

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**125496Orig1s000**

**MEDICAL REVIEW(S)**

## Secondary (Team Leader) Review

<b>Date</b>	February 12, 2014
<b>From</b>	Albert Deisseroth, MD, PhD
<b>Subject</b>	Secondary Review
<b>NDA Number</b>	BLA 125496
<b>Applicant</b>	Janssen Biotech, Inc.
<b>Date of Submission</b>	August 30, 2013
<b>PDUFA Goal Date</b>	April 29, 2014
<b>Established Name/Proprietary Name</b>	Siltuximab/Sylvant
<b>Dosage Regimen</b>	11mg/kg every 3 weeks
<b>Applicant's Proposed Indication</b>	Treatment of Multicentric Castleman's Disease in patients who are immunodeficiency virus negative (HIV) and human herpes virus-8 (HHV-8)
<b>Recommended:</b>	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

## TABLE OF CONTENTS

TABLE OF CONTENTS.....	2
1. EXECUTIVE SUMMARY AND BENEFIT RISK DISCUSSION.....	3
2. BACKGROUND.....	3
3. CMC.....	5
4. NON-CLINICAL (PHARMACOLOGY/TOXICOLOGY).....	5
5. CLINICAL PHARMACOLOGY.....	5
6. EFFICACY OF SILTUXIMAB.....	5
7. SAFETY OF SILTUXIMAB.....	7
8. ADVISORY COMMITTEE MEETING.....	11
9. OTHER RELEVANT REGULATORY ISSUES.....	11
10. LABELING.....	11
11. RECOMMENDATIONS/RISK BENEFIT ASSESSMENT.....	11

**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 September 6, 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 of every 3 week infusions comparing Sylvant (siltuximab) and best supportive care (BSC) to placebo and BSC. The trial met its primary endpoint of durable tumor and symptomatic response based on independent review. 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, 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 secondary TL reviewer concurs with the review of Dr. Patricia Dinndorf and concludes that the benefit risk ratio is favorable and recommends approval.

**2. BACKGROUND:**

**2.a. Regulatory History** (This section was excerpted from the review of Dr. Patricia Dinndorf):

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 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 was 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. Chana Fuchs, TL, DMA, stated on January 29, 2014 that she has not yet found issues that are beyond a relatively easy fix from the sponsor. Candace Gomez-Broughton and Patricia Hughes (TL) BMAB, stated on February 3, 2014 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) (b) (4) May 2014.”

**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 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 significant, 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 <sup>a</sup>
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

<sup>a</sup> 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 treated with siltuximab. My 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.

Three additional studies will be reviewed. These include 2 randomized trials of siltuximab in combination with chemotherapy in multiple myeloma, C0328T06, the randomized trial with bortezomib in multiple myeloma and CNTO328MMY200, the open label randomized trial with VMP in multiple myeloma. 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**

<b>Summary of Clinical Studies in Patients with Castleman's Disease</b>			
<b>Protocol Number</b>	<b>Report Type</b>	<b>Title</b>	<b>Comment</b>
CNT0328MCD2001	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
CNT0328MCD2002	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**

<b>Summary of Clinical Studies in Healthy Volunteers</b>			
<b>Protocol Number</b>	<b>Report Type</b>	<b>Title</b>	<b>Comment</b>
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 ad 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. The incidence of nonfatal serious adverse event is presented in Table 5 based on Body System or Organ Class (SOC) classification. 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 potently immunogenic. There was only incident of significant allergic reaction in over 750 patients suggests the agent. This was a grade 3 anaphylactic reaction, experienced with the first infusion.

**Recommendation of Dr. Dinndorf:** The overall safety profile of situximab 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.

**8. ADVISORY COMMITTEE MEETING:** No Advisory Committee meeting.

**9. OTHER RELEVANT REGULATORY ISSUES:** None

**10. LABELING:** The labeling is currently under negotiation.

**11. RECOMMENDATIONS/RISK BENEFIT ASSESSMENT:** This secondary (TL) reviewer recommends approval.

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

/s/  
-----

ALBERT B DEISSEROTH  
02/26/2014

## Secondary (Team Leader) Review

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

## TABLE OF CONTENTS

TABLE OF CONTENTS.....	2
1. EXECUTIVE SUMMARY AND BENEFIT RISK DISCUSSION.....	3
2. BACKGROUND.....	3
3. CMC.....	5
4. NON-CLINICAL (PHARMACOLOGY/TOXICOLOGY).....	5
5. CLINICAL PHARMACOLOGY.....	5
6. EFFICACY OF DECITABINE FOR INJECTION.....	5
7. SAFETY OF DECITABINE FOR INJECTION.....	7
8. ADVISORY COMMITTEE MEETING.....	11
9. OTHER RELEVANT REGULATORY ISSUES.....	11
10. LABELING.....	11
11. RECOMMENDATIONS/RISK BENEFIT ASSESSMENT.....	11

**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 September 6, 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 of every 3 week infusions comparing Sylvant (siltuximab) and best supportive care (BSC) to placebo and BSC. The trial met its primary endpoint of durable tumor and symptomatic response based on independent review. 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, 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 secondary TL reviewer concurs with the review of Dr. Patricia Dinndorf and concludes that the benefit risk ratio is favorable and recommends approval.

**2. BACKGROUND:**

**2.a. Regulatory History** (This section was excerpted from the review of Dr. Patricia Dinndorf):

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 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 was 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. Chana Fuchs, TL, DMA, stated on January 29, 2014 that she has not yet found issues that are beyond a relatively easy fix from the sponsor. Candace Gomez-Broughton and Patricia Hughes (TL) BMAB, stated on February 3, 2014 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) May 2014.”

**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 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 significant, 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 <sup>a</sup>
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

<sup>a</sup> 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 treated with siltuximab. My 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.

Three additional studies will be reviewed. These include 2 randomized trials of siltuximab in combination with chemotherapy in multiple myeloma, C0328T06, the randomized trial with bortezomib in multiple myeloma and CNTO328MMY200, the open label randomized trial with VMP in multiple myeloma. 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**

<b>Summary of Clinical Studies in Patients with Castleman's Disease</b>			
<b>Protocol Number</b>	<b>Report Type</b>	<b>Title</b>	<b>Comment</b>
CNT0328MCD2001	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
CNT0328MCD2002	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**

<b>Summary of Clinical Studies in Healthy Volunteers</b>			
<b>Protocol Number</b>	<b>Report Type</b>	<b>Title</b>	<b>Comment</b>
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 ad 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. The incidence of nonfatal serious adverse event is presented in Table 5 based on Body System or Organ Class (SOC) classification. 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 potently immunogenic. There was only incident of significant allergic reaction in over 750 patients suggests the agent. This was a grade 3 anaphylactic reaction, experienced with the first infusion.

**Recommendation of Dr. Dinndorf:** The overall safety profile of situximab 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.

**8. ADVISORY COMMITTEE MEETING:** No Advisory Committee meeting.

**9. OTHER RELEVANT REGULATORY ISSUES:** None

**10. LABELING:** The labeling is currently under negotiation.

**11. RECOMMENDATIONS/RISK BENEFIT ASSESSMENT:** This secondary (TL) reviewer recommends approval.

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

/s/  
-----

ALBERT B DEISSEROTH  
02/03/2014

## CLINICAL REVIEW

Application Type	BLA
Application Number(s)	125496
Priority or Standard	Priority Orphan Designation
Submit Date(s)	8/30/13
Received Date(s)	9/6/13
PDUFA Goal Date	4/29/14
Division / Office	DHP/OHOP
Reviewer Name(s)	Patricia Dinndorf
Review Completion Date	1/29/14
Established Name	Siltuximab
(Proposed) Trade Name	Sylvant
Therapeutic Class	Chimeric monoclonal antibody
Applicant	Janssen Biotech, Inc.
Formulation(s)	Lyophilized product for IV infusion
Dosing Regimen	11 mg/kg every 3 weeks
Indication(s)	Castleman's disease
Intended Population(s)	Patients with multicentric Castleman's disease (MCD) who are HIV and HHV-8 negative

## Table of Contents

<b>1</b>	<b>RECOMMENDATIONS/RISK BENEFIT ASSESSMENT</b>	<b>8</b>
1.1	Recommendation on Regulatory Action	8
1.2	Risk Benefit Assessment	9
1.3	Recommendations for Postmarket Risk Evaluation and Mitigation Strategies	9
1.4	Recommendations for Postmarket Requirements and Commitments	10
<b>2</b>	<b>INTRODUCTION AND REGULATORY BACKGROUND</b>	<b>11</b>
2.1	Product Information	11
2.2	Tables of Currently Available Treatments for Proposed Indications	11
2.3	Availability of Proposed Active Ingredient in the United States	13
2.4	Important Safety Issues With Consideration to Related Drugs	13
2.5	Summary of Presubmission Regulatory Activity Related to Submission	14
2.6	Other Relevant Background Information	15
<b>3</b>	<b>ETHICS AND GOOD CLINICAL PRACTICES</b>	<b>16</b>
3.1	Submission Quality and Integrity	16
3.2	Compliance with Good Clinical Practices	16
3.3	Financial Disclosures	16
<b>4</b>	<b>SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES</b>	<b>18</b>
4.1	Chemistry Manufacturing and Controls	18
4.2	Clinical Microbiology	18
4.3	Preclinical Pharmacology/Toxicology	18
4.4	Clinical Pharmacology	18
4.4.1	Mechanism of Action	18
4.4.2	Pharmacodynamics (derived from the clinical pharmacology presentation at the midcycle meeting)	19
4.4.3	Pharmacokinetics (copied from the clinical pharmacologists revisions to the label)	19
<b>5</b>	<b>SOURCES OF CLINICAL DATA</b>	<b>21</b>
5.1	Tables of Studies/Clinical Trials	21
5.2	Review Strategy	23
5.3	Discussion of Individual Studies/Clinical Trials	24
5.3.1	C0328T03 Phase 1 Hematologic Malignancies	24
5.3.2	CNT0328MCD2002 Castleman's Disease Extension Study	28
5.3.3	C0328T08 Bioequivalence of Two Formulations in Healthy Volunteers	29
5.3.4	C0328T06 Multiple Myeloma Placebo or Siltuximab with Bortezomib	31
5.3.5	CNT0328MMY2001 Multiple Myeloma VMP with or without Siltuximab	33
5.3.6	CNT0328MDS2001 Myelodysplastic Syndrome Placebo or Siltuxumab	35
<b>6</b>	<b>REVIEW OF EFFICACY</b>	<b>37</b>

Efficacy Summary.....	37
6.1 Indication.....	37
6.1.1 Methods.....	37
6.1.2 Demographics.....	42
6.1.3 Subject Disposition.....	45
6.1.4 Analysis of Primary Endpoint(s).....	46
6.1.5 Analysis of Secondary Endpoints(s).....	46
6.1.6 Other Endpoints.....	50
6.1.7 Subpopulations.....	52
6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations....	53
6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects.....	53
6.1.10 Additional Efficacy Issues/Analyses.....	53
<b>7 REVIEW OF SAFETY.....</b>	<b>55</b>
Safety Summary.....	55
7.1 Methods.....	56
7.1.1 Studies/Clinical Trials Used to Evaluate Safety.....	56
7.1.2 Categorization of Adverse Events.....	57
7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence.....	57
7.2 Adequacy of Safety Assessments.....	58
7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations.....	58
7.2.2 Explorations for Dose Response.....	58
7.2.3 Special Animal and/or In Vitro Testing.....	59
7.2.4 Routine Clinical Testing.....	59
7.2.5 Metabolic, Clearance, and Interaction Workup.....	59
7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class..	59
7.3 Major Safety Results.....	60
7.3.1 Deaths.....	60
7.3.2 Nonfatal Serious Adverse Events.....	65
7.3.3 Dropouts and/or Discontinuations.....	70
7.3.4 Significant Adverse Events.....	73
7.3.5 Submission Specific Primary Safety Concerns.....	73
7.4 Supportive Safety Results.....	74
7.4.1 Common Adverse Events.....	74
7.4.2 Laboratory Findings.....	86
There were no grade 4 laboratory abnormalities in the either arm. There were no grade 3 chemistry abnormalities reported more frequently in the siltuximab arm (> 3% incidence compared to placebo).....	88
REVIEWER COMMENT:.....	88
7.4.3 Vital Signs.....	88
7.4.4 Electrocardiograms (ECGs).....	88
7.4.5 Special Safety Studies/Clinical Trials.....	88

7.4.6	Immunogenicity (derived from submission 2.7.2 Clinical Pharmacology Studies page 69/89) .....	89
7.5	Other Safety Explorations .....	89
7.5.1	Dose Dependency for Adverse Events .....	89
7.5.2	Time Dependency for Adverse Events .....	89
7.5.3	Drug-Demographic Interactions .....	89
7.5.4	Drug-Disease Interactions .....	89
7.5.5	Drug-Drug Interactions .....	89
7.6	Additional Safety Evaluations .....	89
7.6.1	Human Carcinogenicity .....	89
7.6.2	Human Reproduction and Pregnancy Data .....	90
7.6.3	Pediatrics and Assessment of Effects on Growth .....	90
7.6.4	Overdose, Drug Abuse Potential, Withdrawal and Rebound .....	90
7.7	Additional Submissions / Safety Issues .....	90
<b>8</b>	<b>POSTMARKET EXPERIENCE .....</b>	<b>91</b>
<b>9</b>	<b>APPENDICES .....</b>	<b>92</b>
9.1	Literature Review/References .....	92
9.2	Labeling Recommendations .....	93
9.3	Advisory Committee Meeting .....	95
9.4	Abbreviations .....	96
9.5	Classification of Multicentric Castleman Disease-Related Signs and Symptoms as Defined by Protocol .....	97

## Table of Tables

Table 1: Risk Benefit Assessment.....	9
Table 2: Presubmission Regulatory Activity .....	14
Table 3: Summary of Manufacturing .....	18
Table 4: Summary of Clinical Studies in Patients with Castleman’s Disease .....	21
Table 5: Summary of Clinical Studies in Healthy Volunteers.....	22
Table 6: Summary of Clinical Studies in Patients with Hematologic Malignancies Other Than MCD.....	22
Table 7: Summary of Clinical Studies in Patients with Solid Tumors .....	23
Table 8: Baseline Demographics by Disease in Treated Subjects on C0328T03 Phase 1 Study .....	25
Table 9: Disease Characteristics of Treated Subjects with Castleman’s Disease on C0328T03 Phase 1 Study .....	25
Table 10: Patients with Prolonged Exposure to Siltuximab on C0328T03 Phase 1 Study .....	26
Table 11: Disposition C0328T03 Phase 1 Study.....	26
Table 12: Best Overall Response in Subjects with Castleman's Disease on C0328T03 Phase 1 Study.....	27
Table 13: Demographics and Disease Characteristics - CNT0328MCD2002 Extension Study.....	28
Table 14: Demographics C0328T08 Bioequivalence in Healthy Volunteers .....	29
Table 15: Demographics Study C0328T06 Relapsed Multiple Myeloma.....	31
Table 16: Disposition Study C0328T06 Relapsed Multiple Myeloma .....	32
Table 17: Demographics CNT0328 MMY2001 Newly Diagnosed Multiple Myeloma ....	33
Table 18: Disposition CNT0328 MMY2001 Newly Diagnosed Multiple Myeloma.....	34
Table 19: Exposure CNT0328 MMY2001 Newly Diagnosed Multiple Myeloma .....	34
Table 20: Demographics CNT0328MDS2001 Myelodysplastic Syndrome.....	35
Table 21: Disposition CNT0328MDS2001 Myelodysplastic Syndrome .....	36
Table 22: Exposure CNT0328MDS2001 Myelodysplastic Syndrome.....	36
Table 23: Demographics of the ITT Population in Trial CNT0328MCD2001 .....	43
Table 24: Clinical Characteristics of the ITT Population in Trial CNT0328MCD2001 ...	44
Table 25: Exposure of Subjects in CNT0328MCD2001 to Siltuximab .....	46
Table 26: Response Evaluation of Patients Assigned to Placebo Who Crossed-over to Siltuximab.....	54
Table 27: Clinical Trials Used to Evaluate Safety.....	56
Table 28: Best Overall Response in Subjects with Castleman’s Disease on C0328T03 Phase 1 Trial .....	59
Table 29: CNT0328MCD2001 Deaths.....	60
Table 30: C0328T03 Deaths .....	61
Table 31: C0328T06 Deaths - Placebo .....	62
Table 32: C0328T06 Deaths – Siltuximab.....	63
Table 33: CNT0328MMY2001 Deaths.....	64
Table 34: CNT0328MCD2001 Nonfatal Serious Adverse Events.....	66

Table 35: CNTO328MCD2001 Nonfatal Serious Adverse Events – Infections .....	66
Table 36: C0328T06 Nonfatal Serious Adverse Events .....	68
Table 37: CNTO328MMY2001 Nonfatal Serious Adverse Events .....	69
Table 38: CNTO328MDS2001 Nonfatal Serious Adverse Events .....	70
Table 39: CNTO328MCD2001 Discontinuation Due to Adverse Event – Placebo during Treatment Period .....	71
Table 40: CNTO328MCD2001 Discontinuation Due to Adverse Event – Siltuximab ....	72
Table 41: CNTO328MCD2001 Common Adverse Event by System Organ Class .....	74
Table 42: CNTO328MCD2001 Common Adverse Events - Skin and Subcutaneous Tissue Disorders .....	75
Table 43: CNTO328MCD2001 Common Adverse Events - General Disorders and Administration Site Conditions .....	76
Table 44: CNTO328MCD2001 Common Adverse Events - Gastrointestinal Disorders	76
Table 45: CNTO328MCD2001 Common Adverse Events – Infections .....	77
Table 46: CNTO328MCD2001 Common Adverse Events – Metabolism and Nutrition .	77
Table 47: CNTO328MCD2001 Common Adverse Events – Respiratory, Thoracic and Mediastinal Disorders.....	78
Table 48: CNTO328MCD2001 Common Adverse Events - Nervous System Disorders	78
Table 49: CNTO328MCD2001 Common Adverse Events – Investigations.....	78
Table 50: CNTO328MCD2001 Common Adverse Events - Musculoskeletal and Connective Tissue Disorders .....	79
Table 51: CNTO328MCD2001 Common Adverse Events - Renal and Urinary Disorders .....	79
Table 52: CNTO328MCD2001 Common Adverse Events - Vascular Disorders .....	80
Table 53: CNTO328MCD2001 Common Adverse Events - Injury, Poisoning and Procedural Complications .....	80
Table 54: CNTO328MCD2001 - Cardiac Events in Siltuximab Subjects.....	81
Table 55: C0328T03 Common Adverse Events – All Enrolled Subjects .....	82
Table 56: C0328T03 Common Adverse Events – In Subjects with Castleman’s Disease .....	83
Table 57: Adverse Events Normal Volunteer Study .....	84
Table 58: CNTO328MDS2001 Common Adverse Events System Organ Class and Selected Preferred Terms .....	85
Table 59: CNTO328MDS2001 Adverse Events Reported ≥ 3% in the Siltuximab Arm.	86
Table 60: CNTO328MCD2001 Worst Grade Laboratory Abnormalities .....	87
Table 61: CNTO328MDS2001 Worst Grade Laboratory Abnormalities .....	87
Table 62: Analysis of ΔQTcF for Siltuximab 15 mg/kg .....	88
Table 63: Abbreviations.....	96
Table 64: Classification of Multicentric Castleman Disease-Related Signs and Symptoms .....	97

## Table of Figures

Figure 1: Lymph Node Response to Tocilizumab.....	12
Figure 2: Mean Change in Laboratory Parameters with Tocilizumab.....	13
Figure 3: Median Pre-infusion CRP Level over Time .....	19
Figure 4: Disposition of Subjects During Blinded Phase of Therapy .....	45
Figure 5: Waterfall Plot of Tumor Response During the Blinded Treatment Period .....	47
Figure 6: Time to Treatment Failure During the Blinded Treatment Period .....	48
Figure 7: Improvement of MCD-SS Score During the Blinded Treatment Period .....	49
Figure 8: Overall Survival.....	50
Figure 9: Forest Plot of Durable Tumor and Symptomatic Response .....	52

## 1 Recommendations/Risk Benefit Assessment

### 1.1 Recommendation on Regulatory Action

I recommend siltuximab (chimeric monoclonal antibody (mAb) to interleukin-6 (IL-6), Sylvant®) be granted full approval 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. The indication was evaluated in an international, multicenter, randomized (2:1), phase 2 study of every 3 week intravenous (IV) infusions comparing siltuximab and best supportive care (BSC) to placebo and BSC. The trial met its primary endpoint of durable tumor and symptomatic response based on independent review. The response rate in the siltuximab group compared with the placebo group was 34% (18/53) versus 0% (0/26), (95% confidence interval (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 (Hb) at Week 13 to 15 of 1.5 g/dL in patients who were anemic at study entry, there were no responders in the placebo arm and 19 responders in the siltuximab arm. The difference of Hb 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 Castleman's disease treated with siltuximab on C0328T03, the dose finding trial of siltuximab in patients with hematologic malignancies. The response rate of subjects with Castleman's disease enrolled on the trial was 32% (12/37). There was 1 complete response (CR) and 11 partial responses (PR)s .

## 1.2 Risk Benefit Assessment

**Table 1: Risk Benefit Assessment**

<b>Decision Factor</b>	<b>Evidence and Uncertainties</b>	<b>Conclusions and Reasons</b>
<b>Analysis of Condition</b>	<b>Summary of evidence:</b> MCD is a life-threatening symptomatic lymphoproliferative disorder. Symptoms of MCD are linked to excessive release of IL-6.	<b>Conclusions (implications for decision):</b> Effective symptomatic treatment of this condition represents a clinical benefit for patients with this condition.
<b>Unmet Medical Need</b>	<b>Summary of evidence:</b> There is currently no approved treatment for HIV-negative HHV-8-negative MCD.	<b>Conclusions (implications for decision):</b> Safe and tolerable therapy for this condition will provide therapy for an unmet need.
<b>Clinical Benefit</b>	<b>Summary of evidence:</b> The durable tumor response and symptomatic response was 34% in the siltuximab arm compared to 0% in the placebo arm.	<b>Conclusions (implications for decision):</b> Siltuximab provides symptomatic relief to a substantial number of patients with HIV-negative HHV-8-negative MCD.
<b>Risk</b>	<b>Summary of evidence:</b> Siltuximab was well tolerated. The symptoms of the underlying MCD were much more intolerable than adverse events associated with siltuximab treatment. The most serious adverse event identified in any siltuximab trial (n ≥ 750) was a single case of grade 3 anaphylaxis.	<b>Conclusions (implications for decision):</b> The risk benefit analysis supports approval.
<b>Risk Management</b>	<b>Summary of evidence:</b> The safe administration of siltuximab can be adequately described in the label.	<b>Conclusions (implications for decision):</b> The label is the only required element of a risk management plan.
<b>Benefit-Risk Summary and Assessment</b>		
Patients with MCD have an unmet medical need for treatment of symptoms. Siltuximab has been shown to provide symptomatic relief of the symptoms of MCD. The risk benefit analysis supports approval of this agent for this condition.		

## 1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There are no recommendations for additional risk evaluation or mitigation strategies beyond the label.

#### **1.4 Recommendations for Postmarket Requirements and Commitments**

The applicant will 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.”

## 2 Introduction and Regulatory Background

### 2.1 Product Information

Established Name: Siltuximab (CNTO 328)

Proprietary Name: Sylvant

Applicant: Janssen Research and Development, LLC

Pharmacological Class: Chimeric monoclonal antibody

Proposed Indication: "Treatment of patients with multicentric Castleman's disease (MCD) who are human immunodeficiency virus negative and human herpesvirus-8 negative."

Proposed Dosage and Administration: Infusion of 11 mg/kg over 1 hour every 3 weeks.

Siltuximab is a chimeric (human-murine) immunoglobulin G1k monoclonal antibody that binds with high affinity and specificity to human IL-6, thereby neutralizing the biological activity of IL-6.

### 2.2 Tables of Currently Available Treatments for Proposed Indications

(Derived from UpToDate)

Castleman's disease (angiofollicular lymph node hyperplasia) is a lymphoproliferative disorder (LPD) associated in a subset of cases with the HIV and HHV-8 viruses.

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 (NHL), Hodgkin disease (HD), 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.

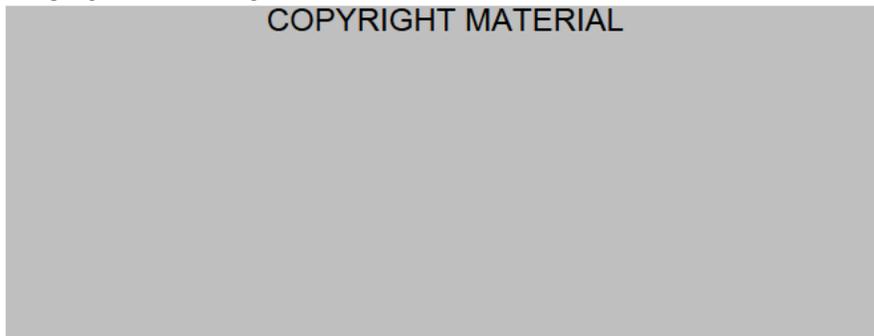
Patients with MCD present at a median age between 52 and 65 with fever, night sweats, weight loss, and weakness or fatigue. Peripheral lymphadenopathy is nearly universal, generalized, and often accompanied by hepatosplenomegaly. Laboratory abnormalities include anemia, hypoalbuminemia, hypergammaglobulinemia, 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 be 26 to 30 months. Almost all treatments using single agents (examples, anti-viral, anti-cytokine, chemotherapy, corticosteroids) are palliative, with disease recurrence once they are stopped.

Tocilizumab, humanized anti-IL-6 receptor monoclonal antibody, 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. (Nishimoto 2005). 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. See Figure 1 copied from Nishimoto 2005. 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. See Figure 2 copied from Nishimoto 2005.

