Clinical Pharmacology Review

BLA 125496
Submission Date: August 29, 2013
Brand Name: Sylvant®
Generic Name: Siltuximab (CNTO 328 IgG)
Formulation: 100 mg of lyophilized siltuximab in 8 mL vial (20 mg/ml after reconstitution) for intravenous infusion.
400 mg of lyophilized siltuximab in 30 mL vial (20 mg/ml after reconstitution) for intravenous infusion

OCP Reviewer: Jeanne Fourie Zirkelbach, PhD
OCP Team Leader: Julie M. Bullock, PharmD
Pharmacometrics Reviewer: Liang Zhao, PhD
Pharmacometrics Team Leader: Nitin Mehrotra, PhD
OND Division: Division of Clinical Pharmacology V
Sponsor: Janssen Biotech Inc.
Submission Type; Code: NME/0000, 0012, 0016/1
Dosing regimen: Siltuximab 11 mg/kg IV every 3 weeks.
Indication: For the treatment of patients with multicentric Castleman’s disease (MCD) who are human immunodeficiency virus negative (HIV-) and human herpes virus 8 negative (HHV-8).

Table of Contents
1 Executive Summary .................................................................2
  1.1 Recommendations .........................................................2
  1.2 Summary of Clinical Pharmacology Findings ..................4
2 Question Based Review ............................................................6
  2.1 General Attributes ..........................................................6
  2.2 General Clinical Pharmacology ........................................7
  2.3 Intrinsic Factors ...............................................................27
  2.4 Extrinsic Factors ............................................................33
  2.5 General Biopharmaceutics ................................................35
  2.6 Analytical Section ...........................................................38
3 Detailed Labeling Recommendations ....................................48
4 Appendices ..............................................................................48
  4.1 PHARMACOMETRICS REVIEW ..................................48
1 Executive Summary
Siltuximab is a chimeric (human-murine) IgG1κ monoclonal antibody that complexes with soluble bioactive forms of IL-6. The proposed indication is 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 primary data to evaluate the efficacy and safety of siltuximab in MCD are from the randomized, double-blind, placebo-controlled trial CNTO328MCD2001. Trial CNTO328MCD2001 determined the safety and efficacy of siltuximab + best supportive care (BSC) compared with placebo + BSC, in subjects with symptomatic MCD. The primary efficacy endpoint was independently reviewed durable tumor and symptomatic response rate. There was a statistically significant improvement in the primary efficacy endpoint in the siltuximab group compared with the placebo group (34% vs. 0%, respectively; 95% CI: 11.1, 54.8; p=0.0012).

The applicant’s proposed dosing regimen is 11 mg/kg q3w. The population PK analysis showed the proposed body weight based dosing is acceptable. The recommended dosing regimen is justified based on the evidence of clinical efficacy in trial CNTO328MCD2001 in MCD. The exposure-response analysis showed a lack of relationship between exposure or serum C-reactive protein (CRP) and durable tumor and symptomatic response rate at the proposed dosing regimen of 11 mg/kg q3w.

The serum siltuximab pharmacokinetics are adequately described by a linear two-compartment intravenous model with first-order elimination. No covariates (including mild to moderate renal and hepatic impairment) warrant a dose adjustment based on the population PK analysis.

1.1 Recommendations
The Office of Clinical Pharmacology has determined that there is sufficient clinical pharmacology and biopharmaceutics information provided in this BLA to support a recommendation of approval of Sylvant. The acceptability of specific drug information is provided below.

<table>
<thead>
<tr>
<th>Decision</th>
<th>Acceptable to OCP?</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>Yes × No NA</td>
<td></td>
</tr>
<tr>
<td>Evidence of Effectiveness†</td>
<td>Yes × No NA</td>
<td>One positive registration trial.</td>
</tr>
<tr>
<td>Proposed dose for general population</td>
<td>Yes × No NA</td>
<td>Siltuximab 11 mg/kg IV every 3 weeks.</td>
</tr>
<tr>
<td>Proposed dose selection for others</td>
<td>Yes × No NA</td>
<td>No dose modifications recommended from a CP perspective.</td>
</tr>
<tr>
<td>Pivotal BE</td>
<td>Yes × No NA</td>
<td>IV administration.</td>
</tr>
<tr>
<td>Labeling</td>
<td>Yes × No NA</td>
<td></td>
</tr>
</tbody>
</table>

†This decision is from a clinical pharmacology perspective only. The overall safety and effectiveness determination is made by the Clinical reviewer.
Labeling Recommendations
Please refer to Section 3 - Detailed Labeling Recommendations.

Phase 4 Requirements
No Phase 4 requirements were identified.
1.2 Summary of Clinical Pharmacology Findings

Siltuximab is a chimeric (human-murine) IgG1κ monoclonal antibody. The intact molecule contains 1324 amino acid residues and is composed of two identical heavy chains (approximately 50 kDa each) and two identical light chains (approximately 24 kDa each).

Mechanism of Action: Siltuximab forms complexes with soluble bioactive forms of IL-6 and prevents the binding of human IL-6 to both soluble and membrane-bound IL-6 receptors (IL-6R), thus inhibiting the formation of the hexameric signaling complex with gp130 on the cell surface.

Efficacy: The primary data to evaluate the efficacy and safety of siltuximab in MCD are from the randomized, double-blind, placebo-controlled trial CNTO328MCD2001. Subjects were randomized in a 2:1 ratio to siltuximab + BSC or placebo + BSC, and were to receive siltuximab (11 mg/kg) or placebo by a 1-hour IV infusion q3w. Seventy-nine subjects were randomized (53 in the siltuximab group, 26 in the placebo group). There was a statistically significant improvement in the primary efficacy endpoint (independently reviewed durable tumor and symptomatic response rate) in the siltuximab group compared with the placebo group (34% vs. 0%, respectively; 95% CI: 11.1, 54.8; p=0.0012).

Exposure-Response (Efficacy and Safety): The exposure-response analysis showed a lack of relationship between exposure or serum C-reactive protein (CRP) and durable tumor and symptomatic response rate at the proposed dosing regimen of 11 mg/kg q3w.

Pharmacokinetics (PK): Based on the population pharmacokinetic analysis, the clearance of siltuximab in patients is 0.23 L/day (51% CV), and body weight was identified as the only statistically significant covariate for siltuximab clearance. The mean terminal half-life (t1/2) for siltuximab in patients after a single oral dose of 11 mg/kg is 20.6 days (range: 14.2 to 29.7 days). Binding bioactive IL-6 by siltuximab may normalize CYP450 enzyme activity, and this may result in increased metabolism of CYP450 substrates compared to metabolism prior to treatment with siltuximab. If siltuximab is co-administered with CYP450 substrates with a narrow therapeutic index, the dose of the concomitant medication may need to be adjusted. Based on the population pharmacokinetic analysis, no initial dosage adjustment is necessary for patients with mild to severe renal impairment or for patients with mild to moderate hepatic impairment.

Immunogenicity: With the immunogenicity assays used, the overall incidence of positive anti-therapeutic antibody (ATA) to siltuximab was determined to be 0.2% in the studies included in the BLA. Further immunogenicity analyses of the single positive sample revealed a low titer of anti-siltuximab antibodies with non-neutralizing capabilities.

QT: No large changes in the mean QT interval (i.e., >20 ms) were detected at the proposed siltuximab dosing regimen.
Signatures:
Reviewer: J Fourie Zirkelbach, PhD
Division of Clinical Pharmacology 5
Team Leader: J Bullock, PharmD
Division of Clinical Pharmacology 5

Reviewer: L Zhao, PhD
Division of Pharmacometrics
Team Leader: Nitin Mehrotra, PhD
Division of Pharmacometrics

Cc: DDOP: CSO - P Garvey; MTL - A Deisseroth; MO - P Dinndorf, Safety MO - R Kane
DCP-5: Reviewers - J Fourie Zirkelbach (CP), L Zhao (PM)
CP TL - J Bullock, PM TL - N. Mehrotra
DDD - B Booth, DD - A Rahman

Reference ID: 3448540
2 QUESTION BASED REVIEW

2.1 GENERAL ATTRIBUTES

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Siltuximab is a chimeric (human-murine) immunoglobulin monoclonal immunoglobulin G1 (IgG1) containing kappa light chains. The intact molecule contains 1324 amino acid residues and is composed of two identical heavy chains (approximately 50 kDa each) and two identical light chains (approximately 24 kDa each) (Figure 1). The heavy and light chains contain 449 and 213 amino acid residues, respectively. The chains are linked together via non-covalent heavy-heavy and heavy-light interactions, and also covalent heavy-heavy and heavy-light disulfide bonds. Predicted molecular masses for the most common siltuximab glycoforms range from 147,128 Da to 147,909 Da.

<table>
<thead>
<tr>
<th>Heavy Chain</th>
</tr>
</thead>
<tbody>
<tr>
<td>EVQLVESGGK LLKPGGSLKL SCASQGFTFS SFAMSWFRQPS FKRLWEVVAE ISSGGSYTYY</td>
</tr>
<tr>
<td>PDVTVGRTKI SRDNAKNTLY LEMSSLRSED TAMYVCARGL WGGYALDYGQ QGTSVTSSA</td>
</tr>
<tr>
<td>STKGPSYFPL APSKSTSSGG TALGCLYKD YFPEPVTVSW NSGALTSGYH TFPAVLGSSG</td>
</tr>
<tr>
<td>LYSLSWSWTV PSSSLGTQTY ICNYNHKPSN TKVDKKEVPEK SGDKTHTCPP CPAPELLGGP</td>
</tr>
<tr>
<td>SVFLFPPKPK DTLMSRTPE VTCVVDVSH EDPEVKFNFY VDGVEVHNAK TKPREEQYN</td>
</tr>
<tr>
<td>TYRVSVLTV LHQDWLNGKE YKCKYNSKAL PAPIETKISK AKGQPREPOY YTLPPRSDEL</td>
</tr>
<tr>
<td>TKNOVSTLCT VKGFYPSDIA VEWESNGQPE NNYKTTPPVY DSDGSFLYSS KLTVDKSRWQ</td>
</tr>
<tr>
<td>QGNVFSCVSVM HEALHNHYTQ KSLLSPRGK</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Light Chain</th>
</tr>
</thead>
<tbody>
<tr>
<td>QIVLQSPA MSASPGEKVT MTCSASSSVS YMYWYQQKPG SSSRLTVYT2 STNLASGVPR</td>
</tr>
<tr>
<td>FSGSGSSTSY SLSRMEAEG DAAYYCCQWS GGGYTFGGG TKEIKRTVA APSVFIFPPS</td>
</tr>
<tr>
<td>DEQLKSGTAS WULLNNFYF REMKVKWD NALQSCNQFE SVTEQSDKDS SYLSSLTLT</td>
</tr>
<tr>
<td>SKADYEHKTV YACEVTHOGL SSVTNSFNR GEC</td>
</tr>
</tbody>
</table>

Figure 1. The Amino Acid Sequences of Siltuximab Heavy and Light Chains.

The siltuximab final lyophilized product is supplied as a sterile, single-use lyophilized dosage form (100 mg or 400 mg vials) for intravenous (IV) infusion. Each 100 mg vial and 400 mg vial must be reconstituted with 5.2 mL or 20.0 mL of sterile water for injection, respectively, to yield a 20 mg/mL solution. Following reconstitution with sterile water, the pH is 5.2. The 20 mg/mL siltuximab solution is further diluted for IV infusion.
Each 100 mg vial drug product contains 100 mg siltuximab, 3.7 mg L-histidine, 0.8 mg polysorbate 80, and 169 mg sucrose. Each 400 mg vial drug product contains 400 mg siltuximab, 14.9 mg L-histidine, 3.2 mg polysorbate 80, and 677 mg sucrose.

2.1.2 What are the proposed mechanisms of action and therapeutic indications?
Siltuximab forms stable complexes with soluble bioactive forms of human Interleukin-6 (IL-6). Siltuximab prevents the binding of human IL-6 to both soluble and membrane-bound IL-6 receptors (IL-6R), thus inhibiting the formation of the hexameric signaling complex with gp130 on the cell surface. IL-6 is a pleiotropic proinflammatory cytokine produced by a variety of cell types including T and B-cells, lymphocytes, monocytes and fibroblasts, as well as malignant cells. IL-6 has been shown to be involved in diverse normal physiologic processes such as induction of immunoglobulin secretion, initiation of hepatic acute phase protein synthesis, and stimulation of hematopoietic precursor cell proliferation and differentiation. Overproduction of IL-6 has been hypothesized to play a central role in driving plasma cell proliferation and systemic manifestations in patients with Castleman’s disease (CD).

The proposed indication is siltuximab 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.

2.1.3 What are the proposed dosage(s) and route(s) of administration?
The recommended dose of siltuximab is 11 mg/kg given over 1 hour by IV infusion every 3 weeks (q3w) until treatment failure.

2.2 GENERAL CLINICAL PHARMACOLOGY
2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?
A summary of completed clinical trials with siltuximab to support the BLA application is shown in Table 1.

Table 1. Summary of completed clinical trials with Siltuximab to support the BLA application.

<table>
<thead>
<tr>
<th>Trial Number</th>
<th>Trial Design</th>
<th>Primary Objectives</th>
<th>No of Subjects</th>
<th>Treatment Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNTO328MCD2001</td>
<td>Phase 2, R, DB, PC in measurable and symptomatic MCD</td>
<td>Tumor and Symptom response</td>
<td>Randomized = 70; S+BSC = 53; P+BSC = 26</td>
<td>S 11 mg/kg over 1 hour q3w +BSC P+BSC</td>
</tr>
<tr>
<td>C0328T03</td>
<td>Phase 1 dose-finding trial. Cohorts 1-6: B cell NHL, MM or MCD Cohort 7: MCD</td>
<td>Safety and PK</td>
<td>Enrolled: 72</td>
<td>Cohort 1 = 3 mg/kg S q2w; Cohort 2 = 6 mg/kg q2w; Cohort 3 = 12 mg/kg; Cohort 4 = 6 mg/kg; Cohort 5 = 12 mg/kg q2w; Cohort 6 = 12 mg/kg q3w; Cohort 7a = 9 mg/kg q3w; Cohort 7b = 12 mg/kg q3w</td>
</tr>
<tr>
<td>C0328T08</td>
<td>Phase 1 Part 1: DB, PL, SJD; Part 2: open label, PL, SJD Healthy men/women</td>
<td>PK comparability of CHO-derived siltuximab vs. Sp2/0-derived siltuximab following 1.4 mg/kg dose</td>
<td>Randomized: 145; Part 1 = 26; Part 2 = 120</td>
<td>Part 1: 2.8 mg/kg S CHO-derived or Sp2/0-derived siltuximab Modified Part 1 and Part 2: 1.4 mg/kg S of CHO-derived or Sp2/0-derived siltuximab</td>
</tr>
<tr>
<td>C0328T01 (Part 1)</td>
<td>Phase 1/2</td>
<td>Safety, PK, PD.</td>
<td>Enrolled: 11</td>
<td>S 1 mg/kg, 3 mg/kg, 6 mg/kg, or</td>
</tr>
<tr>
<td>Trial Number</td>
<td>Trial Design</td>
<td>Primary Objectives</td>
<td>No of Subjects</td>
<td>Treatment Regimen</td>
</tr>
<tr>
<td>---------------</td>
<td>-----------------------------------</td>
<td>----------------------------</td>
<td>----------------</td>
<td>-----------------------------------------------------</td>
</tr>
<tr>
<td>C0328T01 (Part 2)</td>
<td>Phase 1/2 DB, R, 2-treatment Metastatic RCC.</td>
<td>Safety, PK, efficacy.</td>
<td>Randomized: 38 (Stage 1)</td>
<td>S IV infusion 3 mg/kg 6 mg/kg</td>
</tr>
<tr>
<td>C0328T01 (Part 3)</td>
<td>Phase 1/2 OL Metastatic RCC.</td>
<td>Safety, PK, Efficacy.</td>
<td>Enrolled: 20</td>
<td>S 6 mg/kg over no less than 2 hours q2w</td>
</tr>
<tr>
<td>CNT0328SMM1001</td>
<td>Phase 1 OL, SA. MT</td>
<td>GT interval.</td>
<td>Enrolled: 33</td>
<td>S 15 mg/kg over 1 hour q3w, 4 cycles</td>
</tr>
<tr>
<td>CNT0328STM2001</td>
<td>Phase 1/2 OL MD, 2-part, DE, Progressive MST.</td>
<td>CR+PR+STD of duration &gt;6 weeks, PK, Immunogenicity, PD</td>
<td>Enrolled: 84</td>
<td>S Cohort 1= 2.8 mg/kg Day 1, Day 28, then 4 administrations q2w; Cohort 2= 5.5 mg/kg, Day 1, Day 28, then 4 administrations q2w; Cohort 3= 11 mg/kg, Day 1, Day 28, then 4 administrations q3w; Cohort 4= 15 mg/kg, Day 1, Day 28, then 4 administrations q3w; Cohort 5= 15 mg/kg 12 administrations q3w up to 36 weeks</td>
</tr>
<tr>
<td>CNT0328MDS2001</td>
<td>Phase 2 R, DB, PC. Myelodysplastic syndrome.</td>
<td>Clinical efficacy, PK</td>
<td>Treated: 76</td>
<td>Group A: S 15 mg/kg over 1 hour q4w + BSC Group B: P over 1 hr q4w + BSC</td>
</tr>
</tbody>
</table>

An absorptivity constant of 1.4 (mg/mL)^2 cm=1 was used to calculate the dose of siltuximab during early nonclinical development and in early clinical studies, including Studies C0328T01, C0328T03, C0328T04, C0328T05, C0328T06, and C0328T07, that were started before 2007. Therefore, for studies conducted earlier than 2007 the doses reported in the trial protocols (e.g. 12 mg/kg) should be adjusted to the actual dose administered by multiplying them by a factor of 0.92, (12 mg/kg adjusted to 11 mg/kg) which is the ratio of the interim absorptivity constant, 1.4 (mg/mL)^2 cm=1 and the validated absorptivity constant, 1.52 (mg/mL)^2 cm=1.

S = Siltuximab, R = Randomized, DB = Double-Blind, P = placebo, PC = Placebo Controlled, PL = Parallel Group, SD = Single Dose, OL = Open Label, DE = Dose-Escalation, RCC = Renal Cell Carcinoma, SA = Single arm, MM = Multiple Myeloma, MD = Multiple Dose, MST = Malignant Solid Tumors, CR = Complete Response, PR = Partial Response, STD = Stable Disease, PD = pharmacodynamics, BSC = Best Supportive Care.

### 2.2.1.1 Registration Clinical Trial

The clinical development program for evaluating the efficacy and safety of siltuximab in MCD consists of 3 studies. The primary data are from the randomized, double-blind, placebo-controlled trial CNT0328MCD2001 with supportive data from trial C0328T03 in which 35 subjects with MCD and 2 subjects with uniceentric CD were treated, and from an interim analysis of the ongoing trial CNT0328MCD2002 with data from 19 subjects who were previously treated with siltuximab in C0328T03.

Trial CNT0328MCD2001 was a randomized, double-blind, placebo-controlled, multicenter, Phase 2 trial to determine the safety and efficacy of siltuximab + best supportive care (BSC) compared with placebo + BSC, in subjects with symptomatic MCD. Subjects were stratified according to corticosteroid use (yes vs. no). Subjects were randomized in a 2:1 ratio to siltuximab + BSC or placebo + BSC, and were to receive siltuximab (11 mg/kg) or placebo by a 1-hour IV infusion q3w. Seventy-nine subjects were randomized (53 in the siltuximab group, 26 in the placebo group).

**Primary Endpoint:**
The primary efficacy endpoint was durable tumor and symptomatic response rate, assessed by independent central radiology review and investigator-assessed symptomatic response (See definitions below). The trial was powered to test the statistical hypothesis for the primary endpoint (a difference of 25% in durable tumor and symptomatic response rate between the treatment arm and the control arm). Disease assessments (evaluation of signs and symptoms) were performed on Day 1 of every cycle. Radiologic imaging was required at screening, every 9 weeks during the first 6 months of treatment regardless of treatment delays, every 3 months thereafter up to 2 years of treatment, and every 6 months thereafter until the clinical cutoff for the primary analysis.

- **Tumor and Symptomatic Responses were Assessed Using the Following Criteria:**
  - **Complete Response (CR):** Complete disappearance of all measurable and evaluable disease (e.g., pleural effusion) and resolution of baseline symptoms attributed to MCD, sustained for at least 18 weeks.
  - **Partial Response (PR):** A \( \geq 50\% \) decrease in sum of the product of the diameters (SPD) of index lesion(s), with at least stable disease in all other evaluable disease in the absence of treatment failure, sustained for at least 18 weeks.

- **Durable Tumor Response was Defined as Complete Response and Partial Response (CR + PR) as follows:**
  - Tumor response was assessed by Radiology Review. Tumor response was based on the assessment of index lesions (measurable) and nonindex lesions (nonmeasurable).

- To evaluate durable symptomatic response (symptom burden), the MCD-related symptom score was calculated by adding the number of 34 prospectively collected signs and symptoms of MCD by NCI-CTCAE grade. Patient-reported symptom severity data were assessed using a newly developed disease instrument, as no tools were available for this rare indication. This MCD symptom scale (MCDSS), developed based on results of qualitative research with MCD patients and clinical experts, was subsequently field tested with additional MCD patients.

- **Durable Symptomatic Response was Defined as Complete Symptomatic Response and Partial Symptomatic Response (CR + PR):**
  - **Complete symptomatic response:** Complete symptom response, defined as a 100% reduction in the baseline overall MCD symptom score sustained for at least 18 weeks prior to treatment failure.
  - **Partial symptomatic response:** Partial symptom response was defined as a \( \geq 50\% \) reduction but \(< 100\% \) reduction in the baseline overall MCD symptom score sustained for at least 18 weeks prior to treatment failure.
  - **Durable complete symptomatic response was defined as complete response (CR [complete symptom response, defined as a 100% reduction in the baseline overall MCD symptom score sustained for at least 18 weeks prior to treatment failure]).**
The sponsor reported that the trial met its primary endpoint and showed a statistically significant 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: 11.1, 54.8; p=0.0012).

2.2.1.2 Clinical Pharmacology Studies
Siltuximab PK data were reviewed for trials CNTO328MCD2001, C0328T01, C0328T03, and CNTO328STM2001. Trial C0328T08 is included to demonstrate the PK comparability between CHO- and Sp2/0-derived-siltuximab. Trial CNTO328SMM1001 assessed QT/QTc interval prolongation by siltuximab. The immunogenicity of siltuximab was assessed in trials C0328T01, C0328T03, C0328T04, C0328T05, C0328T06, C0328T07, C0328T08, JPN-C0328-MM-101, CNTO328STM2001, CNTO328MDS2001, CNTO328MMY2001, and CNTO328MCD2001.

