

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125496Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

CDTL Review

Date	April 3, 2014
From	Albert Deisseroth, MD, PhD
Subject	CDTL Review
NDA Number	BLA 125496
Applicant	Janssen Biotech, Inc.
Date of Submission	August 30, 2013
PDUFA Goal Date	April 29, 2014
Established Name/Proprietary Name	Siltuximab/Sylvant
Dosage Regimen	11mg/kg every 3 weeks
Applicant's Proposed Indication	Treatment of Multicentric Castleman's Disease in patients who are immunodeficiency virus negative (HIV) and human herpes virus-8 (HHV-8)
Recommended:	Approval

Material Reviewed/Consulted	Reviewer/Author
Medical Officer Review	Patricia Dinndorf, MD
Pharmacology/Toxicology	Pedro L. Del Valle, PhD, and Haleh Saber, PhD
Statistics	Chia-Wen Ko, PhD, and Lei Nie, PhD
Clinical Pharmacology	Jeanne Fourie Zirkelbach, PharmD and Julie Bullock, PharmD
DMA	Audrey Jia, PhD (Drug Substance), Bazarragchaa Damdinsuren PhD (Drug Product), and Chana Fuchs, PhD
BMAB	Maria Candauchacon, PhD (Drug Substance), Candace Gomez-Broughton, PhD (Drug Product), and Patricia Hughes, PhD
Regulatory Program Manager	Patricia Garvey, PhD

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1. EXECUTIVE SUMMARY AND BENEFIT RISK DISCUSSION (This section was excerpted in part from the review of Dr. Patricia Dinndorf):

BLA 125496 was submitted by Janssen Biotech, Inc. on August 30, 2013. The indication proposed was for patients with multicentric Castleman's disease (MCD) who are HIV and HHSV-8 negative.

The indication was evaluated in an international, multicenter, randomized (2:1), phase 2 study comparing every 3 week infusions of Sylvant (siltuximab) and best supportive care (BSC) to placebo and BSC. The trial met its primary endpoint of a statistically significant difference of the proportion of patients showing durable tumor and symptomatic response based on independent review in the siltuximab as compared to the placebo arm. The response rate in the siltuximab group compared with the placebo group was 34% (18/53) versus 0% (0/26), (95% CI of the difference: 11.1, 54.8; $p=0.0012$). This response was supported by the following additional hierarchically pre-specified endpoints:

- The best tumor response in the siltuximab group compared with the placebo group was 38% (20/53) versus 4% (1/26), (95% CI of the difference: 11.1, 54.8; $p < 0.05$).
- The median time to treatment failure was not reached in the siltuximab arm and was 134 days in the placebo arm. (HR 0.418, (95% CI of HR: 0.21 to 0.82; $p < 0.05$).
- Increase in hemoglobin at Week 13 to 15 of 1.5 g/dL in patients who were anemic at study entry: in terms of the response criterion of an increase in the hemoglobin of 1.5 g/dL, there were no responders in the placebo arm and 19 responders in the siltuximab arm. The difference of hemoglobin response rate was 61% (19/31) in the siltuximab arm compared to 0% (0/11) in the placebo arm; 95% CI of the difference: 28.3, 85.1 ($p < 0.05$).

Additional support of the efficacy findings was confirmed by the responses documented in the subset of patients with MCD treated with siltuximab on C0328T03, the dose finding trial of siltuximab in patients with hematologic malignancies. The response rate of subjects with MCD enrolled on the trial was 32% (12/37). There was 1 CR and 11 PRs.

There were no on study deaths. There were no safety signals identified in SAEs or AEs. The adverse events were predominantly constitutional symptoms of MCD including edema, effusions, night sweats, rash, fatigue, malaise, weight loss, ascites, and neuropathy. One subject experienced an anaphylactic reaction with the first infusions of siltuximab, and a second subject experienced symptoms of an infusion reaction. There were rarely discontinuations due to a drug related adverse event.

Recommendation for Regulatory Action: On the basis of the above, this CDTL reviewer concludes that the benefit risk ratio is favorable and recommends approval.

2. BACKGROUND (This section was excerpted from the review of Dr. Patricia Dinndorf):

2.a. Indication: The indication proposed by the Applicant for siltuximab is the treatment of MCD in patients who are immunodeficiency virus negative (HIV) and human herpes virus-8 (HHV-8).