**Figure 1: Lymph Node Response to Tocilizumab**



**Figure 1. Changes in short-axis length of swollen lymph nodes after 4 months and 1 year of treatment with MRA. Size changes of specified lymph nodes (LN) whose short axes were larger than 10 mm at baseline were examined using computed tomography.**

**Figure 2: Mean Change in Laboratory Parameters with Tocilizumab**

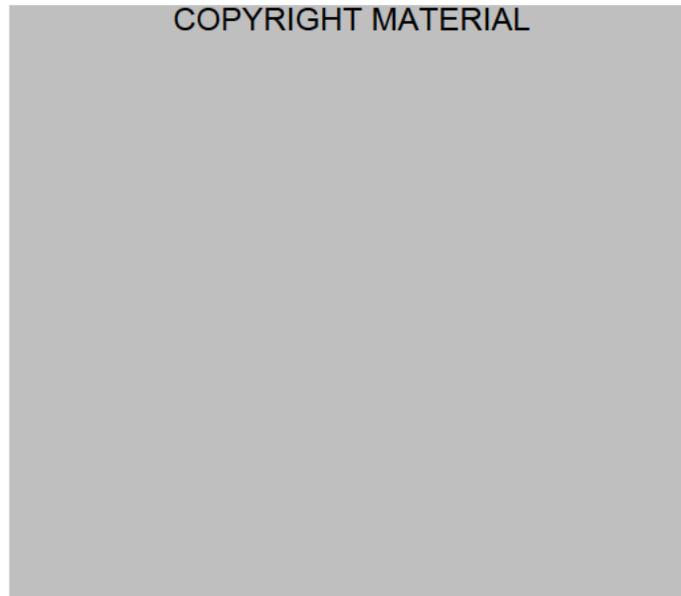


Figure 2. Change of serum CRP, SAA, Hb, Alb, IgG, and total cholesterol levels. Points and vertical bars indicate means and SEs, respectively. Patients treated with MRA up to 48 weeks (n = 28) and up to 60 weeks (n = 27). \* $P < .001$ , paired  $t$  test, compared with baseline. To convert total cholesterol from milligrams per deciliter to millimoles per liter, multiply milligrams per deciliter by 0.02586.

### **2.3 Availability of Proposed Active Ingredient in the United States**

Siltuximab is currently not available in the United States.

### **2.4 Important Safety Issues With Consideration to Related Drugs**

Siltuximab, an anti-IL-6 mAb, is a first-in-class treatment for patients with MCD. No anti-IL-6 antibody or IL-6 antagonist has been approved for commercial use.

Tocilizumab, a mAb against the IL-6 receptor, has been approved in the United States and European Union for treatment of rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, and systemic juvenile idiopathic arthritis; and in Japan for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, and Castleman's disease. The most common adverse reactions ( $\geq 5\%$ ) identified for tocilizumab include upper respiratory tract infection, nasopharyngitis, headache, hypertension, and increased alanine aminotransferase (ALT). Warning and Precautions include serious infections, gastrointestinal perforation, hypersensitivity reactions and need to avoid exposure to live vaccines.

## 2.5 Summary of Presubmission Regulatory Activity Related to Submission

**Table 2: Presubmission Regulatory Activity**

Date	Item
12/22/03	Centacor submits IND 11461 for CNTO 328, a chimeric Antibody against Interleukin-6 Phase 1 study C0328T03 for NHL, MM, or Castleman's Disease
5/4/06	Meeting to discuss MM protocol "A Phase 2 Study of CNTO 328 in Combination with Bortezomib in Multiple Myeloma". (SPA agreed 9/28/06)
5/26/06	Orphan Drug Designation - Treatment of Castleman's disease
10/2/07	<p>Meeting to discuss "evidence of clinical benefit for patients with Castleman's disease."</p> <ul style="list-style-type: none"> <li>- FDA - trial should exclude (b) (4) Castleman's disease</li> <li>- FDA – trial should be randomized &amp; controlled (b) (4).</li> <li>- Centacor proposed best supportive care (BSC) with CNTO 328 versus placebo with crossover for placebo non responders</li> <li>- FDA advised all patients must be symptomatic with measurable disease</li> <li>- Centacor proposed CR &amp; PR (tumor response), and B symptom assessment for the composite endpoint</li> </ul>
8/26/08	<p>FDA denied request for EOP2 Mtg to discuss (b) (4) (b) (4)</p> <p>(b) (4) did not address FDA advice from the 10/2/07 meeting. FDA agreed to provide written responses to Centacor questions. Responses sent 12/5/08</p> <ul style="list-style-type: none"> <li>- 11 mg/kg every 3-week CNTO 328 dose schedule acceptable</li> <li>- Safety database 70 subjects treated with CNTO 238 90% exposed 1 year acceptable</li> <li>- HIV/HHSV-8 positive patients should be excluded or evaluated separately</li> <li>- Recommend subjects with single cutaneous lesions be excluded or justified</li> <li>- Recommend centralized pathology review for eligibility</li> <li>- Recommend study endpoint CR&amp;PR include measure of durability</li> <li>- Recommend independent radiographic committee review of response</li> </ul>
7/13/09	<p>Ortho Biotech (Centacor) submits SPA for "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 to Best Supportive Care in Subjects with Multicentric Castleman's Disease." FDA issued a letter of non-agreement on August 27, 2009.</p> <p>Problems included:</p> <ul style="list-style-type: none"> <li>- Inclusions of subjects with cutaneous disease as only measurable disease not acceptable</li> <li>- Definition of study endpoint, must include durability, disease symptoms</li> <li>- ITT population all randomized subjects</li> <li>- Use of increased doses of corticosteroids problematic</li> <li>- Problems with missing information in CRFs identified</li> <li>- Problems with the (b) (4) include PET/CT not acceptable should be CT only; 1 radiology reviewer not optimal, suggest 2 reviewers with a third to break ties.</li> <li>- (b) (4) review to confirm diagnosis prior to randomization</li> </ul>

Date	Item
10/15/09	Meeting to discuss no agreement to CD SPA <ul style="list-style-type: none"> <li>- FDA agreed to Ortho Biotech's revised endpoint incorporating duration of response and symptoms</li> <li>- Ortho Biotech agreed to disallow courses of corticosteroids as part of best supportive care but can be used at low dose to treat allergic reaction</li> <li>- FDA clarified if justified a single radiology reviewer may be acceptable</li> <li>- Ortho Biotech stated photographs of skin lesion would be centrally reviewed</li> <li>- FDA advised Ortho Biotech that while we cannot agree to a SPA for CNTO 328 in Castleman's disease based on the proposed study, FDA does not object to the proposed trial proceeding.</li> </ul>
1/22/10	Ortho Biotech informs FDA the generic name, siltuximab, has been chosen for CNTO 328
11/18/11	FDA notifies Ortho Biotech the proposed proprietary name Sylvant is acceptable
12/1/11	Notification of corporate name change from Ortho Biotech Oncology Research & Development, Unit of Centocor R&D, Inc. to Janssen Research & Development, LLC.
12/18/12	Pre BLA Meeting to discuss content and format of BLA <ul style="list-style-type: none"> <li>- FDA agreed Approach in statistical analysis plan, but informed Janssen that additional evaluations may be requested at the time of the review.</li> <li>- FDA requested all concentration-time and derived PK parameter datasets for all studies.</li> </ul>
6/7/13	Pre BLA Meeting – Canceled after Janssen received preliminary responses
7/24/13	Pre BLA CMC meeting - Canceled after Janssen received preliminary responses

## 2.6 Other Relevant Background Information

Siltuximab for the treatment of Castleman's disease received orphan designation 5/26/06. Due to this orphan designation this application is not subject to the Pediatric Research Equity Act (PREA).

### 3 Ethics and Good Clinical Practices

#### 3.1 Submission Quality and Integrity

The application is submitted as an eCTD document. It contains all the required and agreed upon sections. The reports contain functional hyperlinks. The data sets are functional. The overall quality and integrity of the submission is adequate to allow substantive review.

#### 3.2 Compliance with Good Clinical Practices

The study report for each study includes the statement: This study was conducted in compliance with Good Clinical Practice, including the archival of essential documents.

#### 3.3 Financial Disclosures

The applicant has adequately disclosed the financial interest forms of investigators participating in the prospective randomized trial submitted to support this indication. There were 325 covered under provision 1 of Form 3454.

There were 3 investigators who submitted Form 3455 indicating they had received Research Funding from Janssen.

(b) (6)	149,443 US Dollar	(b) (4)
	100,000 US Dollar	
	198,000 Euro	

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); 95% CI of the difference: 3.1, 50.3.

Because this is a randomized placebo controlled trial and the endpoint was determined by an independent review committee, this application is reviewable.

I recommend based on the better than average response rate reported in patients treated with siltuximab at site 0102 and 6501 (100% n=5) these sites be considered for the DSI inspection for this application. Because [REDACTED]<sup>(b) (4)</sup>, site 0102 was chosen.

**REVIEWER COMMENT:**

The request for inspection of Site 0102 was cancelled because it was inspected [REDACTED]<sup>(b) (4)</sup> under a for-cause inspection assignment for a clinical investigator. The Office of Regulatory Affairs, Dallas District Office, handled this inspection. A form 483, notice of inspection was issued with a voluntary action indicated regulatory classification recommendation. An Office of Business Informatics close-out letter response was issued to the clinical site with a no action indicated as the final regulatory classification.

## 4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

### 4.1 Chemistry Manufacturing and Controls

The following overview of DMA was presented at the Midcycle Meeting.

**Table 3: Summary of Manufacturing**

	Drug Substance	Drug Product
Formulation:	Final Drug Substance (FDS): (b) (4) siltuximab (b) (4) (b) (4) histidine, (b) (4) sucrose, polysorbate 80, (b) (4) (b) (4)	Sterile, single-use lyophilized dosage forms (100 and 400 mg/vial) for i.v. infusion. Stored at 2-8°C. Formulation is (b) (4). To be reconstituted with 5.2 or 20 mL, respectively, of WFI to a final concentration of 20mg/mL mAb.
Commercial manufacturing	(b) (4)	Cilag AG (Schaffhausen, Switzerland)
Stability (requested by sponsor)	(b) (4)	100 mg/vial: (b) (4) 400 mg/vial: (b) (4)

The final conclusions regarding the acceptability of the manufacturing process for siltuximab were pending at the time of this review.

### 4.2 Clinical Microbiology

Review by product quality microbiology was pending at the time of this review. At the time of the midcycle meeting no problems that would prevent approval were identified.

### 4.3 Preclinical Pharmacology/Toxicology

At the time of the midcycle review the pharmacology toxicology reviewer had determined no additional studies were required. Fertility study and extended embryo-fetal pre and post-natal studies were conducted with surrogate mAbs. The pharmacology toxicology reviewers have decided to designate siltuximab as pregnancy category C.

### 4.4 Clinical Pharmacology

#### 4.4.1 Mechanism of Action

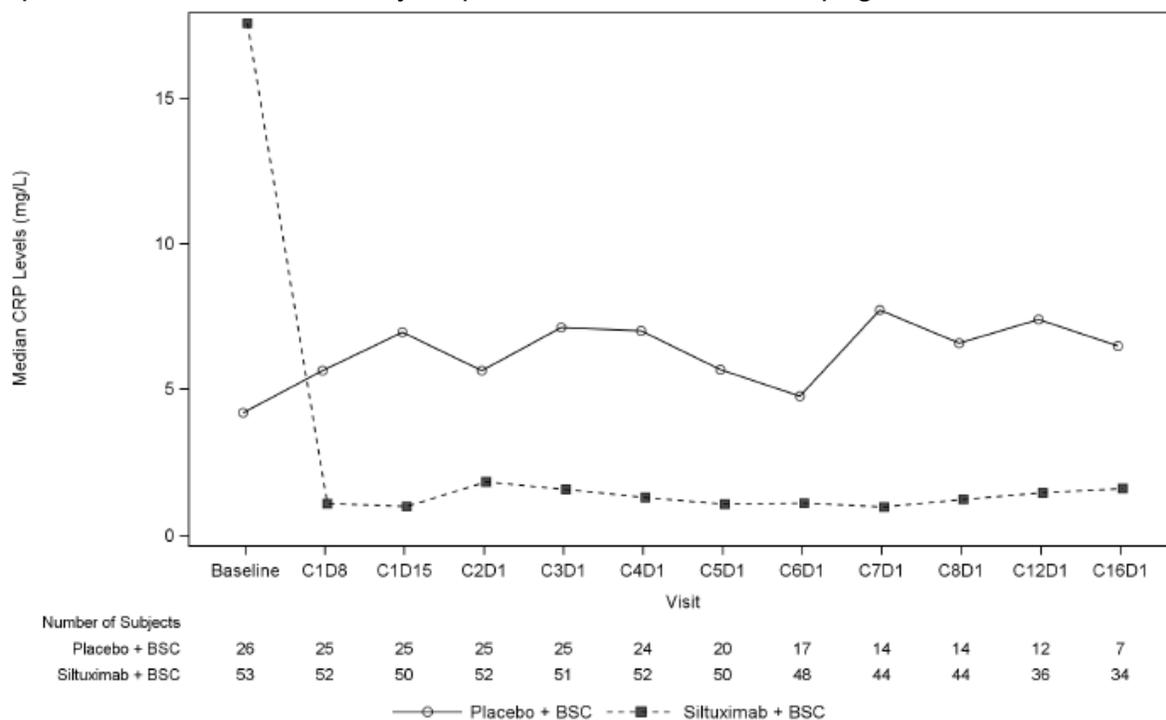
Siltuximab is a human-mouse chimeric mAb that complexes with IL-6. Siltuximab prevents the binding of human IL-6 to both soluble and membrane-bound IL-6

receptors. Castleman's disease has been linked to excessive release of IL-6. Overproduction of IL-6 induces a proinflammatory syndrome that leads to constitutional symptoms, induction of VEGF secretion, and induction of immune dysregulation leading to autoimmune phenomena including cytopenias in patients with MCD.

#### 4.4.2 Pharmacodynamics (derived from the clinical pharmacology presentation at the midcycle meeting)

The pharmacodynamic (PD) effect was measured using CRP levels. CRP levels rise in response to IL-6. Median CRP pre-infusion was suppressed in MCD patients treated with siltuximab compared to patients treated with placebo as presented in Figure 3.

**Figure 3: Median Pre-infusion CRP Level over Time**  
 (copied from submission Study Report CNTO328MCD2001 page 81/766)



There was no relationship detected between dose-exposure to siltuximab and CRP. There was no relationship detected between CRP levels and response. Therefore, CRP is not a useful in identifying non-responders.

#### 4.4.3 Pharmacokinetics (copied from the clinical pharmacologists revisions to the label)

The pharmacokinetics [PK] of siltuximab were evaluated in patients with MCD and hematological and non-hematological malignancies. The serum siltuximab

pharmacokinetics are adequately described by a linear two-compartment intravenous model with first-order elimination.

Following administration of siltuximab (11 mg/kg, once every 3 weeks as 1-hour intravenous infusion), the maximum serum siltuximab concentration ( $C_{max}$ ) occurred close to the end of infusion. At steady state, the serum mean  $C_{max}$  value for siltuximab is 332 mcg/mL, and the serum mean predose trough value is 84 mcg/mL.

With the once every 3 week dosing regimen, siltuximab steady state is achieved by the sixth infusion, and siltuximab accumulates approximately 1.7-fold relative to a single dose. Following multiple dosing, siltuximab showed approximately dose proportional pharmacokinetics over the dose range of 2.8 to 11 mg/kg.

Based on the population pharmacokinetic analysis, the clearance of siltuximab in patients is 0.23 L/day (51% CV [covariance]). Based on population pharmacokinetic analysis (n=378), body weight was identified as the only statistically significant covariate for siltuximab clearance. Therefore, the body weight based dosing is appropriate.

The mean terminal half-life ( $t_{1/2}$ ) for siltuximab in patients after a single oral dose of 11 mg/kg is 20.6 days (range: 14.2 to 29.7 days).

## 5 Sources of Clinical Data

The efficacy of siltuximab in the treatment of MCD is supported by CNTO328MCD2001 a randomized double-blind study in 79 patients. Patients with HIV/HHV-8 associated Castleman’s disease were excluded. 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.

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 (MM) and myelodysplastic syndrome (MDS); 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.

### 5.1 Tables of Studies/Clinical Trials

**Table 4: Summary of 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 5: Summary of 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 6: Summary of Clinical Studies in Patients with Hematologic 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

**Table 7: Summary of Clinical Studies in Patients with Solid Tumors**

Summary of Clinical Studies in Patients with Solid Tumors			
Protocol Number	Report Type	Title	Comment
C0328T01 (Part 1)	Full report	A Phase 1/2 Study of a Chimeric Antibody Against Interleukin-6 (CNTO 328) in Subjects with Metastatic Renal Cell Carcinoma	Siltuximab (1, 3, 6, and 12 mg/kg; Days 1, 29, 43, and 57) n=11
C0328T01 (Part 2)	Full report	A Phase 1/2 Study of a Chimeric Antibody Against Interleukin-6 (CNTO 328) in Subjects with Metastatic Renal Cell Carcinoma	Randomization of 2 doses Siltuximab (3 v 6 mg/kg; Days 1, 22, 43, 64) n=37 treated
C0328T01 (Part 3)	Full report	A Phase 1/2 Study of a Chimeric Antibody Against Interleukin-6 (CNTO 328) in Subjects with Metastatic Renal Cell Carcinoma	Open label dose (6 mg/kg; Days 1, 15, 29, 43, 57, 71) n=20
C0328T04	Abbreviated report	A Phase 1 Study of a Chimeric Antibody Against Interleukin-6 (CNTO 328) Combined with Docetaxel in Subjects with Metastatic Hormone-Refractory Prostate Cancer	Docetaxel 75 mg/m <sup>2</sup> q3w Siltuximab 6, 9, or 12 mg/kg q2wk n=39
CNTO328STM2001	Full report	A Phase 1/2, Multiple-dose, Dose-escalation Study to Assess the Safety, Efficacy, and Pharmacokinetics of Intravenous CNTO 328, an Anti-Interleukin 6 (IL-6) Monoclonal Antibody, in Subjects with Solid Tumors	Siltuximab (2.8, 5.5, 11, and 15 mg/kg); Multiple administrations N=84
C0328T07	Abbreviated report	A Phase 2 Multicenter, Open-label Study of CNTO 328 (Anti-IL-6 Monoclonal Antibody) in Combination with Mitoxantrone versus Mitoxantrone in Subjects with Metastatic Hormone-Refractory Prostate Cancer (HRPC)	Mitoxantrone (12 mg/m <sup>2</sup> q3 wk) n=47 Mitoxantrone + siltuximab (11 mg/kg q2 wk) n=57

## 5.2 Review Strategy

The design and efficacy results of CNTO328MCD2001 will be presented in Section 6. The safety information will be presented in Section 7. The design and background information regarding studies C0328T03, CNTO328MCD2002, C0328T08, C0328T06, CNTO328MMY2001, and CNTO328MDS2001 will be presented in Section 5.3 and the safety results for these studies will be presented in Section 7. The long term safety results of CNTO328MCD2002 will be presented in Section 7.5.2.

### 5.3 Discussion of Individual Studies/Clinical Trials

#### 5.3.1 C0328T03 Phase 1 Hematologic Malignancies

**Number/Clinical Trial Title:** C0328T03 / “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”

**Dose:**

Dose Cohort 1: 3 mg/kg every 2 weeks x 4 administrations (Days 1, 15, 29, 43)

Dose Cohort 2: 6 mg/kg every 2 weeks x 4 administrations (Days 1, 15, 29, 43)

Dose Cohort 3: 12 mg/kg every 3 weeks x 3 administrations (Days 1, 22, 43)

Dose Cohort 4: 6 mg/kg weekly x 7 administrations (Days 1, 8, 15, 22, 29, 36, 43)

Dose Cohort 5: 12 mg/kg every 2 weeks x 4 administrations (Days 1, 15, 29, 43)

Dose Cohort 6: 12 mg/kg every 3 weeks x 3 administrations (Days 1, 22, 43)

Dose Cohort 7a: 9 mg/kg siltuximab every 3 weeks

Dose Cohort 7b: 12 mg/kg siltuximab every 3 weeks

**Route:** IV infusion

**Population:** B-cell NHL, chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL) and Waldenstrom’s macroglobulinemia, MM, or Castleman’s disease

**Enrollment:** Total 72 subjects (5 never treated); included 37 subjects with Castleman’s disease

Cohort 1 - 6 subjects

Cohort 2 - 7 subjects

Cohort 3 - 10 subjects

Cohort 4 - 6 subjects

Cohort 5 - 6 subjects

Cohort 6 - 12 subjects

Cohort 7a - 12 subjects

Cohort 7b - 8 subjects

**Date of Study:** 6/9/05 to 4/29/11

**Substantive Amendments:**

9/28/2007 – Protocol revised to add cohorts 6 and 7; Limited to patients with Castleman’s Disease; Duration of treatment was expanded from 6 weeks to allow extended treatment

2/5/2009 – Cohort 7 was expanded to add cohort 7b

**Results:**

Demographics:

**Table 8: Baseline Demographics by Disease in Treated Subjects on C0328T03 Phase 1 Study**

Demographics				
	Non-Hodgkin's Lymphoma n=17	Multiple Myeloma n=13	Castleman's Disease n=37	Total n=67
<b>Gender n (%)</b>				
Male	9 (53)	6 (46)	19 (51)	34 (51)
Female	8 (47)	7 (54)	18 (49)	33 (49)
<b>Age in Years</b>				
Mean	65	61	47	54
Median	69	57	48	54
Range	23 to 82	43 to 81	18 to 76	18 to 82
<b>Race n (%)</b>				
Caucasian	16 (94)	10 (77)	27 (73)	53 (79)
Black	1 (6)	3 (23)	6 (16)	10 (15)
Asian	0	0	4 (11)	4 (6)

Baseline Characteristics (Castleman's Disease):

**Table 9: Disease Characteristics of Treated Subjects with Castleman's Disease on C0328T03 Phase 1 Study**

Disease Characteristics of Treated Subjects with Castleman's Disease							
Dose Cohort	3 mg/kg q2 weeks n=1	6 mg/kg q2 weeks n=2	9 mg/kg q3 weeks n=12	12 mg/kg q3 weeks n=16	6 mg/kg weekly n=3	12 mg/kg q2 weeks n=3	Combined n=37
<b>Histology n</b>							
Hyaline vascular	0	0	6	8	1	3	18 (49%)
Plasmacytic	1	2	5	7	2	0	17 (46%)
Mixed	0	0	1	1	0	0	2 (5%)
<b>Disease Type n</b>							
Unicentric	0	0	2	0	0	0	2 (5%)
Multicentric	1	2	10	16	3	3	35 (95%)
<b>HHV-8 tested (n=33) n</b>							
Positive	0	0	1	0	0	0	1 (3%)
Negative	1	2	11	14	2	2	32 (97%)
<b>Time from Diagnosis in Months</b>							
Mean	2	11	25	21	10	33	21
Median	2	11	15	7	11	4	8
	NA	5 to 11	1 to 70	1 to 75	1 to 18	2 to 93	1 to 93

Exposure:

**Table 10: Patients with Prolonged Exposure to Siltuximab on C0328T03 Phase 1 Study**

	Prolonged Exposure			Total n=67
	Non-Hodgkin's Lymphoma n=17	Multiple Myeloma n=13	Castleman's Disease n=37	
Subjects Treated ≥ 12 months	2	3	24	29
Subjects Treated ≥ 24 months	0	1	18	10
Subjects Treated ≥ 36 months	0	1	14	15

Disposition: (copied from submission 5.3.3.2 Study Report C0328T03 page 49/1177)

**Table 11: Disposition C0328T03 Phase 1 Study**

**Table 2 Number of subjects who discontinued study agent by reason for discontinuation; treated subjects**

	CNTO 328								
	Cohort 1	Cohort 2	Cohort 3	Cohort 4	Cohort 5	Cohort 6	Cohort 7a	Cohort 7b	Combined
Subjects treated	6	7	10	6	6	12	12	8	67
Subjects who discontinued study treatment	6 (100.0%)	7 (100.0%)	10 (100.0%)	6 (100.0%)	6 (100.0%)	12 (100.0%)	12 (100.0%)	8 (100.0%)	67 (100.0%)
Reason for discontinuation									
Adverse event	0 (0.0%)	1 (14.3%)	1 (10.0%)	1 (16.7%)	1 (16.7%)	0 (0.0%)	2 (16.7%)	1 (12.5%)	7 (10.4%)
Disease progression	2 (33.3%)	2 (28.6%)	2 (20.0%)	1 (16.7%)	1 (16.7%)	4 (33.3%)	1 (8.3%)	0 (0.0%)	13 (19.4%)
Lost to follow-up	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (16.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.5%)
Death	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other	4 (66.7%)	3 (42.9%)	3 (30.0%)	2 (33.3%)	1 (16.7%)	6 (50.0%)	3 (25.0%)	4 (50.0%)	26 (38.8%)
Completed Day 43 administration, but no extension started	2 (33.3%)	2 (28.6%)	0 (0.0%)	2 (33.3%)	1 (16.7%)	1 (8.3%)	0 (0.0%)	0 (0.0%)	8 (11.9%)
Subjects moved to other siltuximab studies	0 (0.0%)	1 (14.3%)	4 (40.0%)	1 (16.7%)	3 (50.0%)	2 (16.7%)	6 (50.0%)	3 (37.5%)	20 (29.9%)

Pharmacokinetic Results: (copied from submission Study Report C0328T03 page 143/1177)

- Following the first dose, serum concentrations of siltuximab declined in a bi-exponential manner with  $t_{1/2}$  ranging from 17.73 to 20.64 days.
- CRP suppression was observed after treatment with siltuximab across all cohorts. Subjects with Castleman's disease treated with 12 mg/kg every 3 weeks showed greater decrease of CRP compared with those treated with 9 mg/kg every 3 weeks, supporting observations from clinical benefit assessments.
- Neutralization of IL-6 also caused a decrease in hepcidin (an iron-regulating peptide hormone) in a majority of subjects, consistent with a general trend toward hemoglobin improvement.
- No apparent treatment-related changes were observed in other serum markers (inflammation, angiogenesis, or bone resorption) examined.