A population PK model (trial report EDMS-ERI-51313826) was developed and validated by the applicant using PK data from 6 Phase 1 and Phase 2 studies (Studies C0328T01, C0328T03, CNTO328STM2001, CNTO328SMM1001, CNTO328MDS2001 and CNTO328MCD2001).

An exposure and response analysis was conducted by the applicant to assess the PK/PD relationship in trial CNTO328MCD2001 between the first dose exposure in terms of Cmax and AUC(0-t) and durable tumor and symptomatic response as defined by the primary efficacy objective.

2.2.2 What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical studies?
The primary efficacy endpoint in the clinical trial used to support the BLA application was the durable tumor and symptomatic response rate, based on independent review (see Section 2.2.1.1).

(b) (d) for protocol CNTO328MCD2001, however the primary endpoint was reviewed by FDA and found generally acceptable (Teleconference: Oct 15, 2009).

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?
Yes. Two electrochemiluminiscent immunoassay (ECLIA) methods were used to determine serum siltuximab concentrations and characterize the PK of siltuximab in the clinical studies supporting this registration.

The applicant provided supportive data of an analysis of serum C-reactive protein (CRP) levels measured as a surrogate marker to evaluate suppression of bioactive IL-6 with siltuximab treatment in trials CNTO328MCD2001 and C0328T03. A immunoturbidometric assay (a) for the in vitro quantitative determination of CRP in human serum and plasma on automated clinical chemistry analyzers was used, and this assay appears
appropriate for qualitative conclusions.

2.2.4 Exposure Response
2.2.4.1 Were efficacy responses similar for different MCD histological subtypes at randomization based on the pivotal phase 2 Trial CNTO328MCD2001?

No. The efficacy response rates for different MCD histological subtypes at randomization, based on the pivotal phase 2 trial, were different. Based on an analysis regarding the imbalance in demographic variable distribution between responders and non-responders, it was found that all 18 patients of hyaline vascular MCD histology failed to respond to treatment for durable tumor and symptomatic response.

As shown in Table 2, most baseline demographic characteristics were balanced between responders and non-responders in the siltuximab treatment arm of trial CNTO328MCD2001. The imbalance was only marginally significant in white vs. non-white (84% of whites as non-responders compared to an overall response rate of 34% in the treatment arm). However, categorizing the patient population into white vs. non-white was an arbitrary choice. If it was chosen to categorize the patient population into Asian vs. non-Asian, given that 27 out of 53 patients were Asians in the treatment arm, the imbalance was no longer statistically significant. Furthermore, there is a lack of mechanistic support to see different response rates from different racial groups based on our current knowledge.

An imbalance was statistically significant for MCD histology based on the Fisher’s exact test. All 18 patients identified with the hyaline vascular subtype failed to show a clinical response (Table 2). In contrast, no strong imbalance in distribution of responders vs. non-responders was found in patients with mixed and plasmacytic subtypes. Therefore, the durable tumor and symptomatic response may not be the same for different MCD histology subtypes, and a potential confounding effect of MCD histology at randomization should be considered for drug exposure-response and CRP level-response relationships.

<p>| Table 2. Summary of the Number of Patients in the Siltuximab Treatment Arm of Trial CNTO328MCD2001 Based on Demographic Information |
|:---:|:---:|:---:|
| <strong>Sex</strong> | <strong>Responders</strong> | <strong>Non responders</strong> |
| Male (N=30) | 33% | 67% |
| Female (N=23) | 35% | 65% |
| <strong>Race</strong> | | |
| Non-white (N=34) | 44% | 56% |
| White (N=19) | 16% | 84% |
| <strong>Race</strong> | | |
| Asian (N=27) | 41% | 59% |
| Non-Asian (N=26) | 27% | 73% |
| <strong>Region</strong> | | |
| Asia (N=26) | 38% | 62% |
| EMEA (N=13) | 23% | 77% |</p>
<table>
<thead>
<tr>
<th></th>
<th>Latin America (N=4)</th>
<th>North America (N=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>25%</td>
<td>75%</td>
</tr>
<tr>
<td>Age (years)</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td></td>
<td>45 ± 15</td>
<td>44 ± 13</td>
</tr>
<tr>
<td>Corticosteroid use at randomization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (N=16)</td>
<td>25%</td>
<td>75%</td>
</tr>
<tr>
<td>No (N=37)</td>
<td>38%</td>
<td>62%</td>
</tr>
<tr>
<td>MCD histology at randomization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyaline Vascular (N=18)</td>
<td>0%</td>
<td>100%</td>
</tr>
<tr>
<td>Mixed (N=22)</td>
<td>45%</td>
<td>55%</td>
</tr>
<tr>
<td>Plasmacytic (N=13)</td>
<td>62%</td>
<td>38%</td>
</tr>
<tr>
<td>Baseline num of MCD symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;=4 (N=25)</td>
<td>28%</td>
<td>72%</td>
</tr>
<tr>
<td>&gt;4 (N=28)</td>
<td>39%</td>
<td>61%</td>
</tr>
</tbody>
</table>

MCD: multicentric Castleman’s disease. SD: standard deviation.

**Data Source:** Sponsor submitted demographic datasets (processed and summarized by Dr. Lei Nie).

It is worthwhile to note that patients with the hyaline vascular subtype did show benefit in terms of other secondary efficacy measures (See Clinical review for details). Therefore, from our perspective the proposed indication, which includes all MCD subtypes, appears reasonable.

### 2.2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?

The pharmacometrics review concluded that there is a lack of relationship between exposure and response (durable tumor and symptomatic response rate) at the proposed dosing regimen of 11 mg/kg q3w (Figure 2), and a lack of relationship between CRP levels and response (Trial CNTO328MCD2001) (Figure 3). See Appendix for more details.
A. Predicted Probability for Response AUClst, 1st dose (µg.day/ml)

B. Predicted Probability for Response AUClst, 1st dose (µg.day/ml)

Figure 2. Predicted Probabilities for Response with 95% Confidence Limits. A) Exposure-response relationship for all patients in siltuximab treatment arm. B) Exposure-response relationship for all patients of mixed and plasmacytic subtypes. Circles: Observed; Line: Predicted; Shaded area: 95% Confidence limits of prediction. (Source: Pharmacometrics Reviewer analysis.)
Figure 3. Predicted Probabilities for Response vs. CRP Level for Patients of Mixed and Plasmacytic Subtypes. A) Response vs. CRP level at baseline. B) Response vs. CRP level at steady state.
Circles: Observed; Line: Predicted; Shaded area: 95% Confidence limits of prediction. (Source: Pharmacometrics Reviewer analysis.)
2.2.4.3 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?

The safety profile, as defined by the incidence of adverse events (AEs), Grade 3 or higher AEs, serious adverse events (SAEs), and mortality, was similar for placebo- and siltuximab-treated subjects in the MCD population. Incidence rates for AEs leading to discontinuation in siltuximab-treated subjects were similar or lower compared with the placebo group. For further details see Appendix.

2.2.4.4 Does this drug prolong the QT or QTc interval?

The effect of siltuximab 15 mg/kg q3w for four cycles on the QTc interval was evaluated in 25 patients with Monoclonal Gammopathy of Undetermined Significance (MGUS), Smoldering Multiple Myeloma (SMM) or Indolent Multiple Myeloma (IMM) in a single arm trial (Trial CNTO328SMM1001). There was no large change (i.e., > 20 ms) in the QTc interval detected when siltuximab 15 mg/kg was administered q3w by a 1-hour IV infusion for four cycles. Using the Frederica corrected QT (QTcF) interval, the largest upper bound of the 2-sided 90% CI mean change from baseline in QTcF was 6.6 ms. The relationship between ΔQTcF and siltuximab concentrations is shown in Figure 4, with no evident exposure-response relationship. There were no placebo or positive control arms in the trail. See the QT/IRT review for further details.

![Figure 4. Relationship between ΔQTcF and Siltuximab Concentration (CNTO328SMM1001)](image)

2.2.4.5 Is the dose and dosing regimen selected by the applicant consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

The recommended dosing regimen appears justified based on the evidence of clinical efficacy in trial C0328T03 and trial CNTO328MCD2001 in MCD at 11 mg/kg q3w, and the lack of dose limiting toxicities (DLTs) at 15 mg/kg q3w in trial CNTO328STM2001. In addition, the applicant based siltuximab dose selection on clinical efficacy and bioactivity rather than the maximum tolerated dose, which is appropriate for biologic agents. The population PK analysis showed that body weight (WT) was a significant covariate on all siltuximab PK parameters (CL, and Vc), and therefore the proposed body weight based dosing is acceptable.
The recommended dose of siltuximab is 11 mg/kg administered q3w as a 1-hour IV infusion. Two dose escalation trials were conducted to identify the recommended siltuximab dose:

- Trial C0328T03 evaluated variable dosing regimens and increasing doses of siltuximab in 37 patients with MCD, and the highest dose level evaluated was 11 mg/kg every 3 weeks as a 1-hour IV infusion. Treatment continued until disease progression or unmanageable treatment-related toxicity. No DLTs were observed with any of the dosing regimens or doses tested. The patients with MCD treated at 11 mg/kg every 3 weeks had higher frequencies of tumor responses and clinical benefit responses than patients with MCD treated at the next lower dose of 8.3 mg/kg every 3 weeks.

- Trial CNTO328STM2001 was a multiple-dose, dose escalation trial in patients with malignant solid tumors. The doses studied were 2.8 and 5.5 mg/kg every 2 weeks and 11 and 15 mg/kg every 3 weeks as a 1-hour IV infusion. No DLTs were observed in the highest dose cohorts, and the siltuximab maximum tolerated dose was not reached at the highest dose of 15 mg/kg.

The proposed dose and dosing regimen are further supported by the 34% response rate in the treatment arm vs. 0% response rate in the placebo arm in the pivotal trial (CNTO328MCD2001).

The applicant provided supportive data for the dose/dosing regimen proposed with an analysis of serum CRP levels as a surrogate marker to evaluate suppression of bioactive IL-6 with siltuximab treatment, measured in trials CNTO328MCD2001, CNTO328MCD2001 and C03328T03. The rationale is based on literature studies that show that IL-6 is the primary factor that drives expression of CRP from hepatocytes in response to inflammatory stimuli such as Castleman’s disease. However, it should be noted that CRP is not considered a validated marker for suppression of bioactive IL-6. The literature indicates that normal levels of serum CRP (0.64 µg/ml) do not differ between healthy adult men and women, but tend to increase slightly with age (Macy et al., Clin Chem, 1997). The applicant provided data to show that subjects with Castleman’s disease treated with 11 mg/kg every 3 weeks in trial C0328T03 showed a greater decrease of systemic CRP levels compared with those treated with 8.3 mg/kg every 3 weeks. This supports the clinical efficacy observations that higher tumor and clinical benefit responses were observed at a siltuximab dose of 11 mg/kg every 3 weeks. Further, in subjects with solid tumors (Trial CNTO328STM2001), similar CRP suppression was observed at 11 mg/kg every 3 weeks and 15 mg/kg every 4 weeks indicating that doses higher than 11 mg/kg every 3 weeks are not needed to neutralize the drug target. CRP suppression at the proposed dose was further sustained throughout the treatment period. The review of the bioanalytical method validation report for CRP quantitation indicates that the applicant’s data on CRP serum levels should serve as qualitative rather than quantitative supportive evidence that the proposed 11 mg/kg q3w dosing regimen is effective in decreasing CRP serum concentrations (see Section 2.6.1 and the Appendix).

### 2.2.5 Pharmacokinetic characteristics of the drug and its major metabolites
#### 2.2.5.1 What are the single-dose and multiple-dose PK parameters?
Trials describing the PK of siltuximab in patients with MCD and hematological and non-hematological malignancies:

- Trial C0823T03 was a dose-escalation trial that characterized the single-dose and
multiple-dose PK of siltuximab in patients with B-cell non-Hodgkin’s lymphoma (NHL), multiple myeloma (MM), or Castleman’s disease (CD). Siltuximab was administered IV at the specified doses and dosing schedule, with an infusion time of 2-hours for Cohorts 1-5 and 1-hour for Cohorts 6 and 7.

The dosing schedules evaluated were:

- 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

Full PK profiles for siltuximab were collected following the first single-dose administration period on Day 1 (Prior to administration, 1 hour after the start of administration, immediately after completion of the administration, and 6 hours, 24 hours, and 72 hours after the start of administration) and during the multiple-dose period on Day 43 (Prior to administration, 1 hour after the start of administration, immediately after completion of the administration, and 6 hours, 24 hours (Day 44), and 72 hours (Day 46) after the start of administration, and at follow-up Weeks 1, 2, 3, and 4). Due to the limited number of samples collected in Cohorts 7a and b, Cmax is the only the pharmacokinetic parameter reported for these cohorts.

- Trial CO328T01 was a dose-escalation trial that characterized the single-dose PK of siltuximab in patients with renal cell carcinoma. Siltuximab was administered intravenously at 4 dose levels (1, 3, 6, and 12 mg/kg as an IV infusion over no less 2-hours). CNTO 328 was administered as 4 doses (Days 1, 29, 43, and 57). A full pharmacokinetic profile was required for all subjects after the first and fourth administration, with peak and trough concentration assessments performed on samples from all other administrations.

- Trial CNTO328STM2001 was a multiple-dose, dose-escalation trial that characterized the single-dose and multiple-dose PK of siltuximab in patients with malignant solid tumors. CHO-derived siltuximab was administered as a 1-hour IV infusion at 2.8 mg/kg, 5.5 mg/kg, 11 mg/kg, and 15 mg/kg. PK was monitored for 3 weeks after the first dose. The second dose in was to be administered 4 weeks after first dose. Full PK profiles for siltuximab were collected following the first single-dose administration on Day 1 (Prior to and immediately after the completion of the infusion, and 4 hours, 6 hours, and 24 hours after the end of the infusion, and on Days 8, 15, and 22).

- Trial CNTO328MCD2001 assessed the PK of siltuximab in patients with MCD. Subjects received siltuximab (11 mg/kg) or placebo by a 1-hour IV infusion every 3 weeks. Siltuximab PK samples were taken in Cycle 1: predose, end of infusion, 2 and 4 hours after the end of infusion, and on Day 8 and Day 15. For subsequent doses (2nd, 3rd, 6th, 9th, and 12th doses only); samples were taken predose and end of infusion, and for the
last dose, samples were taken 1, 2, 4, 8, and 12 weeks post-infusion.

In trial C0823T03, following a dose of 11 mg/kg (Cohorts 3, 5, and 6), mean serum siltuximab concentration-time profiles after the first dose up to 72 hours post-infusion by disease type are presented in Figure 5. This allowed for comparison of the pharmacokinetic profile of siltuximab in subjects with NHL, MM, and MCD. Following a 11 mg/kg dose, the serum concentration-time profiles were similar in subjects with NHL, MM and MCD.

![Figure 5](image-url)

**Figure 5.** Mean serum siltuximab concentration following the first dose of 11 mg/kg by disease type subjects evaluable for PK analysis in Cohort 3, 5, and 6 (C0823T03).

In trial CNTO328STM2001, for Cohorts 1 through 4, mean serum siltuximab concentration time profiles after the first dose and multiple doses are presented in Figure 6 and Figure 7.
Figure 6. Mean Siltuximab Serum Concentration (μg/mL) Following the First Dose through Day 28 in Treated Subjects with Solid Tumors, Cohorts 1 – 4 (CNTO328STM2001).

Figure 7. Mean serum siltuximab (CNTO 328) concentration at Day 43 administration by Cohort; subjects evaluable for PK analysis in Cohort 1 to 6 (C0823T03).

The population PK analysis indicated that a 2-compartment model adequately described the time course of serum siltuximab concentration following multiple IV administrations in 378 subjects with MCD, renal cell carcinoma, NHL, MM, prostate cancer, ovarian cancer and smoldering MM who received single-agent siltuximab at doses ranging from 0.9 to 15 mg/kg. The typical population values for CL and volume of distribution of the central compartment (Vc), in subjects
with a standard body weight of 70 kg were 0.233 L/day and 4.54L, respectively. The between-subject variability (% CV) for CL and Vc were 50.9% and 20.3%, respectively. For details see the Appendix.

Following the first administration at the target dose of 11 mg/kg, the mean (± SD) CL of siltuximab was 4.59 ± 3.064 mL/day/kg and the half-life (t1/2) was 20.6 ± 6.976 days. At 11 mg/kg (cohort 6), the single-dose intersubject variability in AUC_{0-inf} and Cmax were 39% and 27% (%CV), respectively (C0823T03) (Table 3).

Table 3. Summary of siltuximab pharmacokinetic parameter estimates following the first dose; (C0823T03).

<table>
<thead>
<tr>
<th>Subjects evaluable for pharmacokinetic analysis</th>
<th>2.8 mg/kg q2 weeks, 2-hr infusion (Cohort 1)</th>
<th>5.5 mg/kg q2 weeks, 2-hr infusion (Cohort 2)</th>
<th>11 mg/kg q3 weeks, 2-hr infusion (Cohort 3)</th>
<th>5.5 mg/kg Weekly, 2-hr infusion (Cohort 4)</th>
<th>11 mg/kg q2 weeks, 2-hr infusion (Cohort 5)</th>
<th>11 mg/kg q3 weeks, 1 hr Infusion, (Cohort 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC(0-τ) (µg·day/mL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>6</td>
<td>7</td>
<td>6</td>
<td>6</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>400.5 ± 81.14</td>
<td>548.2 ± 162.40</td>
<td>2116.7 ± 787.85</td>
<td>549.6 ± 180.94</td>
<td>2046.5 ± 162.49</td>
<td>1720.4 ± 674.44</td>
</tr>
<tr>
<td>Median</td>
<td>402.5</td>
<td>549.9</td>
<td>2143.7</td>
<td>464.9</td>
<td>2007.1</td>
<td>1730.3</td>
</tr>
<tr>
<td>Range</td>
<td>(286, 513)</td>
<td>(319, 796)</td>
<td>(1109, 3476)</td>
<td>(393, 788)</td>
<td>(1897, 2275)</td>
<td>(902, 2332)</td>
</tr>
<tr>
<td>Cmax (µg/mL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>6</td>
<td>6</td>
<td>5</td>
<td>5</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>550 ± 8.98</td>
<td>910 ± 28.54</td>
<td>3078 ± 102.55</td>
<td>143.5 ± 28.44</td>
<td>328.2 ± 108.89</td>
<td>191.5 ± 52.29</td>
</tr>
<tr>
<td>Median</td>
<td>528</td>
<td>89.5</td>
<td>275.8</td>
<td>148.0</td>
<td>345.9</td>
<td>194.7</td>
</tr>
<tr>
<td>Range</td>
<td>(46, 68)</td>
<td>(49, 135)</td>
<td>(184, 454)</td>
<td>(104, 181)</td>
<td>(182, 439)</td>
<td>(113, 281)</td>
</tr>
<tr>
<td>t1/2 (day)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>NA ± NA</td>
<td>NA ± NA</td>
<td>17.73 ± 6.948</td>
<td>NA ± NA</td>
<td>NA ± NA</td>
<td>20.64 ± 6.976</td>
</tr>
<tr>
<td>Median</td>
<td>NA</td>
<td>NA</td>
<td>16.11</td>
<td>NA</td>
<td>NA</td>
<td>18.59</td>
</tr>
<tr>
<td>Range</td>
<td>(NA, NA)</td>
<td>(NA, NA)</td>
<td>(11.3, 30.0)</td>
<td>(NA, NA)</td>
<td>(NA, NA)</td>
<td>(14.2, 29.7)</td>
</tr>
<tr>
<td>CL (ml/day/kg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>0</td>
<td>0</td>
<td>6</td>
<td>6</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>NA ± NA</td>
<td>NA ± NA</td>
<td>4.03 ± 2.279</td>
<td>NA ± NA</td>
<td>NA ± NA</td>
<td>4.59 ± 3.064</td>
</tr>
<tr>
<td>Median</td>
<td>NA</td>
<td>NA</td>
<td>3.57</td>
<td>NA</td>
<td>NA</td>
<td>2.94</td>
</tr>
<tr>
<td>Range</td>
<td>(NA, NA)</td>
<td>(NA, NA)</td>
<td>(2.1, 8.2)</td>
<td>(NA, NA)</td>
<td>(NA, NA)</td>
<td>(1.9, 8.7)</td>
</tr>
<tr>
<td>VZ (ml/kg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>0</td>
<td>0</td>
<td>6</td>
<td>6</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>NA ± NA</td>
<td>NA ± NA</td>
<td>913 ± 30.79</td>
<td>NA ± NA</td>
<td>NA ± NA</td>
<td>115.4 ± 45.27</td>
</tr>
<tr>
<td>Median</td>
<td>NA</td>
<td>NA</td>
<td>91.2</td>
<td>NA</td>
<td>NA</td>
<td>92.4</td>
</tr>
<tr>
<td>Range</td>
<td>(NA, NA)</td>
<td>(NA, NA)</td>
<td>(45, 133)</td>
<td>(NA, NA)</td>
<td>(NA, NA)</td>
<td>(79, 179)</td>
</tr>
</tbody>
</table>

* 0-τ = the first dose interval following the first administration

Following repeat dose administration at the target dose of 11 mg/kg every 3 weeks, the siltuximab systemic accumulation index was 1.7-fold. At 11 mg/kg, the multiple-dose (Day 43) intersubject variability in AUC_{0-t} and Cmax were 39% and 30% (%CV), respectively (C0328T03) (Table 4).
Table 4. Summary of siltuximab pharmacokinetic parameter estimates following Day 43 administration; subjects evaluable for pharmacokinetic analysis in Cohort 1 to Cohort 6 (C0328T03).

