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RESEARCH**

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

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Supplement #: Original Biologics License Application
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1 EXECUTIVE SUMMARY

This is an initial Biologic Licensing Application (BLA) seeking the approval of intravenous Siltuximab for the treatment of patients with multicentric Castleman’s disease (MCD) who are human immunodeficiency virus negative and human herpesvirus-8 negative.

The main study MCD2001 supporting this application is a phase 2, randomized, double-blind, placebo-controlled study in 79 patients with MCD to assess the efficacy and safety of Siltuximab plus best supportive care (n=53) compared with placebo plus best supportive care (n=26). Patient randomization was stratified by concomitant corticosteroid use at study entry. The major efficacy outcome of the study was durable tumor and symptomatic response, defined as tumor response (complete or partial response based on modified Cheson criteria) assessed by independent review and complete resolution or stabilization of MCD symptoms, sustained for at least 18 weeks.

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

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

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

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

This reviewer recommends approving this application for the proposed indication.

2 INTRODUCTION

2.1 Overview

Product and Proposed Indication

Sylvant (Siltuximab) is an interleukin-6 (IL-6) antagonist indicated for the treatment of patients with multicentric Castleman's disease (MCD) who are human immunodeficiency virus (HIV)-negative and human herpesvirus-8 (HHV-8)-negative.

Disease Overview

MCD is a rare atypical lymphoproliferative disorder, characterized by lymph node swelling and high morbidity. Elevated IL-6 production is the major pathogenic mechanism in MCD. Currently there are no approved therapies for treatment of Castleman's disease in the United States. The Applicant studies siltuximab as a treatment for MCD because siltuximab is a monoclonal antibody that neutralizes human IL-6.

Clinical Studies

Table 1 summarizes the Applicant's MCD studies supporting this application. The main study is a randomized double-blind Phase 2 study having siltuximab plus best supported care (BSC) compared with placebo plus BSC in 79 patients with MCD. The supportive study is a Phase 1 open-label non-randomized dose-finding study in patients with B-cell non-Hodgkin's lymphoma, multiple myeloma, or Castleman's disease. The supporting Phase 1 study will not be discussed in this review, because it is different from the pivotal study in eligibility criteria, dosing regimen, duration of treatment and endpoint definitions.

Table 1: Overview of Clinical Studies

	Pivotal Study	Supportive Study
	MCD2001	C0328T03
No. of patients enrolled	79 (siltuximab 53, placebo 26)	72 (37 patients with Castleman's disease)
Study location	38 study centers in 19 countries, including US	9 study centers in US only
Phase of study	2	1
Study population	Patients with multicentric Castleman's disease	Patients with B-cell non-Hodgkin's lymphoma, multiple myeloma, or Castleman's disease
Study design	randomized, double-blind, placebo-controlled	non-randomized, open-label, dose-finding
Main eligibility criteria	<ul style="list-style-type: none">• Symptomatic with measurable disease confirmed by central pathology review• Age \geq 18 years• HIV negative and HHV-8 negative	<ul style="list-style-type: none">• The disease must be measurable and had either progressed on standard therapy or there was no effective standard therapy• Castleman's disease must be unresectable or multicentric
Siltuximab dosing regimen	11 mg/kg every 3 weeks	Cohort 1: 3 mg/kg q2w; Cohort 2: 6 mg/kg q2w; Cohort 3: 12 mg/kg q3w; Cohort 4: 6 mg/kg weekly; Cohort 5: 12 mg/kg q2w; Cohort 6: 12 mg/kg q3w; Cohort 7a: 9 mg/kg q3w; Cohort 7b: 12 mg/kg q3w
Duration of treatment	Up to 48 weeks after the last patient started treatment	42 days
Primary efficacy endpoint	Durable tumor and symptomatic response	Disease response

Regulatory Interactions

Important recommendations to the Applicant regarding registration are listed below:

- The clinical spectrum of Castleman’s disease is widely divergent. Pooling results across unicentric and multicentric patient populations would be neither appropriate nor representative of either specific population.
- A single-arm trial would not be acceptable for registration, because a single-arm trial is unlikely to provide meaningful data to assess clinical benefit to treatment for such a disease with several patterns of disease progression.
- All study patients should be required to be symptomatic and have measurable disease. Centralized pathology reviews should be used for eligibility.
- The definition for response as the primary study endpoint should also include stabilization or improvement in disease-related symptoms for a partial response and absence of symptoms for a complete response.