Efficacy: (copied from submission 5.3.3.2 Study Report C0328T03 page 92/1177)  
**Table 12: Best Overall Response in Subjects with Castleman's Disease on C0328T03 Phase 1 Study**

**Table 19 Summary of best overall response using modified International Working Group Criteria (Cheson et al, 1999); treated subjects with Castleman's disease**

	CNTO 328						Combined
	3 mg/kg q2 weeks	6 mg/kg q2 weeks	9 mg/kg q3 weeks	12 mg/kg q3 weeks	6 mg/kg Weekly	12 mg/kg q2 weeks	
Treated subjects with Castleman's disease	1	2	12	16	3	3	37
Best overall response							
Complete response	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.3%)	0 (0.0%)	0 (0.0%)	1 (2.7%)
Partial response	0 (0.0%)	1 (50.0%)	2 (16.7%)	6 (37.5%)	0 (0.0%)	2 (66.7%)	11 (29.7%)
Unconfirmed complete response	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Unconfirmed partial response	0 (0.0%)	0 (0.0%)	2 (16.7%)	1 (6.3%)	0 (0.0%)	0 (0.0%)	3 (8.1%)
Stable disease	1 (100.0%)	1 (50.0%)	7 (58.3%)	8 (50.0%)	2 (66.7%)	1 (33.3%)	20 (54.1%)
Progressive disease	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (33.3%)	0 (0.0%)	1 (2.7%)
Nonevaluable	0 (0.0%)	0 (0.0%)	1 (8.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.7%)

Of the 37 treated subjects with Castleman's disease, 1 subject (2.7%) had a best response of CR, 11 subjects (29.7%) had a best response of PR, 3 subjects (8.1%) had unconfirmed PR, and 20 subjects (54.1%) had stable disease (SD). The 1 CR and 8 of 11 PRs were in subjects treated with the highest dose of siltuximab (12 mg/kg). All 24 subjects with Castleman's disease treated long-term ( $\geq 12$  months) in the study had sustained clinical benefit responses, and half ( $n = 12$ ) also had an objective radiologic response, including 1 CR and 11 PRs based on central radiology review. Nine of the 12 responders were treated with the highest dose of siltuximab (12 mg/kg).

Safety is discussed in Section 7.

### 5.3.2 CNTO328MCD2002 Castleman's Disease Extension Study

**Number/Clinical Trial Title:** CNTO328MCD2002 An Open-label, Multicenter Study to Evaluate the Safety of Long-term Treatment with Siltuximab in Subjects with Multicentric Castleman's Disease

**Dose:** 11 mg/kg siltuximab every 3 weeks (or 6 weeks at the investigator's discretion)

**Route:** IV infusion over 1 hour

**Population:** Subjects with Castleman's disease enrolled in study C0328T03 or CNTO328MCD2001.

**Enrollment:** Up to 75 subjects planned; 19 enrolled to date from C0328T03

**Study Period:** 4/1/2011 to 1/2/13 (cut off for interim analysis)

#### Results:

At the time of the interim analysis of this trial all subjects enrolled on this trial were originally enrolled on study C0328T03, the dose finding study.

Demographics:

**Table 13: Demographics and Disease Characteristics - CNTO328MCD2002 Extension Study**

Demographics and Disease Characteristics of Subjects on Extension Study CNTO328MCD2002	
n=19	
<b>Gender n (%)</b>	
Male	12 (63)
Female	7 (37)
<b>Age in Years</b>	
Mean	46
Median	44
Range	18 to 76
<b>Race n (%)</b>	
Caucasian	16 (84)
Black	1 (5)
Asian	2 (11)
<b>Castleman Histology n</b>	
Hyaline vascular	10 (53)
Plasmacytic	9 (47)

Exposure:

All 19 subjects who were enrolled on the CNTO328MDC2002 Extension Study were treated with siltuximab longer than 3 years, 12 were treated longer than 4 years.

Disposition:

None of the 19 patients enrolled on CNTO328MDC2002 Extension Study have discontinued siltuximab treatment.

Safety is discussed in Section 7.5.2.

### 5.3.3 C0328T08 Bioequivalence of Two Formulations in Healthy Volunteers

**Number/Clinical Trial Title:** C0328T08 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

**Dose:** 1.4 and 2.8 mg/kg and placebo

**Route:** IV infusion

**Population:** Healthy adults, 18 to 45 years of age, weight in the range of 60 to 95 kg if male; weight in the range of 50 to 80 kg if female.

**Enrollment:** A total of 145 subjects received a single IV dose in this study as follows in Part 1: placebo (4 subjects); 1.4 mg/kg CHO-derived CNTO 328 (6 subjects); 1.4 mg/kg Sp2/0-derived CNTO 328 (5 subjects); 2.8 mg/kg CHO-derived CNTO 328 (5 subjects); and 2.8 mg/kg Sp2/0-derived CNTO 328 (5 subjects).

In Part 2, subjects were treated as follows: 1.4 mg/kg CHO-derived CNTO 328 (62 subjects) and 1.4 mg/kg Sp2/0-derived CNTO 328 (58 subjects).

**Date of Study:** 6/3/2008 to 6/24/2009

#### Results:

Demographics:

**Table 14: Demographics C0328T08 Bioequivalence in Healthy Volunteers**

Demographics n=145	
Gender n (%)	
Male	50 (34)
Female	95 (66)
Age in Years	
Mean	28
Median	26
Range	19 to 45
Race n (%)	
White	101 (70)
Black	37 (26)
Asian	4 (3)
American Indian/ Alaska Native	2 (1)
Other	1 (<1)

Pharmacokinetic/Pharmacodynamic Results: (copied from submission 5.3.3.1 C0328T08 Synopsis page 3 of 4)

- The maximum observed serum concentration ( $C_{max}$ ) as evaluable in 67 subjects in the 1.4 mg/kg CHO-derived group and 63 subjects in the 1.4 mg/kg Sp2/0-derived CNTO 328 group. The area under the curve ( $AUC$ )<sub>(0-84D)</sub> was evaluable in 64 subjects in the 1.4 mg/kg CHO-derived group and 56 subjects in the 1.4 mg/kg Sp2/0-derived CNTO 328 group.

- The 90% CI of the ratios of the geometric means for  $C_{\max}$  (90% CI: 99.4% to 111.3%) and  $AUC_{(0-84D)}$  (90% CI: 98.1% to 109.6%) were within the pre-specified range of 80% to 125%.
- PK parameters of total systemic clearance of drug (CL), volume of distribution during terminal phase ( $V_z$ ), and  $t_{1/2}$  were similar for each of the groups.
- No samples tested were positive for anti-drug antibodies to CNTO 328.
- Both CHO-derived and Sp2/0-derived CNTO 328 groups showed similar decreases in C-reactive protein (CRP) levels.

Conclusions: (copied from submission 5.3.3.1 C0328T08 Synopsis page 4 of 4)

- The 90% CI of the ratios of the geometric means for  $C_{\max}$  and  $AUC_{(0-84D)}$  were within the pre-specified range of 80% to 125%.
- CHO-derived CNTO 328 and Sp2/0-derived CNTO 328 are pharmacokinetically bioequivalent.
- In general, CNTO 328 was well tolerated by the healthy males and females treated in this study, and none of the subjects with appropriate samples for detection of antibodies against CNTO 328 were positive.

Safety is discussed in Section 7.

### 5.3.4 C0328T06 Multiple Myeloma Placebo or Siltuximab with Bortezomib

**Number/Clinical Trial Title:** 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

**Dose:** Siltuximab or placebo 6 mg/kg was administered as an IV infusion every 2 weeks.

Bortezomib 1.3 mg/m<sup>2</sup> IV bolus;

Treatment Phase (4 cycles of 42 days) Days 1, 4, 8, 11, 22, 25, 29, 32

Maintenance Phase (35 days per cycle) Days 1, 8, 15, 22

Dexamethasone added at time of disease progression or intolerable toxicity

**Route:** IV infusion

**Population:** Adults with measurable MM with documented disease progression, previous bortezomib excluded

**Enrollment:** Planned part 1 – 20 subjects; Part 2 - 270 subjects randomized 1:1; 307 entered and 302 treated

**Date of Study:** 11/7/2006 to 6/17/2011

**Substantive Amendments:**

7/17/2008 – Protocol was amended to add high-dose dexamethasone at the time the disease is refractory to bortezomib.

### Results:

Demographics:

**Table 15: Demographics Study C0328T06 Relapsed Multiple Myeloma**

Demographics Safety Population (By Exposure to Siltuximab not as Randomized)				
	Part 1 Siltuximab 6 mg/kg Bortezomib n=21	Part 2 Siltuximab 6 mg/kg Bortezomib n=142	Part 2 Placebo Bortezomib n=139	Total n=302
<b>Gender n (%)</b>				
<b>Male</b>	8 (38)	73 (51)	80 (58)	161 (53)
<b>Female</b>	13 (62)	69 (49)	59 (42)	141 (47)
<b>Age in Years</b>				
<b>Mean</b>	66	63	62	63
<b>Median</b>	66	64	61	63
<b>Range</b>	39 to 85	36 to 82	37 to 81	36 to 85
<b>Race n (%)</b>				
<b>Caucasian</b>	20 (95)	127 (90)	125 (90)	272 (90)
<b>Black</b>	1 (5)	6 (4)	6 (4)	13 (4)
<b>Asian</b>	0	2 (1)	2 (1)	4 (2)
<b>Other</b>	0	7 (5)	6 (4)	13 (4)
<b>Region n (%)</b>				
<b>North America</b>	10 (48)	16 (11)	11 (8)	37 (12)
<b>Europe</b>	11 (51)	126 (89)	128 (92)	265 (88)

**Table 16: Disposition Study C0328T06 Relapsed Multiple Myeloma**

<b>Disposition Safety Population (By Exposure to Siltuximab not as Randomized)</b>			
<b>n (%)</b>	<b>Part 1 Siltuximab 6 mg/kg Bortezomib n=21</b>	<b>Part 2 Siltuximab 6 mg/kg Bortezomib n=142</b>	<b>Part 2 Placebo Bortezomib n=139</b>
<b>Discontinued Study Agent</b>	14 (67)	106 (75)	91 (61)
<b>Reason for Discontinuation</b>			
<b>Adverse Event</b>	6 (29)	25 (16)	22 (16)
<b>Achieved CR</b>	1 (5)	10 (7)	4 (3)
<b>Withdrew Consent Study Agent</b>	1 (5)	16 (11)	10 (7)
<b>Withdrew Consent Study</b>	1 (5)	5 (4)	5 (4)
<b>Disease Progression</b>	5 (24)	28 (20)	30 (22)
<b>Lost to Follow Up</b>	0	1 (1)	0
<b>Death</b>	0	9 (6)	6 (4)
<b>Physician Decision</b>	0	8 (6)	11 (8)
<b>Other</b>	0	3 (2)	3 (2)

Safety is discussed in Section 7.

Selected Conclusions (copied from submission 5.3.3.2 C0328T06 Synopsis page 11 of 11)

- The siltuximab dose used in this study (6 mg/kg every 2 weeks) is lower than the dose level providing high response rate in subjects with MCD(12 mg/kg every 3 weeks [C0328T03]) and may, therefore, be suboptimal.
- Suppression of CRP levels was much greater in siltuximab plus bortezomib treated group compared to placebo plus bortezomib group and was sustained throughout the treatment period.
- Only 24% of treated subjects showed detectable IL-6 levels (complexed and non-complexed) at baseline, which were not predictive of clinical response.
- The addition of siltuximab to bortezomib did not appear to impact subject perceptions of their overall quality of life, fatigue, or pain.

### 5.3.5 CNTO328MMY2001 Multiple Myeloma VMP with or without Siltuximab

**Number/Clinical Trial Title:** CNTO328MMY2001 / 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.

**Dose:**

Siltuximab 11 mg/kg every 3 weeks

VMP [Velcade, Melphalan, Prednisone]

- Bortezomib (Velcade) - 1.3 mg/m<sup>2</sup> IV bolus injection, biweekly Weeks 1, 2, 4, & 5 for 4 6-week cycles, then weekly Weeks 1, 2, 4, & 5 for 5 6-week cycles
- Melphalan - 9 mg/m<sup>2</sup> Days 1 to 4 of each 6-week cycle
- Prednisone - 60 mg/m<sup>2</sup> oral administration Days 1 to 4 of each 6-week cycle

**Route:** IV infusion

**Population:** Adults with symptomatic MM and measurable secretory disease, not candidates for high-dose chemotherapy with stem cell transplantation

**Enrollment:** Planned Part 1 – 12 subjects, Part 2 – 106 subjects randomized 1:1; 118 enrolled and 117 treated

**Date of Study:** 6/13/2009 to 5/29/2012

**Results:**

Demographics:

**Table 17: Demographics CNT0328 MMY2001 Newly Diagnosed Multiple Myeloma**

Demographics Safety Population				
	Part 1 Siltuximab 11 mg/kg VMP n=12	Part 2 Siltuximab 11 mg/kg VMP n=52	Part 2 VMP n=53	Total n=117
<b>Gender n (%)</b>				
Male	5 (42)	23 (56)	24 (45)	52 (44)
Female	7 (58)	29 (44)	29 (55)	65 (56)
<b>Age in Years</b>				
Mean	74	72	70	71
Median	74.5	71	70	71
Range	64 to 82	50 to 83	48 to 90	48 to 90
<b>Race n (%)</b>				
White	12 (100)	39 (75)	38 (72)	89 (76)
Black	0	0	1 (2)	1 (1)
Asian	0	11 (21)	13 (24)	24 (21)
Other	0	2 (4)	1 (2)	3 (2)
<b>Region n (%)</b>				
North America	0	2 (4)	3 (6)	5 (4)
Europe	12 (100)	34 (65)	31 (58)	77 (66)
Asia		16 (31)	19 (36)	35 (30)

Disposition

**Table 18: Disposition CNT0328 MMY2001 Newly Diagnosed Multiple Myeloma**

Disposition Safety Population			
n (%)	Part 1 Siltuximab 11 mg/kg VMP n=12	Part 2 Siltuximab 11 mg/kg VMP n=52	Part 2 VMP n=53
<b>Discontinued During Treatment Period</b>	8 (67)	25 (48)	20 (38)
<b>Reason for Discontinuation</b>			
<b>Adverse Event</b>	3 (25)	7 (13)	3 (6)
<b>Disease Progression</b>	1 (8)	5 (10)	7 (13)
<b>Physician Decision</b>	3 (25)	3 (6)	3 (6)
<b>Death</b>	1 (8)	5 (10)	3 (6)
<b>Withdrew Consent for Study</b>		5 (10)	4 (8)

Exposure

**Table 19: Exposure CNT0328 MMY2001 Newly Diagnosed Multiple Myeloma**

Exposure Safety Population			
Number of Subjects Who Completed Cycles n (5)	Part 1 Siltuximab 11 mg/kg Day 1 and 22 / Cycle VMP n=12	Part 2 Siltuximab 11 mg/kg Day 1 and 22 / Cycle VMP n=52	Part 2 VMP n=53
≥ 1 Cycle	12 (100)	52 (100)	53 (100)
≥ 2 Cycle	12 (100)	49 (94)	49 (93)
≥ 3 Cycle	11 (92)	46 (89)	47 (89)
≥ 4 Cycle	10 (83)	42 (81)	43 (81)
≥ 5 Cycle	10 (83)	37 (71)	43 (81)
≥ 6 Cycle	7 (58)	35 (67)	42 (79)
≥ 7 Cycle	5 (42)	32 (62)	38 (72)
≥ 8 Cycle	4 (33)	29 (56)	37 (70)
9 Cycles	3 (25)	29 (56)	32 (60)

Safety is discussed in Section 7.

Selected Conclusions (copied from submission 5.3.3.2 CNT0328MMY2001 Synopsis page 9&10 of 10)

- The study did not meet the prespecified hypothesis that the addition of siltuximab to the VMP regimen would increase the CR rate by at least 10% (in this study, the CR rate was 26.5% in the S+VMP arm compared with 22.4% in the VMP arm).
- Patient reported outcomes: The addition of siltuximab to the VMP regimen did not have a positive impact on the subjects perception of their global health, fatigue, or pain.
- Pharmacokinetics: The pharmacokinetic profile of siltuximab in subjects with multiple myeloma appears to be similar to that observed previously in patients with solid tumors treated with single-agent siltuximab.

5.3.6 CNTO328MDS2001 Myelodysplastic Syndrome Placebo or Siltuxumab

**Number/Clinical Trial Title:** CNTO328MDS2001 / 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.

**Dose:** Siltuximab 15 mg/kg every 4 weeks

**Route:** IV infusion

**Population:** Subjects with Low- or INT-1-risk MDS who had received a documented RBC transfusion of at least 2 units of RBC for the treatment of the anemia of MDS in the 8 weeks before the date the informed consent form was signed.

**Enrollment:** Planned 75 2:1 randomization; Enrolled 76 - 50 siltuximab, 26 placebo

**Date of Study:** 10/18/2011 to 9/13/2012

**Results:**

Demographics:

**Table 20: Demographics CNTO328MDS2001 Myelodysplastic Syndrome**

Demographics			
	Siltuximab 15 mg/kg Every 4 weeks n=50	Placebo Every 4 weeks n=26	Total n=76
<b>Gender n (%)</b>			
Male	27 (54)	17 (65)	44 (58)
Female	23 (46)	9 (35)	32 (42)
<b>Age in Years</b>			
Mean	70	72	71
Median	71	71	72
Range	50 to 85	53 to 85	50 to 85
<b>Race n (%)</b>			
White	49 (98)	24 (92)	73 (96)
Black	0	1 (4)	1 (1)
Asian	0	1 (4)	1 (1)
Other	1 (2)	0	1 (1)
<b>Region n (%)</b>			
North America	23 (46)	11 (42)	34 (45)
Europe	27 (54)	15 (58)	42 (55)

Disposition

**Table 21: Disposition CNTO328MDS2001 Myelodysplastic Syndrome**

<b>Disposition</b>		
<b>n (%)</b>	<b>Siltuximab 15 mg/kg Every 4 weeks n=50</b>	<b>Placebo Every 4 weeks n=26</b>
<b>Discontinued During Treatment Period</b>	50 (100)	26 (100)
<b>Reason for Discontinuation</b>		
<b>Adverse Event</b>	3 (6)	2 (8)
<b>Siltuximab Treatment Failure Week 13</b>	27 (54)	1 (4)
<b>MDS Disease Progression</b>	3 (6)	0
<b>Patient Decision</b>	4 (8)	3 (11)
<b>Investigator Decision</b>	0	7 (27)
<b>Study Terminated by Sponsor</b>	13 (26)	13 (50)

Exposure

**Table 22: Exposure CNTO328MDS2001 Myelodysplastic Syndrome**

<b>Exposure</b>		
<b>Number of Infusions of Study Agent</b>	<b>Siltuximab 15 mg/kg Every 4 weeks n=50</b>	<b>Placebo Every 4 weeks n=26</b>
1	10 (20)	3 (12)
2	5 (10)	1 (4)
3	41 (82)	20 (77)
4	5 (10)	2 (8)
5	1 (2)	
7	1 (2)	

Safety is discussed in Section 7.

Selected Conclusions (copied from submission 5.3.5.4 CNTO328MDS2001Synopsis page 6&7 of 7)

- The IDMC [Independent Data Monitoring Committee] recommended stopping this study early due to lack of efficacy and the Sponsor concurred.
- The study did not meet the prespecified hypothesis that a higher proportion of siltuximab-treated subjects would achieve a reduction in RBC transfusions to treat the anemia of MDS, compared with the placebo group, in transfusion dependent Low and INT-1 risk subjects.

## 6 Review of Efficacy

### **Efficacy Summary**

The efficacy is supported by the results of CNTO328MCD2001. Additional support of the efficacy findings was confirmed by the responses documented in the subset of patients with Castleman's disease treated with siltuximab on C0328T03, the dose finding trial of siltuximab in patients with hematologic malignancies. The response rate of subjects with Castleman's disease enrolled on C0328T03 was 32% (12/37). There was 1 CR and 11 PRs. See Section 5.3.1 for a detailed discussion of the results of this trial.

### **6.1 Indication**

The applicant proposed the following indication for siltuximab:  
"Siltuximab is an interleukin-6 antagonist indicated for the treatment of patients with multicentric Castleman's disease who are human immunodeficiency virus - negative and human herpesvirus -negative."

#### 6.1.1 Methods

Title: 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."

Original Protocol Open for Entry:	2/9/10
First Patient Enrolled:	4/7/10
Last Patient Enrolled:	2/29/12
Study Completion Date:	1/31/13
Planned Enrollment:	78
Actual Enrollment:	79 (140 screened/ 79 eligible and randomized)
Terminated Early:	No

#### Treatment

##### Siltuximab or Placebo

Siltuximab (11 mg/kg) or placebo by a 1-hour IV infusion every 3 weeks. No dose modification permitted.

##### Best Supportive Care Measures

Best supportive care should be provided to all study subjects to manage symptoms. These include:

- Management of effusions (eg, drainage, diuretics)

- Antipyretics, antipruritics, antihistamines
- Pain medication
- Management of infections (antibiotics, oral or topical antifungals, and antiviral treatment except for ganciclovir)
- Transfusions
- Standard management of infusion related reactions

#### Prohibited Treatment

Use of these prohibited treatments during the study will result in subjects being withdrawn from the study:

- Other concomitant antitumor therapies for Castleman's disease, for example:
- Anti-CD20 antibodies (eg, rituximab)
- IL-6 targeted therapies (eg, tocilizumab)
- Cytotoxic Chemotherapy
- Biologic treatments such as anti-TNF $\alpha$  [tumor necrosis factor – alpha] antibodies

#### Objectives (copied from protocol)

##### Primary objective

- The primary objective of this study is to demonstrate that CNTO 328 in combination with BSC is superior to BSC in terms of durable tumor and symptomatic response among subjects with multicentric Castleman's disease (MCD).

##### Secondary objective

- To demonstrate additional measures of efficacy (tumor response; duration of response; time to treatment failure; change in hemoglobin levels; ability to discontinue corticosteroids; and improvement in fatigue, physical function, and other disease-related symptoms)
- To study the safety of prolonged dosing
- To determine the pharmacokinetics of CNTO 328 among subjects with MCD
- To determine a baseline hepcidin value predictive of a  $\geq 2$  g/dL increase in hemoglobin

#### Inclusion Exclusion Criteria (copied from protocol)

##### Inclusion Criteria:

- Measurable and symptomatic MCD proven by biopsy and confirmed by central pathology review. Symptomatic disease is defined clinically by the presence of symptoms with NCI-CTCAE grading  $\geq 1$  that are attributable to the disease, and for which treatment is indicated. [See Table 64 in Appendix 9.5] Subjects are required to have measurable disease, which may not 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 do not qualify as symptomatic disease.
- $\geq 18$  years of age

- Pretreatment clinical laboratory values meeting these criteria within 4 weeks before treatment:
  - Absolute neutrophil count (ANC)  $\geq 1.0 \times 10^9/L$
  - Platelets  $\geq 75 \times 10^9/L$
  - ALT within 2.5 x ULN; total bilirubin within 2.5 x ULN; unfractionated alkaline phosphatase within 2.5 x ULN; if unfractionated alkaline phosphatase is above 2.5 x ULN, subjects will be eligible if alkaline phosphatase liver fraction is with 2.5 x ULN
  - Serum creatinine  $\leq 3.0$  mg/dL
- ECOG Performance Status of 0, 1, or 2
- Corticosteroids dose that does not exceed 1 mg/kg/day of prednisone (or equivalent); and has remained stable or decreased over the 4 weeks before randomization

Exclusion Criteria:

- HIV or HHV-8 positive
- Skin lesions as sole measurable manifestation of MCD
- Previous lymphoma
- Malignancies, except for adequately treated basal cell or squamous cell carcinoma of the skin, carcinoma *in situ* of the cervix, or cancer other than lymphoma, from which the subject has been disease-free for  $\geq 3$  years.
- Concurrent medical condition or disease (eg, autoimmune disease, active systemic infection, uncontrolled diabetes, acute diffuse infiltrative pulmonary disease) that is likely to interfere with study procedures or results, or that in the opinion of the investigator would constitute a hazard for participating in this study
- Prior exposure to agents targeting IL-6 or the IL-6 receptor
- Use of disallowed therapies: other concomitant anti-tumor therapies for Castleman's disease (eg, anti-CD20 antibodies, IL-6- or IL-6 receptor-targeted therapies, chemotherapy), biologic treatments such as anti-tumor necrosis factor- $\alpha$  (TNF $\alpha$ ) antibodies, immunosuppressive agents (except stable doses of corticosteroids), and erythropoietin stimulating agents (ESAs)
- Received an investigational drug (including vaccines), ESAs, or any systemic treatment for Castleman's disease within 4 weeks (or in the case of rituximab, within 8 weeks) before the planned start of treatment
- Major surgery within 4 weeks of treatment
- History of uncontrolled heart disease such as unstable angina, congestive heart failure, myocardial infarction within preceding 12 months, hemodynamic instability or known left ventricular ejection fraction (LVEF)  $< 30\%$ , or clinically significant rhythm or conduction abnormality
- Clinically significant infections, including known hepatitis C infection or known to be hepatitis B surface antigen (HBsAg) positive
- History of allogeneic transplant (except corneal transplants)
- Known, unmanageable severe infusion related reactions to monoclonal antibodies or to murine, chimeric, or human proteins or their excipients

- Pregnant or nursing
- Vaccination with live, attenuated vaccines within 4 weeks of first administration of study agent
- Paraneoplastic pemphigus or bronchiolitis obliterans
- Any condition that, in the opinion of the investigator, would compromise the well being of the subject or the study or prevent the subject from meeting or performing study requirements

#### REVIEWER COMMENT

##### Eligibility of Patients

There is documentation in the data sets that all randomized subjects but one met inclusion criteria fulfilling the definition of measurable and symptomatic MCD. A second patient was ineligible because of treatment with 6 mercaptopurine.