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Dose and Dosing Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort 1</td>
<td>2.8 mg/kg q2 weeks, 2-hr infusion</td>
</tr>
<tr>
<td>Cohort 2</td>
<td>5.5 mg/kg q2 weeks, 2-hr infusion</td>
</tr>
<tr>
<td>Cohort 3</td>
<td>11 mg/kg q3 weeks, 2-hr infusion</td>
</tr>
<tr>
<td>Cohort 4</td>
<td>5.5 mg/kg Weekly, 2-hr infusion</td>
</tr>
<tr>
<td>Cohort 5</td>
<td>11 mg/kg q2 weeks, 2-hr infusion</td>
</tr>
<tr>
<td>Cohort 6</td>
<td>11 mg/kg q3 weeks, 1 hr Infusion</td>
</tr>
</tbody>
</table>

Based on the pre-infusion (trough) serum concentrations, steady-state is achieved by the Cycle 6, Day 1 dose. The time to steady-state is consistent with the siltuximab half-life following a single dose of 11 mg/kg. The steady state mean Cmax was 332 μg/mL ± 139 μg/mL (intersubject variability (%CV): 42%) and Cmin was 84 μg/mL ± 66 (μg/mL (intersubject variability (% CV): 78%) (Cycle 6 Day 1) (CNTO328MCD2001).
2.2.5.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

During the clinical development of siltuximab, the sponsor made a change in cell line from a transfected murine Sp2/0 myeloma cell line to a transfected CHO cell line. The effect of changing the manufacturing process was examined in a clinical PK comparability trial of Sp2/0-derived and CHO-derived siltuximab in healthy volunteers (Trial C0328T08). Trial C0328T08 was the only trial conducted in healthy volunteers. In Part 1, subjects were to receive a single IV infusion of either 1.4 or 2.8 mg/kg of Sp2/0-derived CNTO 328 (manufactured from a murine cell line) or CHO-derived CNTO 328 (manufactured from a CHO cell line) or placebo. In Part 2, subjects were to receive a single IV infusion of 1.4 mg/kg of either Sp2/0-derived or CHO-derived CNTO 328.

Following administration of CHO-derived or Sp2/0-derived CNTO 328 at a dose of 1.4 mg/kg, serum concentration of CNTO 328 declined in an apparent biphasic manner (Figure 8).

![Figure 8. Mean CNTO 328 (siltuximab) serum concentration (micrograms/mL) through Day 85 (1.4 mg/kg only)](image)

The summary and derived PK parameters mean ± SD values for T1/2, CL and Vz estimates are provided below (Table 5). The T1/2 appeared longer, and the CL slower, when compared to values reported in the MCD population above.
Table 5. Summary of CNTO 328 pharmacokinetic parameter estimates of $t_{1/2}$, CL, and $V_z$ (1.4 mg/kg and 2.8 mg/kg); evaluable PK population in Part 1 and Part 2 (C0328T08).

<table>
<thead>
<tr>
<th></th>
<th>1.4 mg/kg CHO</th>
<th>1.4 mg/kg Sp2/0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects PK evaluable</td>
<td>67</td>
<td>63</td>
</tr>
<tr>
<td>$t_{1/2}$ (day)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>66</td>
<td>59</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>26.6 ± 5.960</td>
<td>25.8 ± 4.542</td>
</tr>
<tr>
<td>Median</td>
<td>26.53</td>
<td>25.52</td>
</tr>
<tr>
<td>Range</td>
<td>(13.4, 41.6)</td>
<td>(16.3, 44.1)</td>
</tr>
<tr>
<td>CL (mL/day/kg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>66</td>
<td>59</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>2.21 ± 0.479</td>
<td>2.16 ± 0.436</td>
</tr>
<tr>
<td>Median</td>
<td>2.18</td>
<td>2.14</td>
</tr>
<tr>
<td>Range</td>
<td>(1.1, 3.6)</td>
<td>(1.2, 3.4)</td>
</tr>
<tr>
<td>$V_z$ (mL/kg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>66</td>
<td>59</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>82.80 ± 16.381</td>
<td>79.06 ± 13.620</td>
</tr>
<tr>
<td>Median</td>
<td>83.32</td>
<td>78.99</td>
</tr>
<tr>
<td>Range</td>
<td>(39.2, 123.2)</td>
<td>(41.6, 105.0)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>2.8 mg/kg CHO</th>
<th>2.8 mg/kg Sp2/0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects PK evaluable</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>$t_{1/2}$ (day)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>30.72 ± 4.359</td>
<td>21.84 ± 1.897</td>
</tr>
<tr>
<td>Median</td>
<td>30.84</td>
<td>21.60</td>
</tr>
<tr>
<td>Range</td>
<td>(26.2, 36.0)</td>
<td>(19.8, 24.4)</td>
</tr>
<tr>
<td>CL (mL/day/kg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>2.09 ± 0.187</td>
<td>2.53 ± 0.373</td>
</tr>
<tr>
<td>Median</td>
<td>2.01</td>
<td>2.50</td>
</tr>
<tr>
<td>Range</td>
<td>(1.9, 2.3)</td>
<td>(2.2, 2.9)</td>
</tr>
<tr>
<td>$V_z$ (mL/kg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>93.08 ± 18.708</td>
<td>80.09 ± 17.060</td>
</tr>
<tr>
<td>Median</td>
<td>87.90</td>
<td>80.50</td>
</tr>
<tr>
<td>Range</td>
<td>(71.4, 121.7)</td>
<td>(62.5, 96.8)</td>
</tr>
</tbody>
</table>

2.2.5.3 What are the characteristics of drug absorption?

Not applicable. Siltuximab is administered as an IV infusion. No studies of drug absorption have
been performed.

2.2.5.4 **What are the characteristics of drug distribution?**
An assessment of protein binding is not applicable to therapeutic biologics. The population PK model in subjects with MCD and various hematological and non-hematological malignancies reports that following multiple IV administrations of siltuximab, the typical population value for central volume of distribution (Vc) in a male subject with a standard body weight of 70 kg is 4.54 L. The between subject variability (%CV) for Vc is 20.3. Siltuximab is primarily localized to the circulatory system with limited extravascular tissue distribution.

**Transporter Proteins**
Siltuximab is intended for IV administration. Therefore studies with transporter proteins were not applicable, and were not conducted.

2.2.5.5 **Does the mass balance study suggest renal or hepatic as the major route of elimination?**
A mass balance trial was not conducted for siltuximab. Mass balance studies are generally not performed for protein drugs because they are degraded into amino acids that then recycled into other proteins. The molecular weight of siltuximab is greater than 69 kDa, and therefore the impact of renal impairment on siltuximab PK was not studied. In the population PK analysis baseline ALT, albumin and creatinine clearance (CLCr) were evaluated as covariates on clearance (See Section 2.3 and the Appendix).

2.2.5.6 **What are the characteristics of drug metabolism?**
Classic metabolism studies are not required for the evaluation of therapeutic biologics. Therapeutic proteins degrade into small peptides and subsequently amino acids that are recycled into other proteins.

2.2.5.7 **What are the characteristics of drug excretion?**

**Elimination**
As a IgG mAb, siltuximab is presumably metabolized in the same manner as any other endogenous IgG (degraded into small peptides and amino acids via catabolic pathways), and is subject to similar elimination. Therefore, renal excretion and hepatic enzyme-mediated metabolism of intact siltuximab are unlikely to represent major elimination routes. As such, variations in renal and hepatic function are not expected to affect the elimination of siltuximab.

**Clearance**
In the population PK analysis, patients received single agent siltuximab at doses ranging from 0.9 to 15 mg/kg. The typical population value for CL in subjects with a standard body weight of 70 kg was 0.233 L/day. The between-subject variability (% CV) for CL was 50.9%. See the Appendix for details.

**Volume of Distribution**
The population PK analysis was conducted in subjects with MCD and various hematological and non-hematological malignancies following multiple IV administrations of siltuximab at doses ranging from 0.9 to 15 mg/kg. It reports the typical population value for central volume of
distribution (Vc) in a male subject with a standard body weight of 70 kg is 4.54 L. The between subject variability (%CV) for Vc is 20.3. See the Appendix for details.

**Half-life**
Following the first administration at the target dose of 11 mg/kg in patients, the siltuximab mean half-life (t1/2) was 20.6 (range: 14.2 to 29.7 days) (C0328T03).

2.2.5.8 Based on PK parameters, what is the degree of linearity or non-linearity based in the dose-concentration relationship?

**Single-dose:**
The Day 1 single-dose noncompartmental model predicted $\text{AUC}_{0-14\text{days}}$ and $\text{C}_{\text{max}}$ obtained from trial C0328T01 were used to assess the dose proportionality of siltuximab in serum at doses of 0.92, 2.8, 5.5 and 11 mg/kg. Siltuximab was administered on Days 1, 29, 43, and 57 to patients with renal cell carcinoma. Over the dose range of 0.92 to 11 mg/kg, the slope of the line of the log $\text{AUC}_{0-14\text{days}}$ vs. log dose plot was 0.77. Over the dose range of 2.8 to 11 mg/kg, the slope of the line of the log $\text{C}_{\text{max}}$ vs. log dose plot was 0.89. These results from the analyses with $\text{AUC}_{0-14\text{days}}$ and $\text{C}_{\text{max}}$ suggest dose-proportional pharmacokinetics of the single daily dose range of 0.92 to 11 mg/kg siltuximab (Figure 9). The mean apparent clearance of siltuximab after a single oral dose appeared constant over the dose range of 5.5 mg to 15 mg/kg (CNT0328STM2001) (Table 6). Only one patient was studied at the 2.8 mg/kg dose, and thus these data were not included in the evaluation of clearance. The constant mean apparent clearance values are consistent with the approximately linear siltuximab pharmacokinetics observed over the 0.92 to 11 mg/kg dose range.

**Figure 9.** A: Log $\text{AUC}_{0-14\text{days}}$ vs. Log of dose and B: Log $\text{C}_{\text{max}}$ vs. Log of dose over the 0.92 to 11 mg/kg single oral dose range (Cycle 1, Day 1) in patients with renal cell carcinoma. The shaded area is the 90% CI. (Trial C0328T01)
Table 6. Summary of siltuximab pharmacokinetic parameter estimates following the first dose; treated patients with solid tumors (Cohorts 1 to 4) (CNTO328STM2001).

<table>
<thead>
<tr>
<th>Siltuximab</th>
<th>Cohort 1 (2.8 mg/kg q2w)</th>
<th>Cohort 2 (5.5 mg/kg q2w)</th>
<th>Cohort 3 (11 mg/kg q3w)</th>
<th>Cohort 4 (15 mg/kg q3w)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects treated</td>
<td>1</td>
<td>6</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;n&lt;/sub&gt; (µg·day/mL) n</td>
<td>1</td>
<td>6</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>1912.53 ± 3144.89</td>
<td>3198.52 ± 5680.34</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>422.12</td>
<td>1649.40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>(422.1, 422.1)</td>
<td>(1099.1, 3086.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-14days&lt;/sub&gt; (µg·day/mL) n</td>
<td>1</td>
<td>6</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>2267.22 ± 2267.22</td>
<td>2157.07 ± 3946.80</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>344.75</td>
<td>1072.12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>(344.8, 344.8)</td>
<td>(912.6, 1521.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (µg/mL) n</td>
<td>1</td>
<td>6</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>107.26 ± 36.497</td>
<td>340.42 ± 41.182</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>56.60</td>
<td>108.55</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>(56.6, 56.6)</td>
<td>(83.2, 130.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>t&lt;sub&gt;1/2&lt;/sub&gt; (day) n</td>
<td>1</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>16.30 ± 4.247</td>
<td>17.48 ± 4.976</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>12.72</td>
<td>16.15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>(12.7, 12.7)</td>
<td>(11.4, 22.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CL (mL/day/kg) n</td>
<td>1</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>3.54 ± 0.437</td>
<td>3.97 ± 1.306</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>3.64</td>
<td>3.43</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>(6.6, 6.6)</td>
<td>(1.8, 5.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>V&lt;sub&gt;ss&lt;/sub&gt; (mL/kg) n</td>
<td>1</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>105.14 ± 77.49</td>
<td>63.90 ± 2.369</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>105.14</td>
<td>87.58</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>(105.1, 105.1)</td>
<td>(61.2, 67.6)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Multiple-dose:
The multiple-dose noncompartmental model predicted individual $C_{\text{max}}$ and $\text{AUC}_{0-14\text{days}}$ obtained from trial C0328T03 were used to assess the dose proportionality of siltuximab in serum following daily dosing at 2.8, 5.5 and 11 mg/kg. Siltuximab was administered as described above in Section 2.2.5.1 to patients with NHL, MM or MCD. Over the dose range of 2.8 to 11 mg/kg, the slope of the line of the log $C_{\text{max}}$ vs. log dose plot was 0.58. Over the dose range of
2.8 to 11 mg/kg, the slope of the line of the log AUC\textsubscript{0-14days} vs. log dose plot was 0.64. These results from the analyses with multiple-dose C\textsubscript{max} and AUC\textsubscript{0-14days} indicate approximately dose-proportional pharmacokinetics of the daily dose range of 2.8 to 11 mg/kg siltuximab (Figure 10). This is supported by the population PK analysis. See the Appendix for details.

![Graph A](image)

**Figure 10.** A: Log AUC\textsubscript{0-14days} vs. Log of Dose and B: Log C\textsubscript{max} vs. Log of Dose over the 2.8 to 11 mg/kg multiple oral dose range in patients with NHL, MM or MCD. The shaded area is the 90% CL (Trial C0328T03)

2.2.5.9 How do the PK parameters change with time following chronic dosing?

2.2.5.9.1 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

The single-dose and multiple-dose pharmacokinetics reported in the dose ranging trial that enrolled patients with MCD reported low intersubject variability. Following the first administration at the target dose of 11 mg/kg, (cohort 6), the single-dose intersubject variability in AUC\textsubscript{0-inf} and C\textsubscript{max} were 39% and 27% (%CV), respectively (C0823T03). Following repeat dose administration at the target dose of 11 mg/kg every 3 weeks (Day 43), the intersubject variability in AUC\textsubscript{0-24h} and C\textsubscript{max} were 39% and 30% (%CV), respectively (C0328T03).

The between subject variability (%CV) for CL and V\textsubscript{c}, reported in the population PK analysis, were 50.9% and 20.3%, respectively (See the Appendix for details).

2.3 INTRINSIC FACTORS

2.3.1 What intrinsic factors (age, race, weight, height, genetic polymorphisms and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

No formal studies have been conducted to assess the effect of age, race, gender, weight, height, genetic polymorphisms, or organ impairment on siltuximab PK following multiple IV administrations in subjects with MCD and various hematological and non-hematological

Reference ID: 3448540
malignancies.

The population PK analysis evaluated the following factors as covariates on the PK of siltuximab: Categorical creatinine clearance at baseline, clearance, categorical bilirunin and AST based on the NCI classification, body weight, ALT, sex, immune response and disease subtype.

The results showed body weight was the only statistically significant covariate on siltuximab CL and Vc. Of the remaining intrinsic factor covariates, sex was statistically significant on Vc. However, on evaluation of the plots of the Empirical Bayes Estimates (EBEs) of ETAs vs. Covariates, it was found that the medians and the 95% CI for sex largely overlapped. Therefore, sex was not considered clinically relevant and dose adjustment based on sex is not warranted. See the Appendix for more information.

Table 7. Siltuximab Final Population Pharmacokinetic Model Parameter Estimates (See Appendix for details).

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Estimate (%RSE)</th>
<th>Median (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL (L/day)</td>
<td>0.273 (2.92)</td>
<td>0.222 (0.21, 0.235)</td>
</tr>
<tr>
<td>Weight on CL*</td>
<td>0.496 (23.0)</td>
<td>0.499 (0.278, 0.729)</td>
</tr>
<tr>
<td>Vc (L)</td>
<td>4.54 (2.19)</td>
<td>4.53 (4.31, 4.76)</td>
</tr>
<tr>
<td>Weight on Vc</td>
<td>0.381 (15)</td>
<td>0.384 (0.258, 0.501)</td>
</tr>
<tr>
<td>Cell CHO on Vc</td>
<td>-0.17 (11.7)</td>
<td>-0.169 (-0.208, -0.129)</td>
</tr>
<tr>
<td>Female on Vc</td>
<td>-0.14 (16.2)</td>
<td>-0.142 (-0.184, -0.0971)</td>
</tr>
<tr>
<td>Vp (L)</td>
<td>3.39 (6.43)</td>
<td>3.39 (3.01, 3.85)</td>
</tr>
<tr>
<td>Weight on Vp</td>
<td>0.628 (29.8)</td>
<td>0.627 (0.228, 0.975)</td>
</tr>
<tr>
<td>STDY=1 on Vp</td>
<td>-0.327 (24.3)</td>
<td>-0.325 (0.479, -0.163)</td>
</tr>
<tr>
<td>STDY=3 on Vp</td>
<td>0.0594 (207)</td>
<td>0.0597 (-0.18, 0.418)</td>
</tr>
<tr>
<td>STDY=7 on Vp</td>
<td>0.491 (54.2)</td>
<td>0.491 (0.171, 0.946)</td>
</tr>
<tr>
<td>STDY=5 on Vp</td>
<td>0.00532 (6480)</td>
<td>0.00597 (-0.361, 0.624)</td>
</tr>
<tr>
<td>Q (L/day)</td>
<td>0.448 (5.18)</td>
<td>0.451 (0.39, 0.54)</td>
</tr>
<tr>
<td>Weight on Q</td>
<td>1.38 (13.6)</td>
<td>1.37 (0.74, 1.99)</td>
</tr>
<tr>
<td>BSV of CL %</td>
<td>50.9 (8.11)</td>
<td>50.6 (46.2, 55.9)</td>
</tr>
<tr>
<td>BSV of Vc %</td>
<td>20.3 (10.4)</td>
<td>20.1 (17.5, 22.6)</td>
</tr>
<tr>
<td>BSV of Vp %</td>
<td>63.5 (12.9)</td>
<td>62.2 (48.7, 77.8)</td>
</tr>
<tr>
<td>Correlation between</td>
<td>0.488 (14.4)</td>
<td>0.488 (0.423, 0.535)</td>
</tr>
<tr>
<td>BSV of Vp and CL</td>
<td>0.0592 (2.16)</td>
<td>0.0588 (0.0497, 0.0704)</td>
</tr>
<tr>
<td>Proportional error</td>
<td>0.0785 (54.3)</td>
<td>0.0802 (0.0004, 0.243)</td>
</tr>
<tr>
<td>Additive error</td>
<td>0.0785 (54.3)</td>
<td>0.0802 (0.0004, 0.243)</td>
</tr>
</tbody>
</table>

BSV = between-subject variability, calculated as (variance)^1/2*100%; CI = confidence interval; CL = estimated clearance; NA = not applicable.

Q = inter-compartmental flow; RSE = relative standard error; Vc = volume of distribution of the central compartment; Vp = volume of distribution of the peripheral compartment.

Studies C0328TD01 and C0328MCD001 were reference studies; STDY=1, 3, 5 represents Studies C0328TD01, C0328TD31, CNT0328MDS001 and CNT0328MMS1001, respectively.

a. NONMEM derived estimates and corresponding %RSE.
b. Median (95% CI): median value and 95% confidence interval calculated from 1,000 replicates of resampled bootstrap runs.
c. Weight was scaled to 70 kg, ALB was scaled to 3.83 and ALT was scaled to 21.

Reference ID: 3448540
2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dose adjustments, if any, are recommended for each of these groups? If dose adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

The magnitude of effect for the identified statistically significant covariates on siltuximab exposure indicates that body weight based dose adjustments are required. No other covariates produced a clinically relevant effect on siltuximab exposure, and dose adjustment based on the other covariates assessed is not warranted. Refer to section 2.3.1 above and the Appendix for more information.

2.3.2.1 Pediatric patients
Safety and effectiveness of siltuximab have not been established in pediatric patients. Castleman’s disease is rare in children.

2.3.2.2 Body weight
Baseline body weight, normalized to 70 kg, was found to be the only significant covariate on CL and Vc. The impact of body weight on the PK of siltuximab supports the current strategy of body weight-based dosing to minimize the variability of siltuximab exposure when the drug is administered to subjects with different body weights. This body weight-based dosing regimen was used in the clinical trials. See the Appendix for more information.

2.3.2.3 Age
Age (range 18 to 85 years) was evaluated as a covariate on siltuximab CL and Vc. Age was not identified as a significant covariate in population PK analysis, and dose adjustment based on age is not warranted. See the Appendix for more information.

2.3.2.4 Race
The effect of race could not be evaluated. See the Appendix for more information.

2.3.2.5 Renal Impairment
The population PK analysis included assessment of categorical creatinine clearance at baseline, as a covariate on siltuximab exposure. Of the 377 subjects, 176 had normal renal function based on the categorization of CLCr, 122 had Stage 2 (mild) renal function impairment (CLCr 60 to <90 mL/min), 75 had Stage 3 (moderate) renal impairment (CLCr 30 to <60 mL/min), 3 had Stage 4 (severe) renal impairment (CLCr 15 to 29 mL/min) and 1 had Stage 5 (end stage) renal disease (CLCr <15 mL/min). The apparent clearance of siltuximab was similar in patients with pre-existing mild, moderate and severe renal impairment (CLCr 15 to <90 mL/min) compared to patients with normal renal function. To further assess the effect of renal dysfunction on siltuximab exposure, a scatter plot with a lowess smoothing curve was generated for the empirical Bayes estimate of CL vs. creatinine clearance (CLCr). As shown in Figure 11, no obvious pattern was identified. The potential effect of end stage renal disease on siltuximab pharmacokinetics cannot be determined as clinical and pharmacokinetic data are available from only one patient. (Table 8). Overall, renal impairment is not expected to be a major factor
affecting siltuximab exposure as monoclonal antibodies are generally catabolized by ubiquitous proteolytic enzymes. Therefore, no additional trials are recommended at this time. See the Pharmacometrics review in the Appendix for more information.

Table 8. Summary of Categorical Creatinine Clearance (Renal Function) of the Population Pharmacokinetic Dataset

<table>
<thead>
<tr>
<th>Creatinine Clearance Category (%)</th>
<th>C032ST01 n=60</th>
<th>C032ST03 n=66</th>
<th>CNTO328 SMM1001 n=30</th>
<th>CNTO328 STM2001 n=84</th>
<th>CNTO328 MDS2001 n=65</th>
<th>CNTO328 MCD2001 n=66</th>
<th>Total n=377</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1, normal: &gt;90 mL/min</td>
<td>16 (23.33)</td>
<td>32 (48.48)</td>
<td>13 (43.33)</td>
<td>42 (50)</td>
<td>25 (39.68)</td>
<td>48 (72.73)</td>
<td>176 (46.68)</td>
</tr>
<tr>
<td>Stage 2 (60-89 mL/min)</td>
<td>32 (47.06)</td>
<td>23 (34.85)</td>
<td>10 (33.33)</td>
<td>19 (22.62)</td>
<td>27 (42.85)</td>
<td>11 (16.67)</td>
<td>122 (32.36)</td>
</tr>
<tr>
<td>Stage 3 (30-59 mL/min)</td>
<td>18 (28.47)</td>
<td>10 (15.15)</td>
<td>7 (23.33)</td>
<td>22 (26.15)</td>
<td>11 (17.46)</td>
<td>7 (10.61)</td>
<td>75 (19.89)</td>
</tr>
<tr>
<td>Stage 4 (15-29 mL/min)</td>
<td>1 (1.67)</td>
<td>1 (1.52)</td>
<td>0 (0)</td>
<td>1 (1.19)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>3 (0.8)</td>
</tr>
<tr>
<td>Stage 5 (&lt;15 mL/min)</td>
<td>1 (1.67)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (0.27)</td>
</tr>
</tbody>
</table>

a Number of subjects included in analysis data set.

