

Janssen Research & Development

Statistical Analysis Plan

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

Protocol CNTO328MCD2002; Phase 2

CNTO328 (Siltuximab)

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Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

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ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CI	Confidence interval
CR	Complete response
CRF	case report form
CRP	C-reactive protein
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DODC	Duration of disease control
DPS	data presentation specification
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
IA	interim analysis
LDL	Low Density Lipoprotein
HDL	High Density Lipoprotein
LLOQ	lower limits of quantification
MCD	Multicentric Castleman's disease
MCDSS	Multicentric Castleman's Disease Symptom Scale
MedDRA	Medical Dictionary for Regulatory Activities
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse
OS	Overall survival
PD	Progressive disease
PR	Partial response
PRO	Patient-reported outcomes
SAE	serious adverse event
SAP	statistical analysis plan
SD	Stable disease
SOC	system organ class
TEAEs	treatment-emergent adverse events
WBC	White blood cells

1. INTRODUCTION

This statistical analysis plan (SAP) contains definitions of analysis sets, derived variables, and statistical methods for a Phase 2 study to evaluate the safety of long-term treatment with siltuximab in subjects with multicentric Casteman's disease.

1.1. Overview of Trial 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 multicentric Castleman's disease (MCD) (C0328T03 and CNT0328MCD2001) and are either siltuximab-naive or have not progressed on siltuximab in the opinion of the investigator.

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

Up to 75 subjects will be eligible for the study, the majority of whom will be on active therapy with siltuximab and have not progressed at the time of enrollment. Subjects with unmanageable toxicity or discontinuation of treatment from previous sponsor-initiated siltuximab studies due to an adverse event, progression of disease, or withdrawal of consent will be excluded.

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. 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 reason for delay, is required. All subjects will be treated until they progress, withdraw, experience unacceptable toxicity, or until the 6-year data cutoff, whichever comes first.

Throughout the study, 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. Safety evaluations will

include a chest X-ray, or equivalent imaging (ie, computed tomography [CT], magnetic resonance imaging [MRI]), ECG and clinical laboratory tests 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. For those who have discontinued study agent, survival status, occurrence of malignancies, 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.

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
- 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. 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 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.

1.2. Statistical Hypotheses for Trial Objectives

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.

1.3. Sample Size Justification

Up to 75 subjects who were previously enrolled in sponsor-initiated studies of multicentric Castleman's disease (MCD) (C0328T03 and CNTO328MCD2001) and are either siltuximab-naive or have not progressed on siltuximab in the opinion of the investigator will be eligible for the study.

2. GENERAL ANALYSIS DEFINITIONS

2.1. Parent Study and Long-term Safety Extension Study

The parent study refers to study C0328T03 or CNTO328MCD2001. The long-term safety extension study refers to study CNTO328MCD2002.

2.2. Study Data to Be Included in Analysis Tabulation

Subjects treated in the long-term safety extension study of CNTO328MCD2002 were previously enrolled in sponsor-initiated studies of MCD, therefore demographics, baseline characteristics, and prior systemic therapy data will come from parent study of C0328T03 or CNTO328MCD2001. Overall treatment exposure, safety evaluations (i.e., adverse events), and overall survival will be based on parent study and extension study. The data included in these overall summaries are from the start of C0328T03 or CNTO328MCD2001 to the end of CNTO328MCD2002.

Due to quite different schedules in laboratory assessment and vital sign collection between parent study and long-term safety extension study, safety evaluation through laboratory assessment and vital signs will focus on long-term safety extension study of CNTO328MCD2002. Similarly, immunogenicity analyses will also be based on long-term safety extension study.

2.3. By Visit Data Summary

In general, if data (e.g., laboratory and vital sign etc.) are collected by cycle, the nominal cycle will be used to summarize data. However, due to the nature of long-term extension treatment, safety evaluation via laboratory assessment may be summarized by study month/week, by-month/week windowing rules will be applied in the over time data summary.

2.4. Siltuximab Treatment Date

Siltuximab treatment date is the date on which a subject actually received siltuximab (partial or complete) administration.

