

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**125496Orig1s000**

**OFFICE DIRECTOR MEMO**

**Office of Hematology and Oncology Drug Products:  
Office Director Decisional Memo**

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| <b>Date</b>   | Electronic stamp date                        |
| <b>From</b>   | Jonathan P. Jarow, MD Acting Deputy Director |
| <b>Subject</b>  | Office Director Decisional Memo              |
| <b>BLA #</b>  | 125496                                       |
| <b>Applicant Name</b>   | Janssen Biotech, Inc.                        |
| <b>Date of Submission</b>   | August 30, 2013                              |
| <b>PDUFA Goal Date</b>  | April 29, 2014                               |
| <b>Proprietary Name /<br/>Established (USAN) Name</b>                                   | Sylvant<br>Siltuximab                        |
| <b>Dosage Forms / Strength</b>  | Lyophilized product for IV infusion          |
| <b>Proposed Indication(s). See approved<br/>labeling for final approved indication.</b> | Castleman's disease                          |
| <b>Action:</b>  | Approval                                     |

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| <b>Material Reviewed/Consulted: OND Action Package, including:</b> |  |
|  | <b>Names of discipline reviewers</b>                                 |
| Division Director Review   | Ann T Farrell  |
| Regulatory Project Manager Review                                  | Patricia Garvey  |
| Medical Officer Review   | Patricia Dinndorf  |
| Statistical Review   | Chia-Wen Ko and Lei Nie  |
| Pharmacology Toxicology Review                                     | Pedro L Del Valle, Christopher Sheth, Brenda Gehrke, and Haleh Saber |
| DMA  | Audrey Jia, Bazarragchaa Damdinsuren, and Chana Fuchs                |
| BMAB   | Maria Candau-Chacon, Candace Gomez-Broughton, and Patricia Hughes    |
| CMC ONDQA Reviews  | N/A  |
| Biopharmaceutics Review  | N/A  |
| Clinical Pharmacology Review                                       | Jeanne Fourie Zirkelbach and Julie Bullock                           |
| DMPP Consult   | Karen Dowdy and Barbara Fuller                                       |
| IRT/QT Consult   | Moh Jee Ng   |
| SEALD Consult  | Ashley Slagle and Elektra Papadopoulos                               |
| OPDP Reviews   | Nisha Patel and Karen Rulli  |
| OSI Review   | Anthony Orenca   |
| CDTL Review  | Albert Deisseroth  |
| OSE/DMEPA Consult  | Tingting Gao, Yelena Maslov  |
| OSE/DRISK Consult  | Robert Pratt and Cynthia LaCivita                                    |
| Maternal Health Consult  | NA   |

OND=Office of New Drugs

CMC= Chemistry, Manufacturing and Controls OSE= Office of Surveillance and Epidemiology

OPDP= Office of Prescription Drug Promotion DMA = Division of monoclonal antibodies

DMPP=Division of Medical Policy Programs BMAB = Biotechnology Manufacturing Assessment Branch

OSI= Office of Scientific Investigations

CDTL=Cross-Discipline Team Leader

OSE=Office of Surveillance and Epidemiology

DRISK=Division of Risk Management

DMEPA= Division of Medication Error Prevention and Analysis

## 1 Regulatory Action

The Division of Hematology Products is recommending approval of siltuximab, lyophilized powder for intravenous infusion, 11 mg/kg every three weeks, for the treatment of multicentric Castleman's disease in patients who are immunodeficiency virus negative (HIV) and human herpes virus-8 (HHV-8) negative. I concur with their recommendation for approval.

## 2 Introduction

Janssen submitted Biological License Application (BLA) 125496 under section 351(a) of the Public Health Service Act for their anti-interleukin-6 (IL-6) chimeric (human-murine) monoclonal antibody, siltuximab (previously known as CNTO 328), to the Division of Hematology Products on August 30, 2013. The application was complete upon submission.

Siltuximab is an anti-IL-6 antibody. Janssen proposed the indication of "the treatment of patients with multicentric Castleman's disease (MCD) who are human immunodeficiency virus (HIV)-negative and human herpesvirus-8 (HHV-8)-negative". The application is supported by a single randomized, multi-center, double-blind, placebo-controlled trial to assess the efficacy and safety of siltuximab plus best supportive care compared with best supportive care in subjects with multicentric Castleman's disease.

## 3 Background

Castleman's disease (angiofollicular lymph node hyperplasia) is a lymphoproliferative disorder associated in a subset of cases with the HIV and HHV-8 viruses. Overproduction of IL-6 has been linked to systemic manifestation of Castleman's disease (CD). Castleman's disease is a lymphoproliferative disorder that may be localized to a single group of lymph nodes (unicentric) or may occur systemically by affecting multiple groups of lymph nodes and also organs containing lymphoid tissues (multicentric). Multicentric Castleman's disease (MCD) is a rare disease; currently, there are no approved therapies for this disease. Castleman's disease is also associated with a number of malignancies, including Kaposi sarcoma, non-Hodgkin lymphoma, Hodgkin disease, and POEMS syndrome [Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal protein, Skin changes]. This application evaluates siltuximab for the treatment of patients with MCD without HIV or HHV-8.