Figure 11. Relationship between the Empirical Bayes Estimate (EBE) of CL and CLCr (CRCL in figure).

2.3.2.6 Hepatic Impairment
The population PK analysis included assessment of categorical bilirubin and AST based on the NCI classification, as a covariate on siltuximab exposure. The median bilirubin level of the subjects was 8.55 mg/dL (range: 1.71 to 42.75 mg/dL). According to the National Cancer Institute (NCI) organ dysfunction criteria, the majority of subjects (n=302, 80.1%) had normal
hepatic function, and 75 (19.9%) subjects had abnormal hepatic function (mild n=72, moderate n=3) (Table 9). Based on the population PK analysis, there was no statistically significant difference in CL between subjects with normal hepatic function versus those with mild hepatic impairment or moderate hepatic impairment. To further assess the effect of hepatic dysfunction on siltuximab exposure, a scatter plot with a lowess smoothing curve was generated for the empirical Bayes estimate of CL vs. bilirubin level. As shown in Figure 12, no obvious pattern was identified. Patients with severe hepatic impairment were not enrolled in the clinical trials, and therefore the effect of severe hepatic impairment on siltuximab pharmacokinetics could not be determined from the population PK analysis. However, hepatic impairment is not expected to be a major factor affecting siltuximab exposure as monoclonal antibodies are generally catabolized by ubiquitous proteolytic enzymes. Therefore, no additional trials are recommended at this time. See the Appendix for more information.

Table 9. Summary of Categorical Hepatic Function of the Population Pharmacokinetic Dataset.

<table>
<thead>
<tr>
<th>Bilirubin Clearance Category (%)</th>
<th>C032ST01 n=68</th>
<th>C032ST03 n=66</th>
<th>CNT032S n=50</th>
<th>ST0201 n=84</th>
<th>MDS2001 n=63</th>
<th>MCD2001 n=66</th>
<th>Total n=377</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (total bilirubin &lt;ULN and AST&lt;ULN)</td>
<td>59 (86.76)</td>
<td>55 (83.33)</td>
<td>28 (56.67)</td>
<td>56 (66.67)</td>
<td>40 (63.49)</td>
<td>64 (96.97)</td>
<td>302 (80.11)</td>
</tr>
<tr>
<td>Mild (total bilirubin &lt;ULN and AST-ULN or ULN &lt; total bilirubin &lt;1.5xULN)</td>
<td>8 (11.76)</td>
<td>11 (16.67)</td>
<td>2 (6.67)</td>
<td>27 (32.14)</td>
<td>2 (3.05)</td>
<td>2 (3.05)</td>
<td>72 (19.1)</td>
</tr>
<tr>
<td>Moderate (1.5xULN &lt; total bilirubin &lt;3xULN)</td>
<td>1 (1.47)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (1.19)</td>
<td>1 (1.59)</td>
<td>0 (0)</td>
<td>3 (0.8)</td>
</tr>
</tbody>
</table>

* Number of subjects included in analysis data set.

Figure 12. Relationship between the Empirical Bayes Estimate (EBE) of CL and Bilirubin Level.
2.3.3.7 What pregnancy and lactation use information is there in the application?

The safety and effectiveness of the siltuximab have not been established in pregnancy and in lactating women.

2.3.3 Immunogenicity

2.3.3.1 What is the incidence (rate) of the formation of the anti-product antibodies (APA), including the rate of pre-existing antibodies, the rate of APA formation during and after the treatment, time profiles and adequacy of the sampling schedule?

Patients were tested for anti-siltuximab antibodies (APA) in human serum in the clinical trials using two enzyme immunoassay (EIA) methods and one electrochemiluminescent immunoassay (ECLIA) method. Human serum samples from Phase 2 clinical studies identified as containing antibodies to siltuximab were further characterized for the ability of those antibodies to neutralize the bioactivity of siltuximab using an electrochemiluminescent (ECL)-based competitive ligand binding assay. Serum samples were to be screened for antibodies binding to siltuximab. A subject was to be considered to have developed a positive immune response if the result shows any increase from the baseline value following siltuximab administration, so long as the increased reactivity could be demonstrated to specifically bind siltuximab. Serum titer was to be determined from all positive samples. All samples collected for immune response analysis were to be evaluated for siltuximab serum concentration to ensure appropriate interpretation of immune response data.

The immunogenicity sampling schedule in the trials was adequate. The following is the blood sampling schedule for measurement of immune response to siltuximab for each trial in all patients:

- In trial C032801 (Part 1): Immediately prior to infusion, cycle 1 and at 12, 18, and 24 weeks after the last administration (during post-trial follow-up).
- In trial C032801 (Part 2): Immediately prior to the first (Day 1) infusion, and at 6, 12, 18, and 24 weeks following the last infusion.
- In trial C032801 (Part 3): Immediately prior to the first (Day 1) infusion, and at 6, 12, 18, and 24 weeks following the last infusion.
- C0328T03: Immediately prior to the first (Day 1) administration, and at 12, 18, and 24 weeks following the last administration.
- CNTO328MCD2001: Day 1 of Cycles 1, 3, 6, 9, and 12, and every 4 cycles thereafter (at each time point, samples were to be obtained before study agent administration) and 4, 8, and 12 weeks after the last dose.
- CNTO328MMY2001: Blood samples were collected from all subjects in Part 1 and from subjects who received siltuximab + Velcade + melphalan + prednisone in Part 2 (Arm A) at the following time points: Before the first administration of siltuximab on Cycle 1, Day 1 (predose). Six months and 12 months after the first administration of siltuximab (for subjects receiving continuous treatment with siltuximab), and 3, 9, and 12 weeks after the last administration of siltuximab, during the follow-up period (the 3-week sample was collected at the end-of-treatment visit).
- CNTO328STM2001: Immediately prior to the first infusion, and at 4, 8, and 12 weeks following the last infusion during the Follow-up Period.
- CNTO328MDS2001: Blood samples to determine serum concentrations of siltuximab.
were collected from 50 subjects following the first dose (Cycle 1), 2 subjects following the fourth dose (Cycle 4) and 1 subject following the sixth dose (Cycle 6).

In the 620 patients treated with siltuximab as a single agent or in combination with other agents, across all the sponsor’s clinical trials, 583 patients were evaluable (81 subjects with MCD). Of the 583 patients, 401 patients had appropriate blood samples for immunogenicity analysis (APA testing). Antibodies to siltuximab were detectable in one of the 401 patients (0.2% [1/411]) siltuximab-treated subjects evaluated for APAs. This patient was enrolled in trial CNTO328MCD2001. The signal was weak (titer of 1:20) and was detectable in the End-of-Treatment sample only, 45 days after last siltuximab infusion, and was not detectable in prior samples. No other subjects in any other clinical trial with siltuximab had detectable antibodies to siltuximab at any time point assessed.

2.3.3.2 Does the immunogenicity affect the PK and/or PD of the therapeutic protein?
APAs were only detected in one sample from one patient treated with siltuximab. This sample was taken 45 days after the last infusion. Data for a direct comparison of siltuximab PK at the time of the positive APA were available, however the impact of immunogenicity on siltuximab PK could not be determined as only one sample was positive for APAs and available for analysis.

2.3.3.3 Do the anti-product antibodies have neutralizing activity?
The sample that was confirmed to be APA positive was tested for the presence of neutralizing antibodies, and was found to have non-neutralizing activity.

2.3.3.4 What is the impact of anti-product antibodies on clinical efficacy?
Overall, there were not enough data to assess the impact of anti-product antibodies on the clinical efficacy.

2.3.3.5 What is the impact of anti-product antibodies on clinical safety??
The impact of APAs on clinical safety could not be determined due to the low incidence rate of APA following siltuximab treatment.

2.4 EXTRINSIC FACTORS
2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?
The effects of extrinsic factors such as herbal products, diet, smoking, and alcohol use on the dose-exposure and/or dose-response for siltuximab have not been assessed in formal clinical studies.

2.4.2 Drug-drug interactions
2.4.2.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?
No in vitro studies were conducted. This is appropriate, as monoclonal antibodies are generally catabolized by ubiquitous proteolytic enzymes.

The formation of cytochrome P450 (CYP) isozymes is suppressed by increased levels of IL-6 during chronic inflammation such as present in Castleman’s disease. Thus, it is expected that
binding of bioactive IL-6 by siltuximab may normalize the formation of CYP450 enzymes, which may result in increased metabolism of CYP450 substrates compared to patients with Castleman’s disease that are not treated with siltuximab. If siltuximab is administered with CYP450 substrates that have a narrow therapeutic index, the therapeutic effects of the CYP450 substrate may change due to alterations in the CYP450 pathways. Labeling language will adequately address this concern.

2.4.2.2 Is the drug a substrate of CYP enzymes?
Unknown. See Section 2.4.2.1.

2.4.2.3 Is the drug an inhibitor and/or an inducer of CYP enzymes?
Unknown. See Section 2.4.2.1. Monoclonal antibodies do not generally interact directly with CYP isozymes. However, binding of siltuximab to bioactive IL-6 may be an indirect mechanism through which a siltuximab could alter CYP expression (See Section 2.4.2.1).

2.4.2.4 Is the drug a substrate and/or an inhibitor of P-glycoprotein (P-gp) transport processes?
No studies have been conducted to assess if siltuximab is a substrate and/or an inhibitor of P-gp transport.

2.4.2.5 Are other metabolic/transporter pathways important?
No studies have been conducted with transporter proteins.

2.4.2.6 Does the label specify co-administration of another drug and, if so, has the interaction potential between these drugs been evaluated?
No. The proposed dosing regimen involves the use of siltuximab as a monotherapy.

2.4.2.7 What other co-medications are likely to be administered to the target patient population?
The current proposed use of siltuximab is as a monotherapy, however corticosteroids may be co-administered. The concomitant use of corticosteroids was assessed as a covariate in the population PK analysis. Concomitant corticosteroid use was not identified as a significant covariate in the population PK analysis (see the Appendix for details).

2.4.2.8 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?
No dedicated drug-drug interaction studies have been conducted. See Section 2.4.2.7.

2.4.2.9 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?
No.
2.4.3 What issues related to dose, dosing regimens, or administration is unresolved and represents significant omissions?
None.

2.5 GENERAL BIOPHARMACEUTICALS
2.5.1 What is the composition of the to-be-marketed formulation, which was used in the pivotal clinical trial?
The clinical development program for evaluating efficacy and safety of siltuximab in MCD consists of 3 studies: CNTO328MCD2001 (primary), C0328T03 (supportive) and ongoing trial CNTO328MCD2002 (supportive) with data from 19 subjects who were previously treated with siltuximab in trial C0328T03.

Siltuximab used in trial CNTO328MCD2001 and CNTO328MCD2002, was derived from the Chinese Hamster Ovary (CHO) cell line and the final manufacturing process was used. Therefore, the formulation used in these two trials is the same as that of the to-be-marketed formulation. The siltuximab final lyophilized product (FLP) is supplied as a sterile, single-use lyophilized dosage form for IV infusion. The FLP is reconstituted with 5.2 mL of sterile water for infusion 9WFI) prior to use. The quantitative compositions of the siltuximab 100 mg/vial and 400 mg/vial FLP are shown below (Table 10 and Table 11).

<table>
<thead>
<tr>
<th>Table 10. Composition of Siltuximab FLP (100 mg/vial) and the corresponding concentrations post-reconstitution.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Component</td>
</tr>
<tr>
<td>--------------------</td>
</tr>
<tr>
<td>Siltuximab</td>
</tr>
<tr>
<td>Sucrose</td>
</tr>
<tr>
<td>L-Histadine</td>
</tr>
<tr>
<td>Polysorbate 80</td>
</tr>
</tbody>
</table>

\(\text{a}\) Amounts represent overfill to offset losses during withdrawal post-reconstitution
\(\text{b}\) Amounts calculated based on measurements of the drug substance as explained in Section 3.2.P.2.1.2
\(\text{c}\) Amounts calculated without overfill and based on the measurements of drug substance as explained in footnote b
\(\text{d}\) Concentrations of FLP components following reconstitution with 5.2 mL sterile 9WFI
\(\text{e}\) Concentrations calculated based on total combined volume in a vial of FLP components and 9WFI (5.2 mL) after reconstitution and based on the total amounts per vial as explained in footnote a and footnote b.
Table 11. Composition of Siltuximab FLP (400 mg/vial) and the corresponding concentrations post-reconstitution.

<table>
<thead>
<tr>
<th>Component</th>
<th>Amount per Vial (mg) a,b</th>
<th>Nominal Amount Per Vial (mg) c</th>
<th>Concentration Post-reconstitution (mg/mL) d,e</th>
</tr>
</thead>
<tbody>
<tr>
<td>Siltuximab</td>
<td>400</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Sucrose</td>
<td>677</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>L-Histidine</td>
<td>14.9</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td>Polysorbate 80</td>
<td>3.2</td>
<td>0.16</td>
<td></td>
</tr>
</tbody>
</table>

* Amounts represent a overfill to offset losses during withdrawal post-reconstitution
b Amounts calculated based on measurements of the drug substance as explained in Section 3.2.P.2.1.2

c Amounts calculated without overfill and based on the measurements of drug substance as explained in footnote b
d Concentrations of FLP components following reconstitution with 20.0 mL sterile WFI
  Concentrations calculated based on total combined volume in a vial of FLP components
  and WFI (20.0 mL) after reconstitution and based on the total amounts per vial as explained in footnote a and footnote b

For trial C0328T03, siltuximab was supplied as a sterile aqueous formulation for IV infusion at a concentration of 400 mg/mL. This drug product contains siltuximab, monohydrate, polysorbate 80 at (see Section 2.5.2 for PK comparability between this formulation and the to-be-marketed formulation, and the footnote in Table 1).

2.5.2 What is the relationship of the proposed to-be-marketed formulation used in the pivotal clinical trial with previous clinical trial formulations in terms of comparative exposure?
Siltuximab derived from the Chinese Hamster Ovary (CHO) cell line using the final manufacturing process were used for the entire CNTO328MCD2001 trial and ongoing CNTO328MCD2002 trial. Therefore, in terms of comparative exposure, there are no differences between the final lyophilized product (FLP) presentation used in the Phase 2 clinical trials and the siltuximab FLP for commercialization. The formulation development history is described below.

For the start of Phase 1 clinical studies, the drug product was siltuximab derived from the cell line (Sp2/0) process and later from its subcloned cell line (Sp2/0) process. The product was formulated at a concentration of polysorbate 80 for clinical studies up to Phase 2. Prior to the start of Phase 2 clinical trials for registration, a switch was made from the cell line (Sp2/0) to a CHO derived cell line. The change to the -derived siltuximab was accompanied by formulation changes intended to improve the drug product stability, including a change in presentation to a lyophilized form and a change in the formulation composition (Table 12).
The results from trial C0328T03 were used to support the efficacy and safety of siltuximab in the current submission for the treatment of MCD. The Sp2/0 cell line was used for the manufacture of siltuximab in trail C0328T03. Therefore, the effect of changing the manufacturing process was examined in a clinical PK comparability trial of Sp2/0-derived and CHO-derived siltuximab in healthy volunteers (trial C0328T08). Trial C0328T08 assessed the pharmacokinetic (PK) comparability of CHO-derived CNTO 328 with Sp2/0-derived CNTO 328 following administration of a single 1.4 mg/kg IV dose in healthy subjects. Part 2 of the trial was an open-label, parallel group, single-dose design. Subjects were treated as follows: 1.4 mg/kg CHO-derived siltuximab (62 subjects) and 1.4 mg/kg Sp2/0-derived siltuximab (58 subjects). Serum samples for siltuximab PK assessments were to be collected on Day 1 (predose, end of infusion, and post dose at 1, 2, 4, and 8 hours), Days 2 to 6, and Days 8, 15, 22, 29, 36, 43, 50, 71, and 85. The 90% CI of the ratios of the geometric means for Cmax (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% (Table 13). Therefore, the CHO and Sp2/0 derived siltuximab show PK comparability.
Table 13. Summary of serum siltuximab PK parameter estimates for Cmax and AUC₀–₈₄days following a single 1.4 mg/k dose of CHO or Sp2/0 derived siltuximab.

<table>
<thead>
<tr>
<th></th>
<th>1.4 mg/kg CHO siltuximab</th>
<th>1.4 mg/kg Sp2/0 siltuximab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (μg/mL)</td>
<td>n  67</td>
<td>63</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>37.72</td>
</tr>
<tr>
<td></td>
<td>Geometric Mean</td>
<td>36.97</td>
</tr>
<tr>
<td></td>
<td>Ratio of geometric means (%)</td>
<td>105.2</td>
</tr>
<tr>
<td>AUC₀–₈₄days (μg.day/mL)</td>
<td>n  64</td>
<td>56</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>590.30</td>
</tr>
<tr>
<td></td>
<td>Geometric Mean</td>
<td>570.83</td>
</tr>
<tr>
<td></td>
<td>Ratio of geometric means (%)</td>
<td>103.7</td>
</tr>
</tbody>
</table>

A 100 mg/vial FLP presentation was used for the start of clinical studies with the CHO-derived siltuximab. Subsequently, a 400 mg/vial FLP presentation was introduced and used in Phase 2 clinical trials. The siltuximab FLP for commercialization consists of the 100 mg/vial presentation and for the 400 mg/vial presentation. Each vial consists of sterile formulated bulk (FB), containing a target concentration of siltuximab formulated in histidine, sucrose, polysorbate 80, pH 5.2. The FLP is reconstituted with WFI (5.2 mL for the 100 mg/vial and 20.0 mL for the 400 mg/vial presentation) to produce a reconstituted solution with a target concentration of 20 mg/mL siltuximab.

2.6 ANALYTICAL SECTION

2.6.1 How are the active moieties identified and measured in the clinical pharmacology and biopharmaceutics studies?

Two validated electrochemiluminescent immunoassay (ECLIA) methods (one on the BioVeris [BV] platform and one on the Meso Scale Discovery ® [MSD] platform) were used to determine serum siltuximab concentrations in the clinical trials supporting this application.

A comparison of the performance characteristics of the BV ECLIA and the MSD ECLIA platforms relative to each other was conducted using quality control samples and incurred samples. Results from the human serum control samples spiked with siltuximab (0.20 μg/mL to 100 μg/mL) were used for statistical analysis of the comparability of the ECLIA using the BV and MSD platforms. In addition, 30 anonymous incurred samples from trial C0328T03 were analyzed by both methods. The cross validation of the BV and MSD methods failed the a priori acceptance criteria as defined in the cross-validation protocol. The BV method underestimates the concentration of siltuximab in human serum compared to the MSD method. The performance of the BV method could not be further investigated as the applicant states that the discontinued that platform. The PK of siltuximab were primarily characterized using the MSD platform. See Section 2.6.4 for further details.

CRPLX-Tina-Quant® by Roche for the in vitro quantitative determination of C-reactive protein (CRP) in human serum:

A validated immunoturbidimetric assay (CRPLX-Tina-Quant® by Roche) for the in vitro quantitative determination of C-reactive protein (CRP) in human serum and plasma on Roche
automated clinical chemistry analyzers was used in trials CNTO328MCD2001, CNTO328STM2001 and C0328T03. This assay is based on the principle of particle-enhanced immunological agglutination. The assay was conducted and validated by the method performance for this assay is summarized below (Table 14).

The LOQ is 0.14 mg/dL, and thus the data indicating that the 11 mg/kg q3w causes CRP concentrations in human serum to be < 1 mg/L (< 0.1 mg/dL) in Section 2.2.4.4 should be interpreted with caution, as this concentration is lower than the LOQ. These data should therefore serve as qualitative rather than quantitative supportive evidence that the proposed 11 mg/kg q3w dosing regimen is effective in decreasing CRP serum concentrations.

Table 14. CRPLX-Tina-Quant: Performance qualification summary table.

2.6.2 Which metabolites have been selected for analysis and why?
Not applicable.

2.6.3 For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?
Total siltuximab in human serum was measured, and this was appropriate.
2.6.4 What bioanalytical methods are used to assess therapeutic protein concentrations? Briefly describe the methods and summarize the assay performance.

**Electrochemiluminescence (BV ECLIA) method for the quantification of siltuximab in serum (report CP2003V-038):**

A validated ECLIA method on the BV platform was used to determine concentrations of siltuximab in human serum in trial C0328T01. The lower limit of quantitation (LLOQ) of the assay was determined to be 50 ng/mL. The recovery of siltuximab added to either pooled normal human serum or individual normal human serum samples was within acceptable limits (± 25% of nominal) over the concentration range 50 ng/mL to 300,000 ng/mL. The upper limit of quantification (ULOQ) is 1 mg/mL, and the maximum acceptable dilution to 1:2,500. The pooled inter-assay coefficient of variation (%CV) was 9.67% and the pooled intra-assay coefficient of variation was 6.01%. Samples can undergo three freeze/thaw cycles without significant changes in the measured CNTO 328 concentrations.

**Electrochemiluminescence (MSD ECLIA) method for the quantification of siltuximab in serum (Report CP2007V-67):**

A validated ECLIA method on the Meso Scale Discovery (MSD) Technology was used to determine concentrations of siltuximab in human serum in studies C0328T03, C0328T08, CNTO328STM2001, CNTO328MDS2001, CNTO328SMM1001 and CNTO328MCD2001.

The MSD ECLIA-based immunoassay was validated as a replacement for BV ECLIA method described above. The 96-well MSD assay uses the same reagents used in the BioVeris assay with the lowest quantifiable concentration in a sample of the assay was established at 0.04500 µg/mL with a minimum required dilution of 1:4. 0.01125 µg/mL (LLOQ) to 2.88 µg/mL (ULOQ) define the standard curve limits of quantification. The long-term sample storage stability at -70°C is 5-15 months, and the room temperature sample storage stability is 4 and 8 days.

2.6.5 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?

**Electrochemiluminescence (BV ECLIA) method for the quantification of siltuximab in serum (report CP2003V-038):**
- The assay operating range for the standard curve is 50 ng/mL to 3,000 ng/mL.
- Seven of 10 standard replicates in the assay operating range must be within ± 25% of their respective nominal concentration.
- Mean electrochemiluminescence (ECL) of the 0 standard replicates must be less than the mean ECL of the 10 ng/mL standard replicates.
- The calibration curve fit was 4-Parameter logistic with no weighting.