2.2 Data Sources

Material reviewed for this application: protocol, statistical analysis plan, study report, and submitted datasets for the pivotal study MCD2001.

Reviewed data were provided electronically with the standard analysis data formats. SAS programs used to create key efficacy and safety outputs for the pivotal study were submitted in this application. Study MCD2001 datasets for this application are located at:

\\cdsesub1\bla\CTD_Submissions\STN125496\0000\m5\datasets\cnto328mcd2001.

A 4-month safety update report and associated datasets were submitted to the Agency on December 18, 2013. The electronic path for this 4-month safety update is:

\\cdsesub1\bla\CTD_Submissions\STN125496\0018.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

Data from the pivotal study MCD2001 were provided electronically with standard formats. Documentations on datasets and programming for the derivation of key study endpoints and results were included with sufficient details for verification.

3.2 Evaluation of Efficacy

This section shows Study MCD2001 key efficacy results with Reviewer’s comments and evaluations. All the tables shown in this section are based on MCD2001 study report, which has verified by the Reviewer.

3.2.1 Study Design and Endpoints

The pivotal study supporting this application is Study MCD2001. Study MCD2001 was a randomized, double-blind, placebo-controlled, multicenter, Phase 2 study to assess the efficacy and safety of siltuximab + BSC compared with placebo + BSC in patients with symptomatic MCD. The study enrolled a total of 79 patients, randomized in a 2:1 ratio to receive siltuximab at 11 mg/kg (n=53) or placebo (n=26) by a 1-hour intravenous infusion every 3 weeks plus BSC. The randomization was stratified by concomitant corticosteroid use (yes versus no) at study entry. The study consisted of a Screening Period from initial screening visit until randomization, a Blinded Treatment Period starting from the first dose of study agent, an Un-blinded Treatment Period for placebo patients who did not respond and received siltuximab after the Blinded Treatment Period, an End-of-Treatment Visit, and a Follow-up Period.

Symptomatic MCD in Study MCD2001 was defined clinically by the presence of MCD-related symptoms with National Cancer Institute Common Terminology for Adverse Events (NCI-CTCAE) grading ≥ 1 . There were 34 MCD-related signs and symptoms per NCI-CTCAE. The MCD-related overall symptom score was calculated for each patient at baseline and at each cycle as the sum of the severity grades of the MCD-related signs and symptoms.

The primary efficacy endpoint for Study MCD2001 was the durable tumor and symptomatic response. This was a composite endpoint, defined as complete response (CR): complete disappearance of all measurable and evaluable disease and resolution of baseline MCD-related symptoms, sustained for at least 18 weeks + partial response (PR): a $\geq 50\%$ decrease in sum of the product of the diameters of index lesion(s), with at least stable disease in all other evaluable disease in the absence of treatment failure as indicated by no deterioration in disease related symptoms, sustained for at least 18 weeks.

Study MCD2001 had 6 protocol-specified major secondary endpoints, to be tested after the primary endpoint, at a 2-sided 5% level of significance in the following order:

1. Tumor response, defined as a CR or PR according to the modified Cheson criteria
2. Time to treatment failure, defined as the time from randomization to treatment failure
3. Hemoglobin response, assessed by an increase in hemoglobin at Week 13 of 15 g/L or more over baseline
4. Time-to-improvement in the Multicentric Castleman's Disease Symptom Scale (MCD-SS) total score, defined as the time from randomization to the time at which the MCD-SS total score decreases by ≥ 1 point compared with the baseline score
5. Time-to-improvement in the Functional Assessment of Chronic Illness Therapy (FACIT-F) fatigue score, defined as the time from randomization to the time at which the FACIT-F fatigue score decreases by ≥ 3 points compared with the baseline score
6. Discontinuation of corticosteroids, defined as those patients who were on corticosteroids at baseline that were corticosteroid free for at least 9 consecutive weeks during the blinded treatment period

In addition, duration of response was calculated for each of the response endpoints.

