

**Janssen Research & Development\***

**Clinical Protocol**

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**An Open-label, Multicenter Study to Evaluate the Safety of Long-term Treatment  
with Siltuximab in Subjects with Multicentric Castleman's Disease**

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**Protocol CNTO328MCD2002; Phase 2  
Amendment INT-4**

**Siltuximab (CNTO 328)**

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This study will be conducted under US Food & Drug Administration IND regulations (21 CFR Part 312).

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**Compliance:** This study will be conducted in compliance with this protocol, Good Clinical Practice, and applicable regulatory requirements.

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## PROTOCOL AMENDMENTS

Protocol Version	Issue Date
Original Protocol	04 Nov 2010
Amendment INT-1	19 Jan 2012
Amendment INT-2	14 Jun 2012
Amendment INT-3	17 Nov 2012
Amendment INT-4	04 Apr 2014

Amendments are listed beginning with the most recent amendment.

### Amendment INT-4 (04 Apr 2014)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

**The overall reason for the amendment:** To extend the duration of this study to fulfill postmarketing commitments to report safety, efficacy, and survival during long-term treatment with siltuximab, and to stop collecting data that are not required for the final study report.

Applicable Section(s)	Description of Change(s)
<b>Rationale:</b> To extend the duration of this study to fulfill postmarketing commitments to report safety, efficacy, and survival during long-term treatment with siltuximab, and to delete references to treatment until siltuximab is commercially available and replace it with a specified length of treatment.	
Synopsis (Overview of Study Design, Safety Evaluations); 3.1 (Study Design); 6 (Dosage and Administration); 9.6 (Antibodies to Siltuximab); 10.2 (Discontinuation of Treatment); 11.3 (Safety Analyses; Adverse Events); 11.4.3 (Overall Survival); 12.2.1 (All Adverse Events); 12.2.2 (Serious Adverse Events)	The existing data cutoff was changed from 5 years after the first subject is enrolled to approximately 6 years after the first subject is enrolled.  Subjects are not required to stop study treatment when siltuximab is commercially available in their region.
Synopsis (Overview of Study Design, Efficacy Evaluations); 3.1 (Study Design); 9.3.3 (Survival)	Follow-up assessments for survival, occurrence of malignancies, and subsequent therapies for MCD will only be collected until the 6-year data cutoff for subjects who discontinue study agent.
Synopsis (Overview of Study Design, Safety Evaluations); 3.1 (Study Design); 9.2 (Safety Evaluations; Adverse Events) 12.2.1 (All Adverse Events)	For those subjects remaining on treatment after the data cutoff at 6 years, data collection will be limited to pregnancies and serious adverse events (SAEs), including information on study agent administration and concomitant medications associated with an SAE.  Data collected beyond the 6-year data cutoff will be reported to the appropriate health authorities in safety update reports.
Synopsis (Efficacy Evaluations); 9.3.3 (Survival)	Survival status will not be collected twice a year for subjects after the data cutoff.

Applicable Section(s)	Description of Change(s)
Synopsis (Overview of Study Design); 3.1 (Study Design)	The end of study definition was revised.  The end of study is the date of the last assessment for the last subject ( <del>eg, last survival follow up</del> ).
<b>Rationale:</b> To limit assessments and data collection not needed for safety monitoring, and to decrease the burden on the sites.	
Table 2 (Time and Events Schedule per Amendment INT-4; new)	Limit assessments and data collection after Amendment INT-4 is implemented, increase the visit window for siltuximab administration and study procedures, and provide other clarifications for sites.
Throughout the protocol	Add references to the new Time and Events Schedule (Table 2).
Synopsis (Pharmacodynamic Biomarkers); 3.2 (Study Design Rationale, Pharmacodynamic Biomarker Assessments); 9.4 (Pharmacodynamic Biomarker Evaluations)	Collection of samples for biomarker assessments will be stopped after Amendment INT-4 is implemented.
8 (Concomitant Therapy); 9.2 (Safety Evaluations; Hematology Panel, Serum Chemistry Panel)	Limit the collection of concomitant medications and laboratory parameters.
<b>Rationale:</b> To add treatment criteria for hemoglobin as a safety precaution, and add information on the frequency of lipid panel monitoring.	
6.1.1 (Laboratory Assessments and Dose Delays)	If hematology laboratory report indicates hemoglobin >17 g/dL, the dose should be delayed.  Lipid panels are monitored approximately every 6 months, and every 3 months for siltuximab-naïve subjects.
<b>Rationale:</b> To update statistical information based on changes made during Amendment INT-4.	
11 (Statistical Methods); 11.4.3 (Overall Survival)	Updated text is provided for statistical methods.
<b>Rationale:</b> Minor errors were noted.	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

**Amendment INT-3** (17 Nov 2012)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

**The overall reason for the amendment:** To add additional safety evaluations for those subjects entering the study who are naïve to treatment with siltuximab.

Applicable Section(s)	Description of Changes
<b>Rationale:</b> To add additional safety evaluations for those entering the study naïve to treatment with siltuximab.	
Synopsis; Time and Events Schedule (new ECG row and footnote f); 9.2 Safety Evaluations; 11.3 Safety Analyses	ECG performed and analyzed locally at screening and after 1 year of treatment, and as clinically indicated for all subjects.
Time and Events Schedule (hematology and chemistry row and footnote g revised); 6.1.1 Laboratory Assessment and Dose Delays 9.2 Safety Evaluations	Hematology and chemistry laboratory tests performed prior to every study treatment in the first year of treatment, then as specified in the Time and Events Schedule (per treatment regimen) thereafter.
Time and Events Schedule (lipid row revised); 9.2 Safety Evaluations	Lipid panel testing performed every 3 months in the first year of treatment, then every 6 months thereafter.
<b>Rationale:</b> For those subjects who discontinue treatment, the occurrence of malignancies will be collected to evaluate the occurrence with long-term treatment.	
Synopsis; Time and Events Schedule (footnote l); 3.1 Study Design; 10.2 Discontinuation of Treatment; 11.3 Safety Analyses	Data collection of malignancies for subjects who discontinue treatment is added.
<b>Rationale:</b> Other minor changes have been made to enhance the clarity of the protocol.	
Synopsis; 3.1 Study Design; 11.2 Sample Size Determination	The sample size in this study is expected to be approximately 75 subjects instead of 100.
Synopsis; Time and Events Schedule (footnote j); 9.2 Safety Evaluations	If equivalent imaging (eg, CT, MRI) is performed per routine medical care, it is acceptable instead of chest X-ray.
14.4 Preparation, Handling, Storage	A 0.2 micron inline filter is to be used (instead of 0.22 micron).
<b>Rationale:</b> Minor errors were noted	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.



**Amendment INT-2** (14 Jun 2012)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

**The overall reason for the amendment:** To add a data cutoff for an interim analysis, to add survival follow-up for those who discontinue treatment, to remove an exclusion criterion for those on intervening treatment for Castleman’s disease, and to adapt the Time and Events schedule for the 6-week dosing interval.

Applicable Section(s)	Description of Changes
<p><b>Rationale:</b> Interim analysis is added to allow earlier evaluation of the potential benefits and safety of long-term treatment with siltuximab for multicentric Castleman’s disease (MCD), and the data cutoff at 4 years is changed to 5 years to allow sufficient follow-up time because of the later than anticipated enrollment completion date of subjects from study CNTO328MCD2001.</p>	
Synopsis; Time and Events Schedule; 3.1 Study Design; 6 Dosage and Administration 8 Concomitant Therapy; 9.2 Safety Evaluations; 10.2 Discontinuation of Treatment; 11.3 Safety Analyses; 11.7 Interim Analysis; 12.2.1 All Adverse Events; 12.2.2 Serious Adverse Events	Interim analysis added (2 years after the start of enrollment) and existing data cutoff at 4 years changed to 5 years.
<p><b>Rationale:</b> Survival follow-up and data collection for subsequent MCD therapies are added for those subjects who discontinue treatment for more complete analysis of survival.</p>	
Synopsis; Time and Events Schedule; 3.1 Study Design; 9.3.3 Survival; 10.2 Discontinuation of Treatment	Data collection for subjects who discontinue treatment will be limited to survival status and subsequent therapies for MCD, which will be assessed twice per year until the subject has been lost to follow-up or has withdrawn consent for the study, 50% of the subjects have died, or the end of study; whichever occurs first.
<p><b>Rationale:</b> Exclusion Criterion 3 is removed to allow enrollment of subjects who may need treatment while awaiting the unblinding of Study CNTO328MCD2001. Corticosteroid treatment guidelines are also updated to avoid a contradiction in the protocol as a result of removing this criterion.</p>	
Synopsis; 4.3 Exclusion Criteria	Criterion 3 is deleted.
8.2 Guidelines for Corticosteroid Use	Guidelines are updated, including additional details on corticosteroid tapering.

Applicable Section(s)	Description of Changes
<b>Rationale:</b> Other minor changes have been made to enhance the clarity of the protocol.	
4.2 Inclusion Criteria	Corrected unit conversion in Criterion 5a: Absolute neutrophil count (ANC) greater than or equal to $1.0 \times 10^9/L$ ( <del>1,000,500</del> /mm <sup>3</sup> ) with or without neutrophil growth factors  Criterion 7 is aligned with current protocol template wording (Criterion 7.1 is added).
Synopsis; Time and Events Schedule; 9.3.2 Laboratory Evaluations; 11.4.2 Laboratory Evaluations	Moved the assessment and analyses of ESR, CRP, and fibrinogen from safety evaluations (Section 9.2 and 11.3.3) to under efficacy.
Synopsis; 6 Dosage and Administration	Removed the restriction on dose delays up to Week 48, to allow more flexibility in long-term treatment and because almost all subjects are well beyond having 48 weeks of treatment at study entry.
Time and Events Schedule; 6.1 Dose Delays and Retreatment; 9.1.1 Overview	For subjects on the 6-week dosing regimen, laboratory assessments for hematology and chemistry and physical examination are aligned with every other treatment visit to decrease the burden and number of visits.
Synopsis; Time and Events Schedule; 9.2 Safety Evaluations	In addition to a chest X-ray, equivalent imaging (CT, MRI) is allowed.
11.4 Efficacy and Patient-reported Outcomes Analyses; 11.7 Interim Analysis	The Statistical Methods section for efficacy assessments (11.4) includes clarification of the definitions of disease control, overall survival, and patient-reported MCDSS. The laboratory assessments for ESR, CRP, and fibrinogen are added. Subheadings have been added to enhance clarity. Also, the interim analysis at 2 years is described.
<b>Rationale:</b> Minor errors were noted	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

**Amendment INT-1** (19 Jan 2012)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

**The overall reason for the amendment:** To update the secondary objective for biomarkers, implement the legal entity name change, and make small corrections and clarifications.

Applicable Section(s)	Description of Change(s)
<b>Rationale:</b> To comply with current internal standards for the company name (new legal entity).	
Title page	The company name has been changed to Janssen Research & Development and the sponsorship statement has been updated.
<b>Rationale:</b> The IL-6 posttranslational modifications (PTMs) assessments have been removed because it was determined that large sample volumes would be required for PTM evaluation and therefore cannot be evaluated with the sample volumes collected in this study. Also, assessment of IL-6 levels after treatment with siltuximab cannot be performed because of the unavailability of a suitable assay to measure post-treatment IL-6 levels without drug interference. A bioassay to measure IL-6 with acceptable sensitivity and without serum or drug interference could not be developed.	
Synopsis (Secondary Objectives, Pharmacodynamic Biomarkers), 2. Objectives (Secondary objectives), 3. Overview of Study Design (3.1 Study Design, 3.2 Study Design Rationale, Pharmacodynamic Biomarker Assessments), 9.4 Pharmacodynamic Biomarker Evaluations, 11.6 Pharmacodynamic Biomarker Analyses	Assessment of IL-6 levels after siltuximab treatment and IL-6 PTM assessments have been removed. Unusual IL-6 splice variants may be assessed.
<b>Rationale:</b> To clarify frequency of survival assessments after the 4-year data cutoff.	
Synopsis (Overview of Study Design), Time and Events Schedule (new footnote k), 8 Concomitant Therapy, 11.3 Safety Analyses (Adverse Events), 12.2.1 Adverse Events, 12.2.2 Serious Adverse Events	Survival assessments will occur twice per year after the 4-year data cutoff. Adverse event reporting through 30 days after the last siltuximab administration is limited to within the 4-year cutoff (only SAEs, concomitant medications related to SAEs, and pregnancies will be collected after the cutoff).
<b>Rationale:</b> Other changes have been made to enhance the clarity of the protocol.	
Synopsis, Dosage and Administration 6 Dosage and Administration	Up to Week 48, no more than 2 non-consecutive dose delays due to study agent-related toxicity are allowed. After Week 48, documentation of dose delays is required.
Synopsis, Glycoform Clearance and In Vivo Protein Degradation Analysis Time & Events Schedule, footnote d 9.5 Glycoform Clearance and In Vivo Protein Degradation Analysis	For glycoform clearance and in vivo protein degradation analysis it is clarified that blood samples will be collected from former study C0328T03 subjects because more limited sample collection is needed only from subjects who are on longer-term treatment.