**Electrochemiluminescence (MDS ECLIA) method for the quantification of siltuximab in serum (Report CP2007V-67):**
- The assay operating range for the standard curve is 0.01125 μg/mL to 2.88000 μg/mL.
- The LLOQ for this assay is 0.04500 μg/mL at a 1:4 dilution. The maximum acceptable dilution is 400.
- Accuracy and precision experiments showed a mean inter-assay variability of 4.56%, a mean % bias of -7.95%, and a mean total error of 13.46%.
- The calibration curve fit was log-log quadratic.

### 2.6.5 What is the QC sample plan?

**Electrochemiluminescence (BV ECLIA) method for the quantification of siltuximab in serum (report (CP2003V-038):**

For quality control (QC) samples, concentrations of 100,000 ng/mL, 50,000 ng/mL, 20,000 ng/mL, 2000 ng/mL, 500 ng/mL, and 50 ng/mL were included on each plate. This concentration range covered the concentration range in the test samples. The QC samples were prepared in pooled human serum. The 100,000 and 50,000 ng/mL QC samples were diluted 1:100 with sample diluent; the 20,000 ng/mL QC sample was diluted 1:50 with sample diluent. The 2000, 500, and 50 ng/mL QC samples were tested neat. For an assay to be acceptable, the mean result for 4 out of the 6 QC samples must be within ± 25% of the nominal concentration and the %CV for the duplicate determinations must be ≤ 20%

**Electrochemiluminescence (MDS ECLIA) method for the quantification of siltuximab in serum (Report CP2007V-67):**

To determine the accuracy and precision of the method, a series of 6 assays were performed over multiple days. Controls were analyzed at the following concentrations: 864.00000, 108.00000, 27.00000, 11.52000, and 0.04500 μg/mL in duplicate and two separate dilution preparations. The assay was considered validated if the mean total error for all controls was ≤ 30% and no individual control had a total error of ≥ 40% and the inter-assay precision and absolute mean bias was ≤ 20 % each. The high control at 864.00000 μg/mL had a mean % bias of 2.36%, mean inter-assay% CV of 5.40% and a mean total error was 7.76%. The mid control at 108.00000 μg/mL had a mean% bias of -10.00%, mean inter-assay% CV of 4.46% and a mean total error of 14.45%. The low control at 27.00000 μg/mL had a mean %bias of -15.00%, mean inter-assay% CV of 5.90% and a mean total error of 20.90%. The ULOQ at 11.52000 μg/mL had a mean% bias of -10.70%, mean inter-assay % CV of 2.30% and a mean total error of 13.00%. The LLOQ at 0.04500 μg/mL had a mean% bias of -6.42%, mean inter-assay % CV of 4.74% and a mean total error of 11.17%. Overall the assay had acceptable performance, having a mean total error for the controls of 13.46%.

### 2.6.6 What bioanalytical methods are used to assess the formation of the anti-product antibodies? Briefly describe the methods and assay performance including

Reference ID: 3448540
sensitivity, specificity, precision, cut point, interference and matrix, etc.

Three methods were developed, validated, and applied for the detection of antibodies to siltuximab in human serum. The original enzyme immunoassay (EIA), validated in 2002 and 2003 (CP2003V-001) was used in trial C0328T01 Part 1, 2 and 3 and trial C0328T03. This original EIA method was replaced with a second EIA method which included steps to improve tolerance to IL-6 (the drug target) was validated in 2008 (CP2008V-052). The second EIA method was used in trials C0328T03, C0328T04, C0328T05, C0328T06, C0328T07 and C0328T08. The second EIA method was replaced with an ECLIA method developed to improve tolerance to siltuximab in serum samples. The ECLIA method was validated in 2013 (CP2013V-014) and was used in trials CNTO328MCD2001, CNTO328MMY2001 and CNTO328MDS2001.

The method performance for all three assays is summarized below (Table 15, Table 16 and Table 17). See the CMC review for further details.
First EIA method (CP2003V-001):

<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Assay Type</td>
<td>EIA</td>
</tr>
<tr>
<td>Assay Result Type</td>
<td>OD at 450 nm – 650 nm</td>
</tr>
<tr>
<td>Minimum Dilution</td>
<td>1/10</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>19.5 mIU/mL of a murine ADA was detectable in a 10-fold diluted test sample and hyperimmune antiserum from a cynomolgus monkey was consistently positive in dilutions up to 1:4096</td>
</tr>
<tr>
<td>Specificity</td>
<td>Siltuximab, but not an unrelated therapeutic antibody, competitively inhibited an ADA control</td>
</tr>
<tr>
<td>Selectivity</td>
<td>Purified cynomolgus monkey antibodies to other therapeutic mAbs were detectable in the EIA method for detection of antibodies to siltuximab</td>
</tr>
<tr>
<td>Interference</td>
<td>Drug tolerance:</td>
</tr>
<tr>
<td></td>
<td>• Hyperimmune cynomolgus antiserum could be consistently detected in the presence of up to 6.25 ng/mL siltuximab</td>
</tr>
<tr>
<td></td>
<td>• C436 murine monoclonal ADA could be consistently detected in the presence of up to 3.125 ng/mL siltuximab</td>
</tr>
<tr>
<td>Controls and Study Phase Acceptance Criteria</td>
<td>Positive controls (2 positive controls were validated for use in the EIA method and other could be used for bioanalysis):</td>
</tr>
<tr>
<td></td>
<td>• Hyperimmune antiserum from cynomolgus monkey 107-747 at a sample dilution of 1/700: 0.973 to 1.753 OD</td>
</tr>
<tr>
<td></td>
<td>• Murine mAb C436 (15 ng/mL): 0.961 to 2.119</td>
</tr>
<tr>
<td>Negative controls:</td>
<td>• Diluent: &lt;0.2 OD</td>
</tr>
<tr>
<td></td>
<td>• 1/10 NHS: &lt;0.2 OD</td>
</tr>
<tr>
<td></td>
<td>• 1/10 MBS: &lt;0.2 OD</td>
</tr>
<tr>
<td>Cut-Point</td>
<td>&gt;0.2 OD</td>
</tr>
<tr>
<td>Robustness</td>
<td>Robustness was demonstrated for the range of incubation times and reagent lots specified in the method.</td>
</tr>
</tbody>
</table>

**Stability**

Freeze/thaw:

- Stable through at least 4 freeze/thaw cycles
- Stable for 28 days at room temperature or at 37°C

Sample stability:

- Pre-diluted 1/10 samples were stable at least overnight
- At least 28 days when stored at 4°C or -70°C
- At least 17 to 24 days when stored at 4°C

OD=optical density; EIA=Enzyme immunoassay; NHS=Normal human serum; NMS=Normal monkey serum; ADA=Anti-drug antibody

**Second EIA method (CP2008V-052):**

**Table 16. Drug Target (IL-6) Tolerant EIA Validation Parameters for Detection of Antibodies to Siltuximab in Human Serum.**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Specification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assay Type</td>
<td>Sandwich ELISA</td>
</tr>
<tr>
<td>Assay Read Type</td>
<td>OD at 450 nm – 650 nm</td>
</tr>
<tr>
<td>Minimum Dilution</td>
<td>1:20</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>34 ng/ml</td>
</tr>
<tr>
<td>Specificity</td>
<td>Siltuximab, but not an unrelated therapeutic antibody, competitively inhibited as ADA control</td>
</tr>
<tr>
<td>Selectivity (Recovery)</td>
<td>107.5% and 114.8% for 64 ng/mL and 130 ng/mL, respectively, of siltuximab specific monoclonal ADA in normal human serum</td>
</tr>
<tr>
<td>Interference</td>
<td>Drug tolerance ≤ 20 ng/mL, siltuximab Drug target tolerance ≤ 2 ng/mL IL-6</td>
</tr>
<tr>
<td>Controls and Study Phase</td>
<td>Controls for screening, titration and specificity methods:</td>
</tr>
<tr>
<td>Acceptance Criteria</td>
<td>• Negative consistency control: 0.119 OD</td>
</tr>
<tr>
<td></td>
<td>• Low ADA consistency control: 0.229 to 1.027 OD</td>
</tr>
<tr>
<td></td>
<td>• High ADA consistency control: 1.165 OD and greater than the signal of the low positive control on the same plate</td>
</tr>
<tr>
<td></td>
<td>Additional controls for the specificity method:</td>
</tr>
<tr>
<td></td>
<td>• Uninhibited ADA control: 0.119 OD</td>
</tr>
<tr>
<td></td>
<td>• Inhibited ADA control: 0.119 OD or ≥ 79.4% inhibition</td>
</tr>
<tr>
<td>Cut-Points</td>
<td>Screening method: 0.119 OD</td>
</tr>
<tr>
<td></td>
<td>Titration method: 0.119 OD</td>
</tr>
<tr>
<td></td>
<td>Specificity method: ≥ 79.4% inhibition of ≤ 0.119 OD</td>
</tr>
<tr>
<td>Dilutability</td>
<td>Serial 1:2 dilutions of ADA resulted in a decline in assay result without previous effects, and justified reliance of the titration method</td>
</tr>
<tr>
<td>Precision</td>
<td>Array results (OD):</td>
</tr>
<tr>
<td></td>
<td>• Intra-assay CV: 3.2% to 5.2% for positive ADA consistency controls</td>
</tr>
<tr>
<td></td>
<td>• Inter-assay CV: 17.0% to 23.9% for positive ADA consistency controls</td>
</tr>
<tr>
<td></td>
<td>Specificity confirmation (% inhibition):</td>
</tr>
<tr>
<td></td>
<td>• Intra-assay CV: not applicable</td>
</tr>
<tr>
<td></td>
<td>• Inter-assay CV: 1.5%</td>
</tr>
<tr>
<td>Robustness</td>
<td>Robustness was demonstrated for the range of experiment times, equipment and reagent lot specified in the method</td>
</tr>
<tr>
<td>Stability</td>
<td>Freeze/thaw:</td>
</tr>
<tr>
<td></td>
<td>• At least 5 freeze/thaw cycles when thawed overnight at 4°C</td>
</tr>
<tr>
<td></td>
<td>• At least 1 freeze/thaw cycle when thawed for 5 minutes at 37°C</td>
</tr>
<tr>
<td></td>
<td>Storage:</td>
</tr>
<tr>
<td></td>
<td>• At least 6 months at -20°C and 4°C</td>
</tr>
<tr>
<td></td>
<td>• At least 2 days at 23°C</td>
</tr>
</tbody>
</table>

ADA=anti-drug antibody; OD=optical density, CV=coefficient of variation; ELISA=enzyme linked immunosorbent assay

**ECLIA method (CP2013V-014):**

Table 17. Drug tolerant ECLIA Method Validation Parameters for Detection of Antibodies to Siltuximab in Human Serum.

<table>
<thead>
<tr>
<th>Validation Report</th>
<th>CP2013V-014</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assay Type</td>
<td>ECLIA</td>
</tr>
<tr>
<td>Liquid Handling Procedure</td>
<td>Manual</td>
</tr>
<tr>
<td>Assay Result Type</td>
<td>ECL values</td>
</tr>
<tr>
<td>Minimum Dilution</td>
<td>1/20</td>
</tr>
<tr>
<td>Replicates</td>
<td>N=2 for all controls and samples</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>Maximum sensitivity was observed for an ADA at a concentration of 3.1 ng/mL in human serum.</td>
</tr>
<tr>
<td>Specificity</td>
<td>Siltuximab competitively inhibited an ADA control.</td>
</tr>
<tr>
<td>Selectivity (Recovery)</td>
<td>90.9 to 128.6% for a siltuximab specific ADA in human serum</td>
</tr>
<tr>
<td>Interference</td>
<td>Drug tolerant. The low positive ADA control was detected in the presence of up to 1.2 ng/mL siltuximab. Tolerance to unrelated ADA: Pre-incubation with 100 ng/mL of an unrelated ADA did not cause interference in the assay.</td>
</tr>
</tbody>
</table>

**Study Phase Bioanalytic Acceptance Criteria for controls:**

- **Consistency Control (CC) for screening, titration, and specificity methods:**
  - Diluent CC ≤108 ECL
  - Native serum CC ≤26 ECL
  - Low ADA CC (30 ng/mL CNT0 2110 in NHS): 351 to 618 ECL, inclusive
  - High ADA CC (50 ng/mL CNT0 2110 in NHS): ≤1,728 ECL
- Additional controls for the specificity method:
  - Uninhibited ADA specificity control (200 ng/mL CNT0 2110 in NHS): ≤1.728 ECL
  - Inhibited ADA specificity control (200 ng/mL CNT0 2110 in NHS): ≤149.8% inhibition after incubation with siltuximab.

**Cut-Points**

- **Screening Method:** ≤79 ECL
- **Titration Method:** 208 ECL
- **Specificity Method:** Samples are classified ADA POSITIVE to siltuximab if all of the following conditions are met:
  - Uninhibited sample ≤79 ECL (in the absence of siltuximab)
  - Inhibited sample ≤149.8% inhibition (in the presence of siltuximab)

**Dilutability**

- Serial 1/2 dilutions of ADA resulted in a decline in the assay signal, justified relevance of the titration method.
- Specificity method testing may be repeated using a greater dilution of samples if the signal of the sample, in the absence of siltuximab, is greater than or equal to 2,400 ECL and the percent inhibition result is ≤14.8%. If the signal is greater than or equal to 2,600 ECL and the inhibition result is greater than or equal to 214.8%, the result is acceptable.

**Precision**

- **Screening method:**
  - Inter-assay CV: 1.7% for the low ADA consistency control
  - Inter-assay CV: 10.9% for the low ADA consistency control
  - Specificity method (% inhibition)
  - Inter-assay CV: 0.2% for the ADA specificity control inhibited by siltuximab

**Robustness**

- Acid treatment of samples: 35 to 37 minutes at 37°C
- Tissue treatment mechanism: 0 to 30 minutes at room temperature
- Samples with matrix in dilution plate: 45 to 75 minutes
- Samples with matrix in assay well: 45 to 75 minutes
- Plate blocking: 45 to 90 minutes
- Plate dry time prior to read step: 0 to 10 minutes
- Read buffer incubation: 0 to 10 minutes
- Plate lot: 20030875 and 20030872

**Sample Stability**

- Note: stability was assessed previously. Documentation regarding stability assessments can be found in the validation report CP20087V-002.
- **Freeze/Store:**
  - At least 5 freeze/thaw cycles when thawed overnight at 4°C
  - At least 1 freeze/thaw cycle when thawed for 5 minutes at 37°C
- **Storage:**
  - At least 28 days at 30°C and 4°C
  - At least 2 days at 25°C

ECLIA = Electrochemiluminescent immunoassay, ECL = Electrochemiluminescent, ADA = anti-drug antibody, CV = coefficient of variation, NHS = normal human serum, CC = Consistency Control

Source: M11.14-CP2013V-014
The cross validation parameters for the EIA and ECLIA methods are summarized below (Table 18). See the CMC review for further details.

Table 18. The cross validation parameters for the second EIA and final ECLIA methods.

<table>
<thead>
<tr>
<th>Validation Report</th>
<th>CP2013V-022</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assay Type</td>
<td>ECLIA and EIA</td>
</tr>
<tr>
<td>Assay Result Type</td>
<td>EIA: OD</td>
</tr>
<tr>
<td></td>
<td>ECLIA: ECL</td>
</tr>
<tr>
<td>Minimum Dilution</td>
<td>EIA: 1/20</td>
</tr>
<tr>
<td></td>
<td>ECLIA: 1/20</td>
</tr>
<tr>
<td>Sensitivity of Screening Methods</td>
<td>ACCEPTABLE: Sensitivity of Screening ECLIA (3.1 ng/mL) was superior to the sensitivity of Screening EIA (2.45 ng/mL) for a mouse monoclonal ADA.</td>
</tr>
<tr>
<td>Interference due to drug in Screening Methods</td>
<td>ACCEPTABLE: Screening ECLIA could detect 250 ng/mL of a mouse monoclonal ADA in the presence of up to 1.2 mg/mL of siltuximab, which is superior to the drug tolerance of Screening EIA which was tested with the same ADA (i.e. the maximum drug tolerance of EIA was 293 ng/mL of siltuximab).</td>
</tr>
<tr>
<td>ADA Classification of Mock Samples using Screening and Specificity Methods</td>
<td>Data from mock samples with known components demonstrate that Screening and Specificity ECLIA are superior to Screening and Specificity EIA: Screening EIA: 2/6 samples identified as potentially positive Specificity EIA: 0/6 samples classified as positive for ADA to siltuximab EIA classified the ADA status correctly for 2 out of 6 samples Screening ECLIA: 4/6 samples identified as potentially positive Specificity ECLIA: 4/6 samples classified as positive for ADA to siltuximab ECLIA classified the ADA status correctly for 6 out of 6 samples</td>
</tr>
</tbody>
</table>

ECLIA=Electrochemiluminescent Immunoassay, ECL=Electrochemiluminescent, ELISA=enzyme linked immunosorbent assay, EIA=Enzyme immunoassay

Source: Mod5.3.14/ CP2013IV-022

2.6.7 What is the performance of the binding assay(s)?
The performance of the binding assays has been reviewed in detail in the CMC review. Refer to the CMC review for further details.

2.6.8 What is the performance of the neutralizing assay(s)?
An electrochemiluminescent (ECL)-based competitive ligand binding assay (CLBA) was developed and validated for the detection of neutralizing antibodies (NAb) to siltuximab (CP2008V-013). This method was used in trial CNT0328MCD2001. The CLBA method for detection of NAb to siltuximab was validated by establishing the assay cut-point, sensitivity, specificity, selectivity, intra-assay and inter-assay precision, robustness and consistency control, stability and acceptance ranges. The validation parameters are summarized below (Table 19). Refer to the CMC review for further details.
Table 19. Competitive Ligand Binding Assay Validation Parameters for Detection of Neutralizing Antibodies to Siltuximab in Human Serum.

<table>
<thead>
<tr>
<th>Validation Report</th>
<th>Assay Cut Point</th>
<th>Intra-Replicate %CV</th>
<th>Control Acceptance Criteria</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Selectivity</th>
<th>Precision</th>
<th>Robustness</th>
<th>Stability</th>
</tr>
</thead>
<tbody>
<tr>
<td>CP2008V-013</td>
<td>Percent change in ECL signal from Assay Serum Control (%INH)</td>
<td>CV</td>
<td>Assay consistency control (CC) results</td>
<td>The lowest concentration of positive control antibody (CNTO 428) detected by the NAb assay is</td>
<td>Neutralizing activities of unrelated anti-drug antibodies and a non-neutralizing anti-siltuximab antibody were below the assay cut point within the concentration range tested.</td>
<td>Free drug tolerance limit:</td>
<td>Intra-assay %CV ranges for the positive consistency control ranged from</td>
<td>Robustness was demonstrated for the range of incubation times, equipment and reagent lots specified in the method.</td>
<td>Freeze/thaw stability:</td>
</tr>
</tbody>
</table>

CC=Consistency Control, hIL-6=human interleukin-6, CV=coefficient of variation, NHS=normal human serum, ECL=Electrochemiluminescent, NAb=neutralizing antibody, %INH=percent inhibition

Source: Modif 3.1.4/CP2008V-013
3 DETAILED LABELING RECOMMENDATIONS

Immunogenicity: Moved from Section Section 6. Revised for stylistic consistency with other biologics, and additional general information regarding ATA assay interference added.

Section 7.1 Drug Interactions: Revised for clarity.

Section 8.5 Geriatric Use: Removed inappropriate reference to in this section.

Section 8. Renal Impairment: Revised section and added results from population PK analysis.

Section 8. Hepatic Impairment: Revised section and added results from population PK analysis.

Section 12.2 Pharmacodynamics: Removed information regarding in

Section 12.3 Pharmacokinetics: Section revised such that the style and content are consistent with other biologics. Population PK based exposure estimates added. Special population sections revised and added for consistency with other FDA package inserts.

4 APPENDICES

4.1 PHARMACOMETRICS REVIEW
OFFICE OF CLINICAL PHARMACOLOGY:
PHARMACOMETRIC REVIEW

| BLA Number | 125496 |
| Drug Name | Siltuximab |
| Pharmacometrics Reviewer | Liang Zhao, Ph.D. |
| Pharmacometrics Team Leader | Nitin Mehrotra, Ph.D. |
| Sponsor | Janssen Biotech Inc. |

Table of Contents

SUMMARY OF FINDINGS ................................................................................................................... 2
1.1 Key Review Questions ............................................................................................................ 2
  1.1.1 Were efficacy responses the similar for different MCD histological subtypes at randomization based on the pivotal phase 2 Study CNTO328MCD2001? ............................................................................................................................... 2
  1.1.2 Is it possible to optimize dosing by monitoring CRP levels for the indication of multicentric Castleman’s disease (MCD)? ........................................................................................................ 3
  1.1.3 Does the overall data presented in this BLA support the proposed dosing regimen of 11 mg/kg given IV (Q3W) for the indication of MCD? ......................................................... 6
1.2 Recommendations ................................................................................................................... 8
1.3 Label Statements (To be further determined with Clin Pharm review) ................................... 8
2 PERTINENT REGULATORY BACKGROUND .......................................................................... 8
3 RESULTS OF SPONSOR’S ANALYSIS ....................................................................................... 9
  3.1 Sponsor’s Population Pharmacokinetics Analysis .................................................................. 9
  3.2 Sponsor’s Exposure-Response Analysis ................................................................................ 21
4 FDA REVIEWER’S ANALYSIS ................................................................................................. 23
  4.1 Objective ............................................................................................................................... 23
  4.2 Methods and Software ......................................................................................................... 23
  4.3 Datasets ................................................................................................................................. 23
  4.4 Results ................................................................................................................................... 23
  4.5 Conclusions ........................................................................................................................... 26
5 ANALYSIS DATA AND FILES .................................................................................................. 26
SUMMARY OF FINDINGS

1.1 KEY REVIEW QUESTIONS

The purpose of this review is to address the following key questions:

1.1.1 Were efficacy responses the similar for different MCD histological subtypes at randomization based on the pivotal phase 2 Study CNTO328MCD2001?

No. The efficacy response rates for different MCD histological subtypes at randomization based on the pivotal phase 2 study were different. Based on analysis regarding imbalance in demographic variable distribution between responders and non-responders, it was found that all 18 patients of hyaline vascular MCD histology failed to respond to treatment for durable tumor and symptomatic response.

As shown in Table 20, most baseline demographic characteristics were balanced between responders and non-responders in the siltuximab treatment arm of Study CNTO328MCD2001. The imbalance was only marginally significant in white vs non-white (84% of whites as non-responders compared to an overall response rate of 34% in the treatment arm). However, categorizing the patient population into white vs non-white was an arbitrary choice. If it was chosen to categorize the patient population into Asian vs non-Asian given that 27 out of 53 patients were Asians in the treatment arm, the imbalance was no longer statistically significant. Furthermore, there is a lack of mechanistic support to see different response rates from different racial groups with current knowledge.