Reviewer Comment: *MCD-SS is a 15-item patient-reported outcome instrument developed by the Applicant. An instrument validation report, including justification for the 1 point decrease in total score for symptom improvement, is included in this application.*

3.2.2 Statistical Methodologies

The primary efficacy analysis population for Study MCD2001 was the intent-to-treat (ITT) population of all randomized patients. However, the analysis of hemoglobin response was performed only in patients who had a hemoglobin value that was below the lower limit of normal within 2 weeks prior to study treatment (baseline anemia) and had at least one post-baseline hemoglobin evaluation.

The primary efficacy endpoint was durable tumor and symptomatic response during the blinded Treatment Period, based on independently reviewed tumor assessments and investigator determined severity grades for disease related signs and symptoms. The primary analysis of the primary endpoint occurred after all study patients had completed the Week 48 assessment. The durable tumor and symptomatic response rates for the 2 treatment groups were compared using an exact Cochran-Mantel-Haenszel test, adjusted for the stratification factor, baseline corticosteroid use.

The study was sized, with a 2:1 randomization, to detect a 30% response rate in the siltuximab group versus 5% response rate in the placebo group with a 2-sided 5% significance level and 80% power.

Secondary response endpoints were also compared between the treatment groups based on an exact Cochran-Mantel-Haenszel test with adjustment for baseline corticosteroid use. Time-to-event endpoints were compared between the treatment groups using the log-rank test stratified by baseline corticosteroid use. Median time to an event was calculated using the Kaplan-Meier method, except for the duration of response endpoints, whose median was calculated only in responders who had lost their response because the Kaplan-Meier estimate was not reliable due to the heavy censoring at the time of data cut-off for this application.

Reviewer Comment: *Corticosteroids use is known to have an impact on the disease, therefore baseline corticosteroid use was used as a stratification factor at randomization and adjusted for in the efficacy analyses.*

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Table 2 shows patient disposition for Study MCD2001 as of the data cutoff date January 31, 2013. A total of 79 patients enrolled in Study MCD2001, 53 patients were randomized to receive siltuximab + BSC and 26 patients were randomized to receive placebo + BSC. A much higher percentage of patients in the siltuximab group compared to patients in the placebo group had completed their planned treatment. The most common reason for treatment discontinuation

was disease progression, which was reported in 14 of the 26 patients (54%) in the placebo group and in 16 of the 53 patients (30%) in the siltuximab group. At the time of data cutoff, 13 out of the 14 placebo patients who had a treatment failure had cross-over to receive siltuximab.

As required to enter the study, all randomized patients in Study MCD2001 had presented with at least one disease related symptom. The 6 most common symptoms at baseline were fatigue (68 patients; 86%), malaise (48 patients; 61%), night sweats (41 patients; 52%), peripheral sensory neuropathy (30 patients; 38%), and anorexia and pruritus (29 patients; 37%). The proportion of patients with at least one Grade 3 or higher MCD-related symptoms graded according to NCI-CTCAE by investigator was the same in both groups: 10 patients (19%) in the siltuximab group and 5 patients (19%) in the placebo group.

Table 2: Disposition of Patients Enrolled in Study MCD2001 as of January 31, 2013

Study Subjects	Placebo + BSC n (%)	Siltuximab + BSC n (%)
Randomized	26 (100%)	53 (100%)
Received study drug	26 (100%)	53 (100%)
Completed planned treatment	7 (27%)	34 (64%)
Discontinued from trial treatment	20 (77%)	22 (42%)
Primary reason for discontinuation:		
Disease progression (treatment failure)	14 (54%)	16 (30%)
Death	2 (8%)	0
Adverse event	1 (4%)	1 (2%)
Physician decision	0	1 (2%)
Withdrawal consent	3 (12%)	4 (8%)
Crossed-over ¹	13 (50%)	Not applicable

BSC = best supportive care

¹ Placebo patients may crossover to receive siltuximab upon treatment failure

Table 3 gives a summary on demographics and other protocol-specified subgroup analysis factors at baseline. The median age across treatment groups was 48 years. The majority of study patients were men, but the percentage of men was higher in the placebo group compared to the siltuximab group. The randomization factor use of corticosteroid was balanced at baseline between treatment groups. For both treatment groups, the most common disease histology was mixed, followed by hyaline vascular, and plasmacytic. A higher percentage of patients in the placebo group had received a prior therapy in comparison with patients in the siltuximab group.

