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RESEARCH**

APPLICATION NUMBER:

761036Orig1s000

OFFICE DIRECTOR MEMO

Office Director Summary Review
BLA 761036 Darzalex (daratumumab)

Office Director Decisional Memo for Regulatory Action

Date	(electronic stamp)
From	Richard Pazdur, MD
Subject	Office Director Summary Review
NDA/BLA #	761036
Applicant Name	Janssen Biotech, Inc.
Date of Submission	July 9, 2015
PDUFA Goal Date	March 9, 2016
Proprietary Name / Established (USAN) Name	DARZALEX/daratumumab
Dosage Forms / Strength	100 mg/5 mL in a single use vial 400 mg/20 mL in a single use vial
Proposed Indication(s)	a human anti-CD38 monoclonal antibody indicated for the treatment of patients with multiple myeloma who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double-refractory to a PI and immunomodulatory agent
Action/Recommended Action for NME:	Accelerated Approval

Material Reviewed/Consulted	
OND Action Package, including:	
Division Director Review	Ann Farrell, MD
Regulatory Project Manager Review	Jessica Boehmer, MBA
Medical Officer Review	Barry Miller, MSN, CRNP, Albert Deisseroth, MD, PhD,
Statistical Review	Yaping Wang, PhD/Yuan Li-Shen, DrPh/Raji Sridhara, PhD
Pharmacology Toxicology Review	Emily Place, PhD, MPH/Christopher Sheth, PhD/John Leighton, PhD
CMC Review/OBP Review	Jibril Abdus-Samad, PharmD/Tura Camilli, PhD/Wayne Seifert/Laura Fontan/Zhihao (Peter) Qiu, PhD/Jee Chung, PhD/Sarah Kennett, PhD/Kathleen A. Clouse Strebels, PhD
Microbiology	Natalia Pripuzova, PhD/Maria Jose Lopez Barragan, PhD/Patricia Hughes, PhD
Clinical Pharmacology Review	Jeanne Fourie Zirkelbach, PhD/Bahru Habtemariam, PharmD/Lian Ma, PhD/Robert Schuck, PharmD, PhD/Nitin Mehrotra, PhD
OSI	Anthony Orenca, MD/Susan Thompson, MD, MPH/Kassa Ayalew, MD, MPH
CDTL Review	Albert Deisseroth, MD, PhD
OSE	Nisha Patel/Kathleen Davis, RN/Michele Rutledge, PharmD/Yelena Maslov, PharmD/Rowell Medina, PharmD/Barbara Fuller, RN, MSN, CWOCN/LaShawn Griffiths, MSHS-PH, BSN, RN
QT-IRT	Jiang Liu/Moh Jee NG/Qianyu Dang/Michael Y Li/Norman L Stockbridge, MD
CDRH	Jennifer Dickey/Donna Roscoe/Reena Philip
DPMH	Suchitra M. Balakrishnan, MD, PhD/Tamara Johnson, MD, MS/Lynne P. Yao, MD

1. Introduction & Background

On July 9, 2015, Janssen submitted a Biologics Licensing Application (BLA) for daratumumab, a human anti-CD38 monoclonal antibody (IgG1κ) for the treatment of patients with multiple myeloma (MM) who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double-refractory to a PI and immunomodulatory agent.

Breakthrough Therapy Designation was granted on May 1, 2013. This application was given priority review. No monoclonal antibodies directed against CD38 are approved at this time for treatment of multiple myeloma, and Daralex (daratumumab) is not approved in any country at this time.

Multiple myeloma remains a mostly incurable disease with only a few patients who receive an allogeneic transplant cured of their disease. The classes of agents used to treat multiple myeloma include: steroids, alkylators, histone deacetylase inhibitor, proteasome inhibitors, and immunomodulatory agents. The development and approval of proteasome inhibitors and thalidomide analogues has improved the outlook for patients with multiple myeloma with a current median overall survival (OS) of approximately 5 years. However, additional therapies with differing mechanisms of action and adverse event profiles are needed to continue to make progress for patients with multiple myeloma.

The Applicant has submitted the results from a single arm trial enrolling patients with relapsed disease to treatment with daratumumab. This trial is supported by other single arm trial data.

2. CMC/Device

There are no issues that would preclude approval from a CMC perspective.