Castleman's disease has been linked to excessive release of IL-6 or similar polypeptides. Early studies linked local production of IL-6 to the systemic manifestations of unicentric Castleman's disease, since lymph node excision resulted in relief of symptoms along with a decrease in IL-6 levels. IL-6 is a potent growth factor for B lymphocytes and plasma cells. Excess IL-6 induces a proinflammatory syndrome that leads to constitutional symptoms, induction of vascular endothelial growth factor (VEGF) secretion, and induction of immune dysregulation leading to autoimmune phenomena including cytopenias.

The prognosis of untreated MCD is poor. Median survival is reported to be 26 to 30 months. Almost all treatments using single agents (examples, anti-viral, anti-cytokine, chemotherapy, corticosteroids) are palliative, with disease recurrence once they are stopped.

There is no approved therapy for Castleman's disease in the United States, however, tocilizumab, a monoclonal antibody against the IL-6 receptor, has been approved in the US for

treatment of rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, and systemic juvenile idiopathic arthritis. Tocilizumab has been approved in Japan for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, and Castleman's disease.

#### **4 CMC**

The Division of Monoclonal Antibodies (DMA) review concluded that the data submitted in the application are adequate to support their conclusion that the "manufacture of siltuximab is well controlled and leads to a product that is pure and potent." I concur with their conclusion. Multiple postmarketing commitments were requested and these are described in detail in the action letter.

#### **5 Nonclinical Pharmacology/Toxicology**

There are no issues that preclude approval for nonclinical pharmacology/toxicology. Based on the pharmacology of the product and the findings in animals, infants born to pregnant women treated with siltuximab may be at an increased risk of infection. Therefore, pregnancy category C is recommended for siltuximab.

Siltuximab does not bind to IL-6 in rodents. General toxicology studies, the embryo-fetal developmental study, and the enhanced pre- and post-natal developmental study (ePPND) were conducted in the cynomolgus monkey, a pharmacologically relevant species. Fertility studies were conducted in mice with an anti-mouse IL6 monoclonal antibody.

Siltuximab-related adverse findings in general toxicity studies were minimal and mainly related to the pharmacology of the antibody; e.g. reduction in the globulin levels (likely due to decreased production of immunoglobulin), lower anti-KLH IgM and IgG levels in the TDAR assay, and reduction in the size of the splenic germinal centers following KLH immunization. These effects suggest the potential for infection secondary to immune modulation. Although not common, first-dose infusion reaction occurred in a monkey (in 1 out of 52) and included moderate facial swelling. The swelling resolved after the infusion ended and no other instances occurred.

There were no drug-related effects in male or female reproductive organs in general toxicology studies. In addition, the fertility studies conducted in mice with a mouse analog of siltuximab did not reveal any potential for impairment of fertility.

#### **6 Site Inspections**

Janssen maintained adequate oversight of the clinical trial. Monitoring of clinical investigator sites appeared to be adequate. Inspection of the clinical sites revealed several occasions where laboratory testing may have unblinded subject's treatment. These were not felt to affect the reliability of the study results according to the medical officer and the final conclusion of the inspection report was that the results of the clinical study are deemed reliable.

#### **7 Clinical Pharmacology**

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

The applicant's proposed dosing regimen is 11 mg/kg q3 weeks. The population PK analysis showed the proposed body weight based dosing is acceptable. The recommended dosing regimen is justified based on the evidence of clinical efficacy in trial CNTO328MCD2001 in MCD. The exposure-response analysis showed a lack of relationship between exposure or serum C-reactive protein (CRP) and durable tumor and symptomatic response rate at the proposed dosing regimen of 11 mg/kg q3 weeks.

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

## 8 Clinical Microbiology

There were no microbiology issues to preclude approval of siltuximab.

## 9 Clinical/Statistical-Efficacy

The indication was evaluated in an international, multicenter, randomized (2:1), phase 2 study comparing every 3 week infusions of Sylvant (siltuximab) and best supportive care (BSC) to placebo and BSC. The trial met its primary endpoint of a statistically significant difference of the proportion of patients showing durable tumor and symptomatic response based on independent review in the siltuximab as compared to the placebo arm. The response rate in the siltuximab group compared with the placebo group was 34% (18/53) versus 0% (0/26), (95% CI of the difference: 11.1, 54.8;  $p=0.0012$ ). This response was supported by the following additional hierarchically pre-specified endpoints:

- The best tumor response in the siltuximab group compared with the placebo group was 38% (20/53) versus 4% (1/26), (95% CI of the difference: 11.1, 54.8;  $p < 0.05$ ).
- The median time to treatment failure was not reached in the siltuximab arm and was 134 days in the placebo arm. (HR 0.418, (95% CI of HR: 0.21 to 0.82;  $p < 0.05$ ).
- Increase in hemoglobin at Week 13 to 15 of 1.5 g/dL in patients who were anemic at study entry: in terms of the response criterion of an increase in the hemoglobin of 1.5 g/dL, there were no responders in the placebo arm and 19 responders in the siltuximab arm. The difference of hemoglobin response rate was 61% (19/31) in the siltuximab arm compared to 0% (0/11) in the placebo arm; 95% CI of the difference: 28.3, 85.1 ( $p < 0.05$ ).