Applicable Section(s)	Description of Change(s)
4.1 General considerations	Re-testing guidance has been added.
4.2 Inclusion Criterion 7	Clarified that male subjects must also use adequate birth control methods.
6 Dosage and Administration	Added clarifications on adherence to study visits and on switching the dose schedules.
7 Treatment Compliance	Removed the requirement for IV bag weight measurement and added measurement of total volume given if administration was stopped early.
8.2 Guidelines for Corticosteroid Use	Included a crossreference to Section 8.4
8.4 Prohibited Therapies	Bullet added for other investigational agents and “systemic” added to other immunosuppressive therapies.
9.1.1 Overview	Change: The <b>required</b> assessments at every dosing visit are:
9.2 Safety Evaluations	Change: <del>Any areas of disease involvement should be recorded on the disease assessment pages of the CRF.</del> Any clinically significant observation should be recorded on the Adverse Event page of the CRF.
9.4 Pharmacodynamic Biomarker Assessments	The CRP will be analyzed from the chemistry sample, the reference to the hematology sample has been removed.
10.2 Discontinuation of Treatment	Change: The subject initiated any of the prohibited medications requiring discontinuation of treatment (see Section 8.4)
10.3 Withdrawal from Study	Removed: <del>Study drug assigned to the withdrawn subject may not be assigned to another subject.</del>
11.3 Safety Analyses	Vital signs clarification: supine <b>or</b> standing
14.4 Preparation, Handling, and Storage	Change: <del>The study agent is to be reconstituted as specified in the site investigational product manual. The reconstituted vials will be gently swirled to aid in complete dissolution of the lyophilized material.</del>
14.5 Drug Accountability	The text regarding destruction of leftover study drug has been modified.
17.3 Subject Identification, Enrollment, and Screening Logs	Removed reference to subject initials, per current protocol template.
17.4 Source Documentation	Clarified that the MCDSS questionnaire will be completed on paper.
17.6 Data Quality Assurance/Quality Control	Clarification: Written instructions will be provided for collection, preparation, and shipment of blood, plasma, and <del>urine</del> <b>serum</b> samples.

## SYNOPSIS

An Open-label, Multicenter Study to Evaluate the Safety of Long-term Treatment with Siltuximab in Subjects with Multicentric Castleman's Disease

Siltuximab is a chimeric (murine-human) IgG1κ mAb that specifically binds human IL-6 with high affinity and prevents its interaction with the IL-6 receptor, glycoprotein (GP) 80 (Seideman and Peritt, 2002). The mechanism of action of siltuximab is neutralization of IL-6 bioactivity, which can be measured indirectly by C-reactive protein (CRP) suppression.

## OBJECTIVES

### Primary Objectives

The primary objective is to evaluate the long-term safety of siltuximab in subjects with multicentric Castleman's disease (MCD).

### Secondary Objectives

- To determine the proportion of previously responding subjects who maintain disease control
- To determine the proportion of siltuximab-naïve subjects who experience disease control
- To describe the duration of disease control and survival
- To assess reliability of a multicentric Castleman's disease symptom scale (MCDSS)
- To evaluate IL-6 levels
- To assess formation of antibodies to siltuximab (immunogenicity) after long-term treatment in the MCD population

**Hypothesis:** The safety of siltuximab will be acceptable for an extended treatment period. There is no formal hypothesis testing planned for this long-term extension study.

## OVERVIEW OF STUDY DESIGN

This is an open-label, multicenter, non-randomized Phase 2 study designed to study the safety of extended treatment with siltuximab in subjects who were previously enrolled in sponsor-initiated studies of MCD (C0328T03 and CNTO328MCD2001) and are either siltuximab-naïve or have not progressed on siltuximab in the opinion of the investigator. Duration of disease control and survival will also be assessed. Up to 75 subjects will be eligible for the study, the majority of whom will be on active therapy with siltuximab at the time of enrollment. All subjects will be treated until they progress, withdraw, experience unacceptable toxicity, or until the 6-year data cutoff, whichever comes first. Subjects who discontinue study agent will have follow-up assessments for survival, occurrence of malignancies, and subsequent therapies for MCD until the 6-year data cutoff. A data cutoff will occur approximately 6 years after the first subject is enrolled; however, continued drug supply will be ensured for study subjects who would not otherwise have access to siltuximab. For those subjects remaining on treatment after the data cutoff at 6 years, data collection will be limited to pregnancies and serious adverse events (SAEs), including information on study agent administration and concomitant medications associated with an SAE. Data collected beyond the 6-year data cutoff will be reported to the appropriate health authorities in safety update reports. The end of study is the date of the last assessment for the last subject.

## STUDY POPULATION

The main Inclusion/Exclusion Criteria are listed below (see Sections 4.2 and 4.3 for the full list).

### Inclusion Criteria

To be eligible for the study, subjects must meet all of the following criteria:

1. Subjects must have multicentric Castleman's disease.
2. Subjects must have previously been enrolled in study C0328T03 or CNTO328MCD2001 (either treatment arm).
3. Subjects must have had their last administration of study treatment (siltuximab or placebo) less than 6 weeks (window of plus 2 weeks) prior to first dose. Subjects with longer treatment durations since the last study treatment may be allowed after discussion with the medical monitor.
4. Subjects must not have had disease progression while receiving siltuximab. For those subjects originally assigned to placebo in the CNTO328MCD2001 study, subjects who have received less than 4 months of siltuximab following crossover will also be eligible.

**Exclusion Criteria**

1. Unmanageable toxicity, an adverse event, progression of disease, or withdrawal of consent as reason for discontinuing treatment from previous sponsor-initiated siltuximab study.
2. Vaccination with live, attenuated vaccines within 4 weeks of first dose of this study.
3. Criterion removed per amendment INT-2 (see the protocol amendment table before the Synopsis).
4. Known unmanageable allergies, hypersensitivity, or intolerance to monoclonal antibodies or to murine, chimeric, or human proteins or their excipients.

**DOSAGE AND ADMINISTRATION**

Siltuximab will be given as a 1 hour infusion of 11 mg/kg every 3 weeks. The treatment interval may be lengthened to 6 weeks at the investigator's discretion for subjects with confirmed partial or complete response of more than 6 months duration. No dose modifications will be allowed. Documentation of dose delays, including the reason for delay, is required.

**SAFETY EVALUATIONS**

A chest X-ray, or equivalent imaging (ie, computed tomography [CT], magnetic resonance imaging [MRI]) if performed for routine medical care, is required prior to study entry. ECG and clinical laboratory tests are to be performed according to the Time and Events Schedules. Safety monitoring will consist of continuous AE reporting with a focus on infections, hyperlipidemia, neutropenia, thrombocytopenia, GI perforations, infusion-related reactions, liver function, and immunogenicity. Safety reporting will be limited to pregnancies and SAEs, including information on study agent administration and concomitant medications associated with an SAE for subjects remaining on study treatment after the data cutoff at 6 years.

**EFFICACY EVALUATIONS**

Investigator assessment of disease control will be collected during screening, at Cycles 4, 7 and 10, every 6 months thereafter, and at study treatment discontinuation. Laboratory assessments for erythrocyte sedimentation rate (ESR), CRP, and fibrinogen will also be performed at these same timepoints. For those who have discontinued study agent, survival status and subsequent MCD therapies will be collected until the subject has been lost to follow-up or has withdrawn consent for the study, or the 6-year data cutoff, whichever occurs first.

**Patient-reported Outcomes:** The MCDSS will be administered at the screening visit (the first assessment of the day), and predose at Cycles 1 and 2. The questionnaire will only be completed by the subpopulation from the C0328T03 study.

**IMMUNOGENICITY EVALUATIONS**

To detect antibodies to siltuximab (immunogenicity), blood samples will be collected from all subjects in the study every 12 weeks during treatment, and at Week 4, Week 8, and Week 12 after the last siltuximab administration.

**PHARMACODYNAMIC BIOMARKERS**

Biomarker assessments include quantification of IL-6 levels. Exploratory evaluation of putative IL-6 splice variants may also be performed. Collection of samples for these assessments will be stopped after Amendment INT-4 is implemented.

**GLYCOFORM CLEARANCE AND IN VIVO PROTEIN DEGRADATION ANALYSIS**

Blood samples will be collected from former study C0328T03 subjects to study the clearance and degradation of siltuximab glycoforms at several timepoints during Cycle 1.

**STATISTICAL METHODS**

Descriptive statistics will be used to summarize data. For continuous endpoints, number of observations, mean, standard deviation, median, and range will be used. For discrete endpoints, frequencies and percentages will be summarized. No hypothesis testing will be performed.

**Safety Analyses**

The incidence of adverse events (including Grade 3 or higher), deaths, safety-related laboratory tests and antibodies to siltuximab will be summarized.

**Efficacy Analyses**

The proportion of previously responding subjects and siltuximab-naïve subjects who maintain disease control will be summarized, as will the duration of disease control and survival. In addition, the MCDSS total score and the change from baseline in MCDSS total score will be summarized.

**TIME AND EVENTS SCHEDULES**

<b>Table 1: TIME AND EVENTS SCHEDULE THROUGH AMENDMENT INT-3</b>							
Procedures and Evaluations	Screening	Pre-dose Cycle 1	Cycle 1 Day 1, or as indicated	End of treatment/ Follow-Up Week 4	Follow-Up Week 8	Follow-Up Week 12	After 5-year data cutoff
Days	-28 to 0	1					
<b>Screening/Administrative</b>							
Informed consent	X						
Inclusion/exclusion criteria	X						
Medical history/demography	X						
<b>Study Drug</b>							
Administer study drug			X <sup>a</sup>				
<b>Additional blood analyses</b>							
Blood collection: biomarkers <sup>b</sup>		X	Every 12 weeks <sup>b</sup>	X	X	X	
Blood collection for antibodies to siltuximab <sup>c</sup>			Every 12 weeks <sup>c</sup>	X	X	X	
Blood collection for glycoform/in vivo protein degradation analysis <sup>d</sup>		X <sup>d</sup>	Cycle 1 Day 3, Week 1, Week 2, Week 3 <sup>d</sup>				
<b>Safety Evaluations</b>							
Physical examination		X	<ul style="list-style-type: none"> <li>• Every 3 cycles for those on 3-week dosing</li> <li>• Every other administration visit at a minimum for those on 6-week dosing</li> </ul>				
Weight	X	X	X	X			
Vital signs <sup>e</sup>		X	X				
ECG (12-lead) <sup>f</sup>	X		Once, after 1 year				
Hematology, Chemistry <sup>g</sup>	X	X	<ul style="list-style-type: none"> <li>• Every cycle in 1<sup>st</sup> year for siltuximab-naïve subjects</li> <li>• Every 3 cycles for 3-week regimen</li> <li>• Every other administration visit at a minimum for those on 6-week regimen</li> </ul>	X			





<b>Table 1: TIME AND EVENTS SCHEDULE THROUGH AMENDMENT INT-3</b>							
Procedures and Evaluations	Screening	Pre-dose Cycle 1	Cycle 1 Day 1, or as indicated	End of treatment/ Follow-Up Week 4	Follow-Up Week 8	Follow-Up Week 12	After 5-year data cutoff
Days	-28 to 0	1					
<p>a. Siltuximab should be administered after all other study assessments and evaluations required at that visit. The visit window for siltuximab administration is minus 3 or plus 4 days from the scheduled visit date.</p> <p>b. Blood samples for biomarker testing should be collected prior to study agent administration and at the end of treatment visit. A frequency of every 12 weeks means every 4th cycle for those on an every 3-week administration schedule and every 2nd cycle for those on an every 6-week administration schedule.</p> <p>c. Scheduled blood samples for testing antibodies to siltuximab should be collected prior to study agent administration. Serum from venous blood samples (7.5 mL per sample) will be split into 3 aliquots (1 aliquot for analysis of antibodies to siltuximab, 1 aliquot for siltuximab serum concentration analysis to code antibodies to siltuximab data, and 1 aliquot as a backup). Serum concentration of siltuximab will also be determined at these timepoints. In addition, an unscheduled blood sample should be drawn, if possible, for determining antibodies to siltuximab any time an infusion-related reaction is observed during the study. This sample should be obtained as soon as possible after the reaction. A frequency of every 12 weeks means every 4th cycle for those on an every 3-week administration schedule and every 2nd cycle for those on an every 6-week administration schedule.</p> <p>d. Serum samples for glycoform clearance analysis and in vivo protein degradation will be collected from 5 former study C0328T03 subjects (administered 11 mg/kg every 3 weeks) who consented to have these samples collected. These samples should be collected Cycle 1 (pre- and post-dose), and at Cycle 1 Day 3, Week 1 (Day 7 +/- 1 day), Week 2 (Day 14 +/- 2 days), and Week 3 (Day 21 +/- 2 days; before the Cycle 2 dose).</p> <p>e. Vital signs will be measured predose and end of infusion on Day 1 of Cycle 1. Thereafter, vital signs will be measured only before each study agent administration on Day 1 of each cycle, and as clinically indicated.</p> <p>f. ECGs will only be performed for those subjects who are siltuximab naïve at study entry, and as clinically indicated for all subjects.</p> <p>g. Hematology and chemistry panel has to be performed prior to first dose to assess the subject's eligibility. If screening takes place within 7 days prior to first dose, the tests are not required to be repeated pre-dose Cycle 1. Laboratory monitoring will occur prior to each infusion in the first year of treatment for those subjects that are siltuximab-naïve at study entry.</p> <p>h. Fasting sample is required at screening and preferred for subsequent samples. If lipid panel is abnormal, amylase and lipase may be assessed as clinically indicated.</p> <p>i. Coagulation parameters should only be evaluated if clinically indicated.</p> <p>j. If last chest X-ray was performed within 3 months prior to first dose, results can be used for the screening timepoint. If equivalent imaging (ie, CT, MRI) was performed for routine medical care at the timepoint, it is allowed instead of chest X-ray.</p> <p>k. If considered to be clinically indicated, investigator assessment along with ESR, CRP, and fibrinogen evaluations, should be performed more frequently. Quantitative immunoglobulins should be performed if clinically indicated. Subjects who demonstrate disease progression on an once every 6 weeks dosing schedule (see Section 6.1) have to return to the every 3 weeks dosing schedule after reassessment of hematology and chemistry lab panels, physical exam, and, if not done within last 6 weeks, also a reassessment of investigator assessment of disease control and ESR, CRP, and fibrinogen.</p> <p>l. Survival status after 5-year data cutoff will be collected twice a year for subjects still on treatment provided by Sponsor. For these subjects, SAEs, concomitant medications involved in treatment of SAEs, and information on pregnancies will continue to be collected. After treatment discontinuation, survival status, occurrence of malignancies, and subsequent therapies for MCD will be collected twice per year.</p> <p>m. Only for subjects from the C0328T03 study; to be performed at the start of the screening visit, and predose at Cycles 1 and 2 (before other procedures).</p>							