Daratumumab should be stored in a refrigerator at 2°C to 8°C (36°F to 46°F) and protected from light. This product contains no preservative.

The product shelf life recommendation is for 18 months stored at 2-8 C. Based on the Microbiology review, *“Following dilution the infusion bag/container may be stored for up to 24 hours at refrigerated conditions, protected from light. After allowing the bag/container to come to room temperature, DARZALEX solution has to be used immediately. Infusion should be completed within 12 hours. Any unused portion of the infusion solution should not be used”*.

3. Nonclinical Pharmacology/Toxicology

There are no issues that would preclude approval from a nonclinical perspective. Based on the nonclinical secondary review: *The in vitro studies demonstrated that daratumumab and HuMab-CD38 bound to purified human CD38 with high affinity as shown by KD values in the low nanomolar (nM) range. Both antibodies also bound to several lymphoma cell lines. Daratumumab induced myeloma tumor cell lysis through complement-dependent cytotoxicity (CDC), whereas HuMab-CD38 has far less CDC activity. Daratumumab, HuMab-CD38 and rituximab were shown to elicit similar maximal lysis (approximately 40%) of lymphoma cells in vitro through antibody-dependent cell-mediated cytotoxicity (ADCC), and daratumumab is approximately twice as potent as either HuMab-CD38 or rituximab. Daratumumab and a variant (DARA-K322A) with an altered residue in the Fc region were shown to induce macrophage-mediated phagocytosis (antibody-dependent cellular phagocytosis (ADCP)) in malignancies expressing CD38. Daratumumab also promotes apoptosis through Fc mediated cross-linking, in vitro.*

Pharmacology studies also indicate daratumumab modulates CD38 enzyme activity through inhibition of ribosyl cyclase enzyme activity and stimulation of the cyclic adenosine diphosphate ribose (cADPR) hydrolase activity of CD38, whereas the surrogate HuMab-CD38's ability to inhibit ribosyl cyclase enzyme activity is substrate dependent and it conversely inhibits cADPR hydrolase activity. Importantly, the degrees to which the known mechanisms contribute to the clinical efficacy of

daratumumab is still unknown. In vivo pharmacology studies showed that daratumumab reduced tumor growth and burden in human lymphoma xenograft mouse models. Based on the nonclinical data submitted in the BLA and its chemical structure, the Established Pharmacological Class (EPC) of “human CD38-directed monoclonal antibody” was determined to be both clinically meaningful and scientifically valid for Darzalex (daratumumab).

Stand-alone safety pharmacology studies were not conducted with daratumumab. ECG parameters, respiratory rates, body temperatures and pulse rates were assessed during the 6-week repeat-dose toxicology study in chimpanzees and were unremarkable at doses up to 25 mg/kg. ECGs, body temperature and heart rate were assessed during the 2 week repeat dose toxicology study in monkeys and were unremarkable at doses up to 100 mg/kg.

The toxicology data for daratumumab was generated in the chimpanzee (in study that was not designed to be terminal and was not requested by the FDA), and in the monkey using the HuMab-CD38 surrogate antibody. These studies indicated there are no gender differences in exposure in chimpanzees or monkeys. Increases in C_{max} and AUC values are greater than dose proportional in the chimpanzee, and approximately dose proportional in monkeys. Daratumumab was slowly eliminated in the blood following intravenous dosing with half-lives of approximately 15.5 to 18.8 days in chimpanzees, and 9 to 63 hours for HuMab-CD38 in the monkey.

The general toxicology studies reviewed were a 6-week repeat-dose toxicity study in chimpanzee and a 2-week repeat dose toxicity study in the monkey. Both repeat-dose toxicity studies utilized IV dosing, which is the intended route of administration for Darzalex. In animals, daratumumab was found to target the hematopoietic and lymphatic systems, in addition to the liver and spinal cord and nervous system.