2.b. Multicentric Castleman's Disease (This section was excerpted from the review of Dr. Patricia Dinndorf): Castleman's disease (angiofollicular lymph node hyperplasia) is a lymphoproliferative disorder associated in a subset of cases with the human immunodeficiency virus (HIV) and human herpesvirus 8. Castleman's disease comprises at least two distinct diseases (localized and multicentric) with very different prognoses. It is also associated with a number of malignancies, including Kaposi sarcoma, non-Hodgkin lymphoma, Hodgkin lymphoma, and POEMS syndrome [Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal protein, Skin changes]. This application is evaluating siltuximab in patients with MCD without HIV or HHV-8.

Castleman's disease has been linked to excessive release of IL-6 or similar polypeptides. Early studies linked local production of IL-6 to the systemic manifestations of unicentric Castleman's disease, since lymph node excision resulted in relief of symptoms along with a decrease in IL-6 levels. IL-6 is a potent growth factor for B lymphocytes and plasma cells. Excess IL-6 induces a proinflammatory syndrome that leads to constitutional symptoms, induction of vascular endothelial growth factor (VEGF) secretion, and induction of immune dysregulation leading to autoimmune phenomena including cytopenias.

Patients with MCD present at a median age of between 52 and 65 with fever, night sweats, weight loss, and weakness or fatigue. Peripheral lymphadenopathy is nearly universal, generalized, and often accompanied by hepatosplenomegaly. Laboratory abnormalities include anemia, hypoalbuminemia, hypergammaglobulinemia, and an elevated sedimentation rate. There are 2 histologic variants, the hyaline vascular variant and the plasma cell variant.

The prognosis of untreated MCD is poor. Median survival is reported to range from 26 to 30 months. Almost all treatments using single agents (eg, anti-viral, anti-cytokine, chemotherapy, corticosteroids) are palliative, with disease recurrence once they are stopped.

2.c. Approved Therapy for Multicentric Castleman's Disease (This section was excerpted from the review of Dr. Patricia Dinndorf): There is no approved therapy for MCD in the United States. Tocilizumab has been approved for the therapy of MCD in Japan. Tocilizumab is a humanized anti-IL-6 receptor monoclonal antibody which inhibits IL-6 function and is approved in Japan for the treatment of MCD based on a single nonrandomized clinical study of 28 subjects with plasma cell histology conducted in Japan. Subjects were treated with a dose of 8 mg/kg every 2 weeks. After 16 weeks of therapy lymphadenopathy was improved in the 23 subjects with lymph nodes 10 mm or larger. Mean changes in laboratory parameters (C-reactive protein (CRP), amyloid A protein (SAA), hemoglobin (Hb), albumen (Alb), IgG, total cholesterol) known to be associated with active disease were improved in the 28 subjects studied.

3. CMC: Please see the reviews of DMA and BMAB for details. Drs. Candace Gomez-Broughton and Patricia Hughes (TL) of BMAB stated that “BLA 125496, as amended, is recommended for approval from a microbiology product quality perspective with the following post-marketing commitment: To determine the volume of the (b) (4) necessary to achieve consistent (b) (4) test conditions, provide the supportive data, and use the determined volume in the (b) (4) test of the drug product (b) (4) by May 2014.”

Dr. Chana Fuchs, DMA, stated that her review division recommends approval with the following postmarketing commitments:

1. To re-evaluate siltuximab 100 mg/vial final lyophilized product lot release and stability specifications after (b) (4) lots have been manufactured using the commercial manufacturing process. The corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be submitted (Janssen to provide date).
2. To re-evaluate siltuximab 400 mg/vial final lyophilized product lot release and stability specifications after (b) (4) lots have been manufactured using the commercial manufacturing process. The corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be submitted (Janssen to provide date).
3. To re-evaluate siltuximab formulated bulk lot release and stability specifications after (b) (4) lots have been manufactured using the commercial manufacturing process. The corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be submitted (Janssen to provide date)
4. To re-evaluate siltuximab (b) (4) intermediate lot release and stability specifications for lots manufactured using the commercial manufacturing process, once cIEF data from (b) (4) (b) (4) lots are available. The SE-HPLC data from all lots manufactured using the commercial manufacturing process should be included in this evaluation. The corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be submitted (Janssen to provide date).
5. To confirm the anticipated amount of (b) (4) (b) (4) using a validated reduced scale model. Results of the study will be submitted by December 2014.
6. To confirm the anticipated amount (b) (4) (b) (4) using a validated reduced scale