<b>Table 2: TIME AND EVENTS SCHEDULE PER AMENDMENT INT-4</b>							
Procedures and Evaluations	Screening	Pre-dose Cycle 1	Cycle 1 Day 1, or as indicated	End of treatment/ Follow-Up Week 4	Follow-Up Week 8	Follow-Up Week 12	Until 6-year data cutoff
Days	-28 to 0	1					
<b>Screening/Administrative</b>							
Informed consent	X						
Inclusion/exclusion criteria	X						
Medical history/demography	X						
<b>Study Drug</b>							
Administer study drug			X <sup>a</sup>				
<b>Additional blood analyses</b>							
Blood collection for antibodies to siltuximab <sup>b</sup>			Every 12 weeks <sup>b</sup>	X	X	X	
<b>Safety Evaluations</b>							
Physical examination		X	<ul style="list-style-type: none"> <li>• Every 3 cycles for those on 3-week dosing</li> <li>• Every other administration visit at a minimum for those on 6-week dosing</li> </ul>				
Weight	X	X	X	X			
Vital signs <sup>c</sup>		X	X				
ECG (12-lead) <sup>d</sup>	X		Once, after 1 year				
Hematology, Chemistry <sup>e</sup>	X	X	<ul style="list-style-type: none"> <li>• Every cycle in 1<sup>st</sup> year for siltuximab-naïve subjects</li> <li>• Every 3 cycles for 3-week regimen</li> <li>• Every other administration visit at a minimum for those on 6-week regimen</li> </ul>	X			
Lipid panel <sup>f</sup>	X		<ul style="list-style-type: none"> <li>• Every 3 months in 1<sup>st</sup> year for siltuximab-naïve subjects</li> <li>• Every 6 months</li> </ul>	X			
Coagulation <sup>g</sup>			As needed				
Pregnancy test	X			X			
Chest X-ray (or CT/MRI) <sup>h</sup>	X <sup>h</sup>		Annual				
<b>Efficacy Evaluations</b>							
Investigator assessment <sup>i</sup>	X		Cycles 4, 7, 10 and every 6 months <sup>i</sup>	X			
ESR, CRP, and fibrinogen <sup>i</sup>	X		Cycles 4, 7, 10 and every 6 months <sup>i</sup>	X			



**ABBREVIATIONS**

AE	adverse event
ALT/SGPT	alanine aminotransferase/serum glutamate pyruvate transaminase
ANC	absolute neutrophil count
AST/SGOT	aspartate aminotransferase/serum glutamic oxaloacetic transaminase
AUC	area under the curve
BP	blood pressure
BSC	best supportive care
CDM	clinical data manager
CHO	Chinese hamster ovary
CR	complete response
CRF	case report form
CRP	C-reactive protein
CT	computed tomography
DCF	data clarification form
DLT	dose-limiting toxicity
eDC	Electronic Data Capture
ESA	erythropoiesis-stimulating agents
ESR	erythrocyte sedimentation rate
FDA	Food and Drug Administration
GCP	Good Clinical Practices
GI	gastrointestinal
GMR	geometric means
GP	glycoprotein
HDL	high-density lipoprotein
HIV	human immunodeficiency virus
HR	heart rate
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IgA	immunoglobulin A
IgG	immunoglobulin gamma
IgG1κ	immunoglobulin gamma 1 kappa
IgM	immunoglobulin M
IL	Interleukin
IRB	Institutional Review Board
IV	intravenous
LC	liquid chromatography
LDL	low density lipoprotein
LOQ	limit of quantification
mAb	monoclonal antibody
MCD	multicentric Castleman's disease
MCDSS	Multicentric Castleman's Disease Symptom Scale
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MS	mass spectroscopy
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
POEMS	Polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes syndrome
PQC	product quality complaint
PR	partial response
PRO	Patient-reported outcomes
RBC	red blood cell (count)
SAE	serious adverse event

SM	site manager
SOC	system-organ class
SOP	Standard Operating Procedure
TNF $\alpha$	tumor necrosis factor alpha
ULN	upper limit of normal

## 1 INTRODUCTION

Siltuximab is a chimeric (murine-human) IgG1 $\kappa$  mAb that specifically binds human IL-6 with high affinity and prevents its interaction with the IL-6 receptor, glycoprotein (GP) 80 (Seideman and Peritt, 2002). The chimeric antibody contains the variable region of a murine anti-human IL-6 mAb and the constant region from a human immunoglobulin gamma (IgG) 1 molecule. The mechanism of action of siltuximab is neutralization of IL-6 bioactivity, which can be measured indirectly by C-reactive protein (CRP) suppression.

For the most comprehensive nonclinical and clinical information regarding the efficacy and safety of siltuximab, refer to the latest version of the Investigator's Brochure.

The term sponsor used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

### 1.1 Background

Multicentric Castleman's disease (MCD) is a rare lymphoproliferative disease first described by Castleman and Towne, 1954, that is characterized by systemic manifestations such as fever, night sweats, fatigue, anorexia, and wasting, particularly in patients with the plasma cell or mixed-type variants of the disease. Clinical manifestations may vary, and hepatosplenomegaly, lymph node enlargement, and multiple laboratory abnormalities (eg, anemia, hypoalbuminemia, and hypocholesterolemia) are also common (Nishimoto et al, 2005; Casper, 2005; Dham and Peterson, 2007). Other symptoms include fluid retention; neuropathy; skin abnormalities; and polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS) syndrome. MCD can occur in individuals who are infected with HIV as well as in those not infected with HIV, and with similar symptoms. Treatment goals include alleviation of debilitating symptoms that contribute to shortened survival, and reduction of tumor masses. Unlike the unicentric variant of the disease that responds well to surgical resection of affected lymph nodes, or HIV-associated MCD that may respond to antiviral therapy, interferon, or rituximab, there is no established treatment for MCD. In particular, no treatment consistently results in a meaningful or lasting reduction in tumor burden. Consequently, median survival is short (14 to 30 months; Casper, 2005). Patients with MCD are usually managed by treatment of symptoms, with only modest success being reported; therefore, there is an unmet medical need for effective treatment in MCD.

#### 1.1.1 Role of IL-6 in Castleman's Disease

IL-6 is a 22 to 27 Kd secreted GP that is known for its pleiotropic and proinflammatory functions (Kishimoto, 1989; Hirano et al, 1994). Experience with a human IL-6 transgenic murine model clearly supports a pivotal role for IL-6 in the etiology of Castleman's disease (Katsume et al, 1997). These mice overexpress human IL-6, and develop a Castleman's disease-like disorder. Continuous treatment of these mice with

antibodies against the IL-6 receptor significantly reduced or prevented all pathologies examined, confirming the role of IL-6 in the etiology of Castleman's disease (Katsume et al, 2002). The humanized anti-IL-6 receptor mAb, tocilizumab (Actemra<sup>®</sup>), is approved in Japan for its demonstrated benefit in improving symptoms and laboratory findings associated with Castleman's disease, although the impact on tumor burden was not formally studied.

## 1.1.2 Clinical Experience With Siltuximab in Castleman's Disease

### 1.1.2.1 Study C0328T03

This ongoing Phase 1 dose-finding study in subjects with multiple myeloma, B-cell non-Hodgkin's lymphoma, and Castleman's disease (multicentric or unresectable localized disease), has a primary objective of assessing the safety and pharmacokinetics of multiple siltuximab dosing regimens (3 mg/kg to 12 mg/kg dose levels).

In Study C0328T03, 12 (52%) Castleman's disease subjects demonstrated objective tumor response (van Rhee et al, 2010). Duration of overall objective response ranged from 44 to  $\geq$  889 days, and 1 subject had a complete response (CR) for  $\geq$  318 days. Responses were confirmed by independent radiologic review.

A high frequency of clinical benefit response was observed (100% [11/11]; 95% CI 72%-100% of subjects treated at the target dose of 12 mg/kg (corresponding to 11 mg/kg using the current absorptivity constant – see Section 3.2), and 78% [18/23]; 95% CI 56%-93% at all doses studied) (van Rhee et al, 2010). Clinical benefit response was defined as improvement in at least 1 of the following, with all other measures stable or better: hemoglobin, fatigue, anorexia, fever/night sweats, weight, or size of largest lymph node. Nineteen of 23 subjects (83%) had at least 1 g/dL improvement in hemoglobin (median increase 2.1 g/dL; range: 0.2 to 7.2 g/dL) in the absence of transfusion or erythropoiesis-stimulating agents (ESAs). Among the 15 evaluable subjects, serum hepcidin, a biomarker for IL-6 activity, decreased from elevated baseline levels within a short time after siltuximab treatment in 14 subjects (93%). All 6 subjects who required corticosteroids for symptom control at study entry were weaned off corticosteroid dependence. In addition, complete and sustained suppression of CRP, a surrogate for IL-6 activity, was observed in 78% of subjects who had at least 1 postbaseline value, despite the presence of markedly elevated baseline CRP levels in the study population (median 23.4 mg/L [range 1 to 260 mg/L]).

Prolonged exposure at siltuximab dose levels ranging from 3 to 12 mg/kg was observed in this study, with no dose-limiting toxicity (DLT) observed after a median exposure of 331 days (range up to 1148 days). Three (3) subjects had Grade 3 or higher AEs (nausea, upper respiratory tract infection, vomiting, hypertriglyceridemia, and hypertension), which were considered unrelated to treatment with siltuximab by the study investigators. Serious adverse events (SAEs) were reported in 6 of 23 subjects, and none were attributable to siltuximab. Mild infusion reactions (eg, light-headedness, flushing,

hypertension, hives) were observed in 3 subjects, but siltuximab was not discontinued due to these events. No treatment-related deaths have been reported.

### 1.1.2.2 Study CNTO328MCD2001

This is a randomized, double-blind, placebo-controlled, multicenter study to determine the safety and efficacy of siltuximab plus best supportive care (BSC) compared with BSC, in subjects with symptomatic MCD. Approximately 78 subjects will be randomly assigned in a 1:2 ratio to placebo plus BSC or to siltuximab plus BSC. The study will be conducted in a blinded manner with independent, centrally confirmed assessment of the diagnosis and radiographic assessment of tumor response. An Independent Data Monitoring Committee (IDMC) will be commissioned for this study.

Subjects are required to have measurable disease, which may not be limited to cutaneous lesions and will receive siltuximab (11 mg/kg) or placebo by a 1-hour IV infusion every 3 weeks. Results were not available for this study at the time of protocol development.

### 1.1.3 Human Pharmacokinetics in Single-Agent Studies With Siltuximab

Pharmacokinetic results from Study C0328T01, a completed 3-part Phase 1/2 clinical study to evaluate the safety and efficacy of siltuximab in subjects with metastatic renal cell carcinoma at dose levels of 1, 3, 6, and 12 mg/kg, indicated that systemic exposure in terms of C<sub>max</sub> and partial AUC of siltuximab increased in an approximately dose-proportional manner. The mean t<sub>1/2</sub> values for the 3 parts of the study ranged from 17.3 to 22.9 days. In addition, there were no apparent time-dependent changes in the pharmacokinetics of siltuximab. Across the dose levels of 3 mg/kg to 12 mg/kg from all 3 parts of the study, the mean coefficient of variation percentage ranged from 34.0% to 37.8% for C<sub>max</sub> and from 21.7% to 35.1% for AUC(0-14d).

Preliminary pharmacokinetic analysis has also been performed on the available serum concentration-time data for siltuximab in Study C0328T03. Results indicate that the serum concentrations of siltuximab decreased bi-exponentially over 14- or 21-day periods, depending on the dose interval. The terminal t<sub>1/2</sub> for the 12 mg/kg dose every 3 weeks cohort was approximately 18 days. The exposure to siltuximab in terms of C<sub>max</sub> and AUC (0-14d) obtained after the first dose appeared to increase in an approximately dose-proportional manner over doses ranging from 3 mg/kg every 2 weeks to 12 mg/kg every 2 weeks or every 3 weeks. No apparent differences in the pharmacokinetics were observed when comparing subjects with non-Hodgkin's lymphoma, multiple myeloma, and Castleman's disease.

The effect of changing the manufacturing process was examined in a randomized Phase 1 safety and pharmacokinetic comparability study of Sp2/0-derived and Chinese Hamster Ovary (CHO-derived) siltuximab in healthy subjects (Study C0328T08). The pharmacokinetic parameters of C<sub>max</sub> and AUC(0-84d) after a single dose of 1.4 mg/kg siltuximab were compared in this study. The study was designed to conclude



pharmacokinetic comparability of the C<sub>max</sub> and AUC(0-84d) if the 90% confidence interval for the ratios of the geometric means (GMR) for AUC(0-84d) and C<sub>max</sub> both fall within the prespecified range of 80% to 125%.

The C<sub>max</sub> was evaluable in 67 subjects for the CHO-derived siltuximab and 63 subjects for the Sp2/0-derived siltuximab. The GMR 90% CI for C<sub>max</sub> of 99.4 to 111.3% is within the prespecified range of 80 to 125%. The AUC(0-84d) was evaluable in 64 subjects for the CHO-derived siltuximab and 56 subjects for the Sp2/0-derived siltuximab. The GMR 90% CI for AUC(0-84d) of 98.1 to 109.6% is within the prespecified range of 80 to 125%. Therefore, pharmacokinetic comparability of CHO-derived siltuximab and Sp2/0-derived siltuximab was demonstrated.