Findings include:

- *Hematopoietic and lymphatic systems: Increases in red blood cells, hemoglobin, and hematocrit; decreases in white blood cells and platelets (chimpanzee and monkey); lymphoid depletion/atrophy in thymus, mandibular and mesenteric lymph nodes, spleen and peyers patch (monkey only).*
- *Liver: Elevated AST, ALT (chimpanzee only).*
- *Cytokine response reaction (chimpanzees only): Clinical signs include dyspnea, sneezing, increased mucous production, evacuation of bowels, mucous membrane pallor, diarrhea, soft stool, reduced appetite, respiratory arrest, and subsequent cardiac arrest leading to one mortality.*
- *Spinal cord and nervous system (monkey only): Spinal cord myelitis and inflammatory cell infiltrates found in spinal cord and sciatic nerves in recovery animals.*

The Applicant did not conduct genotoxicity, reproductive and developmental toxicology studies, or carcinogenicity studies with daratumumab. Standard genotoxicity studies are not generally applicable to biotechnology-derived pharmaceuticals (per ICH S6) and were not needed. The considerations led to no reproductive and developmental toxicology studies being conducted for daratumumab include: the lack of a pharmacologically relevant species for testing (aside from the chimpanzee wherein these studies are not feasible); that these studies are not warranted to support marketing of pharmaceuticals intended for the treatment of patients with advanced cancer (per ICH S9). ICH S9 also outlines that carcinogenicity studies are not warranted to support marketing for therapeutics intended to treat patients with advanced cancer, and as such no carcinogenicity studies were needed.

4. Clinical Pharmacology/Biopharmaceutics

There are no issues that would preclude approval from a clinical pharmacology perspective. The following is the clinical pharmacology review:

The proposed dosing regimen is 16 mg/kg body weight weekly on Weeks 1 to 8, every two weeks on Weeks 9 to 24 and every four weeks on Weeks 25 onwards until disease progression.

The population pharmacokinetic (PK) analysis included 223 patients with multiple myeloma who received daratumumab (150 subjects received 16 mg/kg). Over the dose range from 1 to 24 mg/kg, AUC increases more than dose-proportionally. Clearance decreases with increasing dose and repeated dosing, indicating target-mediated pharmacokinetics. Following the recommended dose and schedule, the C_{max} at the end of weekly dosing is 2.9-fold higher than following the first infusion. Daratumumab steady state is achieved approximately 5 months into the every 4-week dosing period and the C_{max} at steady-state to C_{max} after the first dose is 1.6. The mean (SD) linear clearance and mean (SD) central volume of distribution are estimated to be 171.4 (95.3) mL/day and 4.7 (1.3) L, respectively. The mean (SD) estimated terminal half-life associated with linear clearance is approximately 18 (9) days.

Population PK analyses indicated that the central volume of distribution and clearance of daratumumab increase with increasing body weight, supporting the body weight-based dosing regimen. Population PK analyses also show that age (31-84 years), gender, mild to severe renal impairment (15 to 89 mL/min) and mild hepatic impairment do not have clinically important effects on the pharmacokinetics of daratumumab.

Exposure-response analyses for efficacy and safety were conducted using data from trials GEN501 and MMY2002. The exposure-efficacy analysis shows that ORR increases with increasing daratumumab concentration, with a plateau achieved at daratumumab maximal pre-infusion concentrations (C_{pre-infusion, max}) ≥ 270 µg/mL. Furthermore, the median progression free survival (PFS) appears shorter in patients with daratumumab C_{pre-infusion, max} < 270 µg/mL (1.9 month) and longer (6.6 months) in those with daratumumab concentrations > 270 µg/mL. However, this analysis was confounded by baseline risk factors such as disease severity. Patients with lower exposure who did not respond to treatment were also the patients with higher disease burden, worse performance status (Eastern Cooperative Oncology Group [ECOG]), and more advanced disease at baseline. Given that there is no control arm available in these open-label trials, it is difficult to differentiate the contribution of exposure from other baseline risk factors on efficacy. As such, we recommend that the applicant should evaluate the possibility of dose optimization in these patients with lower exposure when more data are available from the ongoing controlled clinical trials. There was no exposure-safety relationship for infusion related reactions (IRR), thrombocytopenia, anemia, neutropenia and lymphopenia within the exposure range from 0.1 to 24 mg/kg studied in trials MMY2002 and GEN501.

At the 16 mg/kg dose level, data suggest that patients with baseline mild hepatic impairment have increased rates of ≥ grade 3 treatment emergent adverse events (TEAE), treatment discontinuation due to TEAE and death due to TEAE, compared to patients with normal hepatic function. Patients with moderate and severe hepatic impairment were excluded from the clinical trials, and there are no safety data in these patient populations. Recent literature data suggest that CD38 may play roles in normal hepatic function and liver disease. Therefore, patients with hepatic impairment may be sensitized to daratumumab through yet unknown mechanisms involving CD38. Additional data are needed to confirm this potential safety signal, and to characterize the safety of daratumumab in the patient sub-population with baseline hepatic impairment and multiple myeloma for which daratumumab may provide clinical benefit. A PMR is issued to conduct a study to evaluate the safety of daratumumab in patients with baseline hepatic function.

