpose of extending the expiration dating period of your [redacted] intermediate and your formulated bulk drug substance under 21 CFR 601.12.

FDA LOT RELEASE

You are not currently required to submit samples of future lots of SYLVANT™ (siltuximab) to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1, requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

Any changes in the manufacturing, testing, packaging, or labeling of siltuximab, or in the manufacturing facilities, will require the submission of information to your biologics license application for our review and written approval, consistent with 21 CFR 601.12.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 601.14(b)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, text for the patient package insert). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels and carton and immediate container labels submitted on March 7, 2014, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)". Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Product Correspondence – Final Printed Carton and Container Labels for approved BLA 125496/0**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with final printed labeling (FPL) that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

ADVISORY COMMITTEE

Your application for SYLVANT™ (siltuximab) was not referred to an FDA advisory committee because outside expertise was not necessary; there were no controversial issues that would benefit from advisory committee discussion.

REQUIRED PEDIATRIC ASSESSMENTS

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

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify unexpected serious risks of long-term therapy with SYLVANT™ (siltuximab).

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to identify unexpected serious risks of long-term chronic therapy with SYLVANT™ (siltuximab).

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

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

The timetable you submitted on March 24, 2014, states that you will conduct this trial according to the following schedule:

Trial Completion:	03/2017
Final Report Submission:	08/2017

Submit the final report to your BLA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)", "Required Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o)"**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 601.70 requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 601.70. We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

PMC-2 To determine the volume of the [redacted] (b) (4) necessary to achieve consistent [redacted] (b) (4) test conditions, provide the supportive data, and use the determined volume in the [redacted] (b) (4) test of the drug product [redacted] (b) (4) by August 2014.

The timetable you submitted on March 21, 2014, states that you will conduct this study according to the following schedule:

Final Report Submission: 08/2014

PMC-3 To conduct a study for endotoxin recovery from formulated bulk drug substance held in [redacted] (b) (4) at process conditions and submit summary report to the Agency per 21 CFR 601.12.

The timetable you submitted on March 21, 2014, states that you will conduct this study according to the following schedule:

Final Report Submission: 07/2014

PMC-4 To re-evaluate siltuximab 100 mg/vial final lyophilized drug product (FLP) 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 final report should include the corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications.

The timetable you submitted on April 10, 2014, states that you will conduct this study according to the following schedule:

Study Completion: 04/2019
Final Report Submission: 07/2019

PMC-5 To re-evaluate siltuximab 400 mg/vial final lyophilized drug product (FLP) 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 final report should include corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications.

The timetable you submitted on April 10, 2014, states that you will conduct this study according to the following schedule:

Study Completion:	04/2019
Final Report Submission:	07/2019

PMC-6 To re-evaluate siltuximab formulated bulk drug substance (FB) 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 13 lots which were included in the analysis of specifications submitted in the BLA and any subsequent FB lots manufactured. The final report should include the corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications.

The timetable you submitted on April 10, 2014, states that you will conduct this study according to the following schedule:

Study Completion:	04/2019
Final Report Submission:	07/2019

PMC-7 To re-evaluate siltuximab [redacted] (b) (4) intermediate [redacted] (b) (4) lot release and stability specifications using the commercial manufacturing process 2 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 cIEF specifications submitted in the BLA and any subsequent [redacted] (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 final report should include the corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications.

The timetable you submitted on April 10, 2014, states that you will conduct this study according to the following schedule:

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

PMC-8 To confirm the anticipated amount of [redacted] (b) (4) using a validated reduced scale model.

The timetable you submitted on April 3, 2014, states that you will conduct this study according to the following schedule:

Final Report Submission:	12/2014

PMC-9 To confirm the anticipated amount of [redacted] using a validated reduced scale model [redacted]

The timetable you submitted on April 3, 2014, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/2014

PMC-10 To tighten the [redacted] reference material requalification acceptance criterion for potency 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 CBE-0.

The timetable you submitted on April 10, 2014, states that you will conduct this study according to the following schedule:

Final Report (CBE-0) Submission: 11/2014

PMC-11 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 CBE-0.