## 1.2 Potential Risks With Siltuximab

Because siltuximab is still in clinical development, its safety profile is not yet fully understood. Further investigation is necessary to better understand the safety of siltuximab. Therefore, unanticipated side effects that have not been previously observed may occur. Refer to the latest version of the siltuximab Investigator's Brochure for information regarding the safety of siltuximab.

A brief overview of the potential risks associated with the administration of siltuximab is outlined.

- Hypertriglyceridemia has been observed in some subjects who were administered siltuximab, and has been seen with other agents targeting the IL-6 receptor.
- Serious infections in single-agent studies have been reported in subjects administered agents that target IL-6 or its receptor. IL-6 directed therapy may have potential effects on humoral immunity. In addition, siltuximab may also potentially mask fever and other laboratory markers indicative of acute inflammation (eg, CRP). Therefore, subjects should be actively monitored for potential infection even in the absence of fever. Siltuximab should not be administered when there is evidence of serious active infection.
- Although unlikely, serious infusion related reactions (eg, anaphylaxis) may occur at any time during the administration of mAbs, including siltuximab.
- Administration of siltuximab may result in the development of antibodies against the protein. The risks of an anamnestic response to siltuximab are unknown.
- Gastrointestinal perforation has been reported in siltuximab clinical studies; however, these events are confounded by additional risk factors, including malignancy, abdominal surgery, and recent treatment with bevacizumab.
- Live, attenuated vaccines should not be given concurrently or within 4 weeks of initiating siltuximab, because clinical safety has not been established.
- IL-6 may serve as a growth factor for the bone marrow. Blocking IL-6 may therefore lead to decreases in neutrophils and platelets.

- Drug interactions: In nonclinical studies, IL-6 has been shown to decrease the activity of cytochrome P450 (CYP450; [Jover et al, 2002](#)). In addition, nonclinical and clinical data have shown that biologic agents that inhibit IL-6 activity have the potential to affect CYP450 enzyme activity ([Fujita et al, 2008](#); [Zhang et al, 2009](#)). This may result in increased metabolism of CYP450 substrates, because CYP450 enzyme activity will normalize to baseline activity. Therefore, administering siltuximab with CYP450 substrates that have a narrow therapeutic index has the potential to change drug therapeutic effects and toxicity due to alterations in the CYP450 pathways. Upon initiation or discontinuation of siltuximab in subjects being treated with concomitant medications that are CYP450 substrates and have a narrow therapeutic index, monitoring of the effect (eg, warfarin) or drug concentration (eg, cyclosporine or theophylline) is recommended, and the individual dose of the concomitant medication may be adjusted as needed.

### 1.3 Overall Rationale for the Study

Multicentric Castleman’s disease has an unmet medical need for effective treatment. The overall purpose of this study is to evaluate the long-term safety and disease control of siltuximab in subjects with MCD who have been enrolled in other studies (C0328T03 and CNTO328MCD2001) conducted by the Sponsor.

## 2 OBJECTIVES

### Primary Objective(s)

The primary objective is to evaluate the long-term safety of siltuximab in subjects with MCD.

### Secondary Objective(s)

The secondary objectives are:

- To determine the proportion of previously responding subjects who maintain disease control
- To determine the proportion of siltuximab-naive subjects who experience disease control
- To describe the duration of disease control and survival
- To assess reliability of a multicentric Castleman’s disease symptom scale (MCDSS)
- To evaluate IL-6 levels
- To assess formation of antibodies to siltuximab (immunogenicity) after long-term treatment in the MCD population

In addition, glycoform clearance analysis and in vivo protein degradation of siltuximab will also be assessed (see Section [9.5](#)).

**Hypothesis:** The safety of siltuximab will be acceptable for an extended treatment period. There is no formal hypothesis testing planned for this long-term extension study.

### **3 OVERVIEW OF STUDY DESIGN**

#### **3.1 Study Design**

This is an open-label, multicenter, non-randomized Phase 2 study of the safety of extended treatment with siltuximab in subjects who were previously enrolled in siltuximab studies of MCD (C0328T03 and CNTO328MCD2001). Up to 75 subjects will be eligible for the study, the majority of whom will be on active therapy with siltuximab at the time of enrollment. Duration of disease control and survival will also be assessed. Other secondary objectives include quantification of IL-6 (see Section 9.4) and assessment of the reliability of the MCDSS (see Section 9.3.4).

Subjects must be either siltuximab-naive or have not progressed on siltuximab in the opinion of the investigator. All subjects will be treated until they progress, withdraw, experience unacceptable toxicity, or until the 6-year data cutoff, whichever comes first.

Two data cutoffs will occur:

- No later than 2 years after the start of enrollment, an interim analysis will be conducted to further evaluate the benefit and safety of long-term treatment with siltuximab in subjects with MCD.
- Approximately 6 years after start of enrollment; however, continued drug supply will be ensured for study subjects who would not otherwise have access to siltuximab. A clinical study report (CSR) will be written based on this data cutoff.

Data collection for subjects who discontinue study agent will be limited to survival status, occurrence of malignancies, and subsequent therapies for MCD, which will be assessed twice per year until the subject has been lost to follow-up or has withdrawn consent for the study, or the 6-year data cutoff; whichever occurs first. For subjects still on treatment provided by Sponsor after the 6-year data cutoff, pregnancies and SAEs, including information on study agent administration and concomitant medications associated with an SAE, will continue to be collected. Data collected beyond the 6-year data cutoff will be reported to the appropriate health authorities in safety update reports. The end of study is the date of the last assessment for the last subject.

#### **3.2 Study Design Rationale**

This study is designed to evaluate the long-term safety and disease control in MCD subjects. Because siltuximab is an investigational agent, further evaluation is necessary to better understand the long-term safety of siltuximab in this population. Focused safety monitoring will be performed for key safety events of interest (see the current Investigator's Brochure), including infections, hyperlipidemia, neutropenia,

thrombocytopenia, GI perforations, infusion-related reactions, liver enzyme abnormalities, and immunogenicity.

### **Dose Justification**

The dose of siltuximab for this study is 11 mg/kg administered every 3 weeks by a 1-hour IV infusion. This corresponds to the 12 mg/kg dose used in C0328T03 when the current absorptivity constant is applied (see Section 4.2.1 of the Investigator Brochure). In the C0328T03 study, a dose response in MCD was seen, and was not associated with dose-related toxicity ([van Rhee et al, 2010](#)). Preliminary pharmacokinetic/pharmacodynamic modeling data is also supportive, because suppression of CRP to below the (LOQ; ie, 1 mg/L using high-sensitivity methods) throughout the treatment period does not occur with lower doses that have been tested ([Puchalski et al, 2010](#); data on file).

### **Patient-reported Outcomes**

The MCDSS will be assessed only in the subjects previously treated in the C0328T03 study, to provide an independent assessment of the scale designed for the CNTO328MCD2001 study ([Vernon et al, 2009](#)). The scale, developed based on results of qualitative research with MCD patients and clinical experts, was subsequently field tested with additional MCD patients. Symptom presence/absence and severity are noted on an anchor-based numeric scale. Frequency of occurrence can be generated when the instrument is used as a daily record of symptoms, as the recall period is 24 hours. Completion time is approximately 5 minutes. A summary score is generated based on the scores of 0 (very mild) to 5 (very severe). See Section 9.3.4 for additional information.

### **Pharmacodynamic Biomarker Assessments**

In order to gain further insight into the role of IL-6 in MCD, quantification of IL-6 will be performed and assessment of unusual IL-6 splice variants may also be performed to determine their role in MCD manifestation and response to treatment. The information from these evaluations may contribute to understanding IL-6 biology and siltuximab efficacy in MCD and in predicting or explaining treatment resistance over time. Collection of samples for these assessments will be stopped after Amendment INT-4 is implemented. Assessments are described in Section 9.4 and the planned analyses are described in Section 11.6.

### **Immunogenicity Assessment**

An immunogenic response to siltuximab is possible; therefore, samples to determine the presence of antibodies to siltuximab are planned to be collected from all subjects in the study. The information from these samples and data from other studies will be used to determine the immunogenicity of siltuximab in this population. Assessments are described in Section 9.6.

## Glycoform Clearance Analysis and In Vivo Protein Degradation

Blood samples will be collected from subjects to study the clearance and degradation of siltuximab glycoforms at several timepoints during Cycle 1 (see Section 9.5). Siltuximab contains several different chemical structures due to small differences in glycosylation. Serum collected from these blood samples will be analyzed to determine if there are differences in the clearance of the different glycoforms which could impact clinical efficacy. Changes in the chemical structure of siltuximab will also be monitored after product administration to determine the circulating levels of different protein degradants. Together, this information will be used to refine acceptance specifications for product release and stability.

## 4 STUDY POPULATION

### 4.1 General Considerations

The inclusion and exclusion criteria for enrolling subjects in this study are described in the following sections. No deviations from these criteria are allowed. **NOTE:** Investigators must ensure that all inclusion and exclusion criteria have been met at screening. Re-screening of screening failures is allowed. A subject is considered eligible if the last observation prior to the first dose meets the inclusion and exclusion criteria.

### 4.2 Inclusion Criteria

Potential subjects must satisfy all of the following criteria to be enrolled in the study:

1. Subjects must have multicentric Castleman's disease.
2. Subjects must have previously been enrolled in study C0328T03 or CNTO328MCD2001 (either treatment arm).
3. Subjects must have had their last administration of study treatment (siltuximab or placebo) less than 6 weeks (window of plus 2 weeks) prior to first dose. Subjects with longer treatment durations since the last study treatment may be allowed after discussion with the medical monitor.
4. Subjects must not have had disease progression while receiving siltuximab. For those subjects originally assigned to placebo in the CNTO328MCD2001 study, subjects who have received less than 4 months of siltuximab following crossover will also be eligible.
5. Adequate clinical laboratory parameters within 2 weeks prior to the first dose of siltuximab for this protocol:
  - a. Absolute neutrophil count (ANC) greater than or equal to  $1.0 \times 10^9/L$  ( $1,000/mm^3$ ) with or without neutrophil growth factors

- b. Platelets greater than or equal to  $50 \times 10^9/L$  ( $50,000/mm^3$ ) with or without platelet transfusion, thrombopoietic cytokines, or both
  - c. AST, ALT, total bilirubin and alkaline phosphatase must be within 2.5 x ULN; if alkaline phosphatase is above that, at least alkaline phosphatase liver fraction has to be less than or equal to 2.5 x ULN
6. Any other clinical significant toxicity must be less or equal to Grade 2 or the baseline value of the previous study.
  - 7.1 Women of childbearing potential must agree to use adequate birth control measures during the study and for 3 months after receiving the last dose of study agent, and must have a negative pregnancy test (serum or urine beta-human chorionic gonadotropin [ $\beta$ -HCG]) at screening. Men must agree to use a double barrier method of birth control and to not donate sperm during the study and for 3 months after receiving the last dose of study agent.
  8. Sign an informed consent document indicating that they understand the purpose of and procedures required for the study and are willing to participate in the study.

### 4.3 Exclusion Criteria

Potential subjects who meet any of the following criteria will be excluded from participating in the study:

1. Unmanageable toxicity, an adverse event, progression of disease, or withdrawal of consent as reason for discontinuing treatment from previous sponsor-initiated siltuximab study.
2. Vaccination with live, attenuated vaccines within 4 weeks of first dose of this study.
3. Criterion removed per amendment INT-2 (see protocol amendment table before Synopsis).
4. Known unmanageable allergies, hypersensitivity, or intolerance to monoclonal antibodies or to murine, chimeric, or human proteins or their excipients.

## 5 TREATMENT ALLOCATION

This study is an open-label, single-arm study.

## 6 DOSAGE AND ADMINISTRATION

Siltuximab will be given as a 1-hour infusion at 11 mg/kg every 3 weeks. All subjects will be treated until they progress, withdraw, experience unacceptable toxicity, or until the 6-year data cutoff, whichever comes first. A data cutoff will occur approximately 6 years after the start of enrollment; however, continued drug supply will be ensured for study subjects who would not otherwise have access to siltuximab.

Subjects with confirmed partial or complete remission, defined as a documented radiographic response, for more than 6 months (including those entering the study in PR or CR) may be dosed every 6 weeks at the investigator's discretion. Demonstration of radiographic response is not required for subjects with skin-only disease with confirmed PR/CR for more than 6 months. Subjects on the 6-week schedule should be monitored for safety and disease assessment evaluations as per protocol Time & Events Schedules (see [Table 1](#) and [Table 2](#)). When disease progression is suspected, all screening and pre-dose Cycle 1 evaluations should be repeated and treatment with siltuximab could continue at 11 mg/kg siltuximab every 3 weeks. The effective switch from the 3-week dosing schedule to the 6-week schedule can only occur on odd-numbered cycle visits to match the collection timepoints of biomarkers and immunogenicity samples of every 12 weeks, and has to occur on dosing days. Switching back to a 3-week schedule upon suspected disease progression can occur at any cycle visit.

During the study, no dose modifications of siltuximab will be allowed. Dose delays of up to 3 weeks will be allowed for treatment-related toxicity. Documentation of dose delays, including the reasons for the delay, is required.

## **6.1 Dose Delays and Retreatment**

The dose should be delayed if the subject has an active infection that qualifies for a Grade 3 or 4 NCI-CTCAE toxicity, or that is otherwise considered clinically significant by the investigator.