For subjects who previously received siltuximab treatment, the first siltuximab treatment date is defined as the earliest date of non-zero dose of siltuximab administration from study C0328T03 or CNTO328MCD2001. The last study treatment date is defined as the latest date of non-zero dose of siltuximab administration from CNTO328MCD2002.

For subjects who were siltuximab-naive, the first study treatment date is defined as the earliest date of non-zero dose of siltuximab from study CNTO328MCD2002. The last study treatment date is defined as the latest date of non-zero dose of siltuximab administration from study CNTO328MCD2002.

2.5. Imputation of Partial Dates

Unless specified otherwise, no data imputation will be applied for missing safety and efficacy evaluations. For analysis and reporting purpose, partial dates in adverse event (AE onset date; AE end date), concomitant therapies (start date; end date), MCD diagnosis date, prior MCD therapies (start date; end date) and start date of subsequent MCD therapy will be imputed.

The detailed imputation rules along with other derived variables are specified in the data presentation specification (DPS).

2.6. General Analysis Method

In general, continuous variables will be summarized using descriptive statistics such as mean, standard deviation (SD), median and range. Categorical variables will be summarized using frequency and percentage. For time-to-event variables, the Kaplan-Meier method will be used for descriptive summaries. For the calculation of time-to-event and duration-of-event variables, the difference between the start date and the end date plus 1 day will be used.

2.7. Analysis Sets

Safety population is defined in this study. The safety population will include subjects who have received at least 1 administration of siltuximab treatment (partial or complete). This analysis population will be used for all analyses.

3. 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.

4. SUBJECT INFORMATION

4.1. Demographics and Baseline Characteristics

Because demographics and baseline disease characteristics were not collected in the current long-term safety extension study of CNTO328MCD2002, therefore, demographics and baseline characteristics variables will be summarized based on data collected in the parent study of C0328T03 or CNTO328MCD2001.

Subject demographic and baseline characteristic variables: age (<65 years; ≥65 years), sex, race, weight (kg), height (cm) and ECOG performance score will be summarized.

Baseline disease characteristics including Castleman's disease histology (hyaline vascular; plasmacytic, mixed, undetermined) based on local pathology review, type of disease (unicentric, multicentric), HHV-8 status (positive, negative), and years since disease diagnosis (years) will be tabulated.

The distribution of subject enrollment to the long-term safety extension will be presented according to region and country. Subjects who did not meet inclusion/exclusion criteria for long-term extension study will be listed by subject ID and specific criteria not met.

4.2. Disposition Information

An overview of subject disposition in the long-term safety extension study will be provided. The overview includes number of subjects who previously enrolled to study C0328T03, or CNT0328MCD2001, for subjects who were previously in the study CNT0328MCD2001, a total number of subjects who were in siltuximab arm or placebo arm will be provided, respectively. Among all treated subjects (defined as subjects who have received at least 1 administration of siltuximab treatment), the number and percentage of subjects who discontinued siltuximab treatment including reason for discontinuation as indicated in the “End of Treatment” CRF page will be summarized.

Similar summaries will be presented for all treated subjects who discontinued study (i.e., CNT0328MCD2002).

In addition, a listing of subjects who discontinued siltuximab treatment/study with reason for discontinuation will be provided, separately. The listing may include subject ID, date of siltuximab discontinuation, reason for discontinuation, if reason for discontinuation is due to adverse event, the AE leading to discontinuation will be provided as well.

4.3. Extent of Exposure

Long-term treatment with siltuximab will be summarized and presented based on the safety population by combining parent study and extension study.

Duration of study treatment, defined as the number of years from the date of the first administration of siltuximab treatment to the date of the last administration of siltuximab treatment, will be summarized by descriptive statistics. In addition, the number and percentage of subjects who were on siltuximab treatment for more than 1, 2, 3, 4, 5, 6, 7 and 8 years will be provided.

The total number of siltuximab administrations including cumulative dose (mg/kg) administered across both parent and extension studies will be summarized.

The number of subjects with siltuximab dose delays including reasons (AE or other) for dose delays in the long-term safety extension study of CNT0328MCD2002 will be reported.

4.4. Protocol Deviations

A listing of subjects with major protocol deviations during the long-term safety extension study will be provided. The listing will include subject ID, type of deviation, and reasons for deviation.