- model (b) (4) The results of this study will be submitted by December 2014.
7. To tighten the (b) (4) reference material requalification acceptance criteria of 80 - 125% for potency. This analysis will be 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 (Janssen to provide date).
 8. To implement specific siltuximab master cell bank (MCB) and working cell bank (WCB) stability programs. The protocols (SOP) for the MCB and WCB stability programs and supporting data for the protocols will be submitted as a CBE0 by August 2014.
 9. 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.
 10. (b) (4) (b) (4) (w) (4) The control strategy will be submitted as a CBE0 (Janssen to provide date).
 11. 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. (Janssen to provide study completion date and final report submission date.)
 12. 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. (Janssen to provide study completion date and final report submission date.)
 13. 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. (Janssen to provide study completion date and final report submission date.)
 14. To provide confirmatory data by executing a 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. (Janssen to provide study completion date and final report submission date.)

4. NON-CLINICAL: Please see the Pharmacology/Toxicology Review of Dr. Pedro L. Del Valle for details. Dr. Del Valle recommended approval. Dr. Haleh Saber, Pharmacology/Toxicology Supervisor, stated: “I concur with the pharmacology/toxicology reviewers that from a nonclinical perspective, Sylvant may be approved and that no additional nonclinical studies are needed to support approval of Sylvant in patients with MCD.”

5. CLINICAL PHARMACOLOGY: Please see the review of Dr. Jeanne Fourie Zirkelbach for details. The Clinical Pharmacology team recommended approval.

6. EFFICACY (This section is excerpted from the reviews of Dr. Patricia Dinndorf and Dr. Chia-Wen Ko): This is an initial Biologic Licensing Application (BLA) seeking the approval of intravenous siltuximab for the treatment of patients with MCD who are human immunodeficiency virus negative and human herpesvirus-8 negative. The main study CNTO328MCD2001 supporting this application is a phase 2, randomized, double-blind, placebo-controlled study in 79 patients with MCD to assess the efficacy and safety of siltuximab plus best supportive care (n=53) compared with placebo plus best supportive care (n=26). Supportive information regarding the efficacy is provided by C0328T03 the phase 1 trial conducted in patients with hematologic malignancies. This trial included response data for 37 patients with Castleman’s disease.

Efficacy Results in Study CNTO328MCD2001: All patients had a review of the pathology subtype of Castleman’s Disease by central review: 33% were hyaline vascular, 23 were plasmacytic, and 44 were mixed.

Reviewer Comment: It is relevant to state that in the plasmacytic subset, the plasma cells are more prominent at the histopathological level as compared to the hyaline vascular subset, in which the prominence of plasma cells is decreased. In addition, some studies have shown that the levels of IL-6 in the blood are lower in the hyaline vascular subtype than in the plasmacytic.

Patient randomization was stratified by concomitant corticosteroid use at study entry. The major efficacy outcome of the study was the proportion of patients on each arm who exhibited a durable tumor and symptomatic response, defined as tumor response (complete or partial response based on modified Cheson criteria) assessed by independent review and complete resolution or stabilization of MCD symptoms, sustained for at least 18 weeks.

According to the statistical analysis plan, in the event that the primary endpoint was statistically significantly different on the two arms, the following major secondary endpoints were to be tested hierarchically in support of the primary endpoint, at a two-sided 5% level of significance in the order presented:

- Tumor response
- Time to treatment failure
- Increase in hemoglobin at Week 13 of 15 g/L or more

- Time-to-improvement in the MCD-SS total score
- Time-to-improvement in the FACIT-F fatigue score
- Discontinuation of corticosteroids

Study MCD2001 met its primary objective to demonstrate that siltuximab is superior to placebo in combination of best supportive care in durable tumor and symptom response rate by rituximab over placebo (34% versus 0%). In addition, treatment benefit was supported by significant improvement by siltuximab in tumor response, time to treatment failure, and hemoglobin response. Table 1 below summarizes the efficacy results.