Table 3: Demographics and Other Baseline Factors (MCD2001, ITT Population)

Factor	Placebo + BSC (N = 26)	Siltuximab + BSC (N = 53)	Total (N = 79)
Demographics			
<i>Age (years)</i>			
<65 / >=65	24 / 2 (92 / 8 %)	51 / 2 (96 / 4 %)	75 / 4 (95 / 5 %)
mean (SD), median, min-max	47.7 (13.4), 48, 27-78	44.4 (13.3), 47, 20-74	45.5 (13.4), 48, 20-78
<i>Sex</i>			
Female / Male	4 / 22 (15 / 85 %)	23 / 30 (43 / 57 %)	27 / 52 (34 / 66 %)

Factor	Placebo + BSC (N = 26)	Siltuximab + BSC (N = 53)	Total (N = 79)
<i>Race</i>			
White / Other	12 / 14 (46 / 54 %)	19 / 34 (36 / 64 %)	31 / 48 (39 / 61 %)
<i>Region</i>			
North America / Europe / Asia Pacific / Latin America	5 / 8 / 11 / 2 (19 / 31 / 42 / 8 %)	10 / 13 / 26 / 4 (19 / 25 / 49 / 8 %)	15 [#] / 21 / 37 / 6 (19 / 27 / 47 / 8 %)
Other Subgroup Analysis Factors at Baseline			
<i>Corticosteroid use</i>			
Yes / No	8 / 18 (31 / 69 %)	16 / 37 (30 / 70 %)	24 / 55 (30 / 70 %)
<i>MCD histology</i>			
Hyaline vascular / Plasmacytic / Mixed	8 / 5 / 13 (31 / 19 / 50 %)	18 / 13 / 22 (34 / 25 / 42 %)	26 / 18 / 35 (33 / 23 / 44 %)
<i>Received prior therapy</i>			
Yes / No	17 / 9 (65 / 35 %)	29 / 24 (55 / 45 %)	46 / 33 (58 / 42 %)

BSC = Best Supportive Care; ITT = intent-to-treat

[#] including 14 patients enrolled in the US (4 patients in the placebo group + 10 patients in the siltuximab group)

3.2.4 Efficacy Results

3.2.4.1 The Primary Efficacy Endpoint

The primary efficacy endpoint of Study MCD2001 was durable tumor and symptomatic response, defined as tumor response and complete resolution or stabilization of disease related signs and symptoms, for at least 18 weeks without treatment failure. Tumor response was evaluated based on modified Cheson criteria by central independent review for the primary endpoint. MCD-related signs and symptoms for the determination of primary endpoint were assessed by investigators at each visit using the NCI-CTCAE severity grades, and included: fatigue, malaise, hyperhidrosis, night sweats, fever, weight loss, anorexia, tumor pain, dyspnea, pruritus, autoimmune phenomena, fluid retention, neuropathy, and skin disorders.

Table 4 shows the results of the primary endpoint. Eighteen patients in the siltuximab group and no patient in the placebo group had a durable tumor and symptomatic response. The improvement by siltuximab over placebo in the durable tumor and symptomatic response rate was statistically significant at 34% (95% confidence interval [CI]: 11.1%–54.8%; p-value = 0.0012).

Table 4: Durable Tumor and Symptomatic Response during the Blinded Treatment Period by Independent Review (Study MCD2001, ITT Population)

	Placebo + BSC	Siltuximab + BSC
Randomized patients	26	53
Patients who had a durable tumor and symptomatic response (CR ^a + PR ^b)	0	18 (34.0%)
CR	0	1 (1.9%)
PR	0	17 (32.1%)
Difference in response rates		34.0%
Exact 95% CI for the difference		(11.1% – 54.8%)
p-value ^c for the significance of difference		0.0012

BSC = Best Supportive Care; CI = confidence interval; CR = complete response; PR = partial response

^a CR is defined as complete disappearance of all measurable and evaluable disease and resolution of baseline symptoms attributable to MCD, sustained for at least 18 weeks.