### **6.1.1 Laboratory Assessment and Dose Delays**

Chemistry and hematology laboratory tests are performed every 3 administration visits for subjects on the 3-week dosing schedule and on siltuximab at study entry. If the dosing schedule exceeds the 3-week interval (eg, every 6 weeks), these laboratory assessments should be performed every other administration visit at a minimum, to ensure proper safety evaluation. For subjects who are naïve to siltuximab at study entry, chemistry and hematology laboratory tests are performed at every administration visit for the first year on study. Lipid panels are monitored approximately every 6 months, and every 3 months for siltuximab-naïve subjects.

The siltuximab dose must be delayed if the hemoglobin value measured predose is  $\geq 17$  g/dL, as a safety precaution to avoid clinical consequences of polycythemia.

More frequent laboratory assessment as described above is not required; however, the investigator should consider delaying treatment when laboratory values do not meet those required for inclusion in the study.

## **6.2 Guidelines for Management of Infusion Reactions**

Although unlikely, serious allergic reactions (including anaphylaxis) may occur at any time during the administration of monoclonal antibodies, including siltuximab. Therefore,

before any administration is started, the appropriate personnel, medication (adrenaline, inhaled beta agonists, antihistamines, and possibly corticosteroids) and other requirements to treat anaphylaxis must be available.

A physician must also be immediately available at the site at all times during the administration of study agents. The Medical Monitor must be notified within 24 hours of any infusion reaction requiring interruption of study agent (see Contact Information pages provided separately). Subjects experiencing a reaction during the administration of study agent should be treated according to institutional guidelines.

All subjects should be observed carefully for infusion-site reactions (eg, erythema or induration), symptoms of an allergic reaction/hypersensitivity (eg, urticaria, itching, hives), or cytokine release syndrome/acute infusion reaction. Any adverse reaction should be noted on the AE page of the CRF. The infusion rate may be lowered if clinically indicated.

Infusion must be stopped immediately and permanently discontinued if:

- $\geq$  Grade 3 allergic reaction/hypersensitivity (including drug fever) occurs
- $\geq$  Grade 3 cytokine release syndrome/acute infusion reaction occurs

Subjects with reactions, during or after an infusion, resulting in bronchospasm with wheezing, dyspnea requiring ventilatory support, or symptomatic hypotension with a decrease in systolic blood pressure greater than 40 mm Hg will not be permitted to receive any additional study agent for the remainder of the study. If the infusion reaction results in treatment discontinuation, subjects should undergo all scheduled study evaluations.

Corticosteroid use for allergic reactions to siltuximab should be limited to 2 doses of 100 mg hydrocortisone or equivalent (see [Attachment 1](#)), in addition to standard treatment with antihistamines and acetaminophen (see Section [8.2](#)).

A blood sample should be obtained, if possible, for determining antibodies to siltuximab any time an infusion reaction is observed or reported during the study. Siltuximab serum concentration will also be determined from the sample for the purpose of interpreting data on antibodies to siltuximab. These samples will be stored, and evaluated if deemed necessary.

## 7 TREATMENT COMPLIANCE

Study drug will be administered as an IV infusion by qualified staff and the details of each administration will be recorded in the CRF (including date, start and stop times of the IV infusion, total volume given if administration was stopped early).



## 8 CONCOMITANT THERAPY

Prestudy therapies administered up to 30 days before first dose of study drug in this study must be recorded at screening. Concomitant medications must be recorded throughout the study beginning when the first dose of study drug is administered until 30 days after last dose. All concomitant medications will be collected except for:

- Vitamins
- Herbal medicines
- Dietary supplements (iron is not considered a dietary supplement)

After Amendment INT-4 is implemented, only the following concomitant medications will continue to be collected:

- Anti-infective medications (antibiotics, oral or topical antifungals, and antiviral etc.)
- Lipid modifying agents
- Antihypertensives
- Immunomodulators including corticosteroids
- Hematopoietic cytokines such as colony stimulation factors
- Blood product transfusions
- Clinical important surgery or procedures
- Medications to manage infusion related reactions
- Medications used to treat SAEs

### 8.1 Supportive Care Measures

Allowed supportive care measures for all study subjects to manage symptoms include:

- Management of effusions (eg, drainage, diuretics)
- Antipyretics, antipruritics, antihistamines
- Pain medication
- Management of infections
- Transfusions
- Management of infusion reactions as specified in institutional guidelines (see Section 6.2)

## 8.2 Guidelines for Corticosteroid Use

Concomitant use of immunosuppressive therapy is not permitted during the study, except for:

- Subjects who are receiving corticosteroid treatment at the time of screening may be considered for inclusion in the study. If subjects are taking corticosteroids at the start of the study, they may be tapered during the study. Tapering of corticosteroid dosing should preferably not start before the first disease assessment (ie, Cycle 4). Tapering of corticosteroids should be guided by clinical symptoms of Castleman's disease unless prompted by intolerable or acute and severe corticosteroid-related toxicities.
- Other indications, see Section 8.4
- Treatment of acute allergic reactions according to institution guidelines (see Section 6.2)
- Secondary prophylactic pretreatment with corticosteroids to prevent allergic reactions (eg, to contrast materials or to siltuximab) is allowed after consulting with the Medical Monitor. Corticosteroid use for allergic reactions to siltuximab should be limited to 2 doses of 100 mg hydrocortisone or equivalent (see Attachment 1), in addition to standard treatment with antihistamines and acetaminophen (see Section 6.2).

## 8.3 Guidelines to Manage Hyperlipidemia

Hypertriglyceridemia has been observed in some subjects who were administered siltuximab and has been seen with other agents targeting the IL-6 receptor ([Actemra® PI, 2010](#); [RoActemra EPAR, 2009](#); [Nishimoto et al, 2004](#)). The incidence of hypertriglyceridemia reported as an AE in single-agent studies of siltuximab is low and almost all reported events have been low grade. Monitoring and treatment of lipid profiles (high-density lipoprotein [HDL] and low density lipoprotein [LDL]) and triglycerides as per established guidelines (<http://www.nhlbi.nih.gov/guidelines/cholesterol/dskref.htm>) are recommended since potential effects of chronic siltuximab administration on cardiovascular ischemic events is not well defined.

## 8.4 Prohibited Therapies

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

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

- Other investigational agents
- Increase from baseline or a new course of systemic immunosuppressive agents (including corticosteroids), with the exception of:
  - isolated use of low-dose corticosteroids to treat and prevent allergic reactions (see Section 8.2)
  - increase or new course for another indication such as but not limited to (a flare of) rheumatoid arthritis and psoriasis
- ESAs

The Medical Monitor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

## 9 STUDY EVALUATIONS

### 9.1 Study Procedures

#### 9.1.1 Overview

The Time and Events Schedules (see [Table 1](#) and [Table 2](#)) that follow the Synopsis summarizes the frequency and timing of safety, efficacy, pharmacodynamic biomarker, and other evaluations applicable to this study. Enrolled subjects will be assessed for eligibility according to the inclusion and exclusion criteria (see [Section 4.2](#) and [Section 4.3](#)).

Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy throughout the study. The total blood volume to be collected from each subject will depend on the amount of time they participate in this long-term study. The table in [Attachment 3](#) shows the maximum volume per each assessment. PRO assessments (ie, MCDSS) during a visit should be conducted before any tests, procedures, or other consultations for that visit.

The assessments per visit will vary as indicated per Time and Events schedules (see [Table 1](#) and [Table 2](#)). The required assessments at every dosing visit are:

- Weight
- Vital signs
- Review of adverse events
- Review of concomitant medications
- Administration of siltuximab

The follow-up Week 4 assessment (4 weeks after the last dose) will be considered as the end of treatment visit. During this visit, assessments will be repeated according to the Time & Events Schedules (see [Table 1](#) and [Table 2](#)) to conclude the study treatment and obtain follow-up details. The remainder of the follow-up period constitutes 2 visits, 8 and 12 weeks after the last administration during which serum blood samples will be collected to assess immunogenicity (antibodies to siltuximab) and biomarkers as applicable.

## 9.2 Safety Evaluations

Baseline chest X-ray is required within 3 months of first dose within this study and annually thereafter. If equivalent imaging (ie, CT, MRI) was performed for routine medical care at these timepoints, then it is allowed instead of a chest X-ray. Safety monitoring will consist of continuous AE reporting with a focus on infections, hyperlipidemia, neutropenia, thrombocytopenia, GI perforations, infusion-related reactions, liver enzyme abnormalities, and immunogenicity. ECG and clinical laboratory tests are to be performed according to the Time and Events Schedules. Other laboratory parameters will only be evaluated if clinically indicated. Any of these safety monitoring assessments may be performed more frequently if clinically indicated.

The study will include the following evaluations of safety and tolerability according to the timepoints provided in the Time and Events Schedules (see [Table 1](#) and [Table 2](#)):

- AEs and AEs  $\geq$  Grade 3
- SAEs
- Infusion reactions
- Clinically significant abnormal laboratory parameters
- Antibodies to siltuximab

The Medical Monitor will assess subject safety throughout the study on an ongoing basis. Safety will be evaluated using AEs, vital signs, weight, clinical laboratory parameters (hematology, chemistry, and lipid panel), and ECG as applicable. Any treatment-emergent clinically significant abnormalities persisting at the end of the study will be followed by the investigator until resolution or until a clinically stable endpoint is reached.

## Adverse Events

All toxicities will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE, Version 4.0). Adverse events will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally-acceptable representative) for the duration of the study. Adverse events will be assessed by the investigator as specified in [Section 12](#), Adverse Event Reporting.

For those subjects that do not have access to commercial siltuximab, continued siltuximab supply will be ensured. For all subjects still enrolled in the study after the 6-year data cutoff, only pregnancies and SAEs, including information on study agent administration and concomitant medications associated with an SAE, will be collected, and reported to the appropriate health authorities in safety update reports.

### **Clinical Laboratory Tests**

Blood samples for serum chemistry and hematology are collected according to the Time & Events Schedules (see [Table 1](#) and [Table 2](#)). The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the adverse event section of the CRF. All laboratory reports have to be reviewed prior to the next study administration to evaluate subject's safety for continued treatment.

These tests will be performed by the local laboratory:

- **Hematology Panel**

The screening hematology laboratory sample must be collected > 2 weeks from last RBC transfusion, platelet transfusion, or neutrophil growth factor administration. Hematology results must be reviewed before the scheduled study agent administration to evaluate safety. After Amendment INT-4, only a limited hematology panel is required (see [Table 2](#)).

- hemoglobin
- WBC count with differential
- platelet count

- **Serum Chemistry Panel**

Serum chemistry results must be reviewed before the scheduled study agent administration to evaluate safety. After Amendment INT-4, only a limited serum chemistry panel is required (see [Table 2](#)).

- |                                  |                        |
|----------------------------------|------------------------|
| - sodium                         | - albumin              |
| - potassium                      | - total bilirubin      |
| - blood urea nitrogen/creatinine | - AST                  |
| - glucose                        | - ALT                  |
| - total protein                  | - alkaline phosphatase |

- **Coagulation Tests:** performed if clinically indicated.

- **Lipid Panel**

Fasting sample is required at screening, and is preferred for all subsequent samples. Lipid panel should be performed every 6 months. If the subject is naïve to siltuximab at study entry, the lipid panel should be done every 3 months for the first year of treatment, then every 6 months thereafter. If the lipid panel is abnormal, amylase and lipase may be assessed as clinically indicated.

- cholesterol
- HDL
- triglycerides
- LDL

- **Serum or urine pregnancy testing**

- For women of childbearing potential only at screening and Follow-up Week 4 visit, and as clinically indicated during the study.

- **Other tests**

- Quantitative immunoglobulins (IgG, IgA, IgM), to be performed only as clinically indicated

**Vital Signs (Temperature, Blood Pressure, and Heart Rate)**

Vital signs will be measured predose and end of infusion on Day 1 of Cycle 1. Thereafter, vital signs will be measured only before each study agent administration on Day 1 of each cycle, and as clinically indicated.

**Physical Examination**

Physical examinations will be performed according to the Time & Events Schedules (see [Table 1](#) and [Table 2](#)) with attention to areas of potential tumor involvement (including enlargement of liver and spleen). Any clinically significant observations should be recorded on the Adverse Event page of the CRF. Any clinically significant abnormalities persisting at the end of treatment will be evaluated by the investigator until resolution or until reaching a clinically stable endpoint.

**ECG Assessment**

ECG will be performed and analyzed locally. Subjects entering the study naïve to siltuximab will have ECGs performed according to the Time and Events Schedules (see [Table 1](#) and [Table 2](#)). A focused cardiac investigation including an ECG is recommended if clinically indicated for any subject during the study.

### **9.3 Efficacy Evaluations**

#### **9.3.1 Disease Control**

Investigator assessment of disease control will be collected during screening, at Cycles 4, 7, and 10, every 6 months thereafter, and at study treatment discontinuation (or Follow-up Week 4 visit).

Disease assessments listed in [Attachment 2](#) (including cutaneous assessments), are provided as a guide for assessing multicentric Castleman's disease. If a subject shows disease progression at 2 consecutive assessments the subject must discontinue study treatment.

#### **9.3.2 Laboratory Evaluations**

ESR, CRP, and fibrinogen tests must be performed at the same times as the investigator assessment of disease control. These assessments will be part of the hematology and chemistry panels.

#### **9.3.3 Survival**

For subjects who discontinue study agent, survival status will be assessed twice per year until the subject has been lost to follow-up or has withdrawn consent for the study, or the 6-year data cutoff; whichever occurs first.

#### **9.3.4 Patient-reported Outcomes**

The MCDSS questionnaire will only be completed by the sub-population from the C0328T03 study. The reliability of the MCDSS will be assessed by collecting the completed questionnaire 3 times during the study: at the start of the screening visit, and predose at Cycles 1 and 2.