Table 1: Efficacy Results from MCD2001

Efficacy Endpoint	Siltuximab + BSC n=53	Placebo + BSC n=26	P-value
Durable tumor & symptomatic response	34%	0	0.0012 ^a
Tumor response	38%	4%	<0.05
Median time to treatment failure	Not reached	134 days	<0.05
≥1.5 g/dL increase in hemoglobin at week 13	61% (19/31)	0% (0/11)	<0.05

^a The p-value is from an exact Cochran-Mantel-Haenszel test, adjusted for baseline corticosteroid use

Subset Analysis: None of the 18 patients in the siltuximab arm exhibiting a durable tumor & symptomatic response were hyaline vascular, although some (3/18 or 17%) of the patients who exhibited increases of 1.5 g/L at week 13 as compared to baseline were hyaline vascular.

The durable symptomatic response rate was 57% in the siltuximab group and 19% in the placebo group. This endpoint was not included in the hierarchy of testing of secondary endpoints. It was a component of the primary endpoint. The goal of treatment of MCD with siltuximab is to control symptoms therefore this component is of interest.

No major statistical issues were identified during the review. The primary efficacy endpoint appeared to be robust with respect to missing data. A consistent treatment effect was found by subgroups with the exception of the hyaline vascular histological subtype; however, activity was suggested in this subtype based on change in hemoglobin and median time to failure.

Recommendation of Dr. Ko of Biostatistics and Dr. Dinndorf of DHP: Approval

7. SAFETY (This section is excerpted from the review of Dr. Patricia Dinndorf): The siltuximab safety data base submitted in this application includes 11 company sponsored studies, 7 monotherapy and 4 combination therapy studies. This includes safety data from 997 subjects, 753 of whom were treated with siltuximab. This review will concentrate on 7 studies.

C0328T03, phase 1 trial hematologic malignancies provides dose finding information for siltuximab as monotherapy. The safety information obtained in CNTO328MCD2001, the randomized trial for MCD provides the most relevant information for this application and will be the major focus of the risk benefit analysis. The adverse event information collected in C0328T08, the bioequivalence trial in healthy volunteers will be evaluated to determine the incidence and grade of adverse events associated with siltuximab administration in an

asymptomatic population. Siltuximab is a symptomatic treatment for the IL-6 mediated symptoms of Castleman’s disease, and therefore will be a chronically administered treatment for patients who respond.

CNTO328MCD2002, the Castleman’s disease extension study provides the evidence that that chronic administration of siltuximab is safe and feasible in this population.

CNTO328MDS2001, the randomized trial in myelodysplastic syndrome provides additional data on siltuximab as single agent therapy in another hematologic disease.

The safety of siltuximab for treatment of Castleman’s disease is supported by trials CNTO328MCD2001 and C0328T03. Safety data on long term administration for 19 patients with MCD is included in the extension study CNTO328MCD2002. Additional safety data includes studies in other hematologic malignancies including multiple myeloma and myelodysplastic syndrome; and in solid tumors including renal cell carcinoma, and prostate cancer. This review will concentrate on Castleman’s disease trials, the healthy volunteer study, and randomized trials with control arms in hematologic malignancies. The clinical trials supporting the safety analysis are summarized in Tables 2-4 below.

Table 2: Clinical Studies in Patients with Castleman’s Disease

Summary of Clinical Studies in Patients with Castleman’s Disease			
Protocol Number	Report Type	Title	Comment
CNTO328MCD2001	Full Report	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	Major Supporting Trial BSC+siltuximab n=53 BSC+ placebo n=26
C0328T03	Full report	A Phase 1 Study of Multiple Intravenous Administrations of a Chimeric Antibody Against Interleukin-6 (CNTO 328) in Subjects with B-Cell Non-Hodgkin’s Lymphoma, Multiple Myeloma, or Castleman’s Disease	Supportive Clinical Information for the indication Total treated n=67 Castleman’s Disease n=37
CNTO328MCD2002	Synopsis	An Open-label, Multicenter Study to Evaluate the Safety of Long-term Treatment with Siltuximab in Subjects with Multicentric Castleman’s Disease	Information regarding prolonged administration n=19