4.5. Prior Therapies for Castleman’s Disease

A summary of type of prior therapies (systemic therapy, ASCT, radiotherapy, or cancer-related surgery) for Castleman’s disease will be provided. Specifically, for subjects who received prior systemic therapy, the number of prior therapy regimen will be calculated

and summarized by the following categories: 1, 2, 3, 4 or >4 through frequency and descriptive statistics. In addition, the summary of prior systemic therapies will be presented by the following therapy: cyclophosphamide, rituxan, steroid and thalidomide.

Additionally, the best response to last prior systemic therapy based on investigator assessment will be summarized. Time in days from last prior systemic therapy to the first siltuximab administration will be calculated.

4.6. Concomitant Medications

Concomitant medications reported when subject received siltuximab treatment will be summarized by therapeutic class, pharmacologic class, and drug name. In addition, systemic steroids as concomitant medication use during the study will be summarized.

4.7. Subsequent MCD Therapy

The total number of subjects who received subsequent MCD therapy will be reported. A summary of subsequent anticancer therapy will be presented by therapeutic class, pharmacologic class and drug name.

5. EFFICACY

There is no formal statistical hypothesis testing. All efficacy analyses will be based on safety analysis population.

5.1. Analysis Specifications

5.1.1. Level of Significance

All 95% confidence intervals presented will be 2-sided.

5.1.2. Data Handling Rules

There is no imputation planned for missing efficacy endpoint values.

5.2. Efficacy Endpoints

The efficacy endpoints include proportion of previously responding subjects who maintain disease control, proportion of siltuximab-naive subjects who experience disease control, duration of disease control and overall survival.

5.2.1. Proportion of Subjects Maintaining Disease Control

5.2.1.1. Definition

Proportion of subjects maintaining disease control is defined as the proportion of previously responding subjects who have not progressed during the long-term safety extension based on investigator assessment.

5.2.1.2. Analysis Methods

The number and percentage of subjects who maintain disease control will be provided.

5.2.2. Proportion of Subjects Experiencing Disease Control

5.2.2.1. Definition

Proportion of subjects experiencing disease control is defined as the proportion of siltuximab-naïve subjects who have stable or better response during the long-term safety extension based on investigator's judgment.

5.2.2.2. Analysis Methods

The number and percentage of subjects who experience disease control will be provided.

5.2.3. Duration of Disease Control

5.2.3.1. Definition

For subjects who had/experienced disease control, duration of disease control (DODC) is defined as the time from the first siltuximab administration to disease progression as assessed by the investigator. Subjects with disease control are subjects who had stable or better response assessed by the investigators. Subjects without disease progression will be censored at the date of last disease assessment. Note that disease control was only collected in long-term safety extension study of CNT0328MCD2002.

5.2.3.2. Analysis Methods

Analysis of duration of disease control will be based on Kaplan-Meier method, median DODC with 95% CI will be estimated. The Kaplan-Meier duration of disease control curve will be plotted.

5.2.4. Overall Survival

5.2.4.1. Definition

Overall survival is measured from the date of first siltuximab/placebo (siltuximab-naïve subjects) treatment to the date of death due to any cause. Subjects who withdraw consent from the study or are lost to follow-up will be censored at the time of withdrawal or lost to follow-up. Subjects who are still alive at the cutoff date for the analysis will be censored at the last known alive. The date of last known alive will be determined by the maximum collection/assessment date from among selected data domains within the clinical database.

5.2.4.2. Analysis Methods

OS analysis will be based on safety population. The Kaplan-Meier method will be used to estimate the distribution of OS. Median OS with 95% CI will be provided. In addition, the number and percentage of subjects who died or were censored will be reported. Additionally, the survival rate with 95% CI at 3, 4, 5, 6-years will be estimated using Kaplan-Meier method. The Kaplan-Meier OS curve will also be plotted.

5.3. Efficacy-related Laboratory Assessments

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.

5.4. 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 extension study: at the start of the screening visit, and predose at Cycles 1 and 2.

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

6. SAFETY

Safety analyses will be based on safety population. Safety evaluation will focus on AEs, clinical hematology and chemistry laboratory tests. The overall safety of long-term treatment with siltuximab will be assessed via evaluation of AEs occurred from both parent study and extension study. In the long-term safety extension study, 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.