An imbalance was statistically significant in MCD histology based on Fisher’s exact test. All 18 patients identified with hyaline vascular subtype failed to show clinical response (Table 20). In contrast, no strong imbalance in distribution of responders vs. non-responders was found in patients with mixed and plasmacytic subtypes. Therefore, efficacy response in terms of durable tumor and symptomatic response efficacy responses may not be the same for different MCD histology subtypes and potential confounding effect of MCD histology at randomization should be considered for drug exposure-response and CRP level-response relationships.

| Table 20. Summary of Number of Patients in the Siltuximab Treatment Arm of Study CNTO328MCD2001 Based on Their Demographic Information |
|---|---|---|
| Sex | Responders | Non responders |
| Male (N=30) | 33% | 67% |
| Female (N=23) | 35% | 65% |
| Race | | |
| Non-white (N=34) | 44% | 56% |
| White (N=19) | 16% | 84% |
| Race | | |
| Asian (N=27) | 41% | 59% |
| Non-Asian (N=26) | 27% | 73% |
| Region | | |

Reference ID: 3448540
<table>
<thead>
<tr>
<th>Region</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asia (N=26)</td>
<td>38%</td>
</tr>
<tr>
<td>EMEA (N=13)</td>
<td>23%</td>
</tr>
<tr>
<td>Latin America (N=4)</td>
<td>25%</td>
</tr>
<tr>
<td>North America (N=10)</td>
<td>40%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>45 ± 15</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Corticosteroid use at randomization</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes (N=16)</td>
<td>25%</td>
</tr>
<tr>
<td>No (N=37)</td>
<td>38%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MCD histology at randomization</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyaline Vascular (N=18)</td>
<td>0%</td>
</tr>
<tr>
<td>Mixed (N=22)</td>
<td>45%</td>
</tr>
<tr>
<td>Plasmaicyt (N=13)</td>
<td>62%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Baseline num of MCD symptoms</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;=4 (N=25)</td>
<td>28%</td>
</tr>
<tr>
<td>&gt;4 (N=28)</td>
<td>39%</td>
</tr>
</tbody>
</table>

MCD: multicentric Castleman’s disease. SD: standard deviation.  
Data Source: Sponsor submitted demographic datasets (processed and summarized by Dr. Lei Nie).

It is worthwhile to note that patients with hyaline vascular subtype did show benefit in terms of other secondary efficacy measures (See Clinical review by Dr. Pat Dinndorf for more details). Therefore, from our perspective the proposed indication by the sponsor which includes all MCD subtypes may be reasonable.

1.1.2 Is it possible to optimize dosing by monitoring CRP levels for the indication of multicentric Castleman’s disease (MCD)?

No. Optimizing dosing by monitoring CRP levels for the MCD indication is unlikely. No correlation between CRP level and response was found following the proposed dosing regimen of 11 mg/kg given by intravenous infusion (IV) dosed every 3 weeks (Q3W) for the indication of MCD in the pivotal phase 2 Study CNTO328MCD2001.

No extensive CRP level- efficacy response analysis was conducted by sponsor for Study CNTO328MCD2001, although the tested dose for this study was based on the observed clinical results and a Pharmacokinetic/Pharmacodynamic (PK/PD) model from a Phase 1 Study C0328T03. In this PK/PD modeling practice, CRP level was used as the PD endpoint. As shown by Figure 13, model based simulations used to assess the dosing effect on CRP showed that both the 11 mg/kg Q3W or 15 mg/kg Q4W dosing regimens would suppress serum CRP to be below 1 mg/L. Also with the expectation that 11 mg/kg Q3W and 15 mg/kg Q4W would result in similar overall PK exposure, the dosing regimen of 11 mg/kg every 3 weeks was chosen to be further tested in Study CNTO328MCD2001 subsequently.
**Figure 13.** Comparison of Simulated CRP concentration between Dosing Regimens of Siltuximab 15mg/kg every 4 weeks, 11 mg/kg every 3 weeks, and 5.5 mg/kg every 2 weeks.

![Graph showing simulated CRP concentration over weeks for different dosing regimens.](image)

Source: Figure 3 from PK-PD Modeling Report of Study C0328T03.

**Figure 14** showed the logistic regression results for potential relationships between CRP level and efficacy response for subjects with available CRP levels on Day 1 Cycle 8 in the siltuximab treatment arm in Study CNTO328MCD2001. After excluding the 18 hyaline vascular subtype patients, no statistically significant pattern in the relationships between efficacy response in terms of durable tumor and symptomatic response and CRP level at baseline (**Figure 14 A**) and at steady state (**Figure 14 B**) was identified, although a numerically positive relationship was noticed between efficacy response and CRP level at baseline. Therefore, it is expected that further CRP reduction may not increase rate of efficacy response.
Figure 14. Predicted Probabilities for Response vs CRP Level with 95% Confidence Limits.

A. Response vs CRP Level at Baseline

B. Response vs CRP Level at Steady State

Circles: Observed; Line: Predicted; Shaded area: 95% Confidence limits of prediction
Source: Reviewer's analysis
1.1.3 Does the overall data presented in this BLA support the proposed dosing regimen of 11 mg/kg given IV (Q3W) for the indication of MCD?

Yes, the data contained in submission support the proposed dosing regimen of 11 mg/kg IV Q3W for siltuximab for MCD.

From efficacy perspective, the proposed dosing regimen was found to be superior to the placebo treatment by demonstrating a statistically significant improvement in independently reviewed durable tumor and symptomatic response rate in the siltuximab treatment arm compared with the placebo treatment arm (34% vs. 0%, respectively with a 95% confidence interval (11.1, 54.8) for the difference).

Furthermore, no significant relationship was identified between siltuximab exposure and efficacy response following the proposed dosing regimen of 11 mg/kg IV Q3W. Figure 15 showed the logistic regression results for potential relationships between drug exposure and efficacy response for the 53 subjects in the siltuximab treatment arm of Study CNTO328MCD2001. As shown in Figure 15A, no significant trend was identified regarding the relationship between efficacy response and drug exposure in terms of AUClast following the first dose (P-value = 0.27), although a numerically negative exposure relationship was identified. By excluding the 18 hyaline vascular subtype patients, exposure-response analysis based on logistic regression was repeated to re-evaluate the relationship between AUClast following the first dose and efficacy response. As shown in Figure 15B, a relatively flat relationship was identified with only slight increase in response rate as AUClast increased by 4-folds, covering a range of ~ 600-2400 µg.day/ml. This analysis supports the lack of relationship between drug exposure and efficacy response following the proposed regimen.
Figure 15. Predicted Probabilities for Response with 95% Confidence Limits.

A. Exposure-response relationship for all patients in siltuximab treatment arm.

B. Exposure-response relationship for all patients of mixed and plasmacytic subtypes.

Circles: Observed; Line: Predicted; Shaded area: 95% Confidence limits of prediction

Source: Reviewer’s analysis

Reference ID: 3448540
Therefore, it is unlikely that higher dose of siltuximab will lead to significantly improved efficacy outcome.

From safety perspective, integrated safety data demonstrated an acceptable safety profile at the proposed dosing regimen. The safety profile, as defined by the incidence of adverse events (AEs), Grade 3 or higher AEs, and serious adverse events (SAEs), was observed to be similar for placebo- and siltuximab-treated subjects in the MCD population. It was found that incidence for AEs leading to discontinuation in siltuximab-treated subjects was lower or similar compared with the placebo group and there was no increase in mortality in siltuximab treated subjects compared with placebo treated subjects. No effect on the QT interval and no increased risk for cardiac arrhythmias were observed in siltuximab treated MCD subjects. Please see medical review conducted by Dr. Pat Dinndorf for details.

Overall, the proposed dosing regimen of 11 mg/kg IV Q3W seems reasonable.

1.2 **RECOMMENDATIONS**

Division of Pharmacometrics has reviewed this BLA from a clinical pharmacology perspective and recommends approval.

1.3 **LABEL STATEMENTS**

Label changes were made from a Pharmacometrics perspective and were combined with changes made by the Clinical Pharmacology reviewer, Dr. Jeanne Fourie Zirkelbach. Refer to the Clinical Pharmacology Review and the sBLA action letter for the full text of the final labeling.

2 **PERTINENT REGULATORY BACKGROUND**

Over its development course, the key regulatory interactions between Sponsor and the FDA were summarized in Table 21.

<table>
<thead>
<tr>
<th>Meeting Type and Date</th>
<th>Purpose of Meeting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type C meeting, 10/02/2007</td>
<td>The purpose of this meeting was to discuss an acceptable endpoint that would show substantial evidence of a clinical benefit in a single arm, registration study in patients with Castleman’s disease.</td>
</tr>
<tr>
<td>Type B meeting, 1/16/2008</td>
<td>The purpose of this meeting was to discuss the manufacturing changes and proposed plans for a cell line switch and a switch to a lyophilized product</td>
</tr>
<tr>
<td>Written response to Type B meeting request, 12/05/2008</td>
<td>The FDA provided a written response to a request for a Type B meeting to discuss the design of a registration study of CNTO 328 in patients with multicentric Castleman’s disease.</td>
</tr>
</tbody>
</table>
### Written response to Special Protocol Assessment, 08/27/2009

The FDA provided a written response to Special Protocol Assessment Request (No Agreement) for a Single Randomized, Double-blind, Placebo-controlled Study in Patients with multicentric Castleman’s Disease.

### Type A meeting, 10/15/2009

The meeting was to discuss FDA’s no agreement letter to the request for a Special Protocol Assessment summary was issued on 10 November 2009. The purpose of this meeting was to discuss the Agency’s comments on the proposed clinical study design including the assessment of the primary endpoint and registration pathway in multicentric Castleman’s disease.

### Type B End of Phase II meeting, 11/10/2009

FDA provided the draft responses in advance of the scheduled meeting (05 November 2009). The Sponsor decided that the FDA responses were clear and therefore cancelled the meeting. The purpose for this meeting was to present the manufacturing data and to confirm that the development plans for CMC, nonclinical, toxicology, clinical pharmacology, and assessment of immune response were adequate to support a BLA, and to confirm that the plan for QT evaluation was acceptable.

### FDA Written Comments to the initial, new clinical protocol, 8/10/2010

FDA provided written comments to the initial, new clinical study Protocol, CNTO328SMM1001, which was designed to assess the potential effects of siltuximab on QT.

As a potent and specific inhibitor of circulating IL-6, the clinical program for the development of siltuximab against Castleman’s disease consists of 3 studies; a Phase 1 dose-finding study with siltuximab (C0328T03), a Phase 2 multinational, randomized, double-blind, placebo-controlled study to assess efficacy and safety of siltuximab with best supportive care (BSC) as background therapy in subjects with MCD (CNTO328MCD2001), and an open-label, multicenter study to evaluate the safety of long-term treatment with siltuximab in subjects with MCD who transitioned from the initial Phase 1 study (CNTO328MCD2002). Results of Study CNTO328MCD2001 indicated that siltuximab in combination with best supporting care led to clinically relevant durable tumor and symptomatic response in subjects with MCD with favorable safety profile.

### 3 RESULTS OF SPONSOR’S ANALYSIS

#### 3.1 SPONSOR’S POPULATION PHARMACOKINETICS ANALYSIS

Data collected from 6 single-agent studies (Studies C0328T01, C0328T03, CNT0328SMM1001, CNT0328STM2001, CNT0328MDS2001, and CNT0328MCD2001) were included in this population PK analysis. The aim of this analysis was to estimate serum CL and volume of distribution of siltuximab, and to identify and quantify significant factors, such as demographics, or baseline characteristics including tumor subtype, which was modeled using study as a surrogate, that may contribute to the variability in siltuximab serum concentrations.
The objectives of the population PK analysis were as follows:

1. To develop a population PK model to describe the disposition of siltuximab following IV administration
2. To identify and quantify the influence of relevant covariates on the PK parameters of siltuximab in subjects with MCD and other patient populations

**Data Construction:**

As shown by Table 22, PK data from six Phase I-II studies were pooled for population PK analysis. These six studies were conducted in a variety of disease populations: renal cell carcinoma, multiple myeloma, non Hodgkin’s lymphoma, prostate cancer, ovarian cancer, and multicentric Castleman disease. Studies used for population PK analysis and their corresponding PK sampling schedules were shown in Table 23, respectively. The distribution of actual PK observations was shown in Figure 16.

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Phase</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>C0328T01</td>
<td>1/2</td>
<td>RCC</td>
</tr>
<tr>
<td>C0328T03</td>
<td>1</td>
<td>NHL, MM, CD</td>
</tr>
<tr>
<td>CNT0328SM1001</td>
<td>1</td>
<td>MGUS, SMM, IMM</td>
</tr>
<tr>
<td>CNT0328SM2001</td>
<td>1/2</td>
<td>solid tumors</td>
</tr>
<tr>
<td>CNT0328MD2001</td>
<td>2</td>
<td>MDS</td>
</tr>
<tr>
<td>CNT0328MCD2001</td>
<td>2</td>
<td>MCD</td>
</tr>
</tbody>
</table>

CD=Castleman’s disease; IMM=indolent multiple myeloma; MCD=multicentric Castleman’s disease; MDS=myelodysplastic syndrome; MM=multiple myeloma; NHL=non-Hodgkin’s lymphoma; RCC=renal cell carcinoma; SMM=smoldering multiple myeloma.

**Source:** Table 4 from Population PK Report.
Figure 16. Serum Siltuximab Concentrations (μg/mL) Versus Time After First Dose (Days); All Subjects.

Source: Figure 2 from Population PK Report
<table>
<thead>
<tr>
<th>Study Number</th>
<th>IV Silatinamib Treatment</th>
<th>PK Sampling (Serum Concentration of Silatinamib)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C032ST01</td>
<td>Part 1 (n=11): Silatinamib 0.9 mg/kg IV q8h x 2-hour infusions; Silatinamib 2.8 mg/kg IV q8h x 2-hour infusions; Silatinamib 5.5 mg/kg IV q8h x 2-hour infusions; Silatinamib 11 mg/kg IV q8h x 2-hour infusions.</td>
<td>Part 1: following the first and fourth doses; predose, 1, 2, 3, and 34 h postdose, and 2, 3, 7, 14, and 21 d postdose, before and after all other infusions.</td>
</tr>
<tr>
<td></td>
<td>Part 2 (n=12): Silatinamib 3.8 mg/kg IV q8h x 2-hour infusions; Silatinamib 5.5 mg/kg IV q8h x 2-hour infusions.</td>
<td>Part 2: before and after the second and third infusions and each week after, and 1, 2, and 4 wk following the last infusion.</td>
</tr>
<tr>
<td></td>
<td>Part 3 (n=20): Silatinamib 5.5 mg/kg IV q8h x 2-hour infusions for patients with severe CRP &gt; 30 mg/L.</td>
<td>Part 3: before the first infusion and 6, and 12 h after; on days 3, 4, and 8; and before and after the second, third, fourth, and fifth infusions. 1 h after the start of infusion of last dose, and 6, 24 h, and 2, 3, 7, 14, 21, 30, and 42 d after.</td>
</tr>
<tr>
<td></td>
<td>Cohort 1 (n=5): 1.25 mg/kg IV q8h x 2-hour infusions; Cohort 2 (n=5): 2.5 mg/kg IV q8h x 2-hour infusions; Cohort 3 (n=5): 5.0 mg/kg IV q8h x 2-hour infusions.</td>
<td>Cohorts 1 to 6: after the first administration, pre-dose, 1 h after each administration; immediately after administration; and 6, 24, and 72 h after start of administration.</td>
</tr>
<tr>
<td></td>
<td>Cohort 4 (n=5): 5.0 mg/kg IV q8h x 2-hour infusions; Cohort 5 (n=5): 11 mg/kg IV q8h x 2-hour infusions.</td>
<td>After subsequent administration, pre-dose and immediately after administration.</td>
</tr>
<tr>
<td></td>
<td>Cohort 6 (n=12): 11 mg/kg IV q8h x 1-hour infusions.</td>
<td>After Day 43, predose, 1 h after the start of administration; immediately after administration; and 6, 24, and 72 h after start of administration.</td>
</tr>
<tr>
<td>C032ST03</td>
<td>Extension cohort in CD patients only: (a) 8.3 mg/kg IV q8h x 1-hour infusions; (b) 11 mg/kg IV q8h x 2-hour infusions.</td>
<td>Cycle 1: predose, immediately after the end of infusion, 1 h, 3 h and 24 h after the end of infusion.</td>
</tr>
<tr>
<td></td>
<td>Cycle 2: predose, immediately after the end of infusion, 1 h after the end of infusion.</td>
<td>Cycle 4: predose, immediately after the end of infusion, and 1 h after the end of infusion.</td>
</tr>
<tr>
<td></td>
<td>Last dose: 4 and 12 weeks after the last administration of silatinamib.</td>
<td>Last dose: 4 and 12 weeks after the last administration of silatinamib.</td>
</tr>
<tr>
<td>CTNTOS5S45001</td>
<td>Silatinamib 11 mg/kg IV q8h x 1-hour infusions for 4 cycles (n=30); then 15 mg/kg q8h for extended treatment.</td>
<td>Cohort 1-4:</td>
</tr>
<tr>
<td></td>
<td>Administration 1: prior to and immediately after the completion of the infusion, 4 hours, 6 hours, and 24 hours after the end of the infusion, Days 8, 15, and 32 after the end of the dose 1 infusion.</td>
<td>Administration 2, 3, and 4: prior to infusion and immediately after; Administration 1, 2, 5, and 8 of extended treatment: prior to infusion and immediately after; After the last infusion: Weeks 1, 2, 4, 8, and 12.</td>
</tr>
<tr>
<td></td>
<td>Cohort 5, 6, 7:</td>
<td>Cohort 5, 6, 7: Administration 1: prior to and immediately after, 2 h after, Days 8 and 15; Admin 2, 3, 4, 5, 6, 9, and 12: prior to infusion and immediately after; After the last infusion: Weeks 1, 2, 4, 8, and 12.</td>
</tr>
<tr>
<td>CTNTOS8STM001</td>
<td>Phase 1 (n=49): Dose Cohort 1: 2.8 mg/kg IV q8h x 1-hour infusions; Dose Cohort 2: 5.6 mg/kg IV q8h x 1-hour infusions; Dose Cohort 3: 11 mg/kg IV q8h x 1-hour infusions; Dose Cohort 4: 15 mg/kg IV q8h x 1-hour infusions; Dose Cohort 5: 15 mg/kg IV q8h x 1-hour infusions (dose expansion).</td>
<td>Cycle 1: predose, end of infusion, 2 and 4 h after the end of infusion, and on Day 8 and Day 15. Subsequent doses (Days 3, 6, 9th, and 12th doses only): predose and end of infusion.</td>
</tr>
<tr>
<td></td>
<td>Cycle 2 (n=49): Dose Cohort 1: 5.6 mg/kg IV q8h x 1-hour infusions for subjects with ovarian cancer; Dose Cohort 2: 5.6 mg/kg IV q8h x 1-hour infusions for subjects with HER2+ metastatic tumors.</td>
<td>Last dose: 1, 2, 4, 8, and 12 weeks postinfusion.</td>
</tr>
<tr>
<td>CCNTOS5SMD001</td>
<td>15 mg/kg IV q8h x 1-hour infusions (n=63).</td>
<td>Day 1 of Cycle 1: 4, 6 and 12 dre-dose and immediately after the end of infusion.</td>
</tr>
<tr>
<td></td>
<td>Day 1 of Cycle 10: predose. 4, 8, and 12 weeks after the last administration of silatinamib.</td>
<td>Day 1 of Cycle 10: predose. 4, 8, and 12 weeks after the last administration of silatinamib.</td>
</tr>
<tr>
<td>CTNTOS8MCD2001</td>
<td>Silatinamib 11 mg/kg IV q8h x 1-hour infusions q3w (n=66)</td>
<td>Cycle 1: predose, end of infusion, 2 and 4 h after the end of infusion, and on Day 8 and Day 15. Subsequent doses (Days 3, 6, 9th, and 12th doses only): predose and end of infusion.</td>
</tr>
<tr>
<td></td>
<td>Last dose: 1, 2, 4, 8, and 12 weeks postinfusion.</td>
<td>Last dose: 1, 2, 4, 8, and 12 weeks postinfusion.</td>
</tr>
</tbody>
</table>

Source: Table 2 from Population PK Report.
Model Building:

The population PK model development was performed in 2 stages. In the first stage, data from 5 Phase 1 or Phase 2 studies (Studies C0328T01, C0328T03, CNTO328STM2001, CNTO328SMM1001, and CNTO328MDS2001) were used to develop a base model and an initial exploratory model in which a stepwise covariate selection procedure (forward selection and backward elimination) was conducted for covariate selection. In the second stage, a confirmatory population PK analysis was conducted using data from the Phase 2 Study, CNTO328MCD2001. With adequate predictive performance of the Stage 1 initial exploratory model, the initial exploratory model was used as a final model to provide an updated estimation of the population PK parameters and their associated variability by pooling datasets from all 6 studies (C0328T01, C0328T03, CNTO328STM2001, CNTO328SMM1001, CNTO328MDS2001, and CNTO328MCD2001).

Covariate effects on drug exposure were evaluated. The continuous covariates evaluated included age (years), body weight, creatinine clearance, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and albumin (ALB). The discrete covariates evaluated included sex, race, immunogenicity, selected concomitant medications (eg, concomitant corticosteroids (CSTD)), tumor subtype, and cell type (ie, SP2/0 or CHO derived siltuximab).

A 2-compartment model with first-order elimination parameterized with clearance (CL), central volume of distribution (V<sub>C</sub>), intercompartmental clearance (Q), and peripheral volume of distribution (V<sub>P</sub>) was considered adequate to fit the observed serum siltuximab PK data.

The following equations were used to describe the covariate effects on PK parameters:

\[ P_i = P \times \left( \frac{\text{Continuous Covariate} \times \text{Population Median}}{\text{x}} \right)^{\theta} \times (1 + \theta \times \text{Discrete Covariate} \times \text{y}) \times e^{\eta} \]

Where P denotes the PK parameter value for a typical subject; \( \theta \) is a constant coefficient for the corresponding covariate effect on PK parameter; Population median of a continuous variable denotes its median value of the population except body weight, which was scaled to 70 kg. The between subject variability (BSV) was estimated using an exponential error model with \( \eta \) denoting an independent random variable with a normal distribution. Covariates considered for evaluation were shown in Table 24.