^b PR is defined as a $\geq 50\%$ decrease in sum of the product of the diameters of indicator lesions(s), with at least a stable disease in all evaluable disease in the absence of treatment failure, sustained for at least 18 weeks.

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

Reviewer comments:

- *The study has demonstrated superiority of siltuximab over placebo in the primary efficacy endpoint.*
- *Investigator assessed durable tumor and symptom response rate was 45% in siltuximab treated patients compared to 0% in placebo treated patients*
- *Duration of response could not be reliably estimated, because only one of the 18 responders had lost the response at the time of data cutoff for this application. However, duration of response estimates are not important for approval decision, because: (1) durability of response was incorporated into the primary endpoint (the minimal duration was 18 weeks for all responders by definition); (2) the fact that the majority of responders had not lost their response after a long treatment period is meaningful itself.*
- *The impact of missing data on the determination of the primary endpoint was evaluated. Tumor response assessments by central review were complete in all study patients. Of the 18 responders, all had radiologic imaging performed in the 18-week confirmation period as specified in the protocol. The symptom severity assessments had partial missing data in 4 responders. The Applicant provided justification to absence of treatment failure in those 4 responders based on reviews of adverse events log. Per Dr. Patricia Dinndorf, the medical reviewer, the Applicant's justification is acceptable.*

3.2.4.2 The Secondary Endpoints

Study MCD2001 has 6 protocol-specified major secondary endpoints for sequential testing after the primary endpoint. Table 5 shows the results for the 6 multiplicity-controlled secondary

endpoints in the pre-specified testing sequence. Statistical significance was found for the difference between siltuximab and placebo in tumor response and median time to treatment failure in the ITT population. Statistical significance was also reported for the endpoint of hemoglobin response in the subgroup of anemic patients.

Table 5: Results of the Multiplicity-Adjusted Secondary Endpoints (MCD2001, ITT Population)

Endpoint	Placebo + BSC (n = 26)	Siltuximab + BSC (n = 53)	P-value ¹ < 0.05?
Tumor response by central review	3.8%	37.7%	Yes
Median time to treatment failure ²	134 days	NR	Yes
≥15 g/L increase over baseline in hemoglobin at Week 13	0% (0/11)	61% (19/31)	Yes
Median time to improvement in MCD-SS total score ³	262 days	85 days	No
Median time to improvement in FACIT-F fatigue score ⁴	15 days	22 days	No
Discontinued corticosteroids	11% (1/9)	31% (4/13)	No

BSC = best supportive care; MCD-SS = Multicentric Castleman's Disease Symptom Scale; FACIT-F = Functional Assessment of Chronic Illness Therapy-Fatigue

¹ p-value is calculated based on the exact Cochran-Mantel-Haenszel test for testing the difference in percentages between the placebo and siltuximab groups, and is based on the log-rank test for comparing median times to an event. P-value calculations adjusted for the stratification factor, baseline corticosteroid use.

² Number of time to treatment failure observed: placebo group 16 (61.5%), siltuximab group 20 (37.7%)

³ Number of time to improvement in MCD-SS observed: placebo group 13 (50.0%), siltuximab group 32 (62.4 %)