6.1. Adverse Events

All adverse events, regardless of seriousness, severity, or presumed relationship to study therapy, will be recorded in standard medical terminology. All toxicities will be graded according to graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.0. For AE reporting, the verbatim term used in the CRF by investigators to identify adverse events will be coded to a system organ class (SOC) and a preferred term (PT) using the latest version of Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary.

Unless otherwise specified, at each level (e.g., system organ class and/or preferred term) of subject summarization in reporting the incidence of the AE, a subject is counted once if one or more events were recorded.

All summaries of AEs will be based on treatment-emergent adverse events (TEAEs). TEAEs are defined as any AE that occurs after start of the first siltuximab through 30 days after the last study siltuximab treatment; or the day prior to start of subsequent anticancer therapy, whichever is earlier; or any AE that is considered drug-related (very likely, probably, or possibly related) regardless of the start date of the event; or any AE that is present at baseline but worsens in toxicity grade or is subsequently considered drug-related by the investigator.

The incidence of TEAEs will be summarized overall, by MedDRA system organ class (SOC) and preferred term, by toxicity grade, by relationship to siltuximab treatment, and by number of years of siltuximab exposure. Specifically, the following AE summaries will be presented:

6.1.1. Overview of TEAEs

An overview of TEAEs reported through the study will be provided. The overview will include summaries of subjects with TEAEs, with TEAEs related to siltuximab treatment, with TEAEs of maximum toxicity grade of 1 to 5, SAEs, TEAEs leading to discontinuation of siltuximab treatment.

To account for the different siltuximab exposure times, an exposure-adjusted incidence rates (EAIR) analysis will be performed in the overview of TEAEs summary and for selected TEAEs. More specifically, the incidence rates will be normalized by the exposure time, which is defined as month from first dose date of siltuximab treatment to first onset date of the corresponding TEAE for those who experienced the event and the entire treatment duration for those who never experienced such a TEAE. All reported EAIR is the incidence rate per 100 patient-months at risk.

6.1.2. All TEAEs

- Incidence of TEAEs by MedDRA SOC and preferred term
- Exposure-adjusted analysis of selected TEAEs;
- Incidence of TEAEs by number of years of treatment, MedDRA system-organ class and preferred term;

6.1.3. Toxicity Grade 3 or 4 TEAEs

- Incidence of toxicity Grade 3 or 4 TEAEs, by MedDRA SOC and preferred term
- Exposure-adjusted analysis of selected Grade 3 or higher TEAEs;
- List of subjects with any toxicity Grade 3 or 4 TEAEs

6.1.4. Siltuximab Treatment-Related TEAEs

- Incidence of TEAEs considered by the investigator to be related to siltuximab treatment, by MedDRA SOC, preferred term
- Incidence of TEAEs with toxicity Grade 3 or higher considered by the investigator to be related to siltuximab treatment, by MedDRA SOC and preferred term

6.1.5. Serious Adverse Events (SAEs)

- Incidence of treatment-emergent SAEs, by MedDRA SOC and preferred term
- Incidence of treatment-emergent SAEs considered by the investigator to be related to siltuximab treatment, by MedDRA SOC, preferred term
- List of subjects with any treatment-emergent SAEs

6.1.6. TEAEs Leading to Siltuximab Dose Delays

Siltuximab dose delays were not collected in parent study of C0328T03, therefore, the incidence of TEAEs leading to siltuximab dose delays during the long-term safety extension study will be summarized by MedDRA SOC and preferred term. The summaries will be presented by all grades and grade 3 or higher.

6.1.7. TEAEs Leading to Discontinuation of Siltuximab Treatment

A summary of number of subjects who discontinued siltuximab treatment because of 1 or more TEAEs by MedDRA system-organ class and preferred term will be provided. The summaries will be presented by all Grades and Grade 3 or higher. This table includes associated TEAEs for those subjects who discontinued siltuximab treatment due to an adverse event reported on the “End of Treatment” CRF page.

6.2. Deaths

6.2.1. All Deaths

A summary of all deaths and cause of death for the safety population will be tabulated. The primary cause of death collected on CRF page will be reported. The similar summaries will be presented for subjects who died within 30 days of last siltuximab treatment dose.

