CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125496Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Ann. T. Farrell, M.D., Division Director
Subject	Division Director Summary Review
NDA/BLA # Supplement #	125496
Applicant Name	Janssen Biotech, Inc.
Date of Submission	August 30, 2013
PDUFA Goal Date	April 30, 2014
Proprietary Name / Established (USAN) Name	Sylant/Siltuximab
Dosage Forms / Strength	Lyophilized powder in single-use vial; reconstituted for intravenous injection (100 mg/vial and 400 mg/vial)
Proposed Indication(s)	for the treatment of multicenteric Castleman's Disease (MCD) in patients who are immunodeficiency virus negative and human herpes virus negative.
Action/Recommended Action for NME:	**Approval**

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Patricia Dinndorf, M.D., Ph.D./ Albert Deisseroth, M.D., Ph.D.
Statistical Review	Chia-wen Ko, Ph.D./Lei Nie, Ph.D.
Pharmacology Toxicology Review	Pedro Del Valle, Ph.D., Christopher Sheth, Ph.D., Brenda Gehrke, Ph.D./Haleh Saber, Ph.D.
CMC Review/OBP Review	Audrey Jia, Ph.D., Bazaarragchen Damdinsuren, Ph.D., Chana Fuchs, Ph.D./Maria Canauchacon, Ph.D., Candace Gomez-Broughton, Ph.D. and Patricia Hughes, PhD
Microbiology	Reyes Candau-Chacon, Ph.D. and Patricia Hughes Troost, Ph.D.
Clinical Pharmacology Review	Jeannie Fourie Zirkelbach, Ph.D., Julie Bullock, Pharm.D., Bahru Habtemariam, Pharm.D./Liang Zhao, Ph.D., Nitin Mehotra, Ph.D.
DMPP/OPDP	Nisha Patel, Pharm.D., Karen Dowdy, RN, BSN, LaShawn Griffiths, BSN,RN, Barbara Fuller, RN,MSN, Tingting Gao, Pharm.D./Yelena Maslov, Pharm.D.
OSI	Anthony Orencia, M.D./ Janice Pohlman, M.D./Kassa Ayalew, M.D.
CDTL Review	Albert Deisseroth, M.D., Ph.D.

OSE	Robert Pratt, Pharm.D., Cynthia LaCivita, Pharm.D./ Claudia Manzo, Pharm.D.
QT-IRT	Moh Jee NG, Qianyu Dang, Kevin M Krudys, Monica L Fiszman, Norman L Stockbridge
SEALD	Ashley Slagle, Elektra Papadopoulos, M.D., Sandy Kweder, M.D.

Signatory Authority Review Template

1. Introduction

This submission for BLA 125496 is an application for siltuximab, an interleukin-6 (IL-6) antagonist, for the treatment of multicenteric Castleman's Disease (MCD) in patients who are human immunodeficiency virus negative and human herpes virus negative. The Agency filed the submission on October 29, 2013 and the PDUFA goal date is April 30, 2013.

Siltuximab is not approved in any country at this time.

2. Background

From Dr. Dinndorf's review:

Castleman's disease (angiofollicular lymph node hyperplasia) is a lymphoproliferative disorder (LPD) associated in a subset of cases with the HIV and HHV-8 viruses. Castleman's disease comprises at least two distinct diseases (localized and multicentric) with very different prognoses. It is also associated with a number of malignancies, including Kaposi sarcoma, non-Hodgkin lymphoma (NHL), Hodgkin disease (HD), and POEMS syndrome [Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal protein, Skin changes]. This application is evaluating siltuximab in 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.

Patients with MCD present at a median age between 52 and 65 with fever, night sweats, weight loss, and weakness or fatigue. Peripheral lymphadenopathy is nearly universal, generalized, and often accompanied by hepatosplenomegaly. Laboratory abnormalities include anemia, hypoalbuminemia, hypergammaglobulinemia, and an elevated sedimentation rate. There are 2 histologic variants, the hyaline vascular variant and the plasma cell variant.

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.

3. CMC/Device

No issues were identified that would preclude approval. The following text is from Dr. Fuchs review:

Siltuximab (CNTO 328) is a full length recombinant chimeric (human-mouse) IgG1 kappa monoclonal antibody that is directed to interleukin-6 (IL-6), a proinflammatory cytokine. Siltuximab is comprised of (b) (4) *The total molecular mass of the main isoform of siltuximab,* (b) (4) *is approximately* (b) (4) *Da.*

Siltuximab drug product is supplied as a sterile, preservative free, lyophilized powder in two presentations:
100 mg of lyophilized powder in an 8 mL single-use vial.
400 mg of lyophilized powder in a 30 mL single-use vial.
Each carton of SYLVANT contains one single-use glass vial and one package insert.
Siltuximab is to be reconstituted with sterile Water for Injection (WFI) .. and diluted.