##### Statistical Analysis Plan

The statistical analysis plan dated 3/6/13 was reviewed by the statistical reviewer and team leader 3/27/13.

##### *Trial Design*

This is a randomized, double-blind, placebo-controlled study to determine the efficacy and safety of siltuximab given in combination with best supportive care in subjects with MCD.

Approximately 78 subjects will be randomly assigned in a 1:2 randomization scheme to one of the treatments below:

- Placebo + best supportive care (26 subjects)
- Siltuximab + best supportive care (52 subjects)

The study is stratified by concomitant corticosteroid use at study start.

##### *Study Endpoints*

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

- 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
- PR: a  $\geq 50\%$  decrease in the sum of the product of the diameters 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.

The secondary endpoints are:

- Duration of tumor and symptomatic response, defined as the time from the first tumor and symptomatic response to treatment failure. Responders who have not

had a treatment failure at the time of unblinding will be censored to the last disease assessment (the later of the last radiologic assessment and the last symptom assessment) prior to unblinding.

- Tumor response, defined as a CR or a PR according to the modified Cheson criteria. [Cheson 2007]
- Duration of tumor response, defined as the time from the first documented tumor response to disease progression. Responders who have not had a progression of disease at the time of unblinding will be censored to the last disease assessment prior to unblinding.
- Treatment failure defined as any one of the following:
  - Radiologic progression, as measured by modified Cheson criteria, [positron-emission tomography [PET] scan data, if obtained, will not be taken into Account]: defined as a  $\geq 50\%$  increase in the sum of the product of the diameters (SPD) of index lesion(s) compared with nadir, or at least 1 new lesion that has been confirmed and measures  $> 1.5$  cm in longest dimension. Malignant transformation in a previously defined mass will also be considered progressive disease (PD). For skin lesions, progression is defined as a  $\geq 50\%$  increase in the SPD of index lesion(s) compared with nadir, or at least 1 new lesion that has been confirmed and measures  $> 1.5$  cm in longest dimension. Initiation of any other therapy intended to treat MCD
  - A sustained increase from baseline in disease-related symptoms  $\geq$  Grade 2 persisting for at least 3 weeks despite BSC. This is not applicable to non-debilitating symptoms such as an increase to NCI-CTCAE Grade 2 in anorexia: "Oral intake altered without significant weight loss or malnutrition; oral nutritional supplements indicated", hyperhidrosis: "Involving  $> 1$  site; patient seeks medical intervention; associated with psychosocial impact", or to non-clinically significant laboratory abnormalities.
  - Onset of any new disease-related  $\geq$  Grade 3 symptom despite BSC
  - Sustained (ie, at least 3 weeks) deterioration in performance status (increase from baseline in Eastern Cooperative Oncology Group [ECOG] Performance Status by more than 1 point) despite BSC
- Time to treatment failure, defined as the time from randomization until the subject fails treatment. Subjects who have not failed at the time of unblinding will be censored to the last disease assessment prior to unblinding.
- Increase in hemoglobin at Week 13 of 15 g/L or more, defined as an increase in hemoglobin at Week 13 of 15 g/L or more over baseline.
- Time to improvement in the Multicentric Castleman's Disease Symptom Scale (MCD-SS) total score, defined as the time from randomization to the time at which the MCD-SS total score decreases by  $\geq 1$  point compared with the baseline score. If a subject has not improved by the time of unblinding they will be censored back to the last MCD-SS assessment prior to unblinding.

- Time to improvement in the Functional Assessment of Chronic Illness Therapy (FACIT-F) fatigue score, defined as the time from randomization to the time at which the FACIT-F fatigue score increases by  $\geq 3$  points compared with the baseline score. If a subject has not improved by the time of unblinding they will be censored back to the last FACIT-F assessment prior to unblinding.
- Time to improvement in the Short Form (36) Health Survey (SF-36) physical component score (PCS), defined as the time from randomization to the time at which the SF-36 physical component score increases by  $\geq 5$  points compared with the baseline score. If a subject has not improved by the time of unblinding they will be censored back to the last SF-36 assessment prior to unblinding.
- Increase in hemoglobin at Week 13 of 20 g/L or more, defined as an increase in hemoglobin at Week 13 of 20 g/L or more over baseline.
- Change from baseline for hemoglobin, defined as the maximum change from baseline in the absence of transfusion.
- Discontinuation of corticosteroids, defined as those subjects who were on corticosteroids at baseline that were corticosteroid free for at least 9 consecutive weeks during the blinded treatment period.

#### *Hierarchy of Testing of Select Major Secondary Endpoints*

In the event that the primary endpoint is statistically significant, the following major secondary endpoints will 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 Hb 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

#### 6.1.2 Demographics

The demographics of the subjects enrolled on trial CNTO328MCD2001 (intent to treat (ITT) population) are presented in Table 23 below:

**Table 23: Demographics of the ITT Population in Trial CNTO328MCD2001**

<b>Demographics</b>			
	<b>Siltuximab n=53</b>	<b>Placebo n=26</b>	<b>Total n=79</b>
<b>Gender n (%)</b>			
<b>Male</b>	30 (57)	22 (85)	52 (66)
<b>Female</b>	23 (43)	4 (15)	27 (34)
<b>Age in Years</b>			
<b>Mean</b>	44	48	45
<b>Median</b>	47	48	48
<b>Range</b>	20 to 74	27 to 78	20 to 78
<b>Race Ethnicity n (%)</b>			
<b>Asian</b>	27 (51)	11 (42)	38 (48)
<b>White</b>	16 (30)	11 (42)	27 (35)
<b>White/Hispanic or Latino</b>	3 (5)	1 (4)	4 (5)
<b>Black or African American</b>	3 (5)	0	3 (4)
<b>Hispanic or Latino</b>	1 (2)	1 (4)	2 (3)
<b>Native Hawaiian or Pacific Islander</b>	1 (2)	1 (4)	2 (3)
<b>American Indian Alaska Native</b>	1 (2)	0	1 (1)
<b>Other or Unknown</b>	1 (2)	1 (4)	2 (3)
<b>Region n (%)</b>			
<b>Asia Pacific</b>	26 (49)	11 (42)	37 (47)
<b>Europe (EMEA) (includes Egypt, Israel, and Russia)</b>	13 (25)	8 (31)	21 (27)
<b>North America</b>	10 (19)	5 (19)	15 (19)
<b>Latin America</b>	4 (7)	2 (8)	6 (7)

The clinical characteristics of the ITT population enrolled on trial CNTO328MCD2001 are presented in Table 24.

**Table 24: Clinical Characteristics of the ITT Population in Trial CNTO328MCD2001**

<b>Clinical Characteristics</b>			
	<b>Siltuximab n=53</b>	<b>Placebo n=26</b>	<b>Total n=79</b>
<b>Time from diagnosis (years)</b>			
<b>Mean</b>	1.8	2.8	2.2
<b>Median</b>	0.6	1.1	0.7
<b>Range</b>	0.1 to 12.5	0.1 to 16.6	0.1 to 16.6
<b>Pathologic Subtype of Castleman's Disease by Central Review n (%)</b>			
<b>Hyaline Vascular</b>	18 (34)	8 (31)	26 (33)
<b>Plasmacytic</b>	13 (25)	5 (19)	18 (23)
<b>Mixed</b>	22 (41)	13 (50)	35 (44)
<b>Castleman's Disease-associated Baseline Symptoms</b>			
<b>Number of Baseline Castleman's Disease-associated Symptoms Documented</b>			
<b>1-5</b>	31 (58)	8 (31)	39 (49)
<b>6-10</b>	17 (32)	15 (58)	32 (41)
<b>&gt;10</b>	5 (10)	3 (11)	8 (10)
<b>Elements of POEMS Syndrome Symptoms</b>			
<b>Peripheral Neuropathy</b>	18 (34)	13 (50)	31 (39)
<b>Organomegally</b>	8 (15)	6 (23)	14 (18)
<b>Endocrine Abnormalities</b>	9 (12)	5 (19)	13 (16)
<b>Skin (including pruritis)</b>	23 (43)	18 (69)	41 (52)
<b>Organomegally</b>			
<b>Liver</b>	5 (9)	5 (19)	10 (13)
<b>Spleen</b>	7 (13)	3 (12)	10 (13)
<b>Autoimmune Disorders</b>			
<b>Autoimmune disorder</b>	4 (8)	2 (8)	6 (8)
<b>Fluid Retention and Effusions</b>			
<b>Edema (any)</b>	15 (28)	16 (62)	31 (39)
<b>Ascites</b>	2 (4)	2 (8)	4 (5)
<b>Pericardial Effusion</b>	0	2 (8)	2 (3)
<b>Pleural Effusion</b>	5 (9)	3 (12)	8 (10)
<b>Edema and or Effusion</b>	17 (32)	17 (65)	34 (43)
<b>Constitutional Symptoms</b>			
<b>Fatigue</b>	47 (89)	21 (81)	68 (86)
<b>Malaise</b>	33 (62)	15 (58)	48 (61)
<b>Nightsweats/Hyperhydrosis</b>	29 (55)	17 (65)	46 (58)
<b>Anorexia</b>	23 (43)	6 (23)	29 (37)
<b>Pruritis</b>	17 (32)	12 (46)	29 (37)
<b>Dyspnea</b>	17 (32)	11 (42)	28 (35)
<b>Weight Loss</b>	16 (30)	8 (31)	24 (30)
<b>Tumor Pain</b>	12 (23)	7 (27)	19 (24)
<b>Fever</b>	9 (17)	4 (15)	13 (14)

### 6.1.3 Subject Disposition

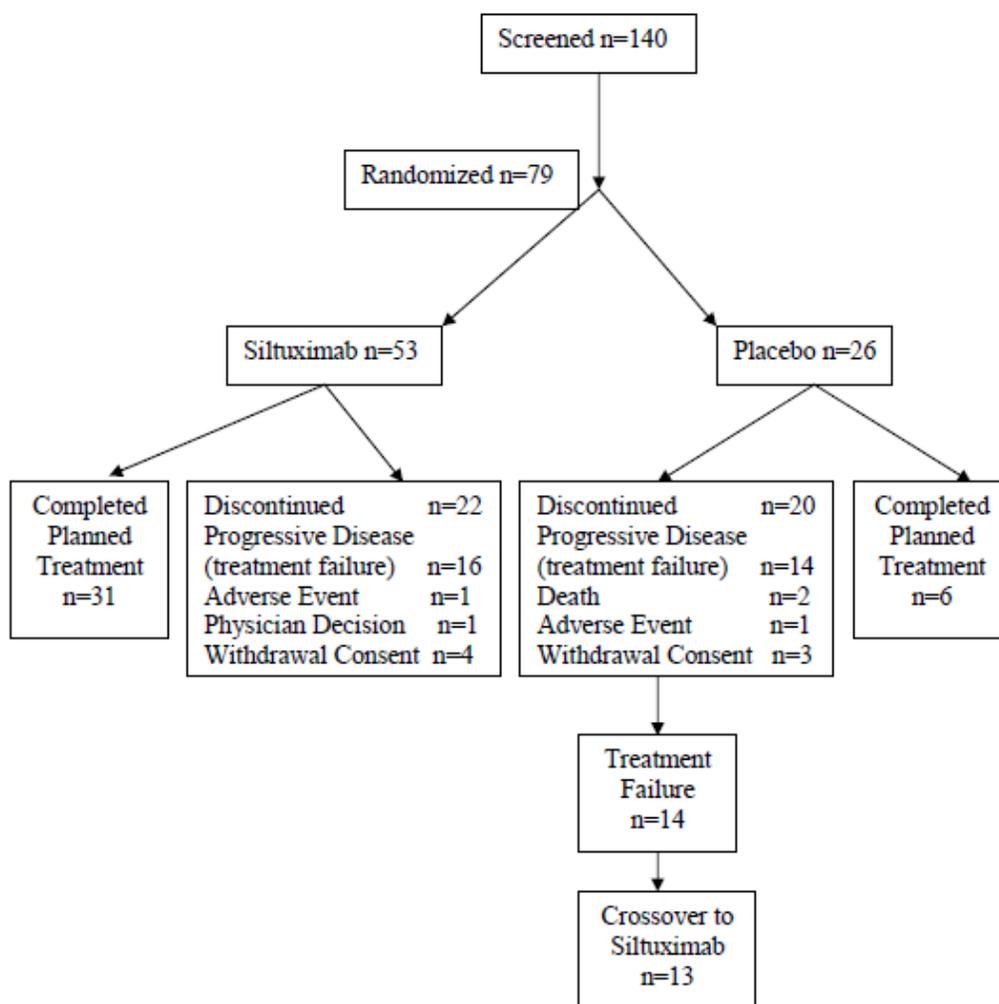
One-hundred and forty subjects were screened for this study; 59 subjects did not meet the study selection criteria at screening. One ineligible subject who was treated with 6 mercaptopurine (CNTO328MCD2001-8605-00103) was randomized. Five subjects withdrew consent prior to randomization. The ITT population includes the 79 randomized subjects.

#### Blinded Treatment Period

The study allowed crossover from placebo to siltuximab after subjects met the criteria for treatment failure.

The disposition of subjects during the blinded treatment period is summarized in Figure 4 below.

**Figure 4: Disposition of Subjects During Blinded Phase of Therapy**



Exposure to Siltuximab

**Table 25: Exposure of Subjects in CNTO328MCD2001 to Siltuximab**

<b>Exposure to Siltuximab in CNTO328MCD2001</b>			
	<b>Randomized Siltuximab Siltuximab Treatment n=53</b>	<b>Randomized Placebo Placebo Treatment n=26</b>	<b>Randomized Placebo Siltuximab Treatment n=13</b>
<b>Courses (Doses)</b>			
<b>Mean</b>	21	11	19
<b>Median</b>	19	8	15
<b>Range</b>	1 to 50	2 to 32	6 to 40
<b>Months</b>			
<b>≥ 6</b>	42	12	10
<b>≥ 12</b>	27	3	6
<b>≥ 24</b>	10	0	2
<b>Mean</b>	14	7	13
<b>Median</b>	12	5	10
<b>Range</b>	<1 to 34	<1 to 22	4 to 28

6.1.4 Analysis of Primary Endpoint(s)

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 (eg, pleural effusion) and resolution of baseline symptoms attributed to MCD, sustained for at least 18 weeks
- PR: a ≥ 50% decrease in the sum of the product of the diameters 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.

REVIEWER COMMENT

Evaluation of the data documented in the case report forms (CRFs) and the data in the dataset ADEF of 8 subjects supported the integrity of the classification of subjects for this endpoint.

Results:

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).

6.1.5 Analysis of Secondary Endpoints(s)

The statistical analysis plan specified the following hierarchy of testing of secondary endpoints:

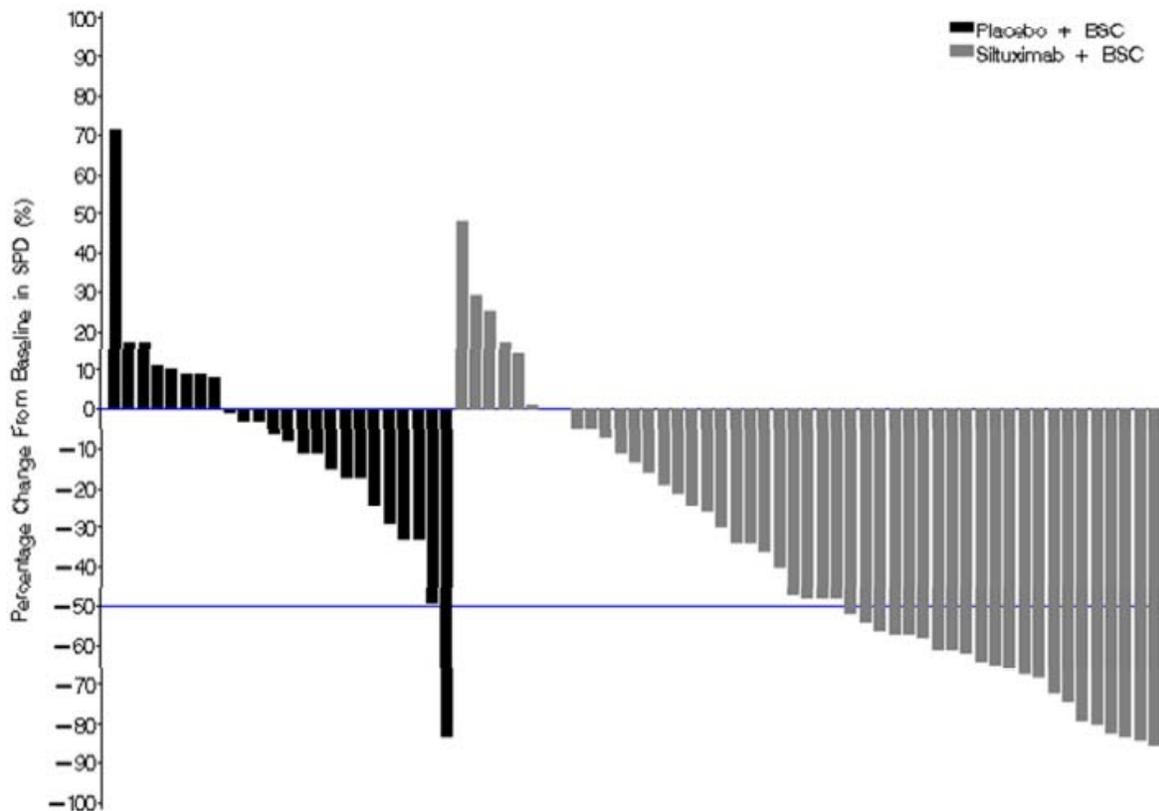
- Tumor response

- Time to treatment failure
- Increase in Hb 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

### Results Tumor Response

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 waterfall plot is presented as Figure 5. (copied from submission Study Report CNTO328MCD2001 page 91/766)

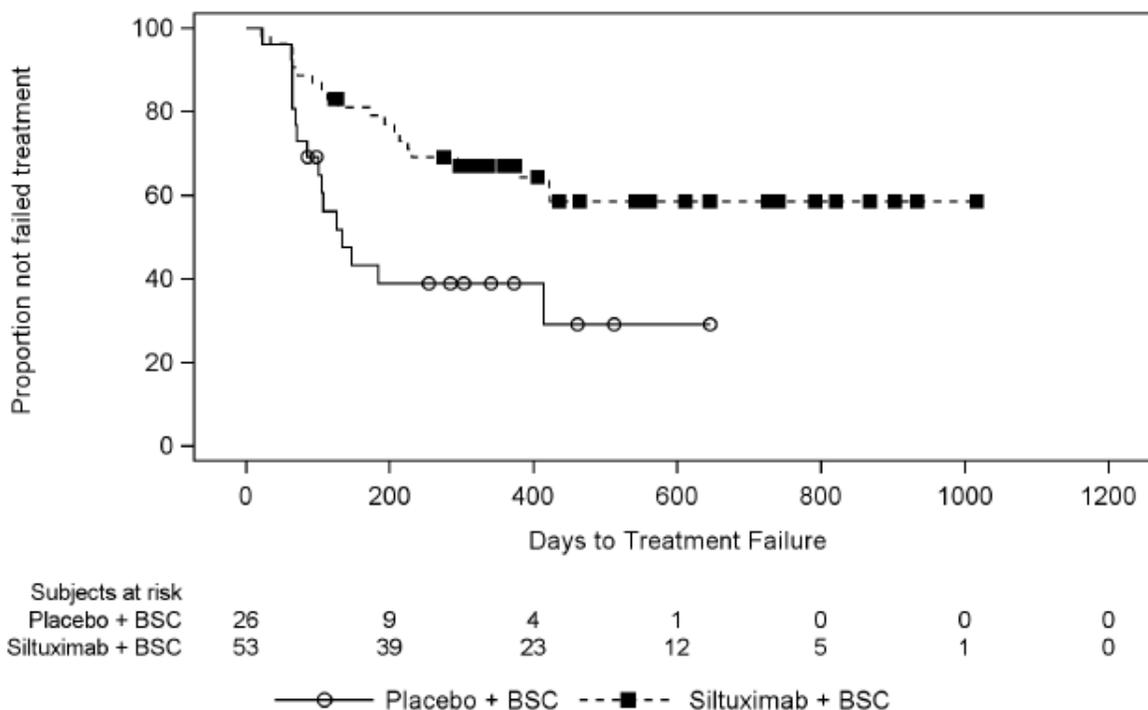
**Figure 5: Waterfall Plot of Tumor Response During the Blinded Treatment Period**



### Results Time to Treatment Failure

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;  $p < 0.05$ )). The Kaplan Meier analysis is presented in Figure 6. (copied from submission Study Report CNTO328MCD2001 page 96/766)

**Figure 6: Time to Treatment Failure During the Blinded Treatment Period**



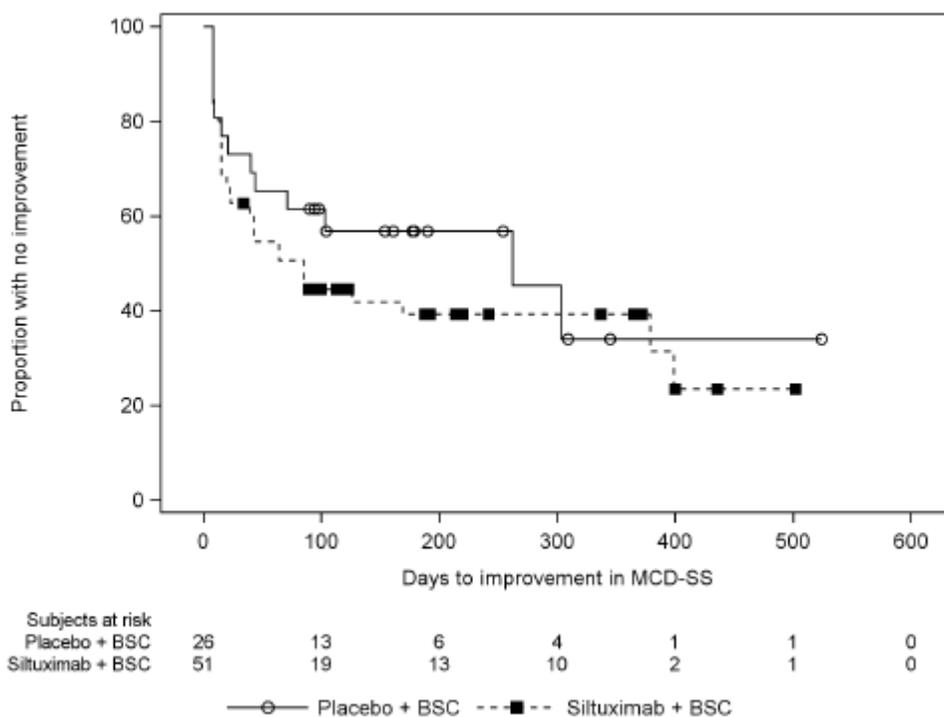
### Results Hemoglobin Week 13

This endpoint was defined as an increase in Hb at Week 13 (~day 91) of 15 g/L (1.5 g/dL) or more over baseline in patients who were anemic at study entry. There were no responders in the placebo arm and 19 responders in the siltuximab arm. The difference of Hb 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 ( $p < 0.05$ ).

### Time-to-improvement in the MCD-SS Total Score

Thirty-two subjects (63%) in the siltuximab group and 13 subjects (50%) in the placebo group achieved the threshold value of improvement ( $\geq 1$  point decrease in the MCD-SS score). The median time to improvement in MCD-SS total score was 85 days (95% CI of median: 22, 379) in the siltuximab arm and 262 days (95% CI of median: 40, NE) in the placebo arm (HR=1.373;  $p= 0.3372$ ). Kaplan Meier analysis of time to improvement in the MCD-SS total score is presented in Figure 7. (copied from submission Study Report CNT0328MCD2001 page 126/766)

**Figure 7: Improvement of MCD-SS Score During the Blinded Treatment Period**



**REVIEWER COMMENT**

(Copied from statistical review)

MCD-SS provides symptom assessments by patient. The result of time to symptom improvement based on MCD-SS total score was supportive of the primary endpoint, but not statistically significant. The reasons for the non-significant result may be related to: lack of symptoms at baseline for an improvement (mean MCD-SS total score at baseline: 2.0, range: 0-6.5, with 10 being the maximum achievable score), missing assessments, small sample size, and mixing specific domain with general domain items in the total score calculation.

Time-to-improvement in the FACIT-F Fatigue Score

Forty-one subjects (79%) in the siltuximab group and 21 subjects (81%) in the placebo group achieved a ≥ 3-point increase in FACIT-F scores during the double-blind treatment period. The median time to improvement was 15 days (95% CI of median: 8, 23) in the siltuximab group and 22 days (95% CI of median: 8, 64) in the placebo group. (HR=1.047; p=0.8627).

Discontinuation of Corticosteroids

There was a trend towards more corticosteroid discontinuation in the siltuximab group compared with the placebo group: 31% versus 11% of subjects, respectively.