### **9.4 Pharmacodynamic Biomarker Evaluations**

From serum samples, pharmacodynamic biomarker evaluations include, but are not limited to:

- Quantification of IL-6.
- Assessment of atypical IL-6 splice variants or cleavage fragments may also be performed along with exploratory assessment to compare IL-6 molecular profiles obtained in MCD patients versus commercially available samples from healthy volunteers. Other assessments related to disease and study agent may be performed based on emerging evidence. Planned biomarker analyses will be deferred if emerging study data show less likelihood of providing useful scientific information. Collection of samples for these assessments will be stopped after Amendment INT-4 is implemented.
- CRP (assessed locally as part of clinical laboratory tests using the chemistry laboratory samples).

## 9.5 Glycoform Clearance and In Vivo Protein Degradation Analysis

To evaluate the clearance and degradation of glycoforms after administration of siltuximab, 6 serum samples will be collected from 5 former C0328T03 subjects (a limited number of samples are needed for this analysis).

Siltuximab will be isolated from the serum samples using an anti-Id antibody. The purified protein will then be analyzed by liquid chromatography/mass spectroscopy (LC/MS) techniques (intact mass and peptide mapping) to evaluate the clearance of different glycoforms over time and to determine the circulating levels of different protein degradants.

## 9.6 Antibodies to Siltuximab

Antibodies to siltuximab will be detected using a validated immunoassay. All samples collected for detection of antibodies to siltuximab will also be evaluated for siltuximab serum concentration to interpret antibody response data. Antibodies to siltuximab may also be assessed at other timepoints. Serum samples will be screened for antibodies binding to siltuximab, and the serum titer of confirmed positive samples will be reported. Other immunogenicity analyses may be performed to further characterize the immune responses. Immunogenicity samples will be analyzed at the 6-year data cutoff.

Blood samples to determine antibodies to siltuximab will be collected from all subjects in the study every 12 weeks while receiving siltuximab in conjunction with a dosing visit, and at Week 4, Week 8, and Week 12 following the last administration of siltuximab.

In addition, a blood sample should be drawn, if possible, to determine antibodies to siltuximab any time an infusion related reaction is observed or reported during the study. This sample should be obtained as soon as possible after the reaction. These samples will be stored, and evaluated if deemed necessary. See Section 6.2 for guidelines for management of infusion related reactions.

All samples should be sent to the central laboratory. The sponsor or its designee will test these samples. Instructions for the collection and shipment of these samples are found in the Laboratory Manual.

## 10 SUBJECT COMPLETION/WITHDRAWAL

### 10.1 Completion

A subject will be considered to have completed the study if he or she has completed assessments at the Follow-up Week 4 assessments, or has experienced a clinical endpoint that precludes further study (eg, disease progression).

### 10.2 Discontinuation of Treatment

All subjects will be treated until they progress, withdraw, experience unacceptable toxicity, or until the 6-year data cutoff, whichever comes first. A data cutoff will occur



approximately 6 years after the start of enrollment; however, continued drug supply will be ensured for study subjects who would not otherwise have access to siltuximab outside this clinical study.

If a subject discontinues study agent, obtain end-of-treatment and follow-up assessments, which are the same assessments done at Follow-up Weeks 4, 8 and 12 as applicable. If a subject's study treatment must be discontinued before the end of the treatment regimen, this will not result in automatic withdrawal of the subject from the study. Subjects will have follow-up assessments for survival, occurrence of malignancies, and subsequent MCD therapies until the 6-year data cutoff (see Section 9.3.3).

A subject's study treatment should be discontinued if:

- The investigator believes that for safety reasons (eg, adverse event) it is in the best interest of the subject to stop treatment.
- The subject becomes pregnant.
- The subject initiated any of the prohibited medications requiring discontinuation of treatment (see Section 8.4)

### 10.3 Withdrawal from Study

A subject will be withdrawn from the study for any of the following reasons:

- Lost to follow-up
- Withdrawal of consent
- Death

If a subject discontinues the study before the end of the treatment phase, obtain end-of-treatment and follow-up assessments.

In case a subject is lost to follow-up, every possible effort must be made by the study site personnel to contact the subject and determine the reason for discontinuation/withdrawal. The measures taken to follow up must be documented.

When a subject withdraws before completing the study, the reason for withdrawal is to be documented in the CRF and in the source document. Subjects who withdraw will not be replaced.

## 11 STATISTICAL METHODS

In general, all continuous endpoints will be summarized using descriptive statistics, which will include the number of subjects, mean, standard deviation, median, minimum, and maximum. All categorical endpoints will be summarized using frequencies and

percentages. For time to event variables (eg, overall survival), the Kaplan-Meier method will be used for descriptive summaries. No formal hypothesis testing will be performed.

### **11.1 Subject Information**

The safety population, which includes all subjects who receive at least one administration of siltuximab, will be used in all statistical analyses.

### **11.2 Sample Size Determination**

The sample size for this study is not designed according to statistical calculation. It is expected that up to 75 subjects could be enrolled. The number of subjects enrolled will be determined by the eligible subjects from the C0328T03 and CNTO328MCD2001 studies.

### **11.3 Safety Analyses**

Adverse events, deaths, and safety-related laboratory tests will be summarized as follows:

- Incidence of all AEs
- Incidence of Grade 3 or higher AEs
- Incidence of SAEs
- Incidence of AEs and SAEs reasonably related to siltuximab
- Incidence of clinically important changes in safety-related laboratory parameters
- Incidence of deaths and malignancies
- Incidence of antibodies to siltuximab

### **Adverse Events**

The original terms used in the CRFs by investigators to identify adverse events will be coded using the MedDRA. All reported adverse events with onset on or after the first siltuximab administration through 30 days after the last siltuximab administration within the 6-year data cutoff (ie, treatment-emergent adverse events) will be included in the analysis. The incidence of treatment-emergent AEs will be summarized overall, by MedDRA system-organ class (SOC) and preferred term, by toxicity grade, and by relationship to siltuximab administration. The adverse events of clinical interest, such as infections, hyperlipidemia, neutropenia, thrombocytopenia, GI perforations, infusion-related reactions, liver enzyme abnormalities, and immunogenicity will be summarized in similar fashion.

Special attention will also be given to those subjects who died, or who discontinued treatment due to an adverse event, or who experienced a severe or a SAE (eg, summaries, listings, and narrative preparation may be provided, as appropriate).

**Clinical Laboratory Tests**

Hematology and chemistry laboratory values will be summarized at baseline and at each scheduled timepoint by descriptive statistics for each type of laboratory test. The changes from baseline results will also be summarized. In addition, the worst toxicity grade experienced by a subject during the study will be summarized, and shift tables from baseline to worst toxicity during the study will be presented.

**Vital Signs**

Descriptive statistics of temperature, pulse, respiratory rate, and blood pressure (systolic and diastolic) (supine or standing) values and changes from baseline will be summarized at each scheduled time point. The percentage of subjects with values beyond clinically important limits will be summarized.

**ECG**

Abnormal 12-lead ECG findings during treatment will be presented in listings.

**11.4 Efficacy and Patient-reported Outcomes Analyses****11.4.1 Disease Control**

Investigator assessment of disease control for all treated subjects will be analyzed. Specifically, the proportion of previously responding subjects and siltuximab-naïve subjects who maintain disease control will be summarized. The duration of disease control, defined as the time from the first siltuximab administration to disease progression as assessed by the investigator, will also be summarized.

**11.4.2 Laboratory Evaluations**

Efficacy-related laboratory assessments of ESR, CRP, and fibrinogen will be summarized by descriptive statistics at baseline and each scheduled timepoint. The changes from baseline results will also be summarized.

**11.4.3 Overall Survival**

Overall survival is defined as the time between the first study siltuximab administration and death. Subjects who died, regardless of the cause of death, will be considered as an event. Subjects who withdraw consent from the study will be censored at the time of withdrawal. Subjects who are still alive at the cutoff date of the final analysis will be censored at the date of last known alive. All subjects who are lost to follow-up before the 6-year data cutoff will be censored at the date they are last known to be alive.

The Kaplan-Meier method will be used to estimate the distribution of overall survival. Median overall survival with 95% CI will be provided. In addition, the Kaplan-Meier overall survival curve will also be provided.

#### **11.4.4 MCDSS Evaluations**

The patient-reported MCDSS total score at each timepoint and the change from baseline in MCDSS total score will be summarized.

#### **11.5 Glycoform Analysis and In Vivo Protein Degradation**

These analyses will be reported in a separate technical report.

#### **11.6 Pharmacodynamic Biomarker Analyses**

Determination of IL-6 levels prior to first administration of siltuximab is planned to be performed. Exploratory evaluation of IL-6 splice variant analysis may also be performed. Results from IL-6 analysis will be summarized at the timepoints tested and association with clinical response may be explored.

#### **11.7 Interim Analysis**

No later than 2 years after start of enrollment, an interim analysis will be conducted to further evaluate the benefit and safety of long-term treatment with siltuximab in subjects with MCD. In addition, the interim analysis results will be used to support internal decision-making.

### **12 ADVERSE EVENT REPORTING**

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures (SOPs) in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

#### **12.1 Definitions**

##### **12.1.1 Adverse Event Definitions and Classifications**

###### **Adverse Event**

An adverse event is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Conference on Harmonisation)

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The sponsor collects adverse events starting with the signing of the informed consent form (refer to Section 12.2.1, All Adverse Events for time of last adverse event recording).

### **Serious Adverse Event**

A serious adverse event as defined by ICH is any untoward medical occurrence that at any dose meets any of the following conditions:

- Results in death
- Is life-threatening  
(The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect

Note: Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in situations other than those listed above. For example, important medical events may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the outcomes listed in the definition above (eg, suspected transmission of an infectious agent by a medicinal product is considered a SAE). Any adverse event is considered a SAE if it is associated with clinical signs or symptoms judged by the investigator to have a significant clinical impact.

### **Unlisted (Unexpected) Adverse Event/Reference Safety Information**

This is defined as an unlisted adverse event, the nature or severity of which is not consistent with the applicable product reference safety information. For an investigational product, the expectedness of an adverse event will be determined by whether or not it is listed in the Investigator's Brochure.

### **Associated With the Use of the Drug**

An adverse event is considered associated with the use of the drug if the attribution is possible, probable, or very likely by the definitions listed in Section 12.1.2.

#### **12.1.2 Attribution Definitions**

##### **Not related**

An adverse event that is not related to the use of the drug.

**Doubtful**

An adverse event for which an alternative explanation is more likely, eg, concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.

**Possible**

An adverse event that might be due to the use of the drug. An alternative explanation, eg, concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

**Probable**

An adverse event that might be due to the use of the drug. The relationship in time is suggestive (eg, confirmed by dechallenge). An alternative explanation is less likely, eg, concomitant drug(s), concomitant disease(s).

**Very likely**

An adverse event that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, eg, concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (eg, it is confirmed by dechallenge and rechallenge).

**12.1.3 Severity Criteria**

Severity of adverse events will be graded according to the NCI-CTCAE Version 4.0, using these descriptors:

- **Grade 1:** Mild AE
- **Grade 2:** Moderate AE
- **Grade 3:** Severe AE
- **Grade 4:** Life-threatening or disabling AE
- **Grade 5:** Death related to the AE

For any event not covered by the NCI-CTCAE, an assessment of severity grade will be made using the following general categorical descriptors:

**Mild:** Awareness of symptoms that are easily tolerated causing minimal discomfort and not interfering with everyday activities.

**Moderate:** Sufficient discomfort is present to cause interference with normal activity.

**Severe:** Extreme distress causing significant impairment of functioning or incapacitation. Prevents normal everyday activities.

The investigator should use clinical judgment in assessing the intensity of events not directly experienced by the subject (eg, laboratory abnormalities).

## **12.2 Procedures**

### **12.2.1 All Adverse Events**

All adverse events, whether serious or non-serious, will be reported from the time a signed and dated informed consent form is obtained until 30 days after last study agent administration. The only exception is for subjects who have withdrawn informed consent for study participation or for subjects who have received additional treatment with therapeutic intent for MCD within 30 days after the last study agent administration. For subjects who have received additional treatment with therapeutic intent for MCD during the AE reporting period, only AEs that are considered to be possibly, probably, or definitely related to study agent must be reported (unless the subject has been withdrawn from the study). Serious adverse events, including those spontaneously reported to the investigator within 30 days after the last dose of study drug, must be reported using the Serious Adverse Event Form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol. Key safety events of interest (see the current Investigator's Brochure), including infections, hyperlipidemia, neutropenia, thrombocytopenia, GI perforations, infusion-related reactions, liver enzyme abnormalities, and immunogenicity.

After the 6-year data cutoff, subjects who do not have access to commercially available siltuximab may continue to receive treatment provided by the Sponsor. For these subjects only, SAEs (information on study agent administration and concomitant medications use to treat the SAEs) and pregnancies will have to be reported and collected after the data cutoff at 6 years. These events will be reported to the appropriate health authorities in safety update reports.

All events that meet the definition of a SAE will be reported as SAEs, regardless of whether they are protocol-specific assessments. All adverse events, regardless of seriousness, severity, or presumed relationship to study therapy, must be recorded using medical terminology in the source document and the CRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as “upper respiratory infection”). Investigators must record in the CRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to sponsor instructions.

The sponsor assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. The sponsor will also report to the investigator all SAEs that are unlisted (unexpected) and associated with the use of the drug. The investigator (or sponsor where required) must report these events to the appropriate Independent Ethics

Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB.

Subjects (or their designees, if appropriate) must be provided with a “study card” indicating the name of the investigational study drug, the study number, the investigator’s name, a 24-hour emergency contact number, and, if applicable, excluded concomitant medications.

Disease progression should not be recorded as an adverse event or SAE term; instead, signs and symptoms of clinical sequelae resulting from disease progression/lack of efficacy will be reported if they fulfill the adverse event or SAE definition (see Section 12.1.1 Adverse Event Definitions and Classifications).