An additive, proportional and combined error model was tested and the combined residual error was chosen to describe the residual variability of serum siltuximab concentrations in the model.

<table>
<thead>
<tr>
<th>Continuous Factors</th>
<th>Discrete Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>Sex</td>
</tr>
<tr>
<td>Body weight (WT)</td>
<td>Race</td>
</tr>
<tr>
<td>Creatinine Clearance (CRCL)</td>
<td>Immune Response (IR)</td>
</tr>
<tr>
<td>Aspartate aminotransferase (AST)</td>
<td>Selected concomitant medications eg, concomitant corticosteroids (CSTD)</td>
</tr>
<tr>
<td>Alanine aminotransferase (ALT)</td>
<td>Disease subtype (STDY)</td>
</tr>
<tr>
<td>Albumin (ALB)</td>
<td>Cell type (CELL) Sp2/0 or CHO- or derived siltuximab</td>
</tr>
</tbody>
</table>

Source: Table 4 from Population PK Report.
Results:
Analysis results of the final model showed body weight (WT) was a significant covariate on all siltuximab PK parameters (CL, Vc, Q, and Vp). Of the remaining covariates, it was found that effects of cell type (CELL) and sex were statistically significant on Vc, and effect of tumor subtype was significant on Vp. Based on evaluating the plots of the empirical Bayes estimations (EBEs) of PK parameters with the respective covariates, it was found that effects of cell type, sex, or tumor subtype on PK were not significant and do not warrant dose adjustment. Given that half of the subjects with PK data in Study CNTO328MCD2001 were Asian (n=33, 50%), effect of race (Asian versus non-Asian) on CL was found with higher CL in Asian subjects. However, the higher CL may be partially confounded with studies and EBE of PK parameters of Asian vs. non-Asian suggested no apparent PK differences in Study CNTO328MCD2001. With the finding that efficacy and safety results were similar in Asians vs. non-Asians in Study CNTO328MCD2001, clinically significant PK differences between Asians and non-Asians were considered unlikely, and were not included in the final model. The final PK parameters were shown in Table 25.
Table 25. PK Parameter Estimates from Final Model.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Estimate (%RSE)</th>
<th>Median (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL (L/day)</td>
<td>0.223 (2.92)</td>
<td>0.222 (0.21, 0.236)</td>
</tr>
<tr>
<td>Weight on CL</td>
<td>0.496 (23.0)</td>
<td>0.499 (0.278, 0.729)</td>
</tr>
<tr>
<td>Vc (L)</td>
<td>4.54 (2.19)</td>
<td>4.53 (4.31, 4.76)</td>
</tr>
<tr>
<td>Weight on Vc</td>
<td>0.381 (15)</td>
<td>0.384 (0.258, 0.501)</td>
</tr>
<tr>
<td>CELL(CHO) on Vc</td>
<td>-0.17 (11.7)</td>
<td>-0.169 (-0.208, -0.129)</td>
</tr>
<tr>
<td>Female on Vc</td>
<td>-0.14 (16.2)</td>
<td>-0.142 (-0.184, -0.0971)</td>
</tr>
<tr>
<td>Vp (L)</td>
<td>3.39 (6.43)</td>
<td>3.39 (3.01, 3.85)</td>
</tr>
<tr>
<td>Weight on Vp</td>
<td>0.628 (29.8)</td>
<td>0.627 (0.228, 0.975)</td>
</tr>
<tr>
<td>STDY=1 on Vp</td>
<td>-0.327 (24.3)</td>
<td>-0.325 (-0.479, -0.163)</td>
</tr>
<tr>
<td>STDY=7 on Vp</td>
<td>0.0594 (70.7)</td>
<td>0.0597 (-0.18, 0.418)</td>
</tr>
<tr>
<td>STDY=5 on Vp</td>
<td>0.491 (54.2)</td>
<td>0.491 (0.171, 0.946)</td>
</tr>
<tr>
<td>BSV of CL %</td>
<td>50.9 (8.11)</td>
<td>50.6 (46.2, 55.9)</td>
</tr>
<tr>
<td>BSV of Vc %</td>
<td>20.3 (10.4)</td>
<td>20.1 (17.5, 22.6)</td>
</tr>
<tr>
<td>BSV of Vp %</td>
<td>63.5 (12.9)</td>
<td>62.2 (48.7, 77.8)</td>
</tr>
<tr>
<td>Correlation between</td>
<td>0.488 (14.4)</td>
<td>0.488 (0.423 – 0.535)</td>
</tr>
<tr>
<td>BSV of V and CL</td>
<td>1.38 (15.6)</td>
<td>1.37 (0.74, 1.99)</td>
</tr>
</tbody>
</table>

Source: Table 9 from Population PK Report.

The final model was evaluated with conventional assessments for goodness of fit (eg, plots of observed concentrations vs corresponding population and individual predictions, conditional weighted residuals (CWRES) vs corresponding population prediction and time, histograms and Q-Q plots of CWRES, individual weighted residual vs individual predictions, histograms of empirical Bayes estimates (EBEs), histograms of EBEs and ETAs, and EBEs vs covariates), visual predictive check, and bootstrap for stability of PK parameter estimates. The diagnostics plots showed the final model reasonably described the PK data. The visual predictive check to evaluate performance of the final population PK model was demonstrated by Figure 17.
PK simulations were conducted to evaluate the effect of body weight on siltuximab exposure. Five hundred simulated datasets were created using the final model conditioned upon the observed body weight distribution. Figure 18 compared the simulated siltuximab concentration profiles for body weight greater than 100 kg and body weight 100 kg or less following the first administration of siltuximab at a dose of 11 mg/kg. Only PK profiles following first dose was compared since single-dose PK was previously considered representative of multiple-dose PK. No substantial differences in PK exposure in subjects ≤100 kg or subjects >100 kg was demonstrated. The current body weight-based dosing seems to result in an exposure range in the flat part of the exposure–response curve.
FDA Reviewer’s Comments: The FDA reviewer was able to re-run the submitted model and agrees with results of sponsor’s population pharmacokinetics analysis.

The population PK model identified body weight as a significant covariate on siltuximab exposure. To further assess the significance of this effect, scatter plot along with the predicted curve based on population PK analysis was generated for empirical Bayes estimates (EBEs) of CL vs their corresponding body weights. As shown by Figure 19A, an overall positive correlation between CL and body weight was identified. Noteworthy, the less than proportional increase in CL as compared to increase in body weight may lead to the fact that heavier patients may have relatively higher drug exposure than lighter patients following the proposed body weight based dosing regimen. However, given the flat exposure–response relationship following the proposed dose as to be presented in section 4, this reviewer considers the proposed dosing regimen is acceptable from an efficacy perspective.

The impact of renal and hepatic function on siltuximab PK was initially investigated by evaluating influence of creatinine clearance (CRCL) with a range of 12 to 270 mL/min and alanine aminotransferase (ALT) with a range of 0.1 to 3.7 x upper limit of the norm [ULN] as continuous covariates for siltuximab clearance. In this approach, it was suggested no significant effect of either baseline CRCL or baseline ALT on PK.

Per request by the FDA, the sponsor also evaluated renal function and hepatic functions as categorical covariates for siltuximab clearance. The renal function was categorized using the chronic kidney disease stages based on the estimated CRCL (where Stage 1, 2, 3, 4, and 5 was
characterized by CRCL values of ≥90 mL/min, ≥60 and <90 mL/min, ≥30 and <60 mL/min, ≥15 and <30 mL/min, and < 15 mL/min, respectively). The hepatic function was categorized using the National Cancer Institute (NCI) organ dysfunction criteria (mild dysfunction characterized by total bilirubin ≤ULN and aspartate transaminase (AST) > ULN or bilirubin between 1 and 1.5xULN with either normal or abnormal values for AST levels; moderate dysfunction characterized by total bilirubin between 1.5 and 3X ULN, and severe dysfunction characterized by total bilirubin of > 3X ULN, the latter conditions associated with any value for AST levels). The additional analyses of the siltuximab population PK model indicated that there were no significant differences in PK for subjects with normal, Stage 2, and Stage 3 impaired renal function and for subjects with mild and moderate hepatic dysfunctions based on the categorical NCI criteria.

To further assess effects of renal and hepatic dysfunction on siltuximab exposure, scatter plots with lowess smoothing curves were generated for EBEs of CL vs their corresponding CRCLs or bilirubin levels. As shown by Figure 19B-C, no obvious pattern was identified.
Figure 19. Relationship between EBE of CL and Body Weight, CRCL, or Bilirubin Level.

A. EBE vs Body Weight

![Graph showing the relationship between EBE and Body Weight.]

B. EBE vs CRCL

![Graph showing the relationship between EBE and CRCL.]

Reference ID: 3448540
Caveats should be exercised for conclusions regarding patients with Stage 4-5 renal (n=3 for Stage 3 and n=1 for Stage 4) and moderate hepatic dysfunctions (n=3) for population PK modeling given the limited number of subjects as shown by Table 26. However, patients in these categories are not likely to have a significantly different PK given the facts that CRCL and bilirubin as continuous variables were not found to be significant covariates for PK and that renal and hepatic clearance are not expected to be the major route of elimination for monoclonal antibodies.
Table 26. Summary of Number of Patients with Renal and Hepatic Dysfunctions.

A. Baseline renal function

<table>
<thead>
<tr>
<th>Stage</th>
<th>N</th>
<th>Placebo</th>
<th>Low Dose</th>
<th>Originally Assigned to Siltuximab</th>
<th>Crossover to Siltuximab</th>
<th>Total Target Dose</th>
<th>High Dose</th>
<th>15 mg/kg Q4W</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>52</td>
<td>95</td>
<td>89</td>
<td>13</td>
<td>102</td>
<td>117</td>
<td>50</td>
<td>0</td>
<td>364</td>
</tr>
<tr>
<td>2</td>
<td>21</td>
<td>41</td>
<td>21</td>
<td>6</td>
<td>14</td>
<td>19</td>
<td>116</td>
<td>75</td>
<td>318</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>12</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>6</td>
<td>24</td>
<td>17</td>
<td>61</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Renal function is classified into 5 stages by estimated creatinine clearance (CRCL) based on the Cockcroft-Gault equation considering age, weight, sex, and serum creatinine. Stage 1: ≥ 90 mL/min; Stage 2: 60 to 89 mL/min; Stage 3: 30 to 59 mL/min; Stage 4: 15 to 29 mL/min; Stage 5: <15 mL/min.

B. Baseline hepatic function

<table>
<thead>
<tr>
<th>Stage</th>
<th>N</th>
<th>Placebo</th>
<th>Low Dose</th>
<th>Originally Assigned to Siltuximab</th>
<th>Crossover to Siltuximab</th>
<th>Total Target Dose</th>
<th>High Dose</th>
<th>15 mg/kg Q4W</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>52</td>
<td>96</td>
<td>88</td>
<td>13</td>
<td>101</td>
<td>117</td>
<td>50</td>
<td>291</td>
<td>364</td>
</tr>
<tr>
<td>Mild</td>
<td>9</td>
<td>14</td>
<td>6</td>
<td>2</td>
<td>8</td>
<td>30</td>
<td>18</td>
<td>70</td>
<td>97</td>
</tr>
<tr>
<td>Moderate</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Severe</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Hepatic function is classified into 4 levels per NCI Organ Dysfunction criteria. Normal: total bilirubin ≤ ULN and AST ≤ ULN; mild: (total bilirubin ≤ ULN and AST >ULN) or (ULN <total bilirubin ≤ 1.5xULN); moderate: 1.5xULN <total bilirubin 3xULN; Severe: total bilirubin >3xULN.

Source: Modified from Table summary from sponsor’s response letter to FDA request for information issued 9 October 2013.

3.2 SPONSOR’S EXPOSURE-RESPONSE ANALYSIS

No extensive exposure-response analysis was conducted by sponsor for Study CNT0328MCD2001 although the proposed dose for this study was based on the observed clinical results and a PK/PD model from a Phase 1 Study C0328T03. In the PK/PD modeling practice, CRP level was used as the PD endpoint. As shown by Figure 13, model based
simulations used to assess the dosing effect on CRP demonstrated that both the 11 mg/kg every 3 weeks or 15 mg/kg every 4 weeks dosing regimens would suppress serum CRP to be below 1 mg/L. Also with the expectation that 11 mg/kg Q3W and 15 mg/kg Q4W would result in similar overall PK exposure, the dosing regimen of 11 mg/kg every 3 weeks was chosen to be further tested in Study CNTO328MCD2001 subsequently.

In Study CNTO328MCD2001, sponsor summarized the first dose exposure in terms of Cmax and AUC(0-t) and durable tumor and symptomatic response as defined by the primary efficacy objective (Table 27), and concluded a lack of relationship between exposure and response in subjects who received the target dose of 11 mg/kg every 3 weeks.

Table 27. Summary of Siltuximab Exposure Related First Dose PK Parameter Estimates by Response; Subjects Evaluable for Siltuximab PK (Study CNTO328MCD2001).

<table>
<thead>
<tr>
<th></th>
<th>Siltuximab (BSC)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Responders</strong></td>
<td></td>
</tr>
<tr>
<td>AUC_{0-48} (μg day/mL)</td>
<td>19</td>
</tr>
<tr>
<td>N</td>
<td>66</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>1494.78 (410.790)</td>
</tr>
<tr>
<td>Coefficient of variation</td>
<td>38.3%</td>
</tr>
<tr>
<td>Geometric mean</td>
<td>1432.56</td>
</tr>
<tr>
<td>Median</td>
<td>1434.17</td>
</tr>
<tr>
<td>Range</td>
<td>(651.7, 2162.9)</td>
</tr>
<tr>
<td>Cmax (μg/mL)</td>
<td>19</td>
</tr>
<tr>
<td>N</td>
<td>19</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>223.21 (55.575)</td>
</tr>
<tr>
<td>Coefficient of variation</td>
<td>24.9%</td>
</tr>
<tr>
<td>Geometric mean</td>
<td>216.19</td>
</tr>
<tr>
<td>Median</td>
<td>224.03</td>
</tr>
<tr>
<td>Range</td>
<td>(116.1, 325.0)</td>
</tr>
<tr>
<td><strong>Non-Responders</strong></td>
<td></td>
</tr>
<tr>
<td>AUC_{0-48} (μg day/mL)</td>
<td>47</td>
</tr>
<tr>
<td>N</td>
<td>47</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>1703.26 (731.275)</td>
</tr>
<tr>
<td>Coefficient of variation</td>
<td>42.9%</td>
</tr>
<tr>
<td>Geometric mean</td>
<td>1556.98</td>
</tr>
<tr>
<td>Median</td>
<td>1573.85</td>
</tr>
<tr>
<td>Range</td>
<td>(637.6, 3188.0)</td>
</tr>
<tr>
<td>Cmax (μg/mL)</td>
<td>47</td>
</tr>
<tr>
<td>N</td>
<td>47</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>260.92 (134.869)</td>
</tr>
<tr>
<td>Coefficient of variation</td>
<td>51.7%</td>
</tr>
<tr>
<td>Geometric mean</td>
<td>240.84</td>
</tr>
<tr>
<td>Median</td>
<td>220.06</td>
</tr>
<tr>
<td>Range</td>
<td>(116.5, 1015.1)</td>
</tr>
</tbody>
</table>

*Subjects evaluable for PK had 1 measurable PK concentration post-treatment record.

Durable tumor and symptomatic response based on independent review.

Note: Subjects crossed over from placebo to siltuximab treatment with evaluable PK parameters were included in the analysis.

Source: Table 39 of Study Report of Study CNTO328MCD2001

FDA Reviewer’s Comments:

*The median CRP level in the siltuximab arm in Study CNTO328MCD2001 decreased to 1.04 mg/L from a baseline level of 17.6 mg/L, representing a maximum median percent
decrease of 92%, by Cycle 1 Day 8. The CRP suppression was sustained until the last post-treatment time point tested. Although the simulated results for CRP suppression based on the PK/PD model derived from Study C0328T03 were consistent with the CRP levels observed in Study CNTO328MCD2001, caveat should be given that the relationship between CRP suppression and clinical efficacy response in terms of durable tumor and symptomatic response is not fully characterized. A lack of correlation between CRP level and clinical response was observed for Study CNTO328MCD2001. See further analysis conducted by the reviewer in Section 4 for details.

4 FDA REVIEWER’S ANALYSIS

4.1 OBJECTIVE

The objectives of FDA reviewer’s analyses for primary efficacy endpoint in terms of durable tumor and symptomatic response were to evaluate:

- Whether there was an evidence of exposure-response relationship following the proposed dosing regimen of 11 mg/kg q3w.
- Whether there was a relationship between CRP levels and response which can aid in optimizing efficacy by monitoring CRP levels

4.2 METHODS AND SOFTWARE

SAS® Version 9.3 (Cary, NC: SAS Institute Inc.) was used for data organization, and graphical and statistical analyses. Sponsor’s population pharmacokinetics analysis was reproduced using NONMEM v7.2.

To explore the relationship between response and exposure or C-reactive protein level (CRP) at baseline, logistic regression analyses were conducted between drug exposure and response and between CRP level at baseline and response.

4.3 DATASETS

Demographic, PK, and efficacy response datasets from Study CNTO328MCD2001 were used for the analysis. Study CNTO328MCD2001 served as the pivotal phase II study in this application. The primary objective of this study was to demonstrate that siltuximab in combination with best supportive care (BSC) is superior to BSC in terms of durable tumor and symptomatic response among subjects with Multicentric Castleman’s Disease (MCD). The secondary objectives of this study were to demonstrate additional measures of efficacy, to study the safety of prolonged dosing, to determine the PK of siltuximab among subjects with MCD, and to determine a baseline hepcidin value predictive of a ≥20 g/L increase in hemoglobin.

Seventy-nine subjects (53 in the siltuximab group, 26 in the placebo group) were used in the analysis.

4.4 RESULTS

Drug exposure used in the analyses was area under the siltuximab serum concentration versus time curve between treatment initiation and last observation following the first dose (AUClast), based on the high correlations between drug exposure after the first dose and the
corresponding steady state exposure and between AUCLast and other PK measures. The median CRP level at baseline in the siltuximab arm in Study CNTO328MCD2001 of 17.6 mg/L decreased to 1.04 mg/L (maximum median percent decrease of 92%) by Cycle 1 Day 8. CRP suppression was sustained in the siltuximab group until the last post-treatment time point tested. Therefore, CRP levels of Cycle 8 Day 1 at the midpoint were used to study the relationship between CRP level after suppression and efficacy response. Efficacy response was based on durable tumor and symptomatic response as used for the primary study objective, defined as complete response (CR: complete disappearance of all measurable and evaluable disease and resolution of baseline symptoms attributed to MCD, sustained for at least 18 weeks) or partial response (PR: a ≥50% decrease in sum of the product of the diameters of index lesion(s), with at least SD in all other evaluable disease in the absence of treatment failure, sustained for at least 18 weeks). Of note, no patient responded following placebo treatment in Study CNTO328MCD2001.

As shown by Table 28, numerically higher exposure, measured in AUClinf, AUCLast, and Cmax, were observed for non responders. This phenomenon was also seen in the exposure-response relationship in the siltuximab treatment arm through logistic regression, although this relationship is not statistically significant. There may be other confounding factors that can explain this observation. Figure 14 and Figure 15 showed the logistic regression results for potential relationships between drug exposure or CRP level and efficacy response for the 53 subjects in the siltuximab treatment arm of Study CNTO328MCD2001. As shown in Figure 15A, no significant trend was identified regarding the relationship between efficacy response and drug exposure in terms of AUCLast following the first dose (P-value= 0.27), although a numerically negative exposure relationship was identified. As shown in Figure 14, a flat relationship between efficacy response and CRP level was identified. Therefore, it is expected that further CRP reduction may not increase rate of efficacy response.

<table>
<thead>
<tr>
<th>Table 28. Summary of Siltuximab Exposure Related First Dose PK Parameter Estimates by Response for Subjects in the Siltuximab Treatment Arm of Study CNTO328MCD2001</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>----------------------</td>
</tr>
<tr>
<td>n=18</td>
</tr>
<tr>
<td>AUCLast (µg.day/ml)</td>
</tr>
<tr>
<td>AUCinf (µg.day/ml)</td>
</tr>
<tr>
<td>Cmax (µg/ml)</td>
</tr>
</tbody>
</table>

AUCLast: area under the siltuximab serum concentration versus time curve between treatment initiation and last observation following the first dose; AUCinf: area under the serum concentration versus time curve from time 0 to infinity following the first dose; Cmin: minimum serum concentration following the first dose; Cmax: maximum concentration following the first dose. SD: standard deviation.

**Data Source:** Sponsor submitted PK parameter estimate and responder datasets (processed by Dr. Lei Nie).
Further analysis regarding imbalance in demographic information between responders and non-responders was conducted to explore potential reasons behind the numerically negative exposure-response relationship. As shown in Table 20, most baseline demographic characteristics were balanced between responders and non-responders in the siltuximab treatment arm of Study CNTO328MCD2001. However, an imbalance was statistically significant in MCD histology based on Fisher’s exact test. The imbalance was only marginally significant in white vs non-white (84% of whites as non responders compared to an overall response rate of 34% in the treatment arm). However, categorizing the patient population into white vs non-white was an arbitrary choice. If it was chosen to categorize the patient population into Asian vs non-Asian given that 27 out of 53 patients were Asians in the treatment arm, the imbalance was no longer statistically significant. Furthermore, there is a lack of mechanistic support to see different response rates from different racial groups with current knowledge. Taken all together, only the potential confounding effect of MCD histology at randomization on the exposure-response relationship was assessed.

As shown in Table 29, further PK summary analysis showed that patients with hyaline vascular subtype at randomization were associated with higher exposure compared to those with mixed and plasmacytic subtypes (eg, 1938, 1486, and 1481 µg.day/ml for AUClast of hyaline vascular, mixed, and plasmacytic subtypes, respectively). In the same time, all 18 patients identified with hyaline vascular MCD histology failed to show clinical response (Table 20). In contrast, no strong imbalance in distribution of responders vs. non-responders was found in patients with mixed and plasmacytic subtypes. Therefore, the numerically negative relationship between AUClast and efficacy response is likely to be attributable to 18 hyaline vascular subtype patients in the non responder group.