## 10 Safety

The safety evaluation of siltuximab is based on 753 patients siltuximab-treated in eleven company-sponsored studies; seven monotherapy and four combination therapy studies and is adequate to characterize the safety profile for the purpose of informing risk-benefit.

The randomized trial in patients with Castleman's disease was the primary source for safety labeling. There were no deaths within 30 days of exposure to siltuximab. The incidence of non-fatal serious adverse events was higher in siltuximab-treated patients (23% versus 12%) even after adjusting for duration of exposure which was more than double for the siltuximab arm (15% versus 8%). Infections were the most frequent nonfatal serious adverse events reported in siltuximab-treated patients in this study at an incidence of 9%. The most common adverse reactions occurring greater than placebo were pruritus, increased weight, rash, hyperuricemia, and upper respiratory infection.

Siltuximab was well tolerated and rarely discontinued due to a drug related adverse event. A single anaphylactic reaction and possibly an infusion reaction in a second subject were probably the only drug related events that led to discontinuation. There does not appear to be signals for significant adverse events associated with siltuximab therapy in this population. Mortality was lower in the siltuximab treated arm, no specific serious adverse event was identified in the siltuximab arm and discontinuation of siltuximab therapy due to adverse events was similar in the siltuximab and placebo arms.

## 11 Advisory Committee Meeting

This application was not referred to ODAC because outside expertise was not necessary as there were no controversial issues that would benefit from advisory committee discussion. The clinical study design was acceptable and the application did not raise significant safety or efficacy issues in the intended population.

## 12 Pediatrics

Orphan designation was granted for siltuximab on May 26, 2006 for treatment of Castleman's disease, therefore siltuximab is exempt from the requirements of PREA for this indication.

## 13 Labeling

Proprietary name: The proprietary name, Sylvant, was determined to be acceptable.

Limitation of Use: "SYLVANT was not studied in patients with MCD who are HIV-positive or HHV-8-positive because SYLVANT did not bind to virally produced IL-6 in a nonclinical study."

- Boxed Warnings: None
- Warnings and Precautions:
  - “Concurrent Active Severe Infections
    - Do not administer SYLVANT to patients with severe infections until the infection resolves.
    - Monitor patients receiving SYLVANT closely for infections. Institute prompt anti-infective therapy and do not administer SYLVANT until the infection resolves.

Vaccinations: Do not administer live vaccines because IL-6 inhibition may interfere with the normal immune response to new antigens.

Infusion Related Reactions: Administer SYLVANT in a setting that provides resuscitation equipment, medication, and personnel trained to provide resuscitation.

Gastrointestinal (GI) perforation: Use with caution in patients who may be at increased risk. Promptly evaluate patients presenting with symptoms that may be associated or suggestive of GI perforation.”

## 14 Decision/Action/Risk Benefit Assessment

### 14.1 Recommended Regulatory Action:

Regular Approval “for the treatment of patients with multicentric Castleman's disease (MCD) who are human immunodeficiency virus (HIV-)-negative and human herpes virus -8 (HHV-8) -negative.”

#### 14.2 Risk Benefit Assessment

The benefit to risk assessment of Sylvant for patients with multicentric Castleman's disease who are human immunodeficiency virus (HIV)-negative and human herpes virus-8 (HHV-8 - )-negative is positive with a substantial improvement in response rate and time to treatment failure as compared to placebo. Patients receiving Sylvant plus best supportive care had a 34% response rate as compared to 0% for best supportive care alone (p=0.0012).

Multicentric Castleman's disease is a serious and life-threatening disease and there are currently no approved therapies in the US. Treatment with Sylvant was well-tolerated in clinical trials with minimal discontinuations due to adverse events, no deaths due to adverse events, and rare serious adverse drug reactions.

Furthermore, the risk-benefit profile of Sylvant was discussed in the reviews of Dr. Farrell, Albert Deisseroth, and Patricia Dinndorf and I concur with their recommendation as well as the review team to approve this BLA.

14.3 Recommendation for Postmarketing Risk Management Activities: No REMS were required for this application.

14.4 Recommendation for other Postmarketing Study Commitments: See action letter

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JONATHAN P JAROW  
04/23/2014