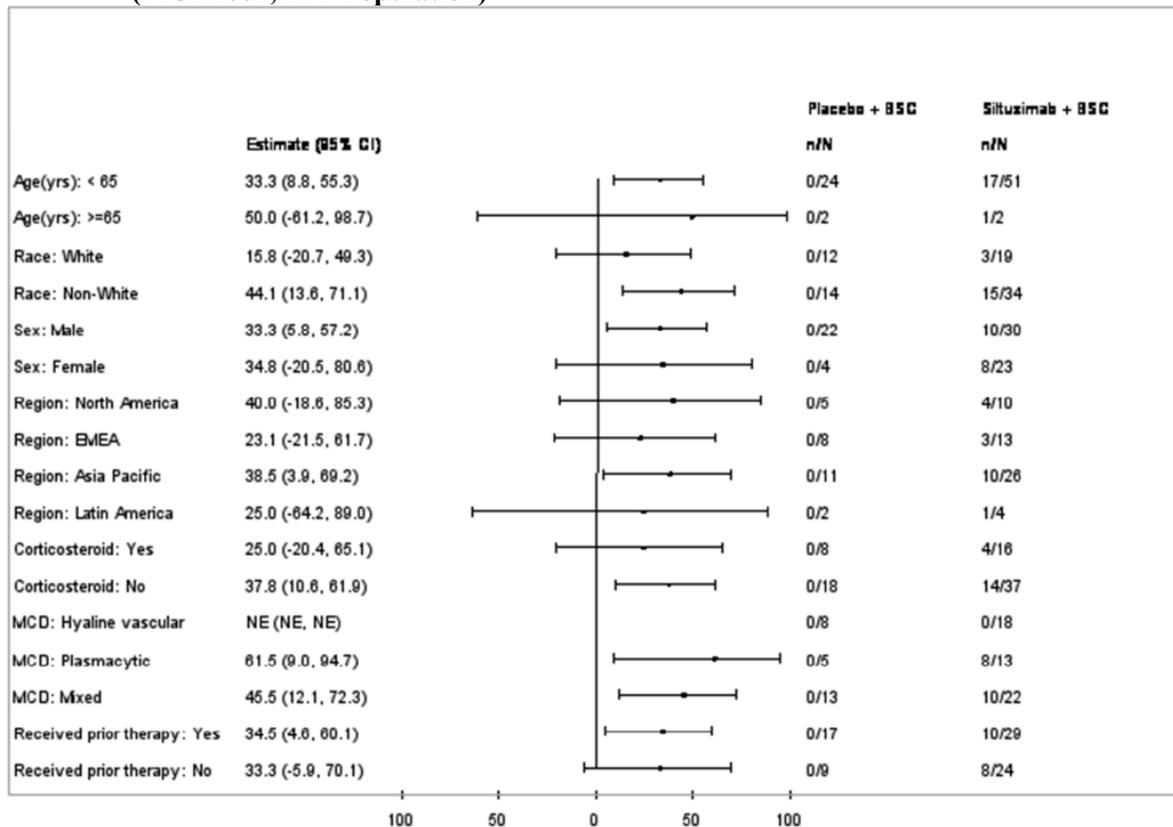
⁴ Number of time to improvement in FACIT-F observed: placebo group 21 (80.8%), siltuximab group 41 (77.4%)

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

3.2.4.3 Primary Efficacy Endpoint by Subgroups

A consistent treatment effect was found on subgroup analysis for all the protocol-specified subgroups with the exception of the hyaline vascular histological subtype (Figure 1). There were no patients with hyaline vascular histology who demonstrated a durable tumor and symptomatic response. However, activity was suggested in this subtype based on change in hemoglobin (siltuximab versus placebo for proportion of anemic patients achieved a ≥15 g/L increase in hemoglobin: 43% versus 0%) and median time to treatment failure (siltuximab versus placebo for median to treatment failure: 206 days versus 70 days).

Figure 1: Durable Tumor and Symptomatic Response during the Blinded Treatment Period (MCD2001, ITT Population)



Source: MCD2001 study report, Figure 13

Note: Estimate = estimated difference, MCD = MCD histology by central pathology, Corticosteroid = corticosteroid use at randomization

3.3 Evaluation of Safety

All the 79 patients randomized in Study MCD2001 received at least 1 dose of study agent. Twenty-five (25) out of the 26 patients in the placebo group and all the patients in the siltuximab group experienced at least one treatment-emergent adverse event during the Treatment Period; but the percentage of patients experienced at least one grade 3 or higher treatment-emergent adverse event was higher in the placebo group (53.8% versus 47.2% in the siltuximab group). Among the siltuximab-treated patients, 21% had at least one adverse event that led to discontinuation of siltuximab.

A 4-month safety update was submitted on December 18, 2013. The overall safety profile did not appear to change from the original submission. Only one additional serious adverse event was reported in patients with ongoing siltuximab treatment in Study MCD2001.

Please refer to the clinical review for more detailed safety results and clinical interpretation.