### **12.2.2 Serious Adverse Events**

All serious adverse events occurring during clinical studies as well as during continued treatment after the 6-year data cutoff, must be reported to the appropriate sponsor contact person by investigational staff within 24 hours of their knowledge of the event.

Information regarding serious adverse events will be transmitted to the sponsor using the Serious Adverse Event Form, which must be completed and signed by a member of the investigational staff, and transmitted to the sponsor within 24 hours. The initial and follow-up reports of a SAE should be made by facsimile (fax).

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject’s participation in the study, or that have not resolved upon discontinuation of treatment beyond the 6-year data cutoff, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value is available
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

The cause of death of a subject in a clinical study, whether or not the event is expected or associated with the investigational agent, is considered a SAE. Suspected transmission of an infectious agent by a medicinal product should be reported as a SAE. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course



of a subject's participation in a clinical study must be reported as a SAE, except hospitalizations for the following:

- Social reasons in absence of an adverse event
- Surgery or procedure planned before entry into the study (must be documented in the CRF)

### **12.2.3 Pregnancy**

All initial reports of pregnancy must be reported to the sponsor by the investigational staff within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes are considered SAEs and must be reported using the Serious Adverse Event Form. Any subject who becomes pregnant during the study must discontinue further study treatment immediately.

Because the study drug may have an effect on sperm, or if the effect is unknown, pregnancies in partners of male subjects included in the study will be reported by the investigational staff within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Men should not donate sperm during this study and for 3 months after receiving the last dose of siltuximab.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

### **12.3 Contacting Sponsor Regarding Safety**

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues or questions regarding the study are listed on the Contact Information page(s), which will be provided as a separate document.

## **13 PRODUCT QUALITY COMPLAINT HANDLING**

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, reliability of a product, including its labeling or package integrity. PQCs may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from clinical studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

### **13.1 Procedures**

All initial PQCs must be reported to the sponsor by the investigational staff as soon as possible after being made aware of the event.

If the defect is combined with a SAE, the investigational staff must report the PQC to the sponsor according to the SAE reporting timelines (refer to Section 12.2.2, Serious Adverse Events). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

### **13.2 Contacting Sponsor Regarding Product Quality**

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product quality issues are listed on the Contact Information page(s), which will be provided as a separate document.

## **14 STUDY DRUG INFORMATION**

### **14.1 Physical Description of Study Drug**

Details regarding the composition of siltuximab can be found in the Investigator's Brochure. The study agents are NOT to be used for any purpose other than that outlined in this protocol, including other human studies, animal investigations, or in vitro testing.

The siltuximab supplied for this study has an approximate molecular weight of 147,750 daltons. Siltuximab will be supplied as a sterile, lyophilized formulation for reconstitution and IV infusion. The drug product after reconstitution of the lyophile contains siltuximab, histidine, sucrose, and polysorbate-80.

### **14.2 Packaging**

The investigational supplies will be uniquely packaged to assure that they are appropriately managed throughout the supply chain process.

### **14.3 Labeling**

Study drug labels will contain information to meet the applicable regulatory requirements for each country.

### **14.4 Preparation, Handling, and Storage**

All study drug must be stored at controlled temperatures ranging from 35.6°F to 46.4°F (2°C to 8°C). Study agent vials should be stored in a secured refrigerator at 2 to 8°C. During extended storage, study agent vials should be stored refrigerated at 2 to 8°C and protected from light. Protection from light is not required during dose preparation or administration.

The pharmacist should prepare study agent using a vertical laminar flow biologic cabinet (hood) and proper aseptic techniques. It is recommended that gloves and protective garments be worn during preparation. Lyophilized vials will be reconstituted with sterile, single-use water for injection, using a syringe with a 21-gauge 1.5-inch needle. The study agent is to be reconstituted as specified in the site investigational product manual. It is recommended to wait 30 minutes to ensure complete reconstitution before preparation of

study agent. DO NOT USE THE VIAL IF DISCOLORATION, OPAQUE PARTICLES, OR OTHER FOREIGN PARTICLES ARE PRESENT.

The study agent will be prepared according to the subject's weight. The drug product will be aseptically withdrawn from the study vials and added to 250 mL 5% dextrose for infusion. A total volume of 250 mL of diluted solution will be administered to the subject over a period of 1 hour. The infusion should be given via a separate line, using the administration set with a 0.2 micron inline filter. Aseptic procedures should be used during the preparation and infusion of study medication. Refer to the Pharmacy Manual for additional guidance on study drug preparation and handling.

#### **14.5 Drug Accountability**

The investigator is responsible for ensuring that all study drug received at the site is inventoried and accounted for throughout the study.

Study drug must be handled in strict accordance with the protocol and the container label and will be stored in a limited access area or in a locked cabinet under appropriate environmental conditions. Unused study drug must be available for verification by the sponsor's site monitor during on-site monitoring visits. The return to the sponsor or designee of unused study drug will be documented on the return or destruction Form. When the site is an authorized destruction unit and study drug supplies are destroyed on site, this must also be documented on the return or destruction Form.

Hazardous materials such as used ampoules, needles, syringes and vials containing hazardous liquids, infusion lines and systems should be disposed of immediately in a safe manner and therefore will not be retained for drug accountability purposes. The immediate destruction of these drug supplies should be documented in the drug accountability records on site.

Study drug should be dispensed under the supervision of the investigator, a qualified member of the investigational staff, or by a hospital/clinic pharmacist. Study drug will be administered only to subjects participating in the study. The investigator agrees neither to dispense the study drug from, nor store it at, any site other than the study sites agreed upon with the sponsor.

### **15 STUDY-SPECIFIC MATERIALS**

The investigator will be provided with the following supplies:

- Study protocol
- Siltuximab drug
- Pharmacy manual
- Laboratory Manual

- Investigator’s Brochure
- MCDSS questionnaire

## **16 ETHICAL ASPECTS**

### **16.1 Study-Specific Design Considerations**

Potential subjects will be fully informed of the risks and requirements of the study and, during the study, subjects will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only subjects who are fully able to understand the risks, benefits, and potential adverse events of the study, and provide their consent voluntarily will be enrolled.

The total blood volume to be collected will be depend on the duration of subject participation in this long-term safety study; however, the volume drawn is well within the limits for blood donation during the time period of study assessments.

### **16.2 Regulatory Ethics Compliance**

#### **16.2.1 Investigator Responsibilities**

The investigator is responsible for ensuring that the clinical study is performed in accordance with the protocol, current ICH guidelines on GCP, and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well being of study subjects are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the clinical study data are credible.

#### **16.2.2 Independent Ethics Committee or Institutional Review Board (IEC/IRB)**

Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents:

- Final protocol and, if applicable, amendments
- Sponsor-approved informed consent form (and any other written materials to be provided to the subjects)
- Investigator’s Brochure (or equivalent information) and amendments
- Sponsor-approved subject recruiting materials
- Information on compensation for study-related injuries or payment to subjects for participation in the study, if applicable

- Investigator’s curriculum vitae or equivalent information (unless not required, as documented by IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for subjects
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any), the informed consent form, applicable recruiting materials, and subject compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

During the study the investigator (or sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments
- Revision(s) to informed consent form and any other written materials to be provided to subjects
- If applicable, new or revised subject recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- Investigator’s Brochure amendments or new edition(s)
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of adverse events that are serious, unlisted, unexpected, and associated with the investigational drug
- New information that may adversely affect the safety of the subjects or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the subjects
- Report of deaths of subjects under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Annual Safety Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or trial conduct), the amendment and applicable informed

consent form revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be asked to review and reapprove this clinical study. The reapproval should be documented in writing (excluding the ones that are purely administrative, with no consequences for subjects, data or trial conduct).

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion.

### **16.2.3 Informed Consent**

Each subject (or a legally-acceptable representative) must give written consent according to local requirements after the nature of the study has been fully explained. The consent form must be signed before performance of any study-related activity. The consent form that is used must be approved by both the sponsor and by the reviewing IEC/IRB. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the investigational staff must explain to potential subjects (or their legally-acceptable representatives) the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the subject will receive for the treatment of his or her disease. Subjects will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the investigator will maintain a subject identification register for the purposes of long-term follow-up if needed and that their records may be accessed by health authorities and authorized sponsor staff without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations. By signing the informed consent form the subject (or legally-acceptable representative) is authorizing such access, and agrees to allow his or her study physician to recontact the subject for the purpose of obtaining consent for additional safety evaluations, if needed, or to obtain information about his or her survival status.

The subject (or legally-acceptable representative) will be given sufficient time to read the informed consent form and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of either the subject's (or his or her legally-acceptable representative's) personally dated signature. After having obtained the consent, a copy of the informed consent form must be given to the subject.

If the subject (or legally-acceptable representative) is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and should personally date and sign the informed consent form after the oral consent of the subject (or legally-acceptable representative) is obtained.

#### **16.2.4 Privacy of Personal Data**

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to investigate the efficacy, safety, quality, and utility of the investigational study drug(s) used in this study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of study subjects confidential.

The informed consent obtained from the subject (or his or her legally-acceptable representative) includes explicit consent for the processing of personal data and for the investigator to allow direct access to his or her original medical records for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The subject has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

#### **16.2.5 Country Selection**

Unless explicitly addressed as a specific ethical consideration in Section 16.1, Study-Specific Design Considerations, this study will only be conducted in those countries where the intent is to help ensure access to the developed product.

### **17 ADMINISTRATIVE REQUIREMENTS**

#### **17.1 Protocol Amendments**

Neither the investigator nor the sponsor will modify this protocol without a formal amendment. All protocol amendments must be issued by the sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the subjects, in which case the amendment must be promptly submitted to the IEC/IRB and relevant

competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor or its designee. When the change(s) involves only logistic or administrative aspects of the study, the IRB (and IEC where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative (see Contact Information pages provided separately). Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the CRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

## **17.2 Regulatory Documentation**

### **17.2.1 Regulatory Approval/Notification**

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A study may not be initiated until all local regulatory requirements are met.

### **17.2.2 Required Prestudy Documentation**

The following documents must be provided to the sponsor before shipment of study drug to the investigational site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator
- A copy of the dated and signed written IEC/IRB approval of the protocol, amendments, informed consent form, any recruiting materials, and if applicable, subject compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed by the chairman or authorized designee.
- Name and address of the IEC/IRB including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the investigational staff is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable
- Documentation of investigator qualifications (eg, curriculum vitae)
- Completed investigator financial disclosure form from the principal investigator, where required



- Signed and dated clinical trial agreement, which includes the financial agreement
- Any other documentation required by local regulations

The following documents must be provided to the sponsor before enrollment of the first subject:

- Completed investigator financial disclosure forms from all clinical subinvestigators
- Documentation of subinvestigator qualifications (eg, curriculum vitae)
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable

### **17.3 Subject Identification, Enrollment, and Screening Logs**

The investigator agrees to complete a subject identification and enrollment log to permit easy identification of each subject during and after the study. This document will be reviewed by the sponsor site contact for completeness.

The subject identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the study will identify subjects by assigned number only.

The investigator must also complete a subject-screening log, which reports on all subjects who were seen to determine eligibility for inclusion in the study.

### **17.4 Source Documentation**

At a minimum, source documentation must be available for the following to confirm data collected in the CRF: subject identification, eligibility, and study identification; study discussion and date of informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all adverse events; and follow-up of adverse events; concomitant medication; drug receipt/dispensing/return records; study drug administration information; and date of study completion, and reason for early discontinuation of study drug or withdrawal from the study, if applicable.

It is recommended that the author of an entry in the source documents be identifiable.

At a minimum, the type and level of detail of source data available for a study subject should be consistent with that commonly recorded at the site as a basis for standard medical care. Specific details required as source data for the study will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

The following data will be recorded directly into the CRFs and will be considered source data:

- Race
- BP/HR (if not primary efficacy or significant safety issue)
- Height (except if primary efficacy or significant safety issue)

MCDSS questionnaires will be completed by the subjects on paper. Once the subject signs and dates the questionnaire, the questionnaire will be regarded as a source document.

### **17.5 Case Report Form Completion**

Case report forms are provided for each subject in printed or electronic format.

Electronic Data Capture (eDC) will be used for this study. The study data will be transcribed by study personnel from the source documents onto an electronic CRF within an agreed upon number of days of the subject's visit. The electronic file will be considered to be the CRF. Worksheets may be used for the capture of some data to facilitate completion of the CRF. Any such worksheets will become part of the subjects' source documentation. All data relating to the study must be recorded in CRFs prepared by the sponsor. Data must be entered into CRFs in English. Designated site personnel must complete CRFs as soon as possible after a subject visit, and the forms should be available for review at the next scheduled monitoring visit.

Every effort should be made to ensure that all subjective measurements (eg, pain scale information or other questionnaires) to be recorded in the CRF are completed by the same individual who made the initial baseline determinations. The investigator must verify that all data entries in the CRFs are accurate and correct.

All CRF entries, corrections, and alterations must be made by the investigator or other authorized study-site personnel. If necessary, queries will be generated in the eDC tool. The investigator or an authorized member of the investigational staff must adjust the CRF (if applicable) and complete the query.

If corrections to a CRF are needed after the initial entry into the CRF, this can be done in 3 different ways:

- Site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool)
- Site manager (SM) can generate a query (field DCF) for resolution by the investigational staff
- Clinical data manager (CDM) can generate a query for resolution by the investigational staff

**17.6 Data Quality Assurance/Quality Control**

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study centers, review of protocol procedures with the investigator and associated personnel before the study, and periodic monitoring visits by the sponsor. Written instructions will be provided for collection, preparation, and shipment of blood, plasma, and serum samples.

Guidelines for CRF completion will be provided and reviewed with study personnel before the start of the study.