REVIEWER COMMENT

The secondary endpoint controlled that demonstrated statistically significant results were

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

The following endpoints were not significant

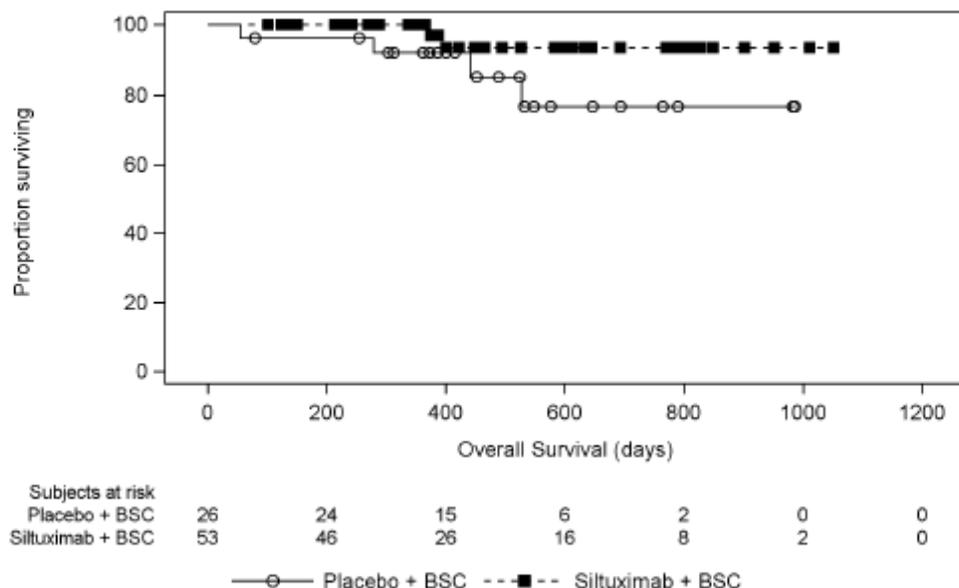
- Time-to-improvement in the MCD-SS total score
- Time-to-improvement in the FACIT-F fatigue score
- Discontinuation of corticosteroids

6.1.6 Other Endpoints

Overall Survival

At the time of analysis, overall survival (OS) data were not mature. The 1-year survival rate was 100% in the siltuximab group and 92% in the placebo group. Two subjects (4%) in the siltuximab group died due to disease progression after treatment had been discontinued (248 and 391 days after the last dose of siltuximab). Four subjects (15%) in the placebo group died; 1 subject had an adverse event (AE) of bronchopneumonia and cardiac failure that led to death. Two subjects died due to disease progression; 1 subject died of development of MDS. See Section 7.3.1. Kaplan Meier analysis of OS is presented in Figure 8. (copied from submission Study Report CNTO328MCD2001 page 114/766)

Figure 8: Overall Survival



Durable Symptomatic Response

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. The durable symptomatic response rate was 57% in the siltuximab group and 19% in the placebo group.

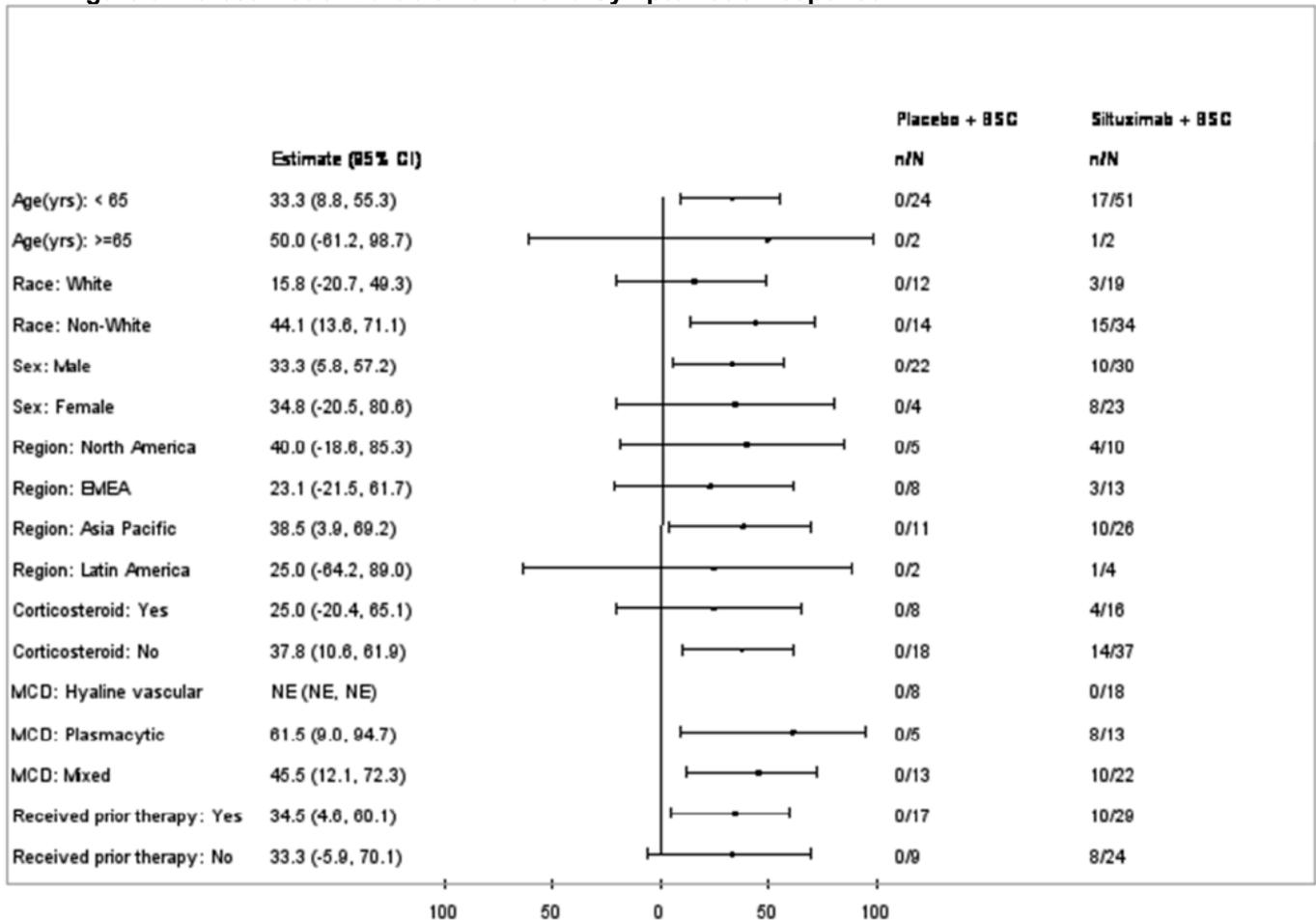
### 6.1.7 Subpopulations

#### Durable Tumor and Symptomatic Response (primary endpoint)

The Forest plot in Figure 9 (copied from the submission 5.3.5.1 Study Report CNTO328MCD2001 page 119/766) summarizes subgroup analysis. The prespecified Groups included:

- Sex (female, male)
- Race (Caucasian, Non-Caucasian)
- Region (North America, EMEA, Asia Pacific, Latin America)
- Age (less than 65, greater than or equal to 65)
- Baseline corticosteroid use (Yes, No)
- MCD histology by independent review (Hyaline vascular, Plasmacytic, Mixed)
- Received prior systemic therapy (Yes, No)

**Figure 9: Forest Plot of Durable Tumor and Symptomatic Response**



#### REVIEWER COMMENT

The treatment effect favored siltuximab in all groups with the exception of hyaline vascular histologic subtype. There is some evidence of activity of siltuximab in the hyaline vascular subtype, although most of the evidence of activity is supported by investigator assessment not by independent review.

- Durable symptomatic response (CR/PR)
  - siltuximab - 33% (6/18)
  - placebo - 13% (1/8)
- Durable tumor and symptomatic response by investigator assessment
  - siltuximab - 17% (3/18)
  - placebo - 0% (0/8)
- Hb increase from baseline at week 13
  - siltuximab - 17% (3/18)
  - placebo - 0% (0/8)
- Median time to treatment failure
  - siltuximab - 206 days
  - placebo - 70 days

#### REVIEWER COMMENT

Although these are not robust results, given the safety profile of siltuximab, (b) (4) as there is some evidence of activity in patients with this subtype. However, the discussion of efficacy in the label should include information on the limitations in the data supporting use of siltuximab in this subset.

#### 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The dose of 11 mg/kg every 3 weeks is acceptable for the following reasons.

- The dose is associated with suppression of CRP, a pharmacodynamic marker of active disease.
- The dose of 12 mg/kg did not exceed the MTD in C0328T03 the phase 1 study in hematologic malignancies.
- The dose demonstrated efficacy and an acceptable safety profile in the CNT0328MCD2001 trial.

#### 6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Evidence of persistent efficacy of prolonged treatment is supported by the interim results of CNT0328MDC2002, the extension study. See Section 5.3.2.

#### 6.1.10 Additional Efficacy Issues/Analyses

In addition to the response rate observed in Castleman's disease patients in the C0328T03, the dose finding trial of siltuximab in patients with hematologic malignancies,

activity was also observed in the placebo patients in the CNTO328MCD2001 trial who crossed over to siltuximab.

Of the 14 patients assigned to the placebo arm determined to experience treatment failure, 13 were subsequently treated with siltuximab. The median number of doses of siltuximab administered to these subjects was 15 (range 6 to 40). The response to treatment is presented in Table 26. Three patients were determined to have disease progression 2 based on radiologic progression and 1 due to sustained progression of Castleman’s disease symptoms.

**Table 26: Response Evaluation of Patients Assigned to Placebo Who Crossed-over to Siltuximab**

Response Evaluation of Placebo Patients Who Crossed-over to Siltuximab					
n=13	PR	SD (≥18 wks)	SD (<18 wks)	SD	PD
Durable tumor and symptomatic response (independent)	1 (8%)	6 (46%)	4 (31%)		2 (15%)
Durable tumor and symptomatic response (investigator)	3 (23%)	5 (38%)	4 (31%)		1 (8%)
Best tumor response (independent)	2 (15%)			9 (69%)	2 (15%)
Best tumor response (investigator)	4 (31%)			9 (69%)	

## **7 Review of Safety**

### **Safety Summary**

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.

## 7.1 Methods

### 7.1.1 Studies/Clinical Trials Used to Evaluate Safety

**Table 27: Clinical Trials Used to Evaluate Safety**

<b>Summary of Clinical Studies Reviewed to Evaluate Safety</b>			
<b>Protocol Number Location in Review</b>	<b>Report Type</b>	<b>Title</b>	<b>Comment</b>
<b>Castleman's Disease</b>			
CNTO328MCD2001  Review Section 6 Safety Section 7	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  Review Section 5.3.1 Safety Section 7	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 (37)
CNTO328MCD2002 Review Section 5.3.2 Safety Section 7.5.2	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
<b>Healthy Volunteers</b>			
C0328T08  Review Section 5.3.3 Safety Section 7	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
<b>Hematologic Malignancies Other Than Castleman's Disease</b>			
C0328T06  Review Section 5.3.4 Safety Section 7	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 Placebo n=139
CNTO328MMY2001  Review Section 5.3.5 Safety Section 7	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 n=53 VMP+siltuximab 11 mg/kg q3 wk n=64
CNTO328MDS2001  Review Section 5.3.6 Safety Section 7	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

### 7.1.2 Categorization of Adverse Events

The original terms used in the CRFs by investigators to identify AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version [15.1]. All reported AEs with onset during the treatment phase (that is treatment-emergent AEs) were included in the analysis.

The verbatim term, AETERM, and the MedDRA preferred term, AEDECOD, of AEs reported for CNTO328MCD2001, the randomized trial of MCD were compared. On initial review the mapping of verbatim terms to MedDRA preferred terms appeared to be appropriate. However, during the review of the application it was noted that AEs of elevated liver enzymes were mapped to the preferred term “hepatic function abnormal” in the system organ classification (SOC) of “hepatobiliary disorders.” Transaminases are not a measure of hepatic function. These AEs should be mapped to the preferred terms “alanine aminotransferase increased” or “aspartate aminotransferase increased” in the SOC of “investigations.” The verbatim term “creatinine higher than normal” was incorrectly mapped to the preferred term renal impairment.

### 7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

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 treated with siltuximab. My review will concentrate on 7 studies.

Three studies included patients with MCD.

- C0328T03, phase 1 trial hematologic malignancies provides dose finding provides safety information for siltuximab as monotherapy.
- CNTO328MCD2001, the randomized trial for MCD provides the most relevant information for this application regarding safety in the MCD population and will be the major focus of the risk benefit analysis.
- CNTO328MCD2002, the MCD extension study provides the evidence that that chronic administration of siltuximab is safe and feasible in this population. Siltuximab is a symptomatic treatment for the IL-6 mediated symptoms of MCD, and therefore will be a chronically administered treatment for patients who respond.

One study involved normal healthy volunteers.

- C0328T08, the bioequivalence trial in healthy volunteers provides safety information regarding the incidence and grade of AEs associated with siltuximab administration in an asymptomatic population.

Three additional studies will be reviewed. These include 2 randomized trials of siltuximab in combination with chemotherapy in MM, and a study in MDS.

- C0328T06, the randomized trial with bortezomib in MM
- CNTO328MMY200, the open label randomized trial with VMP in MM
- CNTO328MDS2001, the randomized trial in MDS (Provides additional data on siltuximab as single agent therapy in another hematologic disease.)

## 7.2 Adequacy of Safety Assessments

### 7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The application includes data from 116 subjects with Castleman's disease 103 who were treated with siltuximab. These include 37 subjects enrolled on C0328T03, a phase 1 trial in subjects with hematologic malignancies, and 66 subjects enrolled on CNTO328MCD2001, the randomized trial in MCD, 53 randomized to siltuximab and 13 of 26 subjects randomized to placebo who crossed over to siltuximab in the trial. CNTO328MCD2001, the randomized trial includes comparative safety data during the randomized blinded phase of the trial.

The application also includes data supporting the safety of prolonged treatment with siltuximab.

The data supplied in this application is adequate to support the dose and duration of therapy in MCD, a rare condition.

### 7.2.2 Explorations for Dose Response

The effect of dose on the incidence and severity of AEs was not explored. Doses up to 12 mg/kg q 2 weeks did not exceed the MTD.

The dose effect on the efficacy of siltuximab was explored in the 37 treated subjects with Castleman's disease on C0328T03, the phase 1 trial. In this study 1 subject (1%) had a best response of CR, 11 subjects (30%) had a best response of PR, 3 subjects (8%) had unconfirmed PR, and 20 subjects (54%) had SD. There were 1 CR and 6 PRs (response rate 44%) in subjects treated with the siltuximab regimen of 12 mg/kg every 3 weeks. This was nominally better than the response rate of 2 PRs (response rate 17%) in subjects treated with the siltuximab regimen of 9 mg/kg every 3 weeks. See Table 28 below copied from the submission 5.3.3.2 C0328T03 Study Report page 92/1177. The dose carried forward to the randomized trial was 11 mg/kg every 3 weeks.

**Table 28: Best Overall Response in Subjects with Castleman’s Disease on C0328T03 Phase 1 Trial**

	CNTO 328						Combined
	3 mg/kg q2 weeks	6 mg/kg q2 weeks	9 mg/kg q3 weeks	12 mg/kg q3 weeks	6 mg/kg Weekly	12 mg/kg q2 weeks	
Treated subjects with Castleman's disease	1	2	12	16	3	3	37
<b>Best overall response</b>							
Complete response	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.3%)	0 (0.0%)	0 (0.0%)	1 (2.7%)
Partial response	0 (0.0%)	1 (50.0%)	2 (16.7%)	6 (37.5%)	0 (0.0%)	2 (66.7%)	11 (29.7%)
Unconfirmed complete response	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Unconfirmed partial response	0 (0.0%)	0 (0.0%)	2 (16.7%)	1 (6.3%)	0 (0.0%)	0 (0.0%)	3 (8.1%)
Stable disease	1 (100.0%)	1 (50.0%)	7 (58.3%)	8 (50.0%)	2 (66.7%)	1 (33.3%)	20 (54.1%)
Progressive disease	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (33.3%)	0 (0.0%)	1 (2.7%)
Nonevaluable	0 (0.0%)	0 (0.0%)	1 (8.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.7%)

### 7.2.3 Special Animal and/or In Vitro Testing

Not discussed in this review.

### 7.2.4 Routine Clinical Testing

See Section 7.4.2.

### 7.2.5 Metabolic, Clearance, and Interaction Workup

Not discussed in this review.

### 7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Tocilizumab, a mAb against the IL-6 receptor, has been approved in the United States and European Union for treatment of rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, and systemic juvenile idiopathic arthritis; and in Japan for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, and Castleman’s disease. The most common adverse reactions ( $\geq 5\%$ ) identified for tocilizumab include upper respiratory tract infection, nasopharyngitis, headache, hypertension, and increased ALT. Warning and Precautions include serious infections, gastrointestinal perforation, hypersensitivity reactions and need to avoid exposure to live vaccines.

### 7.3 Major Safety Results

#### 7.3.1 Deaths

#### CNT0328MCD2001 – Randomized trial Castleman’s disease

Table 29 below summarizes deaths on CNT0328MCD2001. There were no deaths within 30 days of exposure to siltuximab. None of the subjects who were randomized to placebo who died had crossed over to siltuximab. Subject 9721-00066 who died of disease progression was randomized to siltuximab and was only able to receive 1 dose of siltuximab due to an allergic reaction.

**Table 29: CNT0328MCD2001 Deaths**

Deaths CNT0328MCD2001							
ID	Arm	Gender Age	Histologic Type Castleman’s Disease	Months Primary Diagnosis to Study Entry	Days from First Dose to Death	Days from Last Dose to Death	Cause of Death
0102-00027	Placebo	Male 49 years	Hyaline Vascular	83	527	113	Progressive disease
0102-00047	Placebo	Female 60 years	Plasmacytic	2.5	278	14	Bronchopneumonia and CHF
3301-00029	Placebo	Male 78 years	Mixed	7	441	378	Myelodysplastic syndrome Progressive disease
5503-00073	Placebo	Female 44 years	Hyaline Vascular	1.3	55	32	Progressive disease
5503-00113	Siltuximab	Male 49 years	Hyaline Vascular	60	374	247	Progressive disease
9721-00066	Siltuximab	Male 49 years	Hyaline Vascular	1.4	391	391	Progressive disease

C0328T03 - Phase 1 trial in hematologic malignancies

Only 3 subjects died within 90 days of exposure to siltuximab. Details are presented in Table 30.

**Table 30: C0328T03 Deaths**

Deaths within 90 Days C0328T03						
ID	Diagnosis	Gender Age	Dose	Days First Dose to Death	Days Last Dose to Death	Comments Cause of Death
0102-00031	Diffuse Large B-Cell Lymphoma	Female 23 years	12 mg/kg every 3 weeks	14	14	Progressive disease
0105-00006	Multiple Myeloma	Male 57 years	6 mg/kg every 2 weeks	56	42	Siltuximab discontinued after 2 doses for renal impairment attributed to progressive disease not siltuximab.
0104-00002	Castleman's Disease	Male 50 years	6 mg/kg every 2 weeks	393	26	Received 17 administrations of siltuximab. Died of <i>Klebsiella pneumoniae</i> sepsis after subsequently cytotoxic therapy.

CNT0328MCD2002 - Castleman's disease extension study

There were no deaths.

C0328T08 - Bioequivalence trial in healthy volunteers

There were no deaths.

C0328T06 - Randomized trial with bortezomib and dexamethasone in relapsed multiple myeloma

Table 31 and

Table 32 below summarize clinical information on subjects who died within 30 day of study treatment not related to progressive disease. This trial included advanced stage MM. Subjects were treated with bortezomib and dexamthasone and randomized to placebo or siltuximab 6 mg/kg every 2 weeks. There were 139 subjects who received placebo and 163 subjects who received siltuximab (this included 20 non randomized subjects in the phase 2 feasibility population). There were 9 deaths in 139 (6%) placebo treated subjects compared to 13 deaths in 163 (8%) siltuximab treated subjects. Most deaths appear to be related to infections or bleeding complications. Siltuximab added to chemotherapy did not appear to increase risk of death.

Table 31: C0328T06 Deaths - Placebo

<b>Deaths on C0328T03 within 30 Days of Treatment Excluding Those Due to Progression -Placebo</b>					
<b>ID</b>	<b>Gender Age</b>	<b>Study Day Death</b>	<b>Days From Placebo Dose to Death</b>	<b>Days From Bortezomib Dose to Death</b>	<b>Comments Cause of Death</b>
3001-00010	Male 66 years	20	19	12	Grade 4 febrile neutropenia followed by fatal septic shock
3591-00004	Male 67 years	490	27	62	After recent complications including renal failure, anemia and thrombocytopenia subject experienced a fatal gastrointestinal hemorrhage
3591-00006	Male 50 years	534	5	113	Recent grade 2 anemia and grade 1 hepatosplenomegally subject died suddenly at home
3591-00010	Male 59 years	135	22	22	After recent complications of anemia and grade 4 thrombocytopenia subject died of subarachnoid hemorrhage
3591-00011	Female 57 years	6	5	5	After initial dose of bortezomib and placebo the subject died due to pulmonary edema
3591-00013	Male 67 years	4	3	4	Died suddenly after initial bortezomib and placebo therapy
3604-00010	Female 71 years	31	30	23	The subject developed bronchopneumonia and influenza and died of pneumonia
4406-00009	Male 60 years	158	31	10 (another dose on day of death)	The subject developed bronchopneumonia and died of bronchopneumonia and atelectasis
4802-00001	Male 66 years	62	9	9	The subject received reduced dose bortezomib and on day of treatment developed melena and subsequently pulmonary edema which led to death

**Table 32: C0328T06 Deaths – Siltuximab**

<b>Deaths on C0328T03 within 30 Days of Treatment Excluding Those Due to Progression – Siltuximab</b>					
<b>ID</b>	<b>Gender Age</b>	<b>Study Day Death</b>	<b>Days From Siltuximab Dose to Death</b>	<b>Days From Bortezomib Dose to Death</b>	<b>Comments Cause of Death</b>
1022-00006	Male 61 years	61	19	19	After recent complications including renal impairment, CHF, <i>Hemophilus influenza</i> bacteremia, pleural effusion subject died of a respiratory arrest.
3592-00008	Female 63 years	53	38	31	Subject was diagnosed with a meningioma day 22 of study and removed for study. Died of meningioma
3602-00001	Male 69 years	39	10	7	The subject developed grade 4 thrombocytopenia and subsequently died of sepsis
3603-00002	Male 70 years	38	9	6	The subject developed anemia requiring transfusion bronchopneumonia and subsequently died of cardiopulmonary failure
3604-00002	Male 77 years	32	31	28	The subject developed bronchopneumonia and was diagnosed with plasmacytic leukemia, with grade 4 thrombocytopenia. Subject died due to leukemia
4005-00004	Male 53 years	352	11	4	The subject developed lobar pneumonia died following day with ventricular fibrillation
4202-00004	Male 70 years	214	21	13	The subject developed bronchopneumonia and died of pneumonia
4803-00004	Female 71 years	119	27	24	The subjects was diagnosed with pneumonia, shock and renal failure and died 2 days later
4803-00008	Male 64 years	28	11	17	The subject developed pneumonia and subsequently died due to pulmonary edema
4804-00001	Male 64 years	62	14	4	The subject experience pancytopenia and an upper respiratory tract infection and subsequently died of cardiogenic shock
7005-00003	Female 57 years	23	22	12	The subject developed purulent otitis media, renal impairment and subsequently died of hemorrhagic stroke
7005-00005	Male 66 years	337	10	94	Sudden cardiac death
7015-00007	Female 77 years	178	16	13	The subject developed an upper respiratory infection and subsequently died of pulmonary embolism

CNTO328MMY2001 - Open label randomized trial with VMP in newly diagnosed multiple myeloma

Table 33 below summarizes clinical information on subjects who died within 30 day of study treatment not related to progressive disease. Subjects were randomized to VMP with and without siltuximab 11 mg/kg every 3 weeks. There were 53 subjects who received VMP and 64 subjects who received siltuximab and VMP (this included 12 non randomized subjects in the phase 2 feasibility population). There were 4 deaths in 53 (8%) VMP treated subjects compared to 6 deaths in 64 (9%) siltuximab and VMP treated subjects. Most deaths appear to be related to infections and siltuximab added to chemotherapy did not appear to increase risk of death.

**Table 33: CNTO328MMY2001 Deaths**

Deaths on CNTO328MMY2001 within 30 Days of Treatment Excluding Those Due to Progression						
ID	Gender Age	Arm	Study Day Death	Days From Siltuximab Dose to Death	Days From VMP to Death	Comments Cause of Death
4002-00099	Female 53 years	VMP	62		Bortezomib – 15 Melphalan – 15 Prednisone - 15	Subject developed pulmonary edema with a bronchopneumonia and died of cardiac arrest
4003-00100	Male 67 years	VMP	15		Bortezomib – 4 Melphalan – 11 Prednisone - 11	Subject developed bronchitis which progressed to bronchopneumonia subsequent gastrointestinal hemorrhage and progressed to shock and cardiopulmonary arrest
6501-00140	Male 75 years	VMP	82		Bortezomib – 15 Melphalan – 22 Prednisone - 22	Subject developed pneumonia, renal failure and encephalopathy and died of pneumonia
8205-00097	Female 66 years	VMP	143		Bortezomib – 30 Melphalan – 55 Prednisone - 55	Subject developed pneumonia, septic shock and ultimately died of pneumonia
3302-00139	Female 83 years	VMP Siltuxumab 11 mg/kg q 3 weeks	365	6	Bortezomib – 6 Melphalan – 24 Prednisone - 24	Subject died of bronchopneumonia
3402-00017	Female 79 years	VMP Siltuxumab 11 mg/kg q 3 weeks	106	21	Bortezomib – 14 Melphalan – 18 Prednisone - 18	Subject died septic shock
3402-00031	Female 67 years	VMP Siltuxumab 11 mg/kg q 3 weeks	153	8	Bortezomib – 9 Melphalan – 6 Prednisone - 6	Subject committed suicide
3903-00081	Female 70 years	VMP Siltuxumab 11 mg/kg q 3 weeks	260	28	Bortezomib – 70 Melphalan – 46 Prednisone - 46	Subject developed <i>Klebsiella</i> infection with respiratory failure and subsequent cardiac arrest
8203-00084	Female 72 years	VMP Siltuxumab 11 mg/kg q 3 weeks	67	16	Bortezomib – 6 Melphalan – 13 Prednisone - 13	Subject developed pneumonia, renal failure and subsequently died due to the pneumonia
9101-00113	Male 79 years	VMP Siltuxumab 11 mg/kg q 3 weeks	18	18	Bortezomib – 6 Melphalan – 14 Prednisone - 14	Subject died of bronchopneumonia

CNT0328MDS2001 - Randomized trial in myelodysplastic syndrome

This was a randomized trial comparing best supportive care with siltuximab or placebo in subjects with low to intermediate risk myelodysplastic syndrome. There were 50 subjects on the siltuximab arm and 26 subjects on the placebo arm. Two subjects died due to myelodysplastic syndrome that transformed to acute myelogenous leukemia, one in each arm. In retrospect the leukemic transformation had occurred at the time of study entry.