3.4 Benefit-Risk Assessment

Based on the efficacy and safety evaluations from the main study MCD2001, the benefit-risk appears to be positive for siltuximab as a treatment of patients with multicentric Castleman's disease who are human immunodeficiency virus negative and human herpesvirus-8 negative.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

Please refer to Figure 1 for Study MCD2001 primary endpoint results by gender, race, age, and geographic region.

4.2 Other Special/Subgroup Populations

Please refer to Figure 1 for Study MCD2001 primary endpoint results by other protocol-specified subgroup analysis factors.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The clinical efficacy and safety of siltuximab for the treatment of patients with MCD was established in Study MCD2001, a phase 2, multinational, randomized (2:1) double-blind, placebo-controlled study. In this study, 53 patients were randomized to BSC and siltuximab at a dose of 11 mg/kg every 3 weeks and 26 patients were randomized to BSC and placebo. The median age was 48 years (range 20 - 78), and 66% were male. The histological subtype of MCD was similar in both treatment arms, with 33% hyaline vascular subtype, 23% plasmacytic subtype and 44% mixed subtype. Treatment was continued until treatment failure (defined as disease progression based on increase in symptoms, radiologic progression or deterioration in performance status) or unacceptable toxicity.

The major efficacy outcome of Study MCD2001 was durable tumor and symptomatic response, defined as tumor response assessed by central review and complete resolution or stabilization of MCD symptoms graded by investigator, sustained for at least 18 weeks. The primary efficacy result was highly significant, with 34% durable tumor and symptomatic response rate observed in the siltuximab group compared to 0% in the placebo group (95% CI: 11.1, 54.8; p=0.0012). In addition, treatment benefit was supported by significant improvement by siltuximab in tumor response, time to treatment failure, and hemoglobin response.

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

5.2 Conclusions and Recommendations

The pivotal study has demonstrated benefit of siltuximab over placebo in addition to best supportive care for the treatment of patients with MCD. This reviewer recommends approving this application for the proposed indication.

5.3 Labeling Recommendations



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

/s/

CHIA-WEN KO
01/22/2014

LEI NIE
01/22/2014

THOMAS E GWISE
01/22/2014

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

BLA Number: 125496 **Applicant:** Janssen Research & Development **Stamp Date:** 08/30/2013

Drug Name: Siltuximab **NDA/BLA Type:** Original BLA Application

Indication: Treatment of Multicentric Castleman's Disease

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	X			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? ___yes___

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

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X			The treatment efficacy is to be reviewed based on the Phase 2 randomized trial MCD2001. Protocol MCD2001 had a special protocol (SPA) review. The protocol did not receive a SPA agreement, but the Applicant was told they may submit the study results for regulatory consideration.
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X	X		Endpoints and analysis methods are specified, but incomplete. Neither the protocol nor the statistical analysis plan specifies how to determine the efficacy endpoints in presence of missing data. An information request was sent to the sponsor on 09 Oct of 2013. Sponsor's response received on 16 Oct 2013: "The sponsor did not impute any values for missing or incomplete data for the primary and major secondary endpoints." Because the pivotal study does have missing data for symptom assessments, it is not clear, with the sponsor's response, how the primary endpoint of durable tumor and symptom response was determined in presence of missing data. A request for data listings is to be sent.
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			X	The pivotal study does not have any interim analysis for efficacy. An external DSMB met periodically to review unblended safety data.
Appropriate references for novel statistical methodology (if present) are included.			X	Analyses did not involve novel statistical methodology
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	X			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			For the pivotal study, subjects who discontinued from the blinded treatment period are compared between study arms by the frequency and reason of discontinuation.

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Review Issues/Comments to be conveyed:

- For Study MCD2001, neither the protocol nor the statistical analysis plan specified how to determine the primary endpoint in presence of missing data. You indicated in your 16 Oct 2013 response to information request that you did not impute any values for missing data, implying that the primary endpoint was determined based on available individual data. Please provide an individual data listing supporting the determination of the primary endpoint in all study subjects.
- For Study MCD2001, please also provide data listings for secondary endpoints included in your proposed product label.

Chia-Wen Ko	10/22/2013
Reviewing Statistician	Date
Lei Nie	10/22/2013
Team Leader	Date

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

/s/

CHIA-WEN KO
10/22/2013

LEI NIE
10/22/2013