By excluding the 18 hyaline vascular subtype patients, exposure-response analysis based on logistic regression was repeated to re-evaluate the relationship between AUClast following the first dose and efficacy response. As shown in Figure 15C, a relatively flat relationship was identified with only slight increase in response rate as AUClast increased by 4-fold, covering a range of ~ 600-2400 µg.day/ml. This analysis supports the confounding effect of MCD histology on the exposure-response relationship.
Table 29. Summary of Siltuximab Exposure Related First Dose PK Parameter Estimates by MCD Histology in the Siltuximab Treatment Arm of Study CNTO328MCD2001

<table>
<thead>
<tr>
<th>PK Parameters</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUClast (µg.day/ml)</td>
<td></td>
</tr>
<tr>
<td>Hyaline Vascular</td>
<td>1938 ± 818</td>
</tr>
<tr>
<td>Mixed</td>
<td>1486 ± 467</td>
</tr>
<tr>
<td>Plasmacytic</td>
<td>1481 ± 448</td>
</tr>
<tr>
<td>AUCinf (µg.day/ml)</td>
<td></td>
</tr>
<tr>
<td>Hyaline Vascular</td>
<td>2948 ± 1406</td>
</tr>
<tr>
<td>Mixed</td>
<td>1998 ± 859</td>
</tr>
<tr>
<td>Plasmacytic</td>
<td>1942 ± 696</td>
</tr>
<tr>
<td>Cmax (µg/ml)</td>
<td></td>
</tr>
<tr>
<td>Hyaline Vascular</td>
<td>300 ± 59</td>
</tr>
<tr>
<td>Mixed</td>
<td>234 ± 59</td>
</tr>
<tr>
<td>Plasmacytic</td>
<td>209 ± 55</td>
</tr>
</tbody>
</table>

AUClast: area under the siltuximab serum concentration versus time curve between treatment initiation and last observation following the first dose; AUCinf: area under the serum concentration versus time curve from time 0 to infinity following the first dose; Cmax: maximum concentration following the first dose. SD: standard deviation.

Data Source: Sponsor submitted PK parameter estimate and responder datasets (processed by Dr. Lei Nie).

4.5 CONCLUSIONS

No significant relationship was identified between drug exposure or CRP suppression and efficacy response following the proposed dosing regimen of 11 mg/kg given by intravenous infusion every 3 weeks.

5 ANALYSIS DATA AND FILES

Listing of Analyses Codes and Output Files

<table>
<thead>
<tr>
<th>File Name</th>
<th>Description</th>
<th>Location in</th>
</tr>
</thead>
<tbody>
<tr>
<td>SASCodeforNONMEM dataset</td>
<td>SAS code for creating NONMEM dataset</td>
<td>Not submitted</td>
</tr>
<tr>
<td>psn-1.mod</td>
<td>Population pharmacokinetic model (Final)</td>
<td>\Siltuximab_BLA125496_LZ\PPK_Analyses\Modeling</td>
</tr>
<tr>
<td>psn-1.lst</td>
<td>Output of final population pharmacokinetic model</td>
<td>\Siltuximab_BLA125496_LZ\PPK_Analyses\Modeling</td>
</tr>
<tr>
<td>cnto328_6stdy_woduplicate_more_cov.csv</td>
<td>Population pharmacokinetic dataset</td>
<td>\Siltuximab_BLA125496_LZ\PPK_Analyses\Modeling \NM_run1</td>
</tr>
<tr>
<td>ER.sas</td>
<td>ER analysis</td>
<td>\Siltuximab_BLA125496_LZ\ER_Analyses</td>
</tr>
<tr>
<td>all.sas7bdat</td>
<td>Dataset for ER analysis</td>
<td>\Siltuximab_BLA125496_LZ\ER_Analyses</td>
</tr>
</tbody>
</table>
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JEANNE FOURIE ZIRKELBACH  
02/05/2014

LIANG ZHAO  
02/05/2014

NITIN MEHROTRA  
02/05/2014

BAHRU A HABTEMARIAM  
02/05/2014
NDA FILING AND REVIEW FORM

General Information About the Submission

<table>
<thead>
<tr>
<th>NDA Number</th>
<th>BLA 125496</th>
<th>IND 11,461</th>
<th>Brand Name</th>
<th>Sylvant®</th>
</tr>
</thead>
<tbody>
<tr>
<td>OCP Division</td>
<td>DCP V</td>
<td>Generic Name</td>
<td>Siltuximab (CNTO 328)</td>
<td></td>
</tr>
<tr>
<td>OND Division</td>
<td>DHP</td>
<td>Drug Class</td>
<td>Chimeric Antibody against Interlukin-6</td>
<td></td>
</tr>
<tr>
<td>OCP Reviewer</td>
<td>Jeanne Fourie Zirkelbach, Ph.D.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OCP Team Leader</td>
<td>Julie Bullock, Pharm.D.</td>
<td>Dosage Form</td>
<td>100 mg of lyophilized siltuximab in 8 mL vial, 400 mg of lyophilized siltuximab in 30 mL vial</td>
<td></td>
</tr>
<tr>
<td>Sponsor</td>
<td>Janssen Biotech Inc.</td>
<td>Route of Administration</td>
<td>IV infusion</td>
<td></td>
</tr>
<tr>
<td>Date of Submission</td>
<td>8/30/13</td>
<td>Priority Classification</td>
<td>Priority Review</td>
<td></td>
</tr>
<tr>
<td>PDUFA Due Date</td>
<td>4/29/14</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Clinical Pharmacology Information

<table>
<thead>
<tr>
<th>STUDY TYPE</th>
<th>“X” if included at filing</th>
<th>Number of studies submitted</th>
<th>Number of studies reviewed</th>
<th>Critical Comments If any</th>
</tr>
</thead>
<tbody>
<tr>
<td>Table of Contents present and sufficient to locate reports, tables, data, etc.</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tabular Listing of All Human Studies</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPK Summary</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Labeling</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reference Bioanalytical and Analytical Methods</td>
<td>X</td>
<td>5</td>
<td>-Determine serum siltuximab concentrations. -Detect antibodies to siltuximab</td>
<td></td>
</tr>
</tbody>
</table>

1. Clinical Pharmacology

Mass balance:
- Metabolic profiling
- Isozyme characterization:
- Active Metabolites
- Transporters
- Blood/plasma ratio:
- Plasma protein binding:

Pharmacokinetics (e.g., Phase I)

Healthy volunteers
- single dose: X | 1 | C0328T08
- multiple dose: X | 1

Patients-
- multiple dose: X

Dose proportionality - X PK studies above C0328T01

Drug-drug interaction studies

In-vivo effects on primary drug:
## In-vivo effects of primary drug on other drugs:

### In-vitro:

### Subpopulation studies -

- Body size
- gender:
- geriatrics:
- renal impairment:
- Race/Ethnicity:
- hepatic impairment:
- pediatrics:

### PD:

- Phase 2:
- Phase 3:

### PK/PD:

| X | 1 | Study report Mod 5.3.3.5/PopPK C0328T03 –Phase 1 –Datasets, PKPD report not provided. |

### Population Analyses -

| X | 1 | POP PK report –Phase 1 –Datasets and report provided. |

### Biopharmaceutics

#### Absolute bioavailability:

#### Relative bioavailability -

- solution as reference:
- alternate formulation as reference:

### Bioequivalence studies -

| X | 1 | PK comparability of CHO-derived and Sp2/0-derived siltuximab. C0328T08. 2-part, safety and PK study in healthy subjects. Part 1 had a double-blind, staggered parallel, single-dose design, and Part 2 had an open-label, parallel group, single-dose design. |

### Food-drug interaction studies:

#### QTc studies

| X | 1 | CNTO328SMM1001-single arm monotherapy design |

### In-Vitro Release BE

#### (IVIVC):

### Bio-wavier request based on BCS

#### BCS class

### III. Other CPB Studies

#### Genotype/phenotype studies:

#### Chronopharmacokinetics

#### Pediatric development plan

#### Literature References

### Total Number of Studies

---

CC: DHP: (CSO – P Garvey; MTL – A Deisseroth; MO – P Dinndorf)
OCP: (Reviewer – J Fourie Zirkelbach; TL – J Bullock; DDD-B Booth; DD - A Rahman)
On initial review of the NDA/BLA application for filing:

<table>
<thead>
<tr>
<th>Content Parameter</th>
<th>Yes</th>
<th>No</th>
<th>N/A</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Criteria for Refusal to File (RTF)</strong></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 Has the applicant provided metabolism and drug-drug interaction information?</td>
<td>X</td>
<td></td>
<td></td>
<td>No formal studies. Do have label statement that the drug may bind IL-6 (which regulates CYP450 enzyme activity). The label states that if the drug is administered with CYP450 substrates. (3)(4)</td>
</tr>
<tr>
<td>3 Has the sponsor submitted bioavailability data satisfying the CFR requirements?</td>
<td></td>
<td>X</td>
<td></td>
<td>IV formulation</td>
</tr>
<tr>
<td>4 Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 Has a rationale for dose selection been submitted?</td>
<td></td>
<td>X</td>
<td></td>
<td>PK/PD analysis and dose finding studies.</td>
</tr>
<tr>
<td>6 Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7 Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)**
<table>
<thead>
<tr>
<th></th>
<th>Question</th>
<th>X</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?</td>
<td>X</td>
<td>Pop PK analysis data sets provided</td>
</tr>
<tr>
<td>10</td>
<td>If applicable, are the pharmacogenomic data sets submitted in the appropriate format?</td>
<td>X</td>
<td>No PG data, or review.</td>
</tr>
<tr>
<td></td>
<td><strong>Studies and Analyses</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Is the appropriate pharmacokinetic information submitted?</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>Did the applicant submit</td>
<td>X</td>
<td>Waiver.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td>all the pediatric exclusivity data, as described in the WR?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17 Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>General</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18 Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>19 Was the translation (of study reports or other study information) from another language needed and provided in this submission?</td>
<td></td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

**IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?**

*Yes*

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant: N/A
Clinical Pharmacology - NDA Filing Memo

Clinical Pharmacology - NDA Filing Memo

BLA: 125496/0 Original Submission IND: 011,461
Compound: Sylvant (Siltuximab) Injection for intravenous infusion
Sponsor: Janssen Biotech Inc.
Filing Date: Sept 22, 2013
Reviewer: Jeanne Fourie Zirkelbach, PhD

Previous Regulatory History:

- 11/10/2009 EOP2: 1) Siltuximab is produced by the Chinese Hamster Ovary (CHO) cell line (Commercial scale). Siltuximab was originally produced using a Sp2/0 Cell line (presentation used in trial C0328T06). Pharmacokinetic comparability of Chinese hamster ovary (CHO)-derived siltuximab and Sp2/0-derived siltuximab is a review issue but it appears PK comparability is demonstrated (clinical comparability a review issue), 2) Agreed to development plan (including use of a dosing regimen of 11 mg/kg of CNTO 328 every 3 weeks) but stated that studies in special populations and evaluation of potential drug-drug interactions may be requested if clinical signals are identified during clinical studies or the population PK modeling, as well as the PK/PD modeling, 3) proposed immunogenicity testing plan appears acceptable, 4) Proposed QTc study plan appears acceptable.
- 10/9/2013: An information request was sent to the applicant to request datasets and minor clarifications regarding the current submission.

Multicentric Castleman’s disease (MCD) is a rare lymphoproliferative disorder. Clinically, patients with MCD present with lymph node growth in multiple locations and multiple clinical symptoms that can be severe. Overproduction of the cytokine (IL-6) has been hypothesized to play a central role in driving plasma cell proliferation and systemic manifestations in MCD patients.

Siltuximab (CNTO 328) is a chimeric monoclonal antibody (mAb) that specifically binds human interleukin 6 (IL-6) with high affinity and prevents its interaction with the IL-6 receptor. The mechanism of action of siltuximab is neutralization of IL-6 bioactivity, which can be measured indirectly by C-reactive protein repression.

**Efficacy:** The clinical efficacy of siltuximab in patients with MCD who are human immunodeficiency (HIV) negative and human herpes virus 8 (HHV-8) negative is based on the results of three studies (see table below). The primary data came from study CNTO328MCD2001 with supportive results from Study C0328T03 and CNTO328MCD2002.

<table>
<thead>
<tr>
<th>Study #</th>
<th>Study Title</th>
<th>Subjects Treated</th>
<th>Study Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNTO328MCD2001</td>
<td>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</td>
<td>79 subjects with MCD</td>
<td>Ongoing (unblinded and primary analysis is complete)</td>
</tr>
<tr>
<td>C0328T03</td>
<td>A Phase 1 Study of Multiple Intravenous Administrations of a Chimeric Antibody Against Interleukin-6 (CNTO 338) in Subjects With B-Cell Non-Hodgkin’s Lymphoma, Multiple Myeloma, or Castleman’s Disease</td>
<td>57 subjects with Castleman’s disease</td>
<td>Completed</td>
</tr>
<tr>
<td>CNTO328MCD2002</td>
<td>An Open-label, Multicenter Study to Evaluate the Safety of Long-term Treatment with Siltuximab in Subjects with Multicentric Castleman’s Disease</td>
<td>19 subjects with MCD previously treated as C0328T03</td>
<td>Ongoing (interim analysis complete)</td>
</tr>
</tbody>
</table>
In study CNTO328MCD2001, subjects were randomized (2:1 to siltuximab + BSC or placebo + BSC), and stratified for baseline corticosteroid use (yes vs no). Treatment (siltuximab 11 mg/kg every 3 weeks or placebo) was to be continued until treatment failure. The primary endpoint was durable tumor and symptomatic response, defined as tumor response assessed by independent review and complete resolution or stabilization of prospectively collected MCD symptoms, for at least 18 weeks without treatment failure. The primary endpoint was statistically significantly higher in siltuximab-treated subjects compared with placebo-treated subjects (34% vs 0%, respectively; 95% CI: 11.1, 54.8; p=0.0012).

**Dosing Rationale:** The dose and schedule (11 mg/kg every 3 weeks) was selected based on a high frequency of tumor response (both CR and partial response (PR)) as well as a high frequency of clinical benefit response in subjects treated in Study C0328T03 at the highest dose level (11 mg/kg) (van Rhee et al, 2008). Pharmacokinetic/pharmacodynamic modeling results had shown that a dose of 11 mg/kg administered every 3 weeks in subjects with MCD would decrease C-reactive protein (CRP) (to below 1 mg/L) throughout the treatment period. Serum CRP levels are a sensitive marker of IL-6 inhibition (Goransson et al, 1996).

**Safety:** The integrated safety of siltuximab monotherapy in subjects with MCD is supported by 3 trials. Study CNTO328MCD2001, a randomized, placebo-controlled, registration study, provides the primary data within the submission supporting siltuximab monotherapy at the target dose of 11 mg/kg every 3 weeks, with Studies C0328T03 and CNTO328MCD2002 providing supportive data.

In the MCD studies, there was a trend toward a higher incidence of particular AEs related to laboratory parameters in siltuximab-treated subjects compared with placebo-treated subjects, but these were considered of limited clinical significance.

There was a higher incidence of NCI-CTCAE all-grade renal impairment reported as an AE in siltuximab-treated subjects compared with placebo-treated subjects in the MCD studies (0% in the placebo vs 12% and 14% in the target dose and combined siltuximab monotherapy groups, respectively; Table 40; Section 3.1.3). However, the incidence of Grade 3 or higher renal impairment was low and similar among the groups (0% vs 2% each). Dose delays or dose interruptions due to renal impairment were low in siltuximab-treated subjects (0% vs 1% each). There were no SAEs, treatment discontinuations, or deaths due to renal impairment.

<p>| Attachment 4.53 Shif Table of Baseline Versus Maximum Postbaseline NCI-CTCAE Grade for Increases in Creatinine During the Blinded Treatment Period: Safety Population |</p>
<table>
<thead>
<tr>
<th>Baseline</th>
<th>Grade 0</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo + BSC</td>
<td>N=25</td>
<td>72</td>
<td>7</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Grade 0</td>
<td>3 (12.0%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Grade 1</td>
<td>18 (55.9%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Grade 2</td>
<td>1 (4.1%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Grade 3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Grade 4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Siltuximab + BSC</td>
<td>N=40</td>
<td>40</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Grade 0</td>
<td>6 (15.0%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Grade 1</td>
<td>36 (90.0%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Grade 2</td>
<td>4 (10.0%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Grade 3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Grade 4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Reference ID: 3393434
Based on the NCI-CTCAE criteria, a shift from baseline to grade 2 would be a creatinine of 2-3 x above baseline (acute injury).

**Adverse drug reactions:** ADRs identified for siltuximab are pruritus, upper respiratory tract infection, rash maculo-papular, localized edema, weight increased, abdominal pain, nasopharyngitis, thrombocytopenia, renal impairment, hypertriglyceridemia, hypertension, neutropenia, and anaphylactic reaction.

<table>
<thead>
<tr>
<th>Blood and lymphatic system disorders</th>
<th>Placebo + BSC (All Grades (%)</th>
<th>BSC Grade 3-4 (%)</th>
<th>Siltuximab + BSC (All Grades (%)</th>
<th>BSC Grade 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>7.7%</td>
<td>3.8%</td>
<td>11.0%</td>
<td>3.7%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>3.8%</td>
<td>3.8%</td>
<td>15.4%</td>
<td>2.4%</td>
</tr>
<tr>
<td>Gastrintestinal disorders</td>
<td>3.8%</td>
<td>3.8%</td>
<td>15.9%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>3.8%</td>
<td>0.0%</td>
<td>14.0%</td>
<td>2.4%</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>3.8%</td>
<td>0.0%</td>
<td>14.0%</td>
<td>2.4%</td>
</tr>
<tr>
<td>Localised oedema</td>
<td>3.8%</td>
<td>0.0%</td>
<td>14.0%</td>
<td>2.4%</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>3.8%</td>
<td>0.0%</td>
<td>14.0%</td>
<td>2.4%</td>
</tr>
<tr>
<td>Anaphylactic reaction</td>
<td>3.8%</td>
<td>0.0%</td>
<td>14.0%</td>
<td>2.4%</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>3.8%</td>
<td>0.0%</td>
<td>14.0%</td>
<td>2.4%</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>15.4%</td>
<td>3.8%</td>
<td>37.8%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>15.4%</td>
<td>3.8%</td>
<td>37.8%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Investigations</td>
<td>15.4%</td>
<td>3.8%</td>
<td>37.8%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Weight increased</td>
<td>0.0%</td>
<td>0.0%</td>
<td>14.0%</td>
<td>2.4%</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>0.0%</td>
<td>0.0%</td>
<td>13.4%</td>
<td>2.4%</td>
</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td>0.0%</td>
<td>0.0%</td>
<td>13.4%</td>
<td>2.4%</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>0.0%</td>
<td>0.0%</td>
<td>12.2%</td>
<td>2.4%</td>
</tr>
<tr>
<td>Renal impairment</td>
<td>0.0%</td>
<td>0.0%</td>
<td>12.2%</td>
<td>2.4%</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>0.0%</td>
<td>0.0%</td>
<td>12.2%</td>
<td>2.4%</td>
</tr>
<tr>
<td>Rash maculo-papular</td>
<td>11.5%</td>
<td>0.0%</td>
<td>23.2%</td>
<td>1.2%</td>
</tr>
<tr>
<td>Pruritus</td>
<td>11.5%</td>
<td>0.0%</td>
<td>23.2%</td>
<td>1.2%</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>3.8%</td>
<td>0.0%</td>
<td>13.4%</td>
<td>7.3%</td>
</tr>
</tbody>
</table>

![Table 29: Adverse Drug Reactions Identified With Siltuximab](image-url)

**QT:** An assessment of the cardiovascular safety of siltuximab has been performed and no safety issues have been identified among siltuximab-treated subjects. There was no effect on the QT interval and no increased risk for cardiac arrhythmias observed in siltuximab-treated subjects with MCD. In addition, electrocardiogram (ECG) results from Study CNTO328SMM1001, a Phase 1, open-label, single-arm, multicenter study designed to examine siltuximab’s effect on the QT interval indicated that siltuximab, given at the highest dose level used in clinical studies (15 mg/kg every 3 weeks), did not prolong the QT interval.

**Immunogenicity:** There was a very low risk for immunogenicity (generation of antibodies to siltuximab). Specifically, only 1 of 411 (0.2%) evaluable subjects, including 81 subjects with MCD, across multiple clinical studies within this SCS had detectable antibodies to siltuximab at 1 timepoint only and the response was weak and non-neutralizing.

**PK studies:** The PK properties of siltuximab were studied in 473 subjects treated with single-agent therapy in 5 Phase 1 and 2 Phase 2 studies (Table 2). After the earlier Phase 1 single-agent dose-escalation studies (C0328T01, C0328T03, and CNTO328STM2001), single-agent siltuximab Phase 2 studies were conducted at 11 mg/kg every 3 weeks (or equivalent dose intensity 15 mg/kg every 4 weeks).

**Population PK (report and datasets provided):** A population PK model of siltuximab was developed to describe the PK characteristics of siltuximab following IV administration and to identify and quantify the influence of significant covariates on the disposition of siltuximab in subjects with various hematological and non-hematological malignancies including: MCD, CD, RCC, NHL, MM, solid tumors, ovarian cancer, and smoldering multiple myeloma (SMM). Six Phase 1/Phase 2 studies were included in this population PK analysis including C0328T01, C0328T03, CNTO328STM2001, CNTO328SMM1001,
Subject weight, age, sex, race, immunogenicity, baseline 
CRCL, baseline ALB, baseline ALT and AST were considered as intrinsic factors as part of the covariates 
explained in the population PK analysis. Concomitant use of corticosteroids was considered an extrinsic 
factor as part of the covariates explored in the population PK analysis.

**PD Biomarker studies (PK/PD analysis):** IL-6 is the primary factor that drives expression of CRP from 
hepatocytes in response to inflammatory stimuli (Heinrich et al, 1990; Coventry et al, 2009). IL-6 has 
been shown to induce CRP expression by activating transcription factors. Subjects with Castleman’s 
disease treated with 11 mg/kg every 3 weeks in study **C0328T03** showed greater decrease of systemic 
CRP levels compared with those treated with 8.3 mg/kg every 3 weeks, supporting the clinical efficacy 
obserations that higher tumor and clinical benefit responses were observed at a dose of 11 mg/kg every 3 
weeks. Further, in subjects with solid tumors (Study CNTO328STM2001), similar CRP suppression was 
obserated at 11 mg/kg every 3 weeks and 15 mg/kg every 3 weeks indicating that doses higher than 11 
mg/kg every 3 weeks are not needed to neutralize the drug target. Based on these earlier results, serum 
CRP levels were measured in Study CNTO328MCD2001 as a surrogate marker (though not a validated 
marker) to evaluate suppression of bioactive IL-6 with siltuximab treatment.

Two validated electrochemiluminescent immunoassay (ECLIA) methods were used to determine serum 
siltuximab concentrations in the clinical studies supporting this registration. Two enzyme immunoassay 
(EIA) methods and 1 ECLIA method were used to detect antibodies to siltuximab in human serum 
samples.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JEANNE FOURIE ZIRKELBACH
10/21/2013

JULIE M BULLOCK
10/26/2013