REVIEWER COMMENT

The analysis of deaths in these trials supports safety of this agent. Siltuximab did not appear to contribute to the death of any patients.

7.3.2 Nonfatal Serious Adverse Events

CNT0328MCD2001 – Randomized trial Castleman’s disease

During the randomized blind portion of the trial, nonfatal treatment emergent serious adverse event (SAE) occurred in 12 of 53 (23%) subjects in the siltuximab arm and 3 of 26 (12%) subjects in 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 AEs. Therefore the incidence of non-fatal SAEs 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 SAEs. The incidence of nonfatal SAEs is presented in Table 34 based on SOC. No specific type of SAE appears to be associated with siluximab therapy in patients with MCD. Infections were the most frequently reported nonfatal SAEs in this study. Details regarding infections are presented in Table 35.

**Table 34: CNTO328MCD2001 Nonfatal Serious Adverse Events**

CNTO328MCD2001 Nonfatal Serious Adverse Events			
SOC n (%)	Siltuximab n=53	Placebo n=26	Total n=79
Infections and infestations	5 (9)	2 (8)	7 (9)
Respiratory, thoracic and mediastinal disorders	1 (2) Pleural Effusion	2 (8) Dyspnea (n=2)	3 (4)
Gastrointestinal disorders	1 (2) Umbilical hernia	1 (4) Dysphagia	2 (3)
General disorders and administration site conditions	1 (2) Edema	1 (4) Edema	2 (3)
Hepatobiliary disorders	2 (4) Cholelithiasis Cholecystitis chronic *	0	2 (3)
Injury, poisoning and procedural complications	2 (4) Wound Secretion Tibia fracture	0	2 (3)
Endocrine disorders	1 (2) Hyperthyroidism	0	1 (1)
Eye disorders	1 (2) Vitreous hemorrhage	0	1 (1)
Immune system disorders	1 (2) Anaphylactic reaction	0	1 (1)
Musculoskeletal and connective tissue disorders	1 (2) Muscle spasms	0	1 (1)
Renal and urinary disorders	1 (2) Dysuria/Renal colic/ Ureteral disorder (2)**	0	1 (1)
Vascular disorders	0	1 (4) Hypertensive crisis	1 (1)

\*Reported twice in a single patient day 42 and day 190

\*\*Reported 4 separate occasions in a single patient day 63, day 233, day 428, and day 435

**Table 35: CNTO328MCD2001 Nonfatal Serious Adverse Events – Infections**

CNTO328MCD2001 Nonfatal Serious Adverse Events - Infections							
ID	Gender Age	Arm	Infection	Grade	Day on Study	Day from Last Exposure	Comment
0102-00027	Male 49 years	Placebo	Pneumonia	3	438	24	Placebo discontinued day 442 after this event because subject was diagnosed with a T-cell lymphoma.
4402-00054	Male 47 years	Placebo	Lung infection	3	121	8	PCR positive for rhinovirus; Continued further placebo therapy after this event.
4402-00050	Female 64 years	Siltuximab	Anal abscess	3	93	29	After treatment in hospital of the abscess the infection was considered adequately improved for the subject to received continued siltuximab.
4402-00063	Male 52 years	Siltuximab	Lower respiratory tract	3	22	22	The infection was treated with multiple antibiotics and after a week delay siltuximab was restarted.
4402-00063	Male 52 years	Siltuximab	Lower respiratory tract	3	113	21	The infection was treated with multiple antibiotics. Infection suspected to be rhinovirus and bacterial. Siltuximab was restarted.
8521-00087	Female 30 years	Siltuximab	Sepsis	3	21	21	The infection was treated with cephalosporin; the subject continued to receive subsequent siltuximab.
8604-00097	Female 48 years	Siltuximab	Bronchitis	3	20	20	The infection was treated with levofloxacin and ambroxol hydrochloride and after a week delay siltuximab was restarted.

#### C0328T03 - Phase 1 trial in hematologic malignancies

There were 67 subjects who received siltuximab on this trial; 17 experienced nonfatal serious treatment emergent AEs that occurred within 30 days of exposure to siltuximab. Infections were the most common. These included: bacteremia / sepsis (n=5), cellulitis (n=3), abscess (n=3), device related infection (n=2), pneumonia, upper respiratory tract infection, pyelonephritis, wound infection. There were 7 respiratory events in 6 subjects: pleural effusion (n=3), dyspnea, pulmonary hypertension, and a subject with hypoxia and pulmonary embolism. There were 4 cardiac events in 4 subjects: atrioventricular block first degree, pericardial effusion, right ventricular failure, and supraventricular tachycardia. There were 4 gastrointestinal AEs in 4 subjects: abdominal pain (n=2), diverticular perforation, and food poisoning. There were 3 hematologic events in 3 subjects: autoimmune thrombocytopenia, thrombocytopenia, and neutropenia. Two subjects with musculoskeletal disorders osteonecrosis and back and hip pain. There were 3 subjects with vascular disorders: hypertension, hypotension and deep venous thrombosis. There were 2 subjects with renal disorders: renal insufficiency and bladder spasms. The following AEs were reported in 4 subjects tibia fracture, chest pain, hyponatremia and syncope, and POEMS syndrome.

#### CNT0328MCD2002 - Castleman's disease extension study

Of the 19 subjects enrolled on the extension study there were 3 subjects with reported nonfatal serious treatment emergent AEs that occurred after 4/1/11, the date of extension study initiation. These included syncope, dyspnea and polycythemia.

#### C0328T08 - Bioequivalence trial in healthy volunteers

There were no SAEs reported.

#### C0328T06 - Randomized trial with bortezomib and dexamethasone in relapsed multiple myeloma

The per subject incidence of nonfatal SAE based on SOC is presented in Table 36. The most common category was "infections and infestations." The per subject incidence was similar in the bortezomib and siltuximab arm (17%) compared to the bortezomib placebo arm (18%). The addition of siltuximab to bortezomib in this trial did not appear to increase the incidence of serious infections. In the categories of "renal and urinary disorders," and "neoplasms benign, malignant and unspecified" the per subject incidence was  $\geq 3\%$  in the siltuximab arm compared to the placebo arm. The specific preferred term for these categories is included in the Table 36.

**Table 36: C0328T06 Nonfatal Serious Adverse Events**

C0328T06 Nonfatal Serious Adverse Events		
Per subject Incidence n (%) SOC Preferred Term in Categories with $\geq$ 3% Incidence	Siltuximab Bortezomib n=163 (Part 1 - 21; Part 2 -142)	Placebo Bortezomib n=139 (Part 2 - 139)
Infections and infestations	18 (11)	17 (12)
Respiratory, thoracic and mediastinal disorders	6 (4)	7 (5)
Renal and urinary disorders	9 (6)	3 (2)
Renal impairment/failure	8 (5)	3 (2)
Obstructive uropathy	1 (1)	0
Urinary retention	1 (1)	0
General disorders and administration site conditions	5 (3)	5 (4)
Nervous system disorders	7 (4)	3 (2)
Metabolism and nutrition disorders	6 (4)	4 (3)
Gastrointestinal disorders	7 (4)	3 (2)
Blood and lymphatic system disorders	2 (1)	7 (5)
Vascular disorders	6 (4)	3 (2)
Injury, poisoning and procedural complications	5 (3)	3 (2)
Neoplasms benign, malignant and unspecified	6 (4)	1 (1)
Basal Cell	3 (2)	0
Colon	2 (1)	0
Bladder	0	1 (1)
Plasmacytoma	1 (1)	0
Musculoskeletal and connective tissue disorders	4 (2)	2 (1)
Cardiac disorders	4 (2)	1 (1)
Skin and subcutaneous tissue disorders	1 (1)	1 (1)
Eye disorders	1 (1)	1 (1)
Hepatobiliary disorders	0	1 (1)

CNT0328MMY2001 - Open label randomized trial with VMP in newly diagnosed multiple myeloma

The per subject incidence of nonfatal SAE based on SOC is presented in Table 37. The most common category was “infections and infestations.” The per subject incidence was greater in the VMP siltuximab arm (25%) compared to the VMP arm (15%). The addition of siltuximab to VMP in this trial appeared to increase the incidence of serious infections. The specific types of infections are presented in Table 37. In the categories of “respiratory, thoracic and mediastinal disorders,” and “injury, poisoning and procedural complications” the per subject incidence was  $\geq$  3% in the siltuximab arm compared to the placebo arm. The specific preferred terms for the AEs in the respiratory disorders are included in the Table 37. Injuries were fractures in various anatomical locations.

**Table 37: CNTO328MMY2001 Nonfatal Serious Adverse Events**

CNTO328MMY2001 Nonfatal Serious Adverse Events		
Per subject Incidence n (%) SOC Preferred Term in Categories with ≥ 3% Incidence	Siltuximab VMP n=64 (Part 1 - 12; Part 2 - 52)	VMP n=53 (Part 2 - 53)
<b>Infections and infestations</b>	<b>16 (25)</b>	<b>8 (15)</b>
Respiratory (pneumonia, bronchitis, respiratory tract)	15 (23)	8 (15)
Gastroenteritis	1 (2)	1 (2)
Influenza	1 (2)	0
Hepatitis B	1 (2)	0
Parotitis	1 (2)	0
Septic shock	1 (2)	1 (2)
<b>Gastrointestinal disorders</b>	<b>6 (9)</b>	<b>6 (11)</b>
<b>Respiratory, thoracic and mediastinal disorders</b>	<b>7 (11)</b>	<b>3 (6)</b>
Respiratory failure	2 (3)	1 (2)
Pleural effusion	2 (3)	0
Asthma	1 (2)	1 (2)
Pulmonary embolism	1 (2)	0
Pulmonary edema	1 (2)	0
Chronic obstructive pulmonary disease	1 (2)	1 (2)
Dyspnea	0	0
<b>Renal and urinary disorders</b>	<b>5 (8)</b>	<b>5 (9)</b>
<b>Metabolism and nutrition disorders</b>	<b>5 (8)</b>	<b>4 (8)</b>
<b>Nervous system disorders</b>	<b>5 (8)</b>	<b>4 (8)</b>
<b>Blood and lymphatic system disorders</b>	<b>4 (6)</b>	<b>3 (6)</b>
<b>Musculoskeletal and connective tissue disorders</b>	<b>2 (3)</b>	<b>4 (8)</b>
<b>Injury, poisoning and procedural complications (Fractures)</b>	<b>5 (8)</b>	<b>0</b>
Cardiac disorders	3 (5)	2 (4)
Vascular disorders	0	3 (6)
Neoplasms benign, malignant and unspecified	2 (3)	2 (4)
General disorders and administration site conditions	2 (3)	1 (2)
Skin and subcutaneous tissue disorders	1 (2)	0
Psychiatric disorders	1 (2)	0
Investigations	1 (2)	0
Hepatobiliary disorders	1 (2)	0
Endocrine disorders	1 (2)	0

CNTO328MDS2001 - Randomized trial in myelodysplastic syndrome

The per subject incidence of nonfatal SAE based on SOC classification is presented in Table 38. The most common category was “infections and infestations.” The per subject incidence was greater in the siltuximab/BSC arm (14%) compared to the BSC arm (8%). The specific types of infections are presented in Table 38. The per subject incidence of SAEs in the category of “gastrointestinal disorders” was ≥ 3% in the siltuximab arm compared to the control arm. The specific preferred terms are presented in Table 38

**Table 38: CNTO328MDS2001 Nonfatal Serious Adverse Events**

CNTO328MDS2001 Nonfatal Serious Adverse Events		
Per subject Incidence n (%) SOC Preferred Term in Categories with ≥ 3% Incidence	Siltuximab 15 mg/kg every 4 weeks n=50	Placebo n=26
<b>Infections and infestations</b>	<b>7 (14)</b>	<b>2 (8)</b>
Pneumonia	4 (8)	0
Bacteremia / Sepsis	2 (4)	1 (4)
Cellulitis / Soft tissue infection	1 (2)	1 (4)
<b>Gastrointestinal disorders</b>	<b>2 (4)</b>	0
Femoral hernia	1 (2)	0
Bowel Ischemia	1 (2)	0
Nausea /vomiting (separate incident in subject with bowel ischemia")	1 (2)	0
Cardiac disorders	0	2 (8)
Injury, poisoning and procedural complications	1 (2)	1 (4)
Vascular disorders	1 (2)	1 (4)
Blood and lymphatic system disorders	0	1 (4)
General disorders and administration site conditions	0	1 (4)
Hepatobiliary disorders	0	1 (4)
Respiratory, thoracic and mediastinal disorders	1 (2)	0
Metabolism and nutrition disorders	1 (2)	0

### 7.3.3 Dropouts and/or Discontinuations

#### CNTO328MCD2001 – Randomized trial Castleman’s disease

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 AE. The placebo group includes 2 subjects with action taken with study treatment due to the AE categorized as “drug interrupted” rather than “drug withdrawn.” In these 2 cases no subsequent placebo was administered. The subjects on the placebo arm who discontinued the study agent are presented in Table 39.

Most of the AEs 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.

**Table 39: CNTO328MCD2001 Discontinuation Due to Adverse Event – Placebo during Treatment Period**

<b>CNTO328MCD2001 Adverse Events Leading to Discontinuation – Placebo Treatment Period</b>					
<b>ID</b>	<b>AE (PT) Discontinuation (D) or Interruption (I) not restarted</b>	<b>Day AE Started</b>	<b>Day last dose</b>	<b>No. of doses</b>	<b>Attribution Comment</b>
0102-00005	D Abdominal pain (LUQ) D Weight decreased	113 85	113	6	AEs not related to study agent Treatment unblinded; crossed over
0102-00027	D T-cell Lymphoma	442	414	20	AE not related to study agent
1102-00090	D Anemia	106	148	8	AE not related to study agent Treatment unblinded; crossed over
2001-00034	I Anemia I Neutropenia	160 163	71	4	AE not related to study agent Treatment unblinded; crossed over
3301-00029	D Myelodysplastic syndrome	85	64	4	AE not related to study agent
3401-00032	D Tumor Pain	64	64	4	AE not related to study agent
4402-00054	D Peripheral sensory neuropathy	134	156	8	AE not related to study agent Treatment unblinded; crossed over
4701-00008	D Dyspnea D Lymph node pain D Peripheral sensory neuropathy D Pruritus D Rash maculo-papular	137 137 144 144 130	126	7	AEs not related to study agent Treatment unblinded; crossed over
4904-00110	D Localized edema D Night sweats	63 63	85	5	AEs not related to study agent Treatment unblinded; crossed over
5503-00073	I Pleural effusion I Tumor pain	45 45	23	2	Effusion not related to study agent Tumor pain possibly related to study agent
8521-00099	D Fatigue I Anemia	69 89	68	4	Fatigue not related to study agent Doubtful anemia related to study agent Treatment unblinded; crossed over
8601-00089	D Face edema D Edema peripheral	106 106	148	8	Doubtful AE related to study agent Treatment unblinded; crossed over

The subjects on the siltuximab arm who discontinued the study agent are presented in Table 40. In the siltuximab arm, the AEs 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 AE 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 AE 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 AEs leading to discontinuation.

**Table 40: CNTO328MCD2001 Discontinuation Due to Adverse Event – Siltuximab**

CNTO328MCD2001 Adverse Events Leading to Discontinuation – Siltuximab Arm					
ID	AE (PT) Discontinuation (D) or Interruption (I) not restarted	Day AE Started	Day last dose	No. of doses	Attribution
0704-00044	D Face edema D Localized edema	106 106	106	6	AEs not related to study agent
3201-00048	I Chest discomfort (infusion rx) I Erythema (infusion rx) D Night sweats D Edema peripheral	64	64	4	Infusion reaction symptoms related to study agent Sweats and edema not related to study agent
3202-00001	D Night sweats	190	190	10	AE not related to study agent
4402-00063	D Rash maculo-papular D Skin ulcer	99 138	121	6	Possible AE related to study agent
5501-00101	D Fatigue D Malaise	128 128	149	8	AE not related to study agent
5503-00056	D Pleural effusion	206	188	10	Doubtful AE related to study agent
8521-00087	D Peripheral motor neuropathy D Peripheral sensory neuropathy	75 75	89	5	AEs not related to study agent
8601-00092	D Weight decreased	357	378	19	Doubtful AE related to study agent
8602-00122	D Ascites	231	211	11	Doubtful AE related to study agent
8604-00097	D Peripheral sensory neuropathy	186	214	11	Doubtful AE related to study agent
8605-00104	D Night sweats	63	63	4	Doubtful AE related to study agent
9721-00066	I Anaphylactic reaction D Asthenia D Odema peripheral D Pericardial effusion D Rash generalised D Weight increased D Hypoalbuminaemia	1 5 8 8 5 6 16	1	1	Study agent was discontinued due to anaphylactic reaction on the first day of administration.

**REVIEWER COMMENT:**

Siltuximab was well tolerated and rarely discontinued due to a drug related AE. AEs leading to discontinuation that possibly were drug related were an anaphylactic reaction and an infusion reaction.

C0328T03 - Phase 1 trial in hematologic malignancies

There were eight subjects who discontinued situximab therapy due to a treatment emergent AEs. The preferred terms for the AEs included neutropenia, disease progression, renal impairment, thrombocytopenia, peripheral sensory neuropathy, diffuse large B-cell lymphoma, abdominal pain, and drug eruption.

CNTO328MCD2002 - Castleman's disease extension study

None reported.

C0328T08 - Bioequivalence trial in healthy volunteers

A single patient discontinued therapy with CHO-derived CNTO 328 on Day 1 due to infusion site pain due to IV site infiltration. The subject did not receive the intended dose.

C0328T06 - Randomized trial with bortezomib and dexamethasone in relapsed multiple myeloma

The incidence of study discontinuation due to a treatment emergent AE was higher in subjects treated with siltuximab 57 of 163 (35%) subjects compared to subjects treated with placebo 33 of 139 (24%) subjects.

CNTO328MMY2001 - Open label randomized trial with VMP in newly diagnosed multiple myeloma

The incidence of study discontinuation due to a treatment emergent AE during the treatment period (cycles 1-9) was higher in subjects treated on the siltuximab/VMP arm, 12 of 52 (23%) subjects compared to subjects in the control VMP arm 6 of 53 (11%) subjects. The incidence of study agent discontinuations due to infections was 3.8% in the siltuximab/VMP arm and 5.7% in the VMP arm.

CNTO328MDS2001 - Randomized trial in myelodysplastic syndrome

Three subjects in the siltuximab group (thrombocytopenia, chronic obstructive pulmonary disease, pain, palpitations, and paralysis) and 2 subjects in the placebo group (asthenia, weight decreased, and cardiovascular insufficiency) discontinued treatment due to AEs.

#### 7.3.4 Significant Adverse Events

There does not appear to be signals for significant AEs associated with siltuximab therapy in this population. Mortality was lower in the siltuximab treated arm, no specific SAE was identified in the siltuximab arm and discontinuation of siltuximab therapy due to AEs was similar in the siltuximab and placebo arms.

Siltuximab does not appear to be potentially immunogenic. There was only incident of significant allergic reaction in over 750 patients. This was a grade 3 anaphylactic reaction, experienced with the first infusion. The timing of this reaction, that is with the first exposure to siltuximab, casts doubt on the etiologic role of siltuximab.

#### 7.3.5 Submission Specific Primary Safety Concerns

Given the mechanism of action risk of infection is a specific safety concern. See the discussion of infections in Section 7.4.1 below.

## 7.4 Supportive Safety Results

### 7.4.1 Common Adverse Events

CNT0328MCD2001, the randomized trial multicentric Castleman’s disease

Table 41 presents the per subject incidence of treatment emergent AEs that occurred during the randomized blind portion of the trial. Because subjects randomized to siltuximab received a median of 19 doses of study agent compared to the placebo arm who received a median of 8 doses of study agent during the randomized blind portion of the trial, the incidence of AEs that occurred during the first 8 doses of study agent administration was also evaluated.

**Table 41: CNT0328MCD2001 Common Adverse Event by System Organ Class**

CNT0328MCD2001 – Common Adverse Events by System Organ Class				
System Organ Class	Siltuximab	Placebo	Siltuximab 1 <sup>st</sup> 8 Courses	Placebo 1 <sup>st</sup> 8 Courses
Per Subject Incidence n (%)	n=53	n=26	n=53	n=26
Skin and subcutaneous tissue disorders	37 (70)	11 (42)	27 (51)	9 (35)
General disorders and administration site conditions	32 (60)	17 (65)	28 (53)	17 (65)
Gastrointestinal disorders	38 (72)	13 (50)	24 (45)	12 (46)
Infections and infestations	35 (66)	9 (35)	23 (43)	7 (27)
Blood and lymphatic system disorders	20 (38)	8 (31)	13 (25)	8 (31)
Metabolism and nutrition disorders	25 (47)	10 (38)	20 (38)	8 (31)
Respiratory, thoracic and mediastinal disorders	25 (47)	14 (54)	18 (34)	11 (42)
Nervous system disorders	20 (38)	8 (31)	15 (28)	6 (23)
Investigations	20 (38)	7 (27)	16 (30)	7 (27)
Musculoskeletal and connective tissue disorders	16 (30)	8 (31)	11 (21)	7 (27)
Renal and urinary disorders	9 (17)	2 (8)	5 (9)	2 (8)
Eye disorders	12 (23)	4 (15)	8 (15)	3 (12)
Vascular disorders	8 (15)	1 (4)	6 (11)	1 (4)
Neoplasms benign, malignant and unspecified	5 (9)	6 (23)	3 (6)	4 (15)
Psychiatric disorders	8 (15)	3 (12)	4 (8)	3 (12)
Hepatobiliary disorders	5 (9)	2 (8)	2 (4)	1 (4)
Injury, poisoning and procedural complications	7 (13)	2 (8)	6 (11)	1 (4)
Cardiac disorders	5 (9)	0	2 (4)	0
Immune system disorders	5 (9)	1 (4)	4 (8)	0
Reproductive system and breast disorders	3 (6)	2 (8)	2 (4)	2 (8)
Ear and labyrinth disorders	2 (4)	1 (4)	1 (2)	1 (4)
Endocrine disorders	1 (2)	1 (4)		1 (4)

The SOC with a per subject incidence of AEs  $\geq$  to 5% included “skin and subcutaneous tissue disorders,” “gastrointestinal disorders,” “infections and infestations,” “blood and lymphatic system disorders,” “metabolism and nutrition disorders,” “nervous system disorders,” “investigations,” “renal and urinary disorders,” “eye disorders,” “vascular disorders,” “injury, poisoning and procedural complications,” “cardiac disorders,” and “immune system disorders.”

The SOC with a per subject incidence of AEs  $\geq$  5% during the first 8 doses of study agent included “skin and subcutaneous tissue disorders,” “infections and infestations,” “metabolism and nutrition disorders,” “nervous system disorders,” “vascular disorders,” “injury, poisoning and procedural complications,” and “immune system disorders.”

Skin and subcutaneous tissue disorders

For this analysis all categories of “dermatitis” (dermatitis, dermatitis acneiform, dermatitis allergic, and dermatitis contact) were combined, and all categories of rash (rash, rash generalized, rash maculo-papular, rash papular, and rash pruritic ) were combined. The predominant AEs that accounted for the discrepancy between the incidence of AEs in the two arms were rash and pruritis. Of note, pigmentation changes that is vitaligo and hyperpigmentation were only reported in the siltuximab arm as were eczema, psoriasis, dry skin, urticaria, purpura, and skin ulcer. The results are presented in Table 42.

**Table 42: CNTO328MCD2001 Common Adverse Events - Skin and Subcutaneous Tissue Disorders**

CNTO328MCD2001 – Common Adverse Events - Skin and Subcutaneous Tissue Disorders								
System Organ Class Preferred terms	Siltuximab	Placebo	Siltuximab	Placebo	Siltuximab 1 <sup>st</sup> 8 Courses	Placebo 1 <sup>st</sup> 8 Courses	Siltuximab 1 <sup>st</sup> 8 Courses	Placebo 1 <sup>st</sup> 8 Courses
Per Subject Incidence n (%)	n=53	n=26	n=53	n=26	n=53	n=26	n=53	n=26
	All grades		Grade 3&4		All grades		Grade 3&4	
Skin and subcutaneous tissue disorders	37 (70)	11 (42)	6 (11)	1 (4)	27 (51)	9 (35)	5 (9)	1 (4)
Rash	23 (41)	3 (12)	1 (2)	0	15 (28)	3 (12)	1 (2)	0
Pruritis	23 (41)	3 (12)	0	0	15 (28)	2 (8)	0	0
Hyperhidrosis/ Night Sweats	15 (28)	6 (23)	4 (8)	1 (4)	12 (23)	6 (23)	3 (6)	1 (4)
Vitaligo	2 (4)	0	0	0	1 (2)	0	0	0
Skin hyperpigmentation	5 (9)	0	0	0	2 (4)	0	0	0
Dermatitis	7 (13)	2 (8)	0	0	3 (6)	2 (8)	0	0
Eczema	5 (9)	0	0	0	2 (4)	0	0	0
Psoriasis	2 (4)	0	0	0	2 (4)	0	0	0
Dry Skin	4 (8)	0	0	0	2 (4)	0	0	0
Urticaria	2 (4)	0	0	0	1 (2)	0	0	0
Purpura	2 (4)	0	0	0	0	0	0	0
Erythema	2 (4)	1 (4)	0	0	2 (4)	1 (4)	0	0
Skin Ulcer	1 (2)	0	1 (2)	0	1 (2)	0	1 (2)	0

General disorders and administration site conditions

For this analysis all categories of edema (face edema, generalized edema, localized edema, edema, and edema peripheral) were combined. Overall there was a higher incidence of edema and malaise in the siltuximab arm, but the incidence in the siltuximab was not higher during the first 8 cycles of therapy. The results are presented in Table 43.