The sponsor will review CRFs for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the clinical study database they will be verified for accuracy.

**17.7 Record Retention**

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all CRFs and all source documents that support the data collected from each subject, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator must permit access to such reports.

## 17.8 Monitoring

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study center visit log that will be kept at the site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the CRFs with the hospital or clinic records (source documents). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the CRF are known to the sponsor and investigational staff and are accessible for verification by the sponsor site contact. If electronic records are maintained at the investigational site, the method of verification must be discussed with the investigational staff.

Direct access to source documentation (medical records) must be allowed for the purpose of verifying that the data recorded in the CRF are consistent with the original source data. Findings from this review of CRFs and source documents will be discussed with the investigational staff. The sponsor expects that, during monitoring visits, the relevant investigational staff will be available, the source documentation will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

## 17.9 Study Completion/Termination

### 17.9.1 Study Completion

The study is considered completed with the last visit of the last subject participating in the study. The final data from the investigational site will be sent to the sponsor (or designee) after completion of the final subject visit at that site, in the time frame specified in the Clinical Trial Agreement.

### 17.9.2 Study Termination

The sponsor reserves the right to close the investigational site or terminate the study at any time for any reason at the sole discretion of the sponsor. Investigational sites will be closed upon study completion. An investigational site is considered closed when all required documents and study supplies have been collected and a site closure visit has been performed.

The investigator may initiate site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of an investigational site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the sponsor's procedures, or GCP guidelines

- Inadequate recruitment of subjects by the investigator
- Discontinuation of further drug development.

### **17.10 On-Site Audits**

Representatives of the sponsor's clinical quality assurance department may visit the site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection and comparison with the CRFs. Subject privacy must, however, be respected. The investigator and staff are responsible for being present and available for consultation during routinely scheduled site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the sponsor if they have been contacted by a regulatory agency concerning an upcoming inspection.

### **17.11 Use of Information and Publication**

All information, including but not limited to information regarding siltuximab or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including pharmacogenomic research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study, and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the clinical study will be used by the sponsor in connection with the continued development of siltuximab, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain CRF data from all investigational sites that participated in the study. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

The sponsor shall have the right to publish such data and information without approval from the investigator. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and substudy approaches, results may need to be published in a given sequence (eg, substudies) should not generally be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not publishing data derived from the individual site until the combined results from the completed study have been published in full, within 12 months after conclusion, abandonment, or termination of the study at all sites, or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state that the named authors must have made a significant contribution to the design of the study or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version.

**Registration of Clinical Studies and Disclosure of Results**

The sponsor will register or disclose the existence of and the results of clinical studies as required by law.

## REFERENCES

Actemra® (tocilizumab) [prescribing information]. South San Francisco, CA, 94080, USA: Genentech, Inc., 2010

Casper C. The aetiology and management of Castleman disease at 50 years: translating pathophysiology to patient care. *Br J Haematol.* 2005;129(1):3-17.

Castleman B, Towne VW. Case records of the Massachusetts General Hospital; weekly clinicopathological exercises; founded by Richard C. Cabot. *New Engl J Med.* 1954;251(10):396-400.

Dham A, Peterson BA. Castleman disease. *Curr Opin Hematol.* 2007;14(4):354-359.

Fujita T, Yasuda S, Kamata Y, Fujita K, et al. Contribution of down-regulation of intestinal and hepatic cytochrome P450 3A to increased absorption of cyclosporine A in a rat nephrosis model. *J Pharmacol Exp Ther.* 2008;327(2):592-599.

Hirano T, Matsuda T, Nakajima K. Signal transduction through gp130 that is shared among the receptors for the interleukin 6 related cytokine subfamily. *Stem Cells.* 1994;12(3):262-277.

Jover R, Bort R, Gómez-Lechón MJ, Castell JV. Down-regulation of human CYP3A4 by the inflammatory signal interleukin 6: molecular mechanism and transcription factors involved. *FASEB J.* 2002;16(13):1799-1801.

Katsume A, Miyai T, Suzuki H, et al. Interleukin-6 overexpression cannot generate serious disorders in severe combined immunodeficiency mice. *Clin Immunol Immunopathol.* 1997;82(2):117-124.

Katsume A, Saito H, Yamada Y, et al. Anti-interleukin 6 (IL-6) receptor antibody suppresses Castleman's disease like symptoms emerged in IL-6 transgenic mice. *Cytokine.* 2002;20(6):304-311.

Kishimoto T. The biology of interleukin-6. *Blood.* 1989;74(1):1-10.

National Heart, Lung, and Blood Institute (National Institutes of Health). *Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults.* NIH Publication No. 02-5215. September 2002. <http://www.nhlbi.nih.gov/guidelines/cholesterol/dskref.htm>. Accessed October 2010.

Nishimoto N, Yoshizaki K, Miyasaka N, et al. Treatment of rheumatoid arthritis with humanized anti-interleukin-6 receptor antibody: a multicenter, double-blind, placebo-controlled trial. *Arthritis Rheum.* 2004;50(6):1761-1769.

Nishimoto N, Kanakura Y, Aozasa K, et al. Humanized anti-interleukin-6 receptor antibody treatment of multicentric Castleman disease. *Blood.* 2005;106(8):2627-2632.

Puchalski T, Prabhakar U, Jiao Q, Berns B, Davis HM. Pharmacokinetic and Pharmacodynamic Modeling of an Anti-Interleukin-6 Chimeric Monoclonal Antibody (Siltuximab) in Patients with Metastatic Renal Cell Carcinoma. *Clin Cancer Res.* 2010;16(5):1652-1661.

RoActemra, [European Public Assessment Report]. Welwyn Garden City, AL7 1TW, United Kingdom. Roche Registration Limited, 2009.

Seideman J, Peritt D. A novel monoclonal antibody screening method using the Luminex-100 microsphere system. *J Immunol Methods.* 2002;267(2):165-171.

van Rhee F, Fayad L, Voorhees P, et al. Siltuximab, a novel anti-interleukin-6 monoclonal antibody, for Castleman's disease. *J Clin Oncol.* 2010;28(23):3701-3708.

Vernon MK, Teschendorf B, Van Rhee F. Qualitative research in Castleman's disease: exploring patients' perspective of symptoms through qualitative interviews. Paper presented at: International Society for Quality of Life Research; October, 2009; New Orleans, LA.

Zhang X, Schmitt C, Grange S, et al. Disease-drug interaction studies of Tocilizumab with cytochrom P450 substrates in vitro and in vivo. Paper presented at: ASCPT Annual Meeting; March 18-21, 2009; National Harbor, MD. Poster P11-73.



**ATTACHMENT 1: APPROXIMATELY EQUIVALENT DOSES OF CORTICOSTEROIDS**

<b>Steroid</b>	<b>Glucocorticoid anti-inflammatory</b>
Cortisone	100 mg
Hydrocortisone	80 mg
Prednisone	20 mg
Prednisolone	20 mg
Methylprednisolone	16 mg
Dexamethasone	2 mg

Knoben JE, Anderson PO. *Handbook of Clinical Drug Data*, 6th ed. Drug Intelligence Pub, Inc. 1988.

**Steroid Equivalence Converter**

Steroid Equivalence Converter. Available at: <http://www.medcalc.com/steroid.html>. Accessed 22 Jun 2009.

## ATTACHMENT 2: DISEASE ASSESSMENTS

Disease assessment criteria (including cutaneous disease assessments) are provided as a guide for the investigator.

Each subject can be classified as stable, improved, or worsened based on hemoglobin, fatigue, anorexia, fever, weight, and target lymph node assessment (see the first table below). If a subject improves in at least one measure and remains stable for all other measures, the subject is considered to have improved. A worsening in any of the measures will be considered as a progression of the disease. Any other subject will be considered stable for clinical benefit. The investigator's assessment of all lymph node radiologic results will also be recorded.

For subjects who have only cutaneous disease (cutaneous disease must be proven by biopsy), the response assessment for cutaneous lesions is a modified physician's global assessment that has been used in previous oncology clinical studies (Duvic et al, 2001a; Duvic et al, 2001b) and will be one of the clinical benefit components, and be assessed based on the following response criteria.

The extent of disease will be measured by an estimation of BSA involved; single sites of disease must be > 1 cm in diameter. Twelve main body areas will be assessed, as listed in the second table below (Duvic et al, 2001c).

<b>Clinical Benefit Assessments for Castleman's Disease</b>			
<b>Measure</b>	<b>Status</b>		
	<b>Improved</b>	<b>Stable</b>	<b>Worsening</b>
Hemoglobin	Increase of at least 2 g/dL relative to baseline without blood transfusion	Less than 2 g/dL variance relative to baseline without blood transfusion	Decrease of at least 2g/dL relative to baseline without blood transfusion
Fatigue	Decrease of at least 1 CTC grade point relative to baseline	No change in CTC grade relative to baseline	Increase of at least 1 CTC grade point relative to baseline
Anorexia	Decrease of at least 1 CTC grade point relative to baseline	No change in CTC grade relative to baseline	Increase of at least 1 CTC grade point relative to baseline
Fever*	Decrease of at least 2°C relative to baseline or return to normal body temp (37°C)	Less than 2°C variance relative to baseline unless normal body temp is achieved then define as improved	Increase of at least 2°C relative to baseline

Weight	Increase of at least 5% relative to baseline (without new edema or increase in existing edema)	Less than a 5%variance from baseline (without new edema or an increase in existing edema)	Decrease of at least 5% relative to baseline (weight loss not due to decreased edema)
Size of largest lymph node (CT or physical examination) and/or cutaneous disease	Lymph node: Decrease of at least 25% (bidimensionally) compared with baseline.  Cutaneous disease: The disappearance of all visible and palpable evidence of active disease, or an unequivocal reduction in the extent of disease. This must be documented by a $\geq 50\%$ reduction in the disease burden from baseline.	Lymph node: No increase or decrease of at least 25% (bidimensionally) compared with baseline.  Cutaneous disease: Disease not meeting the criteria for improvement or worsening.	Lymph node: Increase of at least 25% (bidimensionally) compared with baseline.  Cutaneous disease: An unequivocal increase in the extent of disease. This must be documented by a $> 50\%$ increase in the disease burden, or at least 1 new lesion. If an existing lesion disappears then reappears, it is considered a new lesion.
*To be assessed in conjunction with subject reported night sweats			

<b>Investigator Estimate of Body Surface Area Involved With Cutaneous Castleman’s Disease</b>				
<b>Area</b>	<b>Total Possible % BSA for Region</b>	<b>% BSA Involved with CD</b>		<b>% BSA CD</b>
Head	7	X	_____	=
Neck	2	X	_____	=
Anterior trunk <sup>a</sup>	13	X	_____	=
Posterior Trunk <sup>b</sup>	13	X	_____	=
Buttocks	5	X	_____	=
Genitalia	1	X	_____	=
Upper arms	8	X	_____	=
Forearms	6	X	_____	=
Hands	5	X	_____	=
Thighs	19	X	_____	=
Lower leg	14	X	_____	=
Feet	7	X	_____	=
<b>Total</b>	<b>100</b>			
<sup>a</sup> : Without neck or genitalia. <sup>b</sup> : Without neck or buttocks.				

**References**

Duvic M, Hymes K, Heald P, et al. Bexarotene is effective and safe for treatment of refractory advanced-stage cutaneous T-cell lymphoma: Multinational Phase II-III trial results. *J Clin Oncol*. 2001a;19(9):2452-2471.

Duvic M, Martin AG, Kim Y, et al. Phase 2 and 3 clinical trial of oral bexarotene (Targretin capsules) for the treatment of refractory or persistent early-stage cutaneous T-cell lymphoma. *Arch Dermatol*. 2001b;137:581-593.

Duvic M, Olsen EA, Omura GA, et al. A phase III, randomized, double-blind placebo-controlled study of peldesine (BCX-34) cream as topical therapy for cutaneous T-cell lymphoma. *J Am Acad Dermatol*. 2001c;44(6):940-947.

**ATTACHMENT 3: BLOOD VOLUMES**

Blood volumes for the assessments in this study are listed below.

<b>Assessment</b>	<b>Blood Volume*</b>
Hematology	10 mL**
Chemistry	10 mL**
Lipid panel	10 mL**
CRP, ESR and fibrinogen	10 mL**
Pharmacodynamic biomarkers	5 mL
Antibodies to siltuximab (immunogenicity)	7.5 mL
Glycoform/degradation analysis	5 mL per sample, 30 mL total
<p>* Volume per sample; total volume depends on length of study participation. Frequency of sample collection is in the Time and Events Schedules (<a href="#">Table 1</a> and <a href="#">Table 2</a>).</p> <p>** Estimated maximal amount; volume could be less or combined (eg, chemistry and lipid panel) depending on local laboratory guidelines.</p>	

**INVESTIGATOR AGREEMENT**

Siltuximab (CNTO 328)

Clinical Protocol CNTO328MCD2002 Amendment INT-4

**INVESTIGATOR AGREEMENT**

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study drug, the conduct of the study, and the obligations of confidentiality.

**Coordinating Investigator (where required):**

Name (typed or printed): \_\_\_\_\_

Institution and Address: \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

Signature: \_\_\_\_\_ Date: \_\_\_\_\_  
(Day Month Year)

**Principal (Site) Investigator:**

Name (typed or printed): \_\_\_\_\_

Institution and Address: \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

Telephone Number: \_\_\_\_\_

Signature: \_\_\_\_\_ Date: \_\_\_\_\_  
(Day Month Year)

**Sponsor's Responsible Medical Officer:**

Name (typed or printed): Ming Qi

Institution: Janssen Research & Development

Signature: \_\_\_\_\_ Date: 4 April 2014  
(Day Month Year)

**Note:** If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

**LAST PAGE**