Table 3: Clinical Studies in Healthy Volunteers

Summary of Clinical Studies in Healthy Volunteers			
Protocol Number	Report Type	Title	Comment
C0328T08	Full report	A Phase 1, Randomized Study to Assess the Safety and Pharmacokinetics of a Single Intravenous Administration of CNTO 328 Derived From 2 Different Cell Lines in Healthy Subjects	Comparability study of Chinese Hamster Ovary (CHO)-derived product and Sp2/0-derived product n=144

Table 4: Clinical Studies in Patients with Hematological Malignancies Other than MCD

Summary of Clinical Studies in Patients with Hematologic Malignancies Other Than Castleman's Disease			
Protocol Number	Report Type	Title	Comment
C0328T05	Full report	A Phase 2 Multicenter Study of CNTO 328 (Anti IL-6 Monoclonal Antibody) in Subjects with Relapsed or Refractory Multiple Myeloma	Siltuximab 6 mg/kg q 2 wk ± Dexamethasone n=53
C0328T06	Full report	A Phase 2, Randomized, Double-blind, Placebo-controlled Study Comparing the Combination of CNTO 328 (Anti-IL-6 Monoclonal Antibody) and VELCADE® versus VELCADE Alone in Subjects with Relapsed or Refractory Multiple Myeloma	Bortezomib + Siltuximab 6 mg/kg q 2 wk (n=163) Or placebo (n=139)
CNTO328MMY2001	Full report	A Randomized, Open-label, Phase 2 Study of CNTO 328 (Anti-IL-6 Monoclonal Antibody) and VELCADE-Melphalan-Prednisone Compared With VELCADE-Melphalan- Prednisone for the Treatment of Previously Untreated Multiple Myeloma	VMP (bortezomib [Velcade] melphalan prednisone) n=53 VMP+siltuximab 11 mg/kg q3 wk n=64
CNTO328SMM1001	Full report	A Study of Siltuximab (Anti-IL-6 Monoclonal Antibody) Effects on the QT Interval in Subjects with Monoclonal Gammopathy of Undetermined Significance, Smoldering Multiple Myeloma, or Indolent Multiple Myeloma	Siltuximab 15 mg/kg q3 wk 4 cycles n=30
CNTO328MDS2001	Abbreviated report	A Phase 2, Randomized, Double-blind, Placebo-controlled, Multicenter Study Comparing Siltuximab Plus Best Supportive Care to Placebo Plus Best Supportive Care in Anemic Subjects with International Prognostic Scoring System Low- or Intermediate-1-Risk Myelodysplastic Syndrome	BSC+siltuximab n=50 BSC+ placebo n=26
JPN-C0328-MM-101	Full report	A Phase 1 Study of CNTO 328 (siltuximab) in Combination with Bortezomib and Dexamethasone for Subjects with Relapsed or Refractory Multiple Myeloma	Siltuximab (5.5, 11 mg/kg) q 21 days with Bortezomib/dexamethasone n=9

Safety Data from CNTO328MCD2001 Randomized Trial of Castleman's Disease:

- A. **Deaths:** There were no deaths within 30 days of exposure to siltuximab.
- B. **Non-fatal SAEs:** There were 12/53 (23%) patients on the siltuximab arm who experienced SAEs and 3/25 (12%) on the placebo arm. The median exposure of subjects to the experimental agent was 12 months in the siltuximab arm and 5 months in the placebo arm. Because subjects were exposed to more courses of siltuximab than courses

of placebo, there is an exposure bias on the incidence of adverse events. Therefore the incidence of non-fatal serious adverse events during the initial 5 months plus 30 days of follow up (185 days) of therapy was analyzed. There were 8 of 53 (15%) subjects in the siltuximab arm and 2 of 26 (8%) subjects in the placebo arm with reported nonfatal serious adverse events. No specific type of serious adverse event appears to be associated with siltuximab therapy in multicentric Castleman's disease patients. Infections were the most frequently reported nonfatal serious adverse events on the siltuximab arm in this study: anal abscess (in one patient), lower respiratory tract infection (in 2 patients), bronchitis (in one patient), and sepsis (in one patient).

- C. **Drop-outs and/or Discontinuations:** The study agent was discontinued in 12 of 26 (46%) subjects in the placebo arm and 12 of 53 (23%) subjects in the siltuximab arm due to an adverse event. The placebo group includes 2 subjects with action taken with study treatment due to the adverse event categorized as "drug interrupted" rather than "drug withdrawn." In these 2 cases no subsequent placebo was administered.

Most of the adverse events reported are known constitutional symptoms of Castleman's disease including pain, anemia, neutropenia, neuropathy, rash edema, night sweats, effusions. In 8 cases the treatment was unblinded and the subject crossed over to siltuximab therapy. There were also 2 patients who developed malignancies.

In the siltuximab arm, the adverse events that led to discontinuation of siltuximab were also predominantly constitutional symptoms of Castleman's disease including edema, effusions, night sweats, rash, fatigue, malaise, weight loss, ascites, neuropathy. One subject experienced an anaphylactic reaction with the first infusion of siltuximab, study treatment due to the adverse event categorized was "drug interrupted" rather than "drug withdrawn" for the anaphylactic reaction. A second subject experienced symptoms of an infusion reaction, treatment due to the adverse event categorized was "drug interrupted" rather than "drug withdrawn." This subject did not receive further siltuximab therapy but night sweats and peripheral edema were identified as the adverse events leading to discontinuation.

Reviewer Comment: Siltuximab was well tolerated and rarely discontinued due to a drug related adverse event. A single anaphylactic reaction and possibly an infusion reaction in a second subject were probably the only drug related events that led to discontinuation. There does not appear to be signals for significant adverse events associated with siltuximab therapy in this population. Mortality was lower in the siltuximab treated arm, no specific serious adverse event was identified in the siltuximab arm and discontinuation of siltuximab therapy due to adverse events was similar in the siltuximab and placebo arms.

Siltuximab does not appear to be potentially immunogenic. There was only incident of a significant allergic reaction in over 750 patients. This was a grade 3 anaphylactic reaction, experienced with the first infusion.

Recommendation of Dr. Dinndorf: The overall safety profile of siltuximab is favorable in the treatment of MCD. AEs were less intense than the symptoms associated with the underlying

disease. A single incidence of grade 3 allergic reaction in more than 750 patients exposed to siltuximab was the most serious event reported. Patients who respond to siltuximab have tolerated extended treatment with siltuximab and have not developed cumulative toxicities. Approval is recommended. Dr. Dinndorf will ask for a post approval commitment for additional follow up of patients on the extension study in terms of safety.

8. ADVISORY COMMITTEE MEETING: No Advisory Committee meeting.

9. OTHER RELEVANT REGULATORY ISSUES: Post Marketing Commitments:

1. The company will be asked to submit a plan with a time line for a post approval safety analysis of patients currently entered in the extension study MCD2002.

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

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

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

5. To re-evaluate siltuximab formulated bulk lot release and stability specifications after (b) (4) lots have been manufactured using the commercial manufacturing process. The corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be submitted (Janssen to provide date).

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

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

8. To confirm the anticipated amount (b) (4)

using a validated reduced scale model (b) (4)

The results of this study will be submitted by December 2014.

9. To tighten the (b) (4) reference material requalification acceptance criteria of 80 - 125% for potency. This analysis will be based on appropriate statistical evaluation and a sufficient amount of datapoints required for such an evaluation. The updated acceptance criterion and supporting data will be submitted as a CBE0 by (Janssen to provide date).

10. 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.

11. To establish a control strategy for the (b) (4)

the updated control strategy and supporting data will be submitted as a CBE0 in August 2014.

12 (b) (4)

(b) (4). The control strategy will be submitted as a CBE0 (Janssen provide date).

13. To provide confirmatory data by executing manufacturing run of the 100 mg/vial FLP batch at (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. (Janssen to provide study completion date and final report submission date.)

14. To provide confirmatory data by executing manufacturing run of the 400 mg/vial FLP batch at (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. (Janssen to provide study completion date and final report submission date.)

15. To provide confirmatory data by executing a manufacturing run of the 100 mg/vial FLP batch at (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. (Janssen to provide study completion date and final report submission date.)

16. To provide confirmatory data by executing a manufacturing run of the 400 mg/vial FLP batch at (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. (Janssen to provide study completion date and final report submission date.)

10. LABELING: The labeling is currently under negotiation.

11. RECOMMENDATIONS/RISK BENEFIT ASSESSMENT: This CDTL reviewer recommends approval.

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/s/

ALBERT B DEISSEROTH
04/03/2014