**Table 43: CNTO328MCD2001 Common Adverse Events - General Disorders and Administration Site Conditions**

CNTO328MCD2001 – Common Adverse Events - General Disorders and Administration Site Conditions								
System Organ Class Preferred terms	Siltuximab	Placebo	Siltuximab	Placebo	Siltuximab 1 <sup>st</sup> 8 Courses	Placebo 1 <sup>st</sup> 8 Courses	Siltuximab 1 <sup>st</sup> 8 Courses	Placebo 1 <sup>st</sup> 8 Courses
Per Subject Incidence n (%)	n=53	n=26	n=53	n=26	n=53	n=26	n=53	n=26
	All grades		Grade 3&4		All grades		Grade 3&4	
General disorders and administration site								
Edema (generalized and localized)	19 (36)	7 (26)	4 (8)	0	14 (26)	7(27)	4 (8)	0
Fatigue	18 (34)	10 (38)	5 (9)	1 (4)	16 (30)	9 (35)	2 (4)	1 (4)
Malaise	15 (28)	5 (19)	0	0	10 (19)	5 (19)	0	0
Pyrexia	6 (11)	2 (8)	0	0	6 (11)	2 (8)	0	0
Pain (all categories)	4 (8)	3 (12)	0	0	2 (4)	2 (8)	0	0

Gastrointestinal disorders

For this analysis all categories of mouth sores (aphthous stomatitis, gingival ulceration, mouth ulceration, and stomatitis) were combined. Overall there was a higher incidence of mouth sores in the siltuximab arm but < 3% when only the first 8 courses were considered. The results are presented in Table 44.

**Table 44: CNTO328MCD2001 Common Adverse Events - Gastrointestinal Disorders**

CNTO328MCD2001 – Common Adverse Events - Gastrointestinal Disorders								
System Organ Class Preferred terms	Siltuximab	Placebo	Siltuximab	Placebo	Siltuximab 1 <sup>st</sup> 8 Courses	Placebo 1 <sup>st</sup> 8 Courses	Siltuximab 1 <sup>st</sup> 8 Courses	Placebo 1 <sup>st</sup> 8 Courses
Per Subject Incidence n (%)	n=53	n=26	n=53	n=26	n=53	n=26	n=53	n=26
	All grades		Grade 3&4		All grades		Grade 3&4	
Gastrointestinal disorders	38 (72)	13 (50)	4 (8)	3 (12)	24 (45)	12 (46)	1 (2)	4 (8)
Abdominal pain/distension/discomfort	15 (28)	3 (12)	1 (2)	3 (12)	7 (13)	2 (8)	1 (2)	2 (8)
Stomatitis/[oral] ulceration (gingival, mouth, tongue)	9 (17)	1 (4)	0	0	3 (6)	1 (4)	0	0
Ascites	3 (6)	2 (8)	1 (2)	0	2 (4)	2 (8)	0	0
Constipation	6 (11)	1 (4)	0	0	4 (8)	1 (4)	0	0
Diarrhea	12 (23)	5 (19)	0	1 (4)	6 (11)	4 (15)	0	1 (4)
Dyspepsia	2 (4)	3 (12)	0	0	1 (2)	3 (12)	0	0
Gastroesophageal reflux disease	3 (6)	0	0	0	1 (2)	0	0	0
Nausea/vomiting	9 (16)	6 (23)	1 (2)	0	4 (8)	6 (23)	0	0

Infections and infestations

For this analysis infections were predominantly grouped by high level term classification. Upper respiratory infections were the predominant AEs that accounted for the discrepancy between the incidence of AEs in the two arms. The results are presented in Table 45.

**Table 45: CNTO328MCD2001 Common Adverse Events – Infections**

CNTO328MCD2001 – Common Adverse Events - Infections and Infestations								
System Organ Class High Level Term or Preferred Term Per Subject Incidence n (%)	Siltuximab n=53	Placebo n=26	Siltuximab n=53	Placebo n=26	Siltuximab 1 <sup>st</sup> 8 Courses n=53	Placebo 1 <sup>st</sup> 8 Courses n=26	Siltuximab 1 <sup>st</sup> 8 Courses n=53	Placebo 1 <sup>st</sup> 8 Courses n=26
	All grades		Grade 3&4		All grades		Grade 3&4	
<b>Infections and infestations</b>								
Lower respiratory tract	4 (8)	2 (8)	2 (4)	2 (8)	4 (8)	1 (4)	2 (4)	1 (4)
Upper respiratory tract	26 (49)	5 (19)	1 (2)	1 (4)	13 (25)	4 (15)	1 (2)	1 (4)
Skin structures and soft tissue	5 (9)	1 (4)	0	0	3 (6)	1 (4)	0	0
Fungal / Tinea / Candida	5 (9)	1 (4)	0	0	3 (6)	1 (4)	0	0
Abdominal and gastrointestinal	5 (9)	2 (8)	1 (2)	0	3 (6)	1 (4)	1 (2)	0
Viral Infection	4 (8)	1 (4)	1 (2)	0	3 (6)	1 (4)	1 (2)	0
Bacterial / Sepsis	3 (6)	2 (8)	1 (2)	0	1 (2)	2 (8)	1 (2)	0
Urinary tract infection	4 (8)	0	0	0	3 (6)	0	0	0

Metabolism and nutrition disorders

The analysis of the SOC “metabolism and nutrition disorders” excluded preferred terms for fluid and electrolyte disorders. The incidence of hypertriglyceridemia, hypercholesterolemia, and hyperuricemia greater in the siltutuximab arm compared to the placebo arm. There were instances of no grade 3 or 4 hypertriglyceridemia or hypercholesterolemia reported during the the first 8 courses of therapy. The results are presented in Table 46.

**Table 46: CNTO328MCD2001 Common Adverse Events – Metabolism and Nutrition**

CNTO328MCD2001 – Common Adverse Events - Metabolism and Nutrition								
System Organ Class Preferred terms Per Subject Incidence n (%)	Siltuximab n=53	Placebo n=26	Siltuximab n=53	Placebo n=26	Siltuximab 1 <sup>st</sup> 8 Courses n=53	Placebo 1 <sup>st</sup> 8 Courses n=26	Siltuximab 1 <sup>st</sup> 8 Courses n=53	Placebo 1 <sup>st</sup> 8 Courses n=26
	All grades		Grade 3&4		All grades		Grade 3&4	
<b>Metabolism and nutrition</b>	18 (34)	6 (23)	4 (8)	0	15 (28)	6 (23)	2 (4)	0
Decreased appetite	9 (17)	4 (15)	1 (2)	0	6 (11)	4 (15)	1 (2)	0
Hypertriglyceridemia	6 (11)	0	1 (2)	0	4 (8)	0	0	0
Hypercholesterolemia	3 (6)	0	0	0	2 (4)	0	0	0
Hyperuricemia	7 (13)	0	2 (4)	0	6 (11)	0	1 (2)	0
Hypoalbuminemia	2 (4)	1 (4)	0	0	2 (4)	1 (4)	0	0

Respiratory, thoracic and mediastinal disorders

No AE except oropharyngeal pain in the SOC “respiratory, thoracic and mediastinal disorders” occurred more frequently in the siltuximab arm. The results are presented in Table 47.

**Table 47: CNTO328MCD2001 Common Adverse Events – Respiratory, Thoracic and Mediastinal Disorders**

CNTO328MCD2001 – Common Adverse Events - Respiratory, Thoracic and Mediastinal Disorders								
System Organ Class Preferred terms	Siltuximab	Placebo	Siltuximab	Placebo	Siltuximab 1 <sup>st</sup> 8 Courses n=53	Placebo 1 <sup>st</sup> 8 Courses n=26	Siltuximab 1 <sup>st</sup> 8 Courses n=53	Placebo 1 <sup>st</sup> 8 Courses n=26
Per Subject Incidence n (%)	n=53	n=26	n=53	n=26	n=53	n=26	n=53	n=26
	All grades		Grade 3&4		All grades		Grade 3&4	
Respiratory, thoracic and mediastinal disorders	25 (47)	14 (54)	1 (2)	1 (4)	18 (34)	11 (42)	1 (2)	1 (4)
Dyspnea	13 (25)	9 (35)	1 (2)	1 (4)	9 (17)	8 (31)	1 (2)	1 (4)
Cough	9 (17)	6 (23)	0	0	6 (11)	3 (12)	0	0
Pleural effusion	3 (6)	3 (12)	0	1 (4)	2 (4)	2 (8)	0	1 (4)
Oropharyngeal pain	4 (8)	1 (4)	0	0	4 (8)	1 (4)	0	0

Nervous system disorders

The per subject incidence of AEs  $\geq$  to 5% during the first 8 doses of study agent identified in the SOC “nervous system disorders” was not due to any individual AE. See Table 48 below.

**Table 48: CNTO328MCD2001 Common Adverse Events - Nervous System Disorders**

CNTO328MCD2001 – Common Adverse Events - Nervous system disorders								
System Organ Class Preferred terms	Siltuximab	Placebo	Siltuximab	Placebo	Siltuximab 1 <sup>st</sup> 8 Courses n=53	Placebo 1 <sup>st</sup> 8 Courses n=26	Siltuximab 1 <sup>st</sup> 8 Courses n=53	Placebo 1 <sup>st</sup> 8 Courses n=26
Per Subject Incidence n (%)	n=53	n=26	n=53	n=26	n=53	n=26	n=53	n=26
	All grades		Grade 3&4		All grades		Grade 3&4	
Nervous system disorders	20 (38)	8 (31)			15 (28)	6 (23)		
Peripheral neuropathy (motor and sensory)/burning sensation	14 (26)	7 (27)	0	1 (4)	10 (19)	5 (19)	0	1 (4)
Dizziness	6 (11)	2 (8)	1 (2)	0	3 (4)	2 (8)	1 (2)	0
Headache	6 (11)	1 (4)	0	0	4 (8)	1 (4)	0	0
Somnolence	1 (2)	1 (4)	0	0	1 (2)	1 (4)	0	0

Investigations

Laboratory values are excluded from this evaluation. See Section 7.4.2 for a comprehensive evaluation of laboratory results. The only preferred terms were weight increased and weight decreased. There were no placebo subjects with weight increased and 11 subjects in the siltuximab arm were reported to have increased weight. More subjects in the placebo arm were documented to have decreased weight. The analysis is presented in Table 49 below.

**Table 49: CNTO328MCD2001 Common Adverse Events – Investigations**

CNTO328MCD2001 – Common Adverse Events - Investigations								
System Organ Class Preferred terms	Siltuximab	Placebo	Siltuximab	Placebo	Siltuximab 1 <sup>st</sup> 8 Courses n=53	Placebo 1 <sup>st</sup> 8 Courses n=26	Siltuximab 1 <sup>st</sup> 8 Courses n=53	Placebo 1 <sup>st</sup> 8 Courses n=26
Per Subject Incidence n (%)	n=53	n=26	n=53	n=26	n=53	n=26	n=53	n=26
	All grades		Grade 3&4		All grades		Grade 3&4	
Investigations	14 (26)	4 (15)	2 (4)	0	12 (23)	4 (15)	1 (2)	0
Weight increased	11 (21)	0	2 (4)	0	10 (19)	0	1 (2)	0
Weight decreased	4 (8)	4 (15)	0	0	2 (4)	4 (15)	0	0

Musculoskeletal and Connective Tissue Disorders

The incidence of musculoskeletal AEs was higher in the placebo arm. See Table 50 below.

**Table 50: CNTO328MCD2001 Common Adverse Events - Musculoskeletal and Connective Tissue Disorders**

CNTO328MCD2001 – Common Adverse Events - Musculoskeletal and Connective Tissue Disorders								
System Organ Class Preferred terms	Siltuximab	Placebo	Siltuximab	Placebo	Siltuximab 1 <sup>st</sup> 8 Courses	Placebo 1 <sup>st</sup> 8 Courses	Siltuximab 1 <sup>st</sup> 8 Courses	Placebo 1 <sup>st</sup> 8 Courses
Per Subject Incidence n (%)	n=53	n=26	n=53	n=26	n=53	n=26	n=53	n=26
	All grades		Grade 3&4		All grades		Grade 3&4	
Musculoskeletal and connective tissue disorders	16 (30)	8 (31)	1 (2)	0	11 (21)	7 (27)	1 (2)	0
Pain (any location, arthralgia, myalgia)	12 (23)	7 (27)	0	0	8 (15)	7 (27)	0	0
Muscle spasm/muscle weakness/ muscle stiffness	5 (9)	2 (8)	1 (2)	0	3 (6)	2 (8)	1 (2)	0

Renal and urinary disorders

The per patient incidence of renal impairment and/or azotemia was greater in the siltuximab arm but not when this arm was corrected for exposure. See Table 51 below.

**Table 51: CNTO328MCD2001 Common Adverse Events - Renal and Urinary Disorders**

CNTO328MCD2001 – Common Adverse Events - Renal and Urinary Disorders								
System Organ Class Preferred terms	Siltuximab	Placebo	Siltuximab	Placebo	Siltuximab 1 <sup>st</sup> 8 Courses	Placebo 1 <sup>st</sup> 8 Courses	Siltuximab 1 <sup>st</sup> 8 Courses	Placebo 1 <sup>st</sup> 8 Courses
Per Subject Incidence n (%)	n=53	n=26	n=53	n=26	n=53	n=26	n=53	n=26
	All grades		Grade 3&4		All grades		Grade 3&4	
Renal and urinary disorders	8 (15)	2 (8)	2 (4)	0	4 (8)	2 (8)	1 (2)	0
Renal impairment/azotemia	4 (8)	1 (4)	1 (2)	0	3 (6)	1 (4)	0	0
Dysuria/bladder pain/renal colic	2 (4)	1(4)	1 (2)	0	1 (2)	1 (4)	1 (2)	0

Note: 8602-00122 CREATINE KINASE HIGHER THAN NORMAL improperly coded to renal impairment. Removed from my evaluation.

Eye disorders

The per subject incidence of AEs reported in the SOC “eye disorders” were “periorbital edema” (siltuximab n=3, placebo n=1); conjunctivitis (siltuximab n=2, placebo n=2); “conjunctival hemorrhage” (siltuximab n=1); “eye irritation” (siltuximab n=1); “eye pruritus” (placebo n=1); “orbital pseudotumour” (placebo n=1); “vision blurred” (siltuximab n=1); “visual acuity reduced” (siltuximab n=1); “vitreous haemorrhage” (n=1).

Vascular disorders

The per subject incidence of AEs ≥ to 5% during the first 8 doses of study agent identified in the SOC “vascular disorders” was not due to any individual AE. See Table 52 below.

**Table 52: CNTO328MCD2001 Common Adverse Events - Vascular Disorders**

CNTO328MCD2001 – Common Adverse Events - Vascular Disorders								
System Organ Class Preferred terms	Siltuximab n=53	Placebo n=26	Siltuximab n=53	Placebo n=26	Siltuximab 1 <sup>st</sup> 8 Courses n=53	Placebo 1 <sup>st</sup> 8 Courses n=26	Siltuximab 1 <sup>st</sup> 8 Courses n=53	Placebo 1 <sup>st</sup> 8 Courses n=26
Per Subject Incidence n (%)	All grades		Grade 3&4		All grades		Grade 3&4	
Vascular Disorders	8 (15)	1 (4)	6 (11)	1 (4)	8 (15)	1 (4)	6 (11)	1 (4)
Hypertension/Hypertensive crisis	4 (8)	1 (4)	2 (4)	1 (4)	2 (4)	1 (4)	0	0
Hypotension/Orthostatic hypotension	3 (6)	0	1 (2)	0	2 (4)	0	1 (2)	0
Flushing	2 (4)	0	0	0	1 (2)	0	0	0
Vasculitis	1 (2)	0	0	0	0	0	0	0

Psychiatric disorders

Insomnia was the most commonly reported AE in the SOC “psychiatric disorders” (siltuximab n=5, placebo n=2). Depression was reported in one subject on each arm, and a single report of “libido decreased,” “night mare,” and “somatic delusion” were reported in subjects treated on the siltuximab arm.

Hepatobiliary disorders

The majority of AEs reported in the SOC “hepatobiliary disorders” were elevated transaminases grade 1 and 2. This is an incorrect classification. These should be classified as elevated transaminase in the “investigations” category. (For details see Section 7.4.2.) In the siltuximab arm the following AEs were reported in a single subject “hepatic cirrhosis,” “cholelithiasis,” “cholecystitis chronic.”

Injury, poisoning and procedural complications

Table 53 lists the preferred terms for AEs listed under this SOC. There dose not appear to be an obvious association with the study agent.

**Table 53: CNTO328MCD2001 Common Adverse Events - Injury, Poisoning and Procedural Complications**

ID	Arm	Preferred Term	Dose of Experimental Agent
0102-00027	Placebo	Fall	2
8602-00083	Placebo	Ligament sprain	12
0102-00003	Siltuximab	Excoriation	15
0104-00065	Siltuximab	Contusion	3
0106-00086	Siltuximab	Wound secretion	2
0107-00031	Siltuximab	Wound complication	3
		Tibia fracture	16
3401-00058	Siltuximab	Clavicle fracture	3
5501-00135	Siltuximab	Fall	8
8521-00087	Siltuximab	Fall	1

Cardiac disorders

There were no nonfatal cardiac events reported in the placebo subjects. Table 54 lists the AEs reported in the siltuximab arm. There did not appear to be any specific common cardiac AE reported.

**Table 54: CNTO328MCD2001 - Cardiac Events in Siltuximab Subjects**

Cardiac Events in Siltuximab Subjects		
ID	Preferred Term	Dose of Experimental Agent
0102-00003	Atrial fibrillation	31
0107-00037	Palpitations	30
8521-00035	Palpitations	3 / 6
8602-00084	Ventricular extrasystoles	12
9721-00066	Bradycardia	1
	Pericardial effusion	
	Sinus tachycardia	

Immune system disorders

All AEs but one were reported in siltuximab subjects. As reported in Section 7.3.2, subject 9721-00066 experience an anaphylactic reaction with the first dose of siltuximab. There were 3 subjects (2 siltuximab, 1 placebo) with seasonal allergies. Siltuximab subjects reported to have “elevate immuno adenosine triphosphate” and “contrast media allergy.” There did not appear to be any specific common immune system AE reported.

C0328T03, phase 1 trial hematologic malignancies

Preferred terms reported  $\geq 15\%$  for all subjects enrolled on this trial are presented in Table 55. Preferred terms reported  $\geq 15\%$  for subjects with Castleman’s disease enrolled on this trial are presented in Table 56 (copied from submission Study Report C0328T03 page 101-2/1177). Note: Elevated transaminases are incorrectly classified as “hepatic function abnormal.”

**Table 55: C0328T03 Common Adverse Events – All Enrolled Subjects**

	All Grades	Grade 3 or higher
Subjects treated	67	67
Avg exposure (number of administrations)	27.7	27.7
Subjects with any adverse events	66 (98.5%)	40 (59.7%)
<b>Preferred terms</b>		
Upper respiratory tract infection	26 (38.8%)	1 (1.5%)
Nausea	25 (37.3%)	3 (4.5%)
Thrombocytopenia	21 (31.3%)	5 (7.5%)
Vomiting	21 (31.3%)	3 (4.5%)
Diarrhoea	20 (29.9%)	1 (1.5%)
Headache	17 (25.4%)	1 (1.5%)
Hypertriglyceridaemia	17 (25.4%)	2 (3.0%)
Neutropenia	16 (23.9%)	14 (20.9%)
Hepatic function abnormal	14 (20.9%)	1 (1.5%)
Anaemia	13 (19.4%)	3 (4.5%)
Arthralgia	13 (19.4%)	1 (1.5%)
Back pain	13 (19.4%)	1 (1.5%)
Cough	13 (19.4%)	0 (0.0%)
Hyperuricaemia	13 (19.4%)	0 (0.0%)
Leukopenia	13 (19.4%)	1 (1.5%)
Hypercholesterolaemia	12 (17.9%)	0 (0.0%)
Hypertension	12 (17.9%)	6 (9.0%)
Oedema peripheral	12 (17.9%)	0 (0.0%)
Pain in extremity	11 (16.4%)	1 (1.5%)
Rash	11 (16.4%)	1 (1.5%)
Urinary tract infection	11 (16.4%)	0 (0.0%)

**Table 56: C0328T03 Common Adverse Events – In Subjects with Castleman’s Disease**

	All Grades	Grade 3 or higher
Subjects treated	37	37
Avg exposure (number of administrations)	40.3	40.3
Subjects with any adverse events	37 (100.0%)	20 (54.1%)
<b>Preferred terms</b>		
Nausea	18 (48.6%)	3 (8.1%)
Upper respiratory tract infection	18 (48.6%)	1 (2.7%)
Vomiting	18 (48.6%)	3 (8.1%)
Diarhoea	15 (40.5%)	1 (2.7%)
Headache	14 (37.8%)	1 (2.7%)
Hypertriglyceridaemia	12 (32.4%)	1 (2.7%)
Arthralgia	11 (29.7%)	1 (2.7%)
Hyperuricaemia	11 (29.7%)	0 (0.0%)
Hepatic function abnormal	10 (27.0%)	1 (2.7%)
Hypercholesterolaemia	10 (27.0%)	0 (0.0%)
Back pain	9 (24.3%)	1 (2.7%)
Hypertension	9 (24.3%)	3 (8.1%)
Dizziness	8 (21.6%)	0 (0.0%)
Pain in extremity	8 (21.6%)	1 (2.7%)
Urinary tract infection	8 (21.6%)	0 (0.0%)
Abdominal pain	7 (18.9%)	2 (5.4%)
Anxiety	7 (18.9%)	1 (2.7%)
Constipation	7 (18.9%)	0 (0.0%)
Cough	7 (18.9%)	0 (0.0%)
Oedema peripheral	7 (18.9%)	0 (0.0%)
Rash	7 (18.9%)	1 (2.7%)
Renal impairment	7 (18.9%)	0 (0.0%)
Sinusitis	7 (18.9%)	0 (0.0%)
Anaemia	6 (16.2%)	2 (5.4%)
Dyspepsia	6 (16.2%)	0 (0.0%)
Hyperglycaemia	6 (16.2%)	1 (2.7%)
Hypokalaemia	6 (16.2%)	0 (0.0%)
Muscle spasms	6 (16.2%)	0 (0.0%)
Peripheral sensory neuropathy	6 (16.2%)	2 (5.4%)
Thrombocytopenia	6 (16.2%)	0 (0.0%)

C0328T08, Bioequivalence trial in healthy volunteers  
 Table 57: Adverse Events Normal Volunteer Study

System Organ Class Preferred Term Per Subject Incidence (n)	Placebo n=4	CHO n=73	SP2 n=68	Total Anti-IL-6 n=141 (n (%))
<b>Blood and lymphatic system disorders</b>	2	9	9	20 (14%)
Neutropenia	2	8	6	14 (10%)
Lymphadenopathy	0	1	1	2 (1%)
Eosinophilia	0	0	2	2 (1%)
Leukopenia	0	1	0	1 (1%)
Thrombocytopenia	0	0	1	1 (1%)
<b>Cardiac disorders</b>	0	0	1	1 (1%)
Palpitations	0	0	1	1 (1%)
<b>Ear and labyrinth disorders</b>	0	2	2	4 (3%)
Ear pain	0	2	1	3 (2%)
Tinnitus	0	0	1	1 (1%)
Eustachian tube disorder	0	1	0	1 (1%)
<b>Eye disorders</b>	1	1	1	3 (2%)
Lacrimation increased	0	1	0	1 (1%)
Conjunctivitis	1	0	0	1 (1%)
Conjunctival hemorrhage	0	0	1	1 (1%)
<b>Gastrointestinal disorders</b>	0	16	8	24 (17%)
Abdominal discomfort/pain Stomach discomfort	0	4	6	10 (7%)
Nausea/Vomiting	0	10	1	11 (8%)
Diarrhea	0	3	0	3 (2%)
Toothache	0	3	1	4 (3%)
Aphthous stomatitis	0	3	0	3 (2%)
Flatulence	0	2	1	3 (2%)
Dyspepsia	0	1	1	2 (1%)
Constipation	0	1	0	1 (1%)
Feces discoloured	0	0	1	1 (1%)
<b>General disorders and administration site conditions</b>	1	10	10	21 (15%)
Infusion site problems (multiple terms)	0	3	6	9 (6%)
Pain	1	2	0	3 (2%)
Fatigue	0	2	2	4 (3%)
Edema	0	1	1	2 (1%)
Infusion related reaction	0	0	1	1 (1%)
Chills	0	1	1	2 (1%)
Asthenia	0	1	0	1 (1%)
Feeling hot	0	1	0	1 (1%)
<b>Infections and infestations</b>	0	12	10	22 (16%)
Upper respiratory tract infection	0	10	6	16 (11%)
Gastroenteritis	0	2	3	5 (4%)
Bronchitis	0	1	0	1 (1%)
Gingival infection	0	1	0	1 (1%)
Mononucleosis syndrome	0	0	1	1 (1%)
Pharyngitis streptococcal	0	1	0	1 (1%)
Rhinitis	0	0	1	1 (1%)
Sinusitis	0	1	0	1 (1%)
Urinary tract infection	0	1	0	1 (1%)
<b>Injury, poisoning and procedural complications</b>	0	7	3	10 (7%)
<b>Investigations</b>	0	4	3	7 (5%)
Blood creatine phosphokinase increased	0	3	1	4 (3%)
Transaminase increased	0	1	1	2 (1%)

In this study patients received a single dose of 1.4mg/kg, or 2.8 mg/kg of two formulations of anti-IL-6. No grade 3 or higher AEs were reported. The AEs that

occurred with an incidence of  $\geq 5\%$  were neutropenia, abdominal discomfort/pain abdominal distension, nausea and or vomiting, and upper respiratory infection.