Further details for dilution and infusion and type of infusion bags and testing are found in her review. In summary Dr. Fuchs states:

The Division of Monoclonal Antibodies, Office of Biotechnology Products, OPS, CDER, has completed review of BLA 125496 for siltuximab (SYLVANT™) manufactured by Janssen Research and Development, LLC. The data submitted in this application are adequate to support a conclusion that the manufacture of

siltuximab is well controlled and leads to a product that is pure and potent. It is recommended that this product be approved for human use under the conditions specified in the package insert….

The dating period for SYLVANT 100 mg vial shall be 24 months from the date of manufacture when stored at 2-8°C. The dating period for SYLVANT 400 mg vial shall be 24 months from the date of manufacture when stored at 2-8°C. The date of manufacture shall be defined as (b) (4)

The dating period for siltuximab (b) (4) *intermediate shall be* (b) (4)

The dating period for siltuximab formulated bulk drug substance (b) (4)

The dating period for siltuximab formulated bulk drug substance (b) (4)

The following text lists the 14 PMCs recommended:

1. *To re-evaluate siltuximab 100 mg/vial final lyophilized product lot release and stability specifications using the commercial manufacturing process 5 years from the PDUFA date of April 2014 or after the manufacture of 30 lots, whichever occurs first. The 30 lots will include the 9 lots which were included in the analysis of specifications submitted in the BLA and any subsequent FLP lots manufactured. The corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications* (b) (4)

2. *To re-evaluate siltuximab 400 mg/vial final lyophilized product lot release and stability specifications using the commercial manufacturing process 5 years from the PDUFA date of April 2014 or after the manufacture of 30 lots, whichever occurs first. The 30 lots will include the 7 lots which were included in the analysis of specifications submitted in the BLA and any subsequent FLP lots manufactured. The corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications* (b) (4)

3. *To re-evaluate siltuximab formulated bulk lot release and stability specifications using the commercial manufacturing process 5 years from April 2014 or after the manufacture of 30 lots, whichever occurs first. The 30 lots will include the 13 lots which were included in the analysis of specifications submitted in the BLA and any subsequent FB lots manufactured.* (b) (4)

[redacted]

4. *To re-evaluate siltuximab [redacted] intermediate lot release and stability specifications using the commercial manufacturing process 2 years from April 2014 or after the manufacture of 30 lots, whichever occurs first. The 30 lots will include the 7 lots which were included in the analysis of cIEF specifications submitted in the BLA and any subsequent [redacted] lots manufactured. The cIEF and SE-HPLC data from all lots manufactured using the commercial manufacturing process will be included in this evaluation. The corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications [redacted]*

5. *To confirm the anticipated amount of [redacted] using a validated reduced scale model. Results of the study will be submitted by December 2014.*

6. *To confirm the anticipated amount of [redacted] using a validated reduced scale model [redacted] The results of this study will be submitted by December 2014.*

7. *To tighten the [redacted] reference material requalification acceptance criteria based on appropriate statistical evaluation and a sufficient amount of data points required for such an evaluation. The updated acceptance criterion and supporting data will be submitted as a CBE0 by November 2014.*

8. *To implement specific siltuximab master cell bank (MCB) and working cell bank (WCB) stability programs. The protocols (SOP) for the MCB and WCB stability programs and supporting data for the protocols will be submitted as a CBE0 by August 2014.*

9. *To establish a control strategy for the [redacted] The updated control strategy and supporting data will be submitted as a CBE0 in August 2014.*

10. *To re-evaluate the [redacted] using data from drug substance batches manufactured up to October 2016. The analysis and supporting data will be submitted as a CBE30 by December 2016.*

11. *To provide confirmatory data by executing manufacturing run of the 100 mg/vial* [redacted] *The drug product from this run will be placed on a stability protocol. The study report, release and stability data will be submitted in Annual Reports.*
Study Completion Date: 09/2017
Final Report Submission Date: 12/2017

12. *To provide confirmatory data by executing manufacturing run of the 400 mg/vial FLP batch at* [redacted] *The drug product from this run will be placed on a stability*
protocol. The study report, release and stability data will be submitted in Annual Reports.
Study Completion Date: 09/2017
Final Report Submission Date: 12/2017

13. *To provide confirmatory data by executing a manufacturing run of the 100 mg/vial FLP batch at* [redacted] *The drug product from this run will be placed on a stability protocol. The study report, release and stability data will be submitted in Annual Reports.*
Study Completion Date: 09/2017
Final Report Submission Date: 12/2017

14. *To provide confirmatory data by executing a manufacturing run of the 400 mg/vial FLP batch at* [redacted] *The drug product from this run will be placed on a stability protocol. The study report, release and stability data will be submitted in Annual Reports.*
Study Completion Date: 09/2017
Final Report Submission Date: 12/2017

No inspectional issues were identified which would preclude approval.

4. Nonclinical Pharmacology/Toxicology

No issues that would preclude approval were identified. From the secondary review:

Siltuximab binds to IL6 and prevents the binding of IL6 to the soluble or membrane bound IL6-receptor, thus inhibiting the IL-6 related signaling pathway. Based on its mechanism of action, the pharmacologic class assigned to siltuximab is "IL-6 antagonist"…

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….