6.2.2. Death Due to TEAEs

The number of subjects who died due to TEAEs will be summarized by preferred term and relationship to study siltuximab treatment. The TEAEs included in this table are AEs with outcome death or toxicity Grade 5 recorded in the AE CRF page.

A listing of subjects who died due to treatment-emergent adverse events will be provided.

6.3. Adverse Events of Clinical Interest

6.3.1. Infusion-Related Reactions (IRR)

Number of subjects with any IRR associated with siltuximab administration during the long-term extension study will be summarized by MedDRA system-organ class and preferred term. Note that IRR was not collected in parent study C0328T03.

A listing of subjects with Grade 3 or higher treatment-emergent infusion-related reactions associate with siltuximab administration will be provided.

6.3.2. Infections and Infestations

A summary of number of subjects with 1 or more toxicity Grade 3 or 4 treatment-emergent infections and infestations by MedDRA preferred term and relationship to siltuximab treatment will be provided.

6.3.3. Secondary Malignancies

A listing of subjects who reported secondary malignancies during the study will be provided. The listing will include subject ID, diagnosis, study day of diagnosis, recurrence of a prior existing malignancy (yes, no) and stage of disease etc. information whenever a second primary malignancy is observed. In addition, treatment related to secondary malignancy, a total of siltuximab dose received, whether or not subject received subsequent MCD therapy information will also be presented in the listing.

6.4. Clinical Laboratory Tests

Safety evaluation of clinical laboratory tests will focus on the following selected laboratory analytes based on long-term safety extension study.

- Hematology panel: hemoglobin, platelet count, white blood cell (WBC) count with absolute neutrophils and lymphocytes
- Blood chemistry panel: sodium, potassium, creatinine, glucose, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, alkaline phosphatase, uric acid, creatinine, phosphate and albumin.
- Lipid panel: cholesterol, triglycerides, HDL and LDL

Blood samples for serum hematology and biochemistry were taken at the screening visit, every cycle in 1st year for siltuximab-naïve subjects, every 3 cycles for 3-week regimen and every other administration visit at a minimum for those on 6-week regimen.

Descriptive statistics (mean, standard deviation, median, range) will be used to summarize observed laboratory values and change from baseline in observed value at each scheduled visit. Line plot of mean with SE for each laboratory analyte over time up to 6 years will be displayed for hematological parameters: hemoglobin, neutrophils, platelets, WBC, and biochemistry parameters: AST, ALT, creatinine, albumin, bilirubin, HDL, LDL, cholesterol, and triglycerides.

The worst toxicity grade in hematology and chemistry during siltuximab treatment will be summarized by toxicity grade. Shift tables from baseline to worst toxicity grade during siltuximab treatment will be provided for each laboratory analyte listed above. These tables will summarize the number of subjects with each baseline CTC grade and changes to the maximum CTC grade.

6.5. Vital Signs and ECG Findings

In the long-term safety extension study, vital signs (temperature, blood pressure, and heart rate) will be measured predose and end of siltuximab infusion on Day 1 of Cycle 1. Thereafter, vital signs will be measured only before each siltuximab administration on Day 1 of each cycle, and as clinically indicated.

The observed values in vital signs and change from baseline in observed value at each scheduled visit will be descriptively summarized.

Similar summaries will be provided for weight at each assessment visit.

A listing of ECG findings will be provided for siltuximab-naïve subjects who enrolled into extension study.

6.6. Other Safety Assessment

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.

A listing of chest X-Ray or equivalent imaging results during long-term safety extension study will be provided.

7. IMMUNOGENICITY

7.1. Sampling Timepoints

Blood samples to determine antibodies to siltuximab will be collected from all subjects in the long-term safety extension 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.

7.2. Analysis Methods

Immunogenicity samples will be analyzed at the 6-year data cutoff. Immunogenicity analysis will be based on long-term safety extension study. The incidence of antibodies to siltuximab (immunogenicity) will be summarized for all subjects who receive a dose of siltuximab and have appropriate samples for detection of antibodies to siltuximab. In addition, subjects who are positive for antibodies to siltuximab will also be listed.