CNTO328MDS2001, the randomized trial in myelodysplastic syndrome

Table 58 presents the per patient incidence of treatment emergent AEs by SOC including preferred terms for SOCs with a  $\geq 3\%$  incidence of per patient AEs. Only preferred terms reported in more than 1 patient are included.

**Table 58: CNTO328MDS2001 Common Adverse Events System Organ Class and Selected Preferred Terms**

Per Subject Incidence n (%) System Organ Class Preferred Term	Siltuximab BSC n=50	Placebo BSC n=26
Skin and subcutaneous tissue disorders	7 (14%)	4 (15%)
General disorders and administration site conditions	16 (32%)	7 (27%)
Asthenia/fatigue/malaise	3 (6%)	2 (8%)
Chest discomfort/pain	3 (6%)	1 (4%)
Chills	2 (4%)	1 (4%)
Edema peripheral	8 (16%)	2 (8%)
Gastrointestinal disorders	17 (34%)	8 (31%)
Nausea/vomiting	4 (8%)	4 (15%)
Abdominal pain/distention	6 (12%)	0
Stomatitis (tongue ulceration)	3 (6%)	1 (4%)
Constipation	3 (6%)	1 (4%)
Diarrhea	2 (4%)	2 (8%)
Infections and infestations	15 (30%)	6 (23%)
Upper respiratory tract	4 (8%)	3 (12%)
Lower respiratory tract	4 (8%)	0
Urinary tract	2 (4%)	1 (4%)
Sepsis/bacteremia	2 (4%)	1 (4%)
Blood and lymphatic system disorders	4 (8%)	3 (12%)
Metabolism and nutrition disorders	11 (22%)	3 (12%)
Abnormal electrolytes (PO <sub>4</sub> , Mg, K)	4 (8%)	3 (12%)
Decreased appetite	2 (4%)	0
Dehydration	2 (4%)	0
Hypertriglyceridemia	1 (2%)	0
Respiratory, thoracic and mediastinal disorders	10 (20%)	8 (31%)
Nervous system disorders	11 (22%)	3 (12%)
Dizziness	4 (8%)	2 (8%)
Headache	3 (6%)	1 (4%)
Transient Paralysis*	1 (2%)	0
Investigations	2 (4%)	1 (4%)
Musculoskeletal and connective tissue disorders	11 (22%)	7 (27%)
Renal and urinary disorders	2 (4%)	0
Eye disorders	2 (4%)	0
Vascular disorders	6 (12%)	0
Hypotension (one episode infusion related)	3 (6%)	0
Neoplasms benign, malignant and unspecified	0	1 (4%)
Psychiatric disorders	3 (6%)	2 (8%)
Hepatobiliary disorders	8 (16%)	4 (15%)
Injury, poisoning and procedural complications	5 (10%)	1 (4%)
Cardiac disorders	5 (10%)	3 (12%)
Ear and labyrinth disorders	4 (8%)	1 (4%)

\*Transient paralysis was associated with an infusion reaction

The adverse reactions identified in this study are relevant to the safety profile of siltuximab. Because MCD is associated with multiple constitutional symptoms it is difficult to identify AEs associated with siltuximab treatment in the MCD population. Constitutional symptoms are not a prominent feature of MDS. The CNTO328MDS2001 study isolates the effect of siltuximab treatment, and provides a better determination of the AEs likely to be associated with siltuximab treatment. This information contributes to the risk benefit analysis of siltuximab. The preferred term for AEs reported with and incidence  $\geq 3\%$  in the siltuximab arm of CNTO328MDS2001 are presented in Table 59.

**Table 59: CNTO328MDS2001 Adverse Events Reported  $\geq 3\%$  in the Siltuximab Arm**

Per Subject Incidence n (%) System Organ Class Preferred Term	Siltuximab + BSC N=50		Placebo + BSC N=26	
	All Grades	Grade 3&4	All Grades	Grade 3&4
Infections				
Lower respiratory tract	4 (8%)	4 (8%)	0	0
General Disorders				
Edema (peripheral)	8 (16%)	0	2 (8%)	0
Gastrointestinal disorders				
Abdominal pain/distention	6 (12%)	0	0	0
Metabolism				
Decreased appetite	2 (4%)	0	0	0
Dehydration	2 (4%)	1 (2%)	0	0
Vascular Disorders				
Hypotension	3 (6%)	0	0	0

The Grade 3 and 4 infections reported for siltuximab included pneumonia (n=3), pneumonia and sepsis (n=1), bacteremia (*E. coli*) (n=1), cellulitis (n=1). One patient treated with placebo was reported to have sepsis.

#### 7.4.2 Laboratory Findings

##### CNTO328MCD2001 – Randomized trial Castleman’s disease

During the study, laboratory tests for safety evaluations were to be performed at specified timepoints. The following routine safety laboratory parameters were analyzed at local laboratories:

- Hematology: Complete blood count (CBC) (Hb, white blood cell (WBC) count with differential, and platelet count) reticulocyte count.
- Serum Chemistry: sodium, potassium, calcium, blood urea nitrogen (BUN), creatinine, uric acid, glucose, total protein, Alb, total bilirubin, aspartate aminotransferase (AST), ALT, lactate dehydrogenase (LDH), alkaline phosphatase.
- Lipid panel: cholesterol (high-density lipoprotein [HDL] and low-density lipoprotein [LDL]) and triglycerides.

The Table 60 is the applicant’s summary of the worst grade of laboratory abnormalities documented during the blinded treatment period of the trial (copied from submission Study Report CNTO328MCD2001 page 158/766).

**Table 60: CNTO328MCD2001 Worst Grade Laboratory Abnormalities**

**Table 50: Summary of Hematology and Chemistry Worst NCI-CTCAE Grade During the Blinded Treatment: Safety Population (Study CNTO328MCD2001)**

	Total N	Placebo + BSC					Total N	Siltuximab + BSC				
		NCI-CTCAE Grade, n (%)						NCI-CTCAE Grade, n (%)				
		0	1	2	3	4		0	1	2	3	4
<b>Hematology</b>												
WBC	26	22 (84.6)	2 (7.7)	2 (7.7)	0	0	53	33 (62.3)	11 (20.8)	9 (17.0)	0	0
Neutrophils	26	22 (84.6)	3 (11.5)	0	1 (3.8)	0	53	35 (66.0)	10 (18.9)	6 (11.3)	2 (3.8)	0
Platelet	26	22 (84.6)	3 (11.5)	0	0	1 (3.8)	53	39 (73.6)	8 (15.1)	4 (7.5)	2 (3.8)	0
Hemoglobin	26	10 (38.5)	9 (34.6)	4 (15.4)	3 (11.5)	0	53	14 (26.4)	27 (50.9)	11 (20.8)	1 (1.9)	0
Lymphocytes	26	18 (69.2)	2 (7.7)	4 (15.4)	2 (7.7)	0	53	32 (60.4)	5 (9.4)	13 (24.5)	3 (5.7)	0
<b>Chemistry</b>												
AST	26	22 (84.6)	4 (15.4)	0	0	0	53	40 (75.5)	12 (22.6)	1 (1.9)	0	0
ALT	26	22 (84.6)	4 (15.4)	0	0	0	53	34 (64.2)	19 (35.8)	0	0	0
Bilirubin	26	24 (92.3)	2 (7.7)	0	0	0	53	41 (77.4)	9 (17.0)	3 (5.7)	0	0
Alkaline Phosphatase	26	18 (69.2)	8 (30.8)	0	0	0	53	39 (73.6)	14 (26.4)	0	0	0
Creatinine	26	3 (11.5)	21 (80.8)	2 (7.7)	0	0	53	6 (11.3)	38 (71.7)	8 (15.1)	1 (1.9)	0
Hypercalcemia	26	26 (100.0)	0	0	0	0	53	51 (96.2)	2 (3.8)	0	0	0
Hypocalcemia	26	20 (76.9)	3 (11.5)	3 (11.5)	0	0	53	37 (69.8)	9 (17.0)	6 (11.3)	1 (1.9)	0
Hyperkalemia	26	26 (100.0)	0	0	0	0	53	47 (88.7)	3 (5.7)	0	3 (5.7)	0
Hypokalemia	26	20 (76.9)	0	5 (19.2)	1 (3.8)	0	53	43 (81.1)	0	9 (17.0)	1 (1.9)	0
Hyponatremia	26	16 (61.5)	10 (38.5)	0	0	0	53	33 (62.3)	19 (35.8)	0	1 (1.9)	0
Cholesterol	25	24 (92.3)	1 (3.8)	0	0	0	53	36 (67.9)	16 (30.2)	1 (1.9)	0	0
Triglycerides	25	15 (57.7)	6 (23.1)	3 (11.5)	1 (3.8)	0	53	34 (64.2)	10 (18.9)	7 (13.2)	2 (3.8)	0

There were no grade 4 laboratory abnormalities in the siltuximab arm. Incidences of grade 3 hematologic abnormalities were similar in the placebo and siltuximab arms. The only grade 3 chemistry abnormality reported more frequently in the siltuximab arm (> 3% incidence compared to placebo) was hyperkalemia.

CNTO328MDS2001, the randomized trial in myelodysplastic syndrome

A similar analysis of applicant's summary of the worst grade of laboratory abnormalities in the randomized MDS trial is presented in presented in Table 61(copied from submission Study Report CNTO328MDS2001 page 71/323).

**Table 61: CNTO328MDS2001 Worst Grade Laboratory Abnormalities**

	N	Placebo					N	Siltuximab				
		NCI-CTCAE Grade						NCI-CTCAE Grade				
		0	1	2	3	4		0	1	2	3	4
Analysis set: subjects in safety population	26						50					
<b>Chemistry</b>												
ALT	26	14 (53.8%)	10 (38.5%)	1 (3.8%)	1 (3.8%)	0	50	24 (48.0%)	22 (44.0%)	3 (6.0%)	1 (2.0%)	0
AST	26	19 (73.1%)	5 (19.2%)	1 (3.8%)	1 (3.8%)	0	50	28 (56.0%)	21 (42.0%)	1 (2.0%)	0	0
Alkaline phosphatase	26	24 (92.3%)	2 (7.7%)	0	0	0	49	41 (83.7%)	8 (16.3%)	0	0	0
Bilirubin	26	19 (73.1%)	4 (15.4%)	3 (11.5%)	0	0	50	30 (60.0%)	13 (26.0%)	6 (12.0%)	1 (2.0%)	0
Creatinine	26	8 (30.8%)	17 (65.4%)	1 (3.8%)	0	0	50	16 (32.0%)	31 (62.0%)	3 (6.0%)	0	0
Albumin	26	23 (88.5%)	1 (3.8%)	2 (7.7%)	0	0	50	46 (92.0%)	3 (6.0%)	1 (2.0%)	0	0
eGFR/CrCl	18	2 (11.1%)	14 (77.8%)	2 (11.1%)	0	0	36	6 (16.7%)	19 (52.8%)	11 (30.6%)	0	0
<b>Lipid</b>												
Cholesterol	24	24 (100.0%)	0	0	0	0	48	43 (89.6%)	5 (10.4%)	0	0	0
Triglycerides	25	24 (96.0%)	0	1 (4.0%)	0	0	48	39 (81.3%)	4 (8.3%)	4 (8.3%)	1 (2.1%)	0

There were no grade 4 laboratory abnormalities in the either arm. There were no grade 3 chemistry abnormalities reported more frequently in the siltuximab arm (> 3% incidence compared to placebo).

REVIEWER COMMENT:

No significant trends of laboratory abnormalities associated with siltuximab therapy were identified in the analysis of prospectively collected data in either of the randomized controlled (BSC) studies in MCD or MDS.

7.4.3 Vital Signs

No findings.

7.4.4 Electrocardiograms (ECGs)

(Copied from IRT Review (12/6/14))

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 62.

**Table 62: Analysis of  $\Delta$ QTcF for Siltuximab 15 mg/kg**

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

The suprathereapeutic 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.

7.4.5 Special Safety Studies/Clinical Trials

CNTO328MCD2002 – Extension trial Castleman’s disease

In order to evaluate the safety of extended exposure to siltuximab, AEs reported on subjects enrolled on study CNTO328MCD2002 after the first year of therapy were evaluated. There were 19 subjects enrolled on the extension study. The median length of exposure to siltuximab, excluding the first year of therapy, was 4.1 years (range 2.4 to 6.2).

No patients were removed from therapy for any reason. There were no deaths. There does not appear to be any cumulative toxicities identified with prolonged treatment with siltuximab.

#### 7.4.6 Immunogenicity (derived from submission 2.7.2 Clinical Pharmacology Studies page 69/89)

The immunogenicity of siltuximab was evaluated across multiple indications using validated antigen-bridging enzyme immunoassay (EIA) and electrochemiluminescence (ECL)-based immunoassay (ECLIA) methods. There was 1 sample from 583 evaluable subjects including 81 subjects with MCD determined to be positive for anti-siltuximab antibodies. Further immunogenicity analyses of the single positive sample revealed a low titer of 1:20 and non-neutralizing capabilities. The positive response was in Study CNTO328MCD2001 and was limited to the end of treatment visit; no anti-siltuximab antibodies were detected in samples taken prior to the end of treatment visit.

### **7.5 Other Safety Explorations**

#### 7.5.1 Dose Dependency for Adverse Events

Not done.

#### 7.5.2 Time Dependency for Adverse Events

Not done.

#### 7.5.3 Drug-Demographic Interactions

Not done.

#### 7.5.4 Drug-Disease Interactions

Not done.

#### 7.5.5 Drug-Drug Interactions

Not done.

### **7.6 Additional Safety Evaluations**

#### 7.6.1 Human Carcinogenicity

Not done.

7.6.2 Human Reproduction and Pregnancy Data

Not done.

7.6.3 Pediatrics and Assessment of Effects on Growth

Not applicable.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Not applicable.

**7.7 Additional Submissions / Safety Issues**

Not applicable.

## **8 Postmarket Experience**

Siltuximab is not an approved agent in any market at this time. There is no postmarketing experience.

## 9 Appendices

### 9.1 Literature Review/References

Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, et al., 2007, Revised Response Criteria for Malignant Lymphoma, *J Clin Oncol*, 25(5): 579-86.

Dispenzieri, A, 2012, POEMS Syndrome: Update on Diagnosis, Risk-stratification, and Management, *Am J Hematol* 87:804-14.

Kurzrock R, PM Voorhees, C Casper, et al., 2013, A Phase I, Open-Label Study of Siltuximab, an Anti-IL-6 Monoclonal Antibody, in Patients with B-cell Non-Hodgkin Lymphoma, Multiple Myeloma, or Castleman Disease, *Clin Cancer Res*, 19(13):3659–70.

Nishimoto N, Y Kanakura, K Aozasa, et al., 2005, Humanized Anti-interleukin-6 Receptor Antibody Treatment of Multicentric Castleman Disease, *Blood*, 106:2627–32.

van Rhee F, L Fayad, P Voorhees, et al., 2010, Siltuximab, a Novel Anti-interleukin-6 Monoclonal Antibody, for Castleman's Disease, *J Clin Oncol*, 28:3701–8.

#### UpToDate

Aster J, J Brown, Castleman's Disease; Literature review current through Sept 2013, Last updated July 2013, <http://www.uptodate.com/contents/castleman-s-disease>

## 9.2 Labeling Recommendations

### 1 INDICATIONS AND USAGE

The indication as proposed by Janssen is acceptable. I recommend adding the following Limitation of use to the indication:

#### Limitation of Use

SYLVANT should not be used in patients with MCD who are HIV - positive or HHV-8 – positive because SYLVANT does not bind to virally produced IL-6.

### 5 WARNING AND PRECAUTIONS

I have changed the language to imperative sentences.

I agree with the items Janssen proposed, with the exception of [REDACTED] (b) (4)

I have revised the common adverse reactions to reflect an analysis of safety data in the MCD2001 randomized study during the first 8 courses of therapy.

### 6.1 Clinical Trials Experience

I do not agree with Janssen's approach to this section. [REDACTED] (b) (4)

[REDACTED] his comparison obscures the adverse reaction profile of siltuximab in this population. Patients with MCD experience multiple disease-related constitutional symptoms. On the CNTO328MCD2001 trial patients treated with siltuximab received a median of 19 infusions compared to patients treated with placebo who received a median of 8 infusions. There was no comparison group of patients with Castleman's disease on the C0328T03, phase 1 trial. Therefore, the revised table only compares adverse reactions reported during the first 8 infusions of patients enrolled on the CNTO328MCD2001 trial, and does not include patients with Castleman's disease from the single arm phase 1 trial or the adverse reactions reported in patients on the placebo arm who crossed over to siltuximab.

Janssen also conducted a single agent randomized study in MDS. Patients with MDS do not experience as many constitutional symptoms as patients with MCD. Therefore

this experience further isolates the effect of siltuximab. A summary of this experience has been included.

Siltuximab has been administered to patients with MCD for prolonged periods (up to 7 years). A discussion of the long term safety has been added.

Finally the discussion of anaphylaxis and infusion related reactions did not provide an accurate idea of the incidence. The discussion was revised to reflect the entire experience with siltuximab in all the clinical trials.

#### 14 CLINICAL STUDIES

This section has been revised to limit discussion to pre-specified endpoint that were statistically significant. It was also revised to discuss the response in the hyaline vascular subtype.

### **9.3 Advisory Committee Meeting**

This application was not discussed at an advisory committee.

## 9.4 Abbreviations

Table 63: Abbreviations

Abbreviations	
AE	Adverse event
Alb	Albumen
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BSC	Best supportive care
CI	Confidence interval
C <sub>max</sub>	Maximum observed serum concentration
CR	Complete response
CRF	Case report form
CRP	C-reactive protein
ESA	Erythropoietin stimulating agents
ESR	Erythrocyte sedimentation rate
Hb	Hemoglobin
HHV-8	Human herpesvirus -8
HIV	Human immunodeficiency virus
HR	Hazard ratio
IL-6	Interleukin-6
ITT	Intent to treat
IV	Intravenous
mAb	Monoclonal antibody
MCD	Multicentric Castleman's disease
MDS	Myelodysplastic syndrome
MM	Multiple myeloma
NHL	Non-Hodgkin lymphoma
OS	Overall survival
PD	Pharmacodynamic / Progressive disease
PK	Pharmacokinetic
POEMS	Peripheral neuropathy, Organomegally, Endocrine abnormality, Monoclonal gamopathy, Skin [Syndrome]
PR	Partial response
SAE	Serious adverse event
SD	Stable disease
SOC	System organ classification
TNF- $\alpha$	Tumor necrosis factor – alpha
t <sub>1/2</sub>	Mean terminal half-life
VEGF	Vascular endothelial growth factor
VMP	Velcade, Melphalan, Prednisone [Regimen]

## 9.5 Classification of Multicentric Castleman Disease-Related Signs and Symptoms as Defined by Protocol

Table 64: Classification of Multicentric Castleman Disease-Related Signs and Symptoms

Disease Related Symptoms		
Sign or symptom of MCD	CTCAE Version 4.0 System organ class	CTCAE Version 4.0 term
Fatigue, malaise, lethargy, asthenia, weakness	General disorders and administration site conditions	Fatigue, malaise
Sweating, Night sweats	Skin and subcutaneous tissue disorders, General disorders and administration site conditions	Hyperhidrosis, General disorders and administration site conditions other specify as "nightsweats"
Fever	General disorders and administration site conditions	Fever
Weight loss	Investigations	Weight loss
Anorexia	Metabolism and nutrition disorders	Anorexia
Discomfort or pain due to compression by tumor mass	Neoplasms benign, malignant & unspecified	Tumor pain, or as specified by location in CTCAE terms
Autoimmune phenomena, autoimmune reaction, autoimmune hemolytic anemia autoimmune thrombocytic purpura	Immune system disorders	Autoimmune disorder, Immune system disorders - Other, specify as appropriate
Fluid retention, edema, cardiac effusion, pleural effusion, ascites, anasarca	Reproductive system and breast disorders Respiratory, thoracic and mediastinal disorders Skin and subcutaneous tissue disorders Vascular disorders General disorders and administration site conditions/  Gastrointestinal disorders Cardiac disorders	Specify as appropriate: Genital edema  Pleural effusion  Periorbital edema  Capillary leak syndrome Edema face, edema limbs, edema trunk, localized edema, neck edema/ General disorders and administration site conditions - other, specify as generalized edema Ascites Pericardial effusion
Dyspnea	Respiratory, thoracic, and mediastinal disorders	Dyspnea
Neuropathy	Neuropathy	Peripheral motor neuropathy, Peripheral sensory neuropathy, Nervous system disorders others, specify as appropriate
Skin rash, skin nodules, hyperpigmentation, pruritus	Skin and subcutaneous tissue disorders	Specify as appropriate: Rash acneiform, Rash maculopapular, Papulopustular rash, Purpura, Skin hyperpigmentation, Skin induration, Pruritus, Skin and subcutaneous tissue disorders - other, specify
Clinical signs and symptoms of endocrinopathy	Endocrine disorders	As per clinical symptoms or specify endocrine disorder as appropriate CTCAE v4 term

Signs and symptoms of MCD listed below will be scored where applicable according to the NCI-CTCAE criteria (Version 4.0) to evaluate treatment failure. For signs and symptoms (such as lymphadenopathy, hepatomegaly, or splenomegaly) not readily evaluable according to CTCAE grading, assess as appropriate according to modified Cheson criteria or by physical examination.

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

/s/  
-----

PATRICIA A DINNDORF  
01/29/2014

ALBERT B DEISSEROTH  
01/29/2014

# CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

**BLA Number:** 125496

**Applicant:** Janssen Biotech Inc **Stamp Date:** 8/30/13

**Drug Name:** Siltuxumab

**NDA/BLA Type:** Priority

**PDUFA Date:** 4/29/13

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
<b>FORMAT/ORGANIZATION/LEGIBILITY</b>					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	x			eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	x			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	x			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	x			
5.	Are all documents submitted in English or are English translations provided when necessary?	x			
6.	Is the clinical section legible so that substantive review can begin?	x			
<b>LABELING</b>					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	x			
<b>SUMMARIES</b>					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	x			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	x			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	x			
11.	Has the applicant submitted a benefit-risk analysis for the product?	x			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505(b)(1)
<b>DOSE</b>					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)? Study Number: CO328T03 Study Title: "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" Sample Size: 72 Arms: Approved 25 Feb 2012 2 Dose Cohort 1: 3 mg/kg q 2 wks x 4 (Days 1, 15, 29, 43) Dose Cohort 2: 6 mg/kg q 2 wks x 4 (Days 1, 15, 29, 43) Dose Cohort 3: 12 mg/kg q 3 wks x 3 (Days 1, 22, 43)	x			

File name: 5\_Clinical Filing Checklist for NDA\_BLA or Supplement 010908

## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Dose Cohort 4: 6 mg/kg q wk x 7 Days 1, 8, 15, 22, 29, 36, 43) Dose Cohort 5: 12 mg/kg q 2 wks x 4 (Days 1, 15, 29, 43) Dose Cohort 6: 12 mg/kg q 3 wks x 3 (Days 1, 22, 43) Dose Cohort 7a: 9 mg/kg q 3 wks Dose Cohort 7b: 12 mg/kg q 3 wks Location in submission: 5.3.5.2				
<b>EFFICACY</b>					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application?  Pivotal Study #1 - 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” Indication: Multicentric Castleman’s Disease  Supportive Study #2 - CO328T03 “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” Indication: Castleman’s Disease n=37	x			Orphan indication – The application includes a prospective blinded randomized trial and a supportive trial with a response rate of in
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	x			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	x			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			x	Not required. Study population includes adequate number of US subjects (17%)
<b>SAFETY</b>					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	x			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?	x			
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	x			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure <sup>1</sup> )			x	

<sup>1</sup> For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	been exposed at the dose (or dose range) believed to be efficacious?				
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	x			
23.	Has the applicant submitted the coding dictionary <sup>2</sup> used for mapping investigator verbatim terms to preferred terms?	x			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	x			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	x			
<b>OTHER STUDIES</b>					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			x	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			x	
<b>PEDIATRIC USE</b>					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?			x	Although Janssen asked for full waiver, PREA is not triggered because agent was granted orphan status.
<b>ABUSE LIABILITY</b>					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			x	
<b>FOREIGN STUDIES</b>					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			x	
<b>DATASETS</b>					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	x			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	x			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	x			
34.	Are all datasets to support the critical safety analyses available and complete?	x			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	x			
<b>CASE REPORT FORMS</b>					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and	x			

<sup>2</sup> The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comment</b>
	adverse dropouts)?				
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	x			
<b>FINANCIAL DISCLOSURE</b>					
38.	Has the applicant submitted the required Financial Disclosure information?	x			
<b>GOOD CLINICAL PRACTICE</b>					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	x			

### IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? Yes

1. The “[Comments](#)” hyperlinks in the CRFs for trial CNT0328MCD2001 are not functional. Please submit revised CRFs with functional hyperlinks facilitate review of the comments.

Patricia Dinndorf

10/22/13

---

Reviewing Medical Officer

Date

Albert Deisseroth

10/22/13

---

Clinical Team Leader

Date

File name: 5\_Clinical Filing Checklist for NDA\_BLA or Supplement 010908

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

/s/  
-----

PATRICIA A DINNDORF  
10/22/2013

ALBERT B DEISSEROTH  
10/22/2013