An embryofetal developmental toxicology study was conducted in cynomolgus monkeys with siltuximab and an ePPND study was conducted in the same species with a humanized version of siltuximab. Siltuximab crossed the placenta and resulted in reduced globulin levels in pregnant animals and in the offspring; this may be secondary to a decreased production of immunoglobulin as expected from the pharmacology of this product. (b) (4)
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. This is also consistent with the pregnancy category for the approved product Actemra (IL6-receptor antagonist), a drug that inhibits the same pathway.

5. Clinical Pharmacology/Biopharmaceutics

No issues that would preclude approval were identified.

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

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

From the OT-IRT review:
No large change (i.e., > 20 ms) in the QTc interval was detected when siltuximab 15 mg/kg administered every 3 weeks by a 1-hour IV infusion for 4 cycles. Using Fridericia corrected QT (QTcF) interval, the largest upper bound of the 2-sided 90% CI mean change from baseline in QTcF was 6.6 ms. There are no placebo or positive control arms.

6. Microbiology

No issues that would preclude approval were identified. However the following text is taken from the review:

Recommendation: BLA 125496, as amended, is recommended for approval from a microbiology product quality perspective with the following post-marketing commitment:

To determine the volume of the [redacted] *necessary to achieve consistent* [redacted] *test conditions, provide the supportive data, and use the determined volume in the* [redacted] *test of the drug product* [redacted] *by May 2014.*

7. Clinical/Statistical-Efficacy

From the primary clinical review:

I recommend siltuximab (chimeric monoclonal antibody (mAb) to interleukin-6 (IL-6), Sylvant®) be granted full approval for the treatment of patients with multicentric Castleman's disease (MCD) who are human immunodeficiency virus (HIV)-negative and human herpesvirus-8 (HHV-8)-negative. The indication was evaluated in an international, multicenter, randomized (2:1), phase 2 study of every 3 week intravenous (IV) infusions comparing siltuximab and best supportive care (BSC) to placebo and BSC. The trial met its primary endpoint of durable tumor and symptomatic response based on independent review. The response rate in the siltuximab group compared with the placebo group was 34% (18/53) versus 0% (0/26), (95% confidence interval (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 (Hb) at Week 13 to 15 of 1.5 g/dL in patients who were anemic at study entry, there were no responders in the placebo arm and 19 responders in the siltuxumab arm. The difference of Hb 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).*

Additional support of the efficacy findings was confirmed by the responses documented in the subset of patients with Castleman's disease treated with siltuximab on C0328T03, the dose finding trial of siltuximab in patients with hematologic malignancies. The response rate of subjects with Castleman's disease enrolled on the trial was 32% (12/37). There was 1 complete response (CR) and 11 partial responses (PR)s .

I concur with the findings of the clinical and statistical review teams.

8. Safety

The major safety issues identified with use of this product in clinical trials include: infection, myelosuppression, hyperlipidemia, and immune suppression.

9. Advisory Committee Meeting

No clinical efficacy or safety issues arose that required an Advisory Committee meeting.

10. Pediatrics

This product has orphan designation.

11. Other Relevant Regulatory Issues

Financial Disclosure information was provided and reviewed. The Office of Scientific Investigation reported that the data were reliable in support of the indication.

12. Labeling

All disciplines made recommendations for labeling.

13. Decision/Action/Risk Benefit Assessment

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- Recommended regulatory action
  Approval with a PMR under 505 (o) to provide long term follow up from this trial
- Risk Benefit Assessment
  The trial data demonstrated a favorable risk benefit. Castleman's disease is associated with significant symptomatology as well as lymphadenopathy. This trial demonstrated an effect on tumor response as well as symptoms resulting in an improvement for patients. The major safety issues identified with use of this product in clinical trials include: infection, myelosuppression, hyperlipidemia, and immune suppression.

- Recommendation for Post marketing Risk Management Activities
  None except for routine surveillance

- Recommendation for other Post marketing Study Requirements/ Commitments

  Draft Clinical PMR: Complete the trial and submit the final study report of CNTO328MCD2002 *"An Open-label, Multicenter Study to Evaluate the Safety of Long-term Treatment with Siltuximab in Subjects with Multicentric Castleman's Disease."*

2 Draft PMCs from Microbiology:

To determine the volume of the [redacted] necessary to achieve consistent [redacted] test conditions, provide the supportive data, and use the determined volume in the [redacted] test of the drug product [redacted] by August 2014.

To conduct a study for endotoxin recovery from formulated drug substance held in [redacted] at process conditions and submit summary report to the Agency per 21CFR601.12 by July [redacted] 2014.

14 PMCs were identified from the Office of Biotechnology Products see draft list in section 3 of this review. For final language PMC/PMR, please see the approval letter.

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

/s/

ANN T FARRELL
04/23/2014