From the QT-IRT review:

No clear dose-dependent QT_c effect was observed (see Table 8 and Table 9). Based on concentration-QT_c analysis, no evident exposure-response relationship was observed after adjusting for infusion effect (Figure 5). The predicted ΔQT_cF is less than 10 ms with upper bound less than 20 ms at the therapeutic C_{max} of 1000 µg/mL, suggesting no clinically relevant QT prolongation of daratumumab.

5. Microbiology

There are no issues that would preclude approval from a microbiology perspective.

6. Clinical/Statistical-Efficacy

The Applicant submitted data from two single arm trials: MMY2002 and GEN501.

GEN501 was a first-in-human phase 1/2 monotherapy dose-escalation trial in patients with relapsed or refractory multiple myeloma. The trial included dose escalation cohorts and explored various dosing schedules.

MMY2002 was an open-label, single arm, phase 2 trial enrolling patients with relapsed multiple myeloma who had received prior treatments including proteasome inhibitors and immunomodulatory agents. The trial tested two weekly dosing regimens. The clinical review focused on the 16 mg/kg weekly treatment. In this cohort, 106 individuals received 16 mg/kg of daratumumab until disease progression. The dosing regimen was 16 mg/kg intravenously once every week for 8 weeks, then once every 2 weeks for 16 weeks, and then once every four weeks.

For both trials, the primary endpoint was ORR, calculated as the proportion of subjects who achieved a partial response (PR) or better during treatment or the follow-up phase. The MMY2002 trial results showed an ORR of 29% (95% CI: 21-39%) and with a median duration of response of 7.4 months. The GEN501 trial results for those 42 patients receiving 16 mg/kg dose regimen showed an ORR of 36% (95% CI: 22-52%) with a median DOR of 6.9 months.

7. Safety

The major safety issues identified with use of this product in clinical trials include: infection, infusion-related reactions (needing pretreatment with steroids), fatigue, nausea, back pain, fever, and cough. The most common laboratory abnormalities were lymphopenia, neutropenia, anemia and thrombocytopenia.

8. Advisory Committee Meeting

This application was not referred to an advisory committee because there were no clinical efficacy or safety issues or controversial issues that would benefit from committee discussion.

9. Pediatrics

This product has orphan designation for this indication and is therefore exempt from PREA studies.

10. Decision/Action/Risk Benefit Assessment

- Recommended regulatory action: Accelerated Approval.

- Risk Benefit Assessment

Relapsed multiple myeloma is a serious and life-threatening illness without a curative therapy except for an allogeneic stem cell transplant. The typical clinical course for those who do not undergo a transplant is characterized by multiple relapses. While significant improvement in median survival for patients with multiple myeloma has been achieved with the recent approval of thalidomide analogues and proteasome inhibitors, additional therapies with different modes of action and adverse event profiles are needed. Daratumumab is a novel monoclonal antibody targeted against CD38 which is present on the surface of plasma cells and B-cells and through effector mechanisms such as complement-dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity, and macrophage-mediated phagocytosis. In the single arm trial data submitted, daratumumab produced durable response rates of 29-36%. Patients need pre-treatment with steroids to avoid infusion-related reactions.

The major safety issues identified with use of this product in clinical trials include: infection, infusion-related reactions (needing pretreatment with steroids and other products), fatigue, nausea, back pain, fever, and cough. The most common laboratory abnormalities were lymphopenia, neutropenia, anemia and thrombocytopenia.

The risk:benefit profiles were also discussed in the reviews of Dr. Farrell, Dr. Deisseroth and Barry Miller. Furthermore, the review team recommends approval of this application. I concur with this recommendation, and therefore this application will be approved.

- Recommendation for Post marketing Risk Management Activities
A REMS is not required for this drug.
- Recommendation for PMRs under accelerated approval
See action letter.

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/s/

TAMY E KIM
11/16/2015

RICHARD PAZDUR
11/16/2015