The timetable you submitted on April 3, 2014, states that you will conduct this study according to the following schedule:

Final (CBE-0) Report Submission: 08/2014

PMC-12 To establish a control strategy for the [redacted] The updated control strategy and supporting data will be submitted as a CBE-0.

The timetable you submitted on April 3, 2014, states that you will conduct this study according to the following schedule:

Final Report (CBE-0) Submission: 08/2014

PMC-13 To re-evaluate the [redacted] using data from formulated bulk drug substance batches manufactured up to October 2016. The analysis and supporting data will be submitted as a CBE-30.

The timetable you submitted on April 10, 2014, states that you will conduct this study according to the following schedule:

Study Completion:	10/2016
Final Report (CBE-30) Submission:	12/2016

PMC-14 To provide confirmatory data by executing a manufacturing run of the 100 mg/vial final lyophilized drug product batch at (b) (4) The drug product from this run will be placed on a stability protocol. The final report, release and stability data will be submitted as an Annual Report.

The timetable you submitted on April 3, 2014, states that you will conduct this study according to the following schedule:

Study Completion:	09/2017
Final Report Submission:	12/2017

PMC-15 To provide confirmatory data by executing a manufacturing run of the 400 mg/vial final lyophilized drug product batch at (b) (4) The drug product from this run will be placed on a stability protocol. The final report, release and stability data will be submitted as an Annual Report.

The timetable you submitted on April 3, 2014, states that you will conduct this study according to the following schedule:

Study Completion:	09/2017
Final Report Submission:	12/2017

PMC-16 To provide confirmatory data by executing a manufacturing run of the 100 mg/vial final lyophilized drug product batch at (b) (4) (b) (4). The drug product from this run will be placed on a stability protocol. The final report, release and stability data will be submitted as an Annual Report.

The timetable you submitted on April 3, 2014, states that you will conduct this study according to the following schedule:

Study Completion:	09/2017
Final Report Submission:	12/2017

PMC-17 To provide confirmatory data by executing a manufacturing run of the 400 mg/vial final lyophilized drug product batch at (b) (4) (b) (4). The drug product from this run will be placed on a stability protocol. The final report, release and stability data will be submitted as an Annual Report.

The timetable you submitted on April 3, 2014, states that you will conduct this study according to the following schedule:

Study Completion:	09/2017
Final Report Submission:	12/2017

Submit clinical protocols to your IND 011461 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

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

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (21 CFR 600.80). You should submit postmarketing adverse experience reports to:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Prominently identify all adverse experience reports as described in 21 CFR 600.80.

You must submit distribution reports under the distribution reporting requirements for licensed biological products (21 CFR 600.81).

You must submit reports of biological product deviations under 21 CFR 600.14. You should promptly identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA-3486 to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
5901-B Ammendale Road
Beltsville, MD 20705-1266

Biological product deviations, sent by courier or overnight mail, should be addressed to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
10903 New Hampshire Avenue, Bldg. 51, Room 4206
Silver Spring, MD 20903

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from

improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

PDUFA V APPLICANT INTERVIEW

FDA has contracted with Eastern Research Group, Inc. (ERG) to conduct an independent interim and final assessment of the Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs under PDUFA V ('the Program'). The PDUFA V Commitment Letter states that these assessments will include interviews with applicants following FDA action on applications reviewed in the Program. For this purpose, first-cycle actions include approvals, complete responses, and withdrawals after filing. The purpose of the interview is to better understand applicant experiences with the Program and its ability to improve transparency and communication during FDA review.

ERG will contact you to schedule a PDUFA V applicant interview and provide specifics about the interview process. Your responses during the interview will be confidential with respect to the FDA review team. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final assessments. Members of the FDA review team will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to these assessments.

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

Sincerely,

{See appended electronic signature page}

Richard Pazdur, MD
Director
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURES:
Content of Labeling
Carton and Container Labeling

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

/s/

RICHARD PAZDUR
04/23/2014