CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761036Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

CDTL (Cross Discipline Team Leader) Review

Date	October 26, 2015
From	Albert Deisseroth, MD, PhD
Subject	Cross Discipline Team Leader Review
BLA Number	BLA 761036
Applicant	Janssen Biotech, Inc.
Date of Submission	July 9, 2015
PDUFA Goal Date/ Planned Action Date	March 9, 2016/November 17, 2015
Established/Proprietary Name	Daratumumab/Darzalex™
Dosage Regimen	16 mg/kg weekly during weeks 1-8; every two weeks during weeks 9-24; Every four weeks from week 25 onwards until progression
Dosage Form/Strength	100 mg/5mL and 400 mg/20 mL (20 mg/mL) for injection
Approved Indication	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 (IMiD) or who are double-refractory to a PI and an IMiD
Recommendation:	Accelerated Approval

Material Reviewed/Consulted	Reviewer/Author
Medical Officer Review	Barry Miller
Clinical Pharmacology	Jeanne Fourie Zirkelbach, PhD and Bahru Habtermariam, PharmD
Pharmacometrics	Lian Ma, PhD and Nitin Mehrotra, PhD
Genomics	Robert Schuck, PhD
CMC Product Quality	Tura Camilli, PhD and Jee Chung, PhD
CDER, OPQ, OPF, DIA	Laura Fontan, PhD and Peter Qiu, PhD
CMC (Drug Product)	Natalia Pripuizova, PhD and Patricia Hughes, PhD
CMC (Drug Substance)	Maria Jose Lopez-Barragan and Patricia Hughes, PhD
Nonclinical	Emily Place, PhD, and Christopher Sheth, PhD
Biostatistics	Yaping Wang, PhD and Yuan Li Shen, PhD
DRISK	Joyce Weaver, PharmD and Cynthia LaCivita, PharmD
Project Manager	Jessica Boehmer

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1. EXECUTIVE SUMMARY: (This section was derived in part from the reviews of Barry Miller, Jeanne Fourie Zirkelbach and Emily Place).

On July 9, 2015, Janssen Biotech, Inc. submitted BLA 761036 which requested approval for daratumumab (Darzalex) for the treatment of patients with multiple myeloma who have received at least three prior lines of therapy including a proteasome inhibitor and an immunomodulatory agent or who are double-refractory to a proteasome inhibitor and an immunomodulatory agent.

According to the Applicant, daratumumab is designed to target CD38 positive B-cells and plasma cells and cause depletion of these cells via several effector-based mechanisms. CD38 is a 45 kDa type II transmembrane glycoprotein that has been described as both a receptor and a multifunctional enzyme (cyclic ADP ribose hydrolase), which is involved in the production of nucleotide metabolites. CD38 is expressed in human hematopoietic cells such as lymphocytes (CD4+ and CD8+ T cells and B cells), as well as natural killer cells and at a lower level in pancreas, Purkinje cells, pituitary, eye, kidney, prostate, smooth muscle cells, and bone.

Daratumumab (HuMax-CD38) bound to human and chimpanzee CD38, but it did not bind to CD38 from the mouse, rat, rabbit, pig, and cynomolgus and rhesus monkey. Another anti-CD38 mAb, HuMab-CD38 or HuMab- 3003-003, that binds human and cynomolgus monkey CD38 was also characterized and used in some exploratory studies.

In vitro pharmacology studies were generally conducted with one or more antibodies including daratumumab, HuMab-CD38, and/or the human isotype (negative) control antibody (HuMab-KLH). 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. According to the Applicant, binding of daratumumab to CD38 on NK cells results in their death, whereas this is not necessarily the case with normal T cell lymphocytes.

The key registration trial (MMY2002) was an open-label, single arm, phase 2 trial in which the proposed patient population of 106 individuals who received 16mg/kg of daratumumab until disease progression. The primary endpoint was independent review committee–assessed overall response rate (ORR), calculated as the proportion of subjects who achieved a partial response (PR) or better during treatment or the follow-up phase. The final analysis for trial MMY2002 showed an ORR of 29%, with a median time to response of 1 month, and a median duration of response of 7.4 months.

Daratumumab efficacy was supported by GEN501, a first-in-human phase1/2 monotherapy dose-escalation trial in patients with relapsed or refractory multiple myeloma. Trial GEN501 was the first-in-human, open-label, multicenter, phase 1 and 2 trial of daratumumab in patients with relapsed and refractory with multiple myeloma. The trial included dose escalation cohorts and explored various dosing

schedules. The primary objective was to establish the safety profile of daratumumab. The primary efficacy endpoint was overall response rate (ORR). Trial GEN501 was divided into 2 parts. Part 1 was a dose-escalation phase; Part 2 was a single-arm phase with multiple cohorts, based on the dose levels established in Part 1. Eligible were patients with multiple myeloma relapsed or refractory to at least 2 different cytoreductive therapies and without further established treatment options. In Part 2, 42 patients were treated at the 16 mg/kg dose of daratumumab.

Patients entered into these trials were heavily pretreated and refractory to multiple lines of a PI and IMiD:

a. 97% were refractory to the last line of therapy
b. 77% were refractory to alkylating agents
c. 95% were double refractory
d. 66% were refractory to 3 of the 4 following therapies: bortezomib, lenalidomide, carfilzomib or pomalidomide.
e. 63% were refractor to pomalidomide
f. 48% were refractory to carfilzomib

Patients entered into MMY2002 were very heavily pretreated:

a. 100% prior PI
b. 100% prior IMiD
c. 100% prior alkylating agents
d. 80% prior bone marrow transplant

The response rates are shown below in Table 1:

Table 1: Efficacy Results from MMY002 and GEN501

Trial	MMY002 (16 mg/kg) N=106	GEN501 (16 mg/kg) N=42
ORR	29.2%	35.7%
sCR	2.8%	0.0%
CR	0.0%	4.8%
VGPR	9.4%	4.8%
PR	17.0%	26.2%
DOR (median in months)	7.4	Not reached with 65% responders disease free at 12 months

The analysis in a safety population of 156 patients treated with 16 mg/kg of daratumumab showed that there were no deaths attributable to daratumumab and no TEAEs considered by the investigator to be related to study drug which led to a discontinuation of treatment. There were no cases of febrile neutropenia, no increase in infection over time, and no patients positive for

anti-daratumumab antibodies. Only 3% of patients had grade 3 infusion reactions and none of these led to discontinuation of daratumumab.

In addition to these two completed single arm trials (MMY002 and GEN501), the Applicant has the following Phase 3 trials under development in previously untreated patients with myeloma:

a. Velcade/Melphalan and Prednisone with and without daratumumab
b. Lenalidomide and low dose dexamethasone with and without daratumumab
c. Velcade/thalidomide and low dose dexamethasone with and without daratumumab.

The Applicant also has the following Phase 3 trials under development in relapsed refractory patients with myeloma:

a. Lenalidomide and low dose dexamethasone with and without daratumumab
b. Velcade and low dose dexamethasone with and without daratumumab.

In view of these results, the CDTL recommends accelerated approval on the basis of his conclusion that there is a positive risk/benefit ratio for the use of daratumumab in the proposed indication of 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 (IMiD) or who are double-refractory to a PI and an IMiD

Regulatory Recommendation of the CDTL Reviewer: Accelerated Approval.

2. BACKGROUND: (This section was derived in part from the review of Barry Miller).

Multiple Myeloma: Multiple myeloma (MM) is a plasma cell neoplasm characterized by the proliferation and accumulation of clonal plasma cells that produce a monoclonal immunoglobulin. The clinical features of the disease result from bone marrow infiltration by the malignant clone, high levels of circulating immunoglobulin and/or free light chains, depressed immunity, and end-organ damage.

Multiple myeloma accounts for an estimated 1.6% of all cancers and 16.6% of hematologic malignancies. An estimated 26,850 new cases of myeloma will occur in the U.S. in 2015 with an estimated 11,240 deaths. The diagnosis is most common in the 6^{th} and 7^{th} decades of life. Myeloma is more common in men than women (7.9 vs. 5.1 per 100,000 persons per year). African Americans or Blacks are the most affected race and account for twice as many new cases of myeloma than Whites: 12.8 vs. 5.8 per 100,000 persons per year.

With the introduction of chemotherapy, median survival extended to 24 to 30 months from a natural history median survival of 7 months. The introduction of corticosteroids, proteasome inhibitors, immunomodulatory agents, and stem cell transplants has further extended median survival to 5 to 6 years.

Current Treatment Options in Myeloma: Treatment of multiple myeloma is typically initiated when symptoms develop. Patients with symptomatic myeloma often respond to

cytotoxic chemotherapy. However, responses are often transient; myeloma is not considered curable with available treatments. 2 lists all FDA approvals for multiple myeloma.

Current treatment regimens tend to be comprised of two to three agents; most all patients receive a proteasome inhibitor (bortezomib or carfilzomib) and an immunomodulatory agent (lenalidomide, pomalidomide, thalidomide) both early and late in the course of treatment of their disease.

Treatment for relapsed and/or refractory myeloma depends on disease- and patient-specific features, initial treatment regimen, and the duration of responses to initial and subsequent treatment. Single drug or combination regimens, stem cell transplant, or clinical trial therapy are all options for patients with relapsed or refractory myeloma. In patients who are refractory or relapsed to both an immunomodulating agent and the proteasome inhibitor bortezomib, ORR (≥PR) ranged from 24% to the first therapy to 6% after the 5th regimen. The median overall survival of patients with multiple myeloma who have received multiple salvage therapies is 9 months.

Approvals for drugs in multiple myeloma have been supported by improvements in time-to-progression (TTP) or progression-free survival (PFS). Both include objective tumor progression measured in time from randomization; TTP does not include deaths. Accelerated approvals have been supported by overall response rate (ORR) results from single-arm trials.

When compared to dexamethasone alone as a single agent or in combination with dexamethasone, the agents bortezomib, lenalidomide, and thalidomide demonstrated improvements of 2.7 to 16 months in TTP. In trials adding an investigational agent to a known single- or double-agent treatment regimen, differences in median PFS or TTP ranged from 2.8 to 8.7 months.

Table 2 Currently Available Treatment for Multiple Myeloma

Drug Name *Indication*	**Trial Type**	**Approval** *Date, Type*	**Approval Basis**	**Survival Benefit?**
Cytoxan (cyclophosphamide) *For treatment of MM*		1959 *Regular*	Case series	NE
Alkeran tablet (melphalan) *For palliative treatment of MM*		1964 *Regular*	Case series	NE
BiCNU (carmustine) *For MM, with prednisone*		1977 *Regular*	Case series	NE
Alkeran injection (melphalan) *For palliative treatment of MM for whom oral therapy is not appropriate*	Alkeran IV injection + pred (n=203) vs. oral melphalan + pred (n=107)	1992 *Regular*	Response rate at 22 weeks: Oral 44% vs. IV 38%	NE
Velcade (bortezomib) *For 3rd line MM*	Single arm trial (n=256)	2003 *Accelerated*	ORR 28%	NE
Velcade (bortezomib) *For 2nd line MM*	RCT of Velcade vs. dex (n=669)	2005 *Regular*	TTP: 6.2 m. vs. 3.5 m. ΔTTP 2.7 m.	Yes HR 0.57, p<0.05 (median f/u 8.3 m.)

Drug Name *Indication*	Trial Type	Approval *Date, Type*	Approval Basis	Survival Benefit?
Velcade (bortezomib) *For untreated MM*	RCT of Velcade + melphalan + pred (VMP) vs. melphalan + pred (MP) (n=682)	2008 *Regular*	PFS: 18.3 m. vs. 14 m. Δ PFS 4.3 m.	Yes HR 0.61, p=0.0078
Revlimid (lenalidomide) *For 2nd line MM, with dex*	Two RCTs of Revlimid + dex vs. dex (n=341, n=351)	2006 *Accelerated*	Trial 1 TTP: 8.5 m. vs. 4.6 m. Δ TTP 3.9 m. Trial 2 TTP: NE (Rev+dex) vs. 4.6 m.	No
Thalomid (thalidomide) *For newly diagnosed MM*	Two RCTs: Thalomid + dex vs. dex (n =207) Thalomid + dex vs. placebo (n=470)	2006 *Accelerated*	Trial 1 ORR: 52% vs. 36% Trial 2 TTP: 22.5 m. vs. 6.5 m. Δ TTP 16 m.	Difference not statistically significant
Doxil (doxorubicin HCL liposome) *For 2nd line MM (no prior Velcade)*	RCT of Doxil + bort vs. bort (n=646)	2007 *Regular*	TTP: 9.3 m. vs. 6.5 m. Δ TTP 2.8 m.	No
Kyprolis (carfilzomib) *For 3rd line MM*	Single arm trial (n=266)	2012 *Accelerated*	ORR (sCR, CR, VGPR, PR): 23%. mDOR: 7.8 m.	NE
Kyprolis (carfilzomib) *For 2nd, 3rd, or 4th line MM, with len and dex*	Kyprolis + len/dex vs. len/dex (n=792)	2015 *Regular*	PFS: 26.3 m. vs. 17.6 m. Δ PFS 8.7 m.	Difference not statistically significant
Pomalyst (pomalidomide) *For 3rd line MM*	Pomalyst + dex vs. Pomalyst (n=221)	2013 *Accelerated*	PFS not evaluable; ORR (PR, CR): 29% vs. 7%. mDOR for Pom+dex: 7.4 m.	NE
Pomalyst (pomalidomide) *For 3rd line MM*	Pomalyst + dex vs. Dex (n=455)	2015 *Regular*	PFS: 3.6 m. vs. 1.8 m. OS: 12.4 m. vs. 5.8m.	Yes HR 0.70, p=0.009
Farydak (panobinostat) *For 3rd line MM, with bort and dex*	RCT Farydak + bort/dex vs. bort/dex (n=768)	2015 *Accelerated*	Subgroup: prior tx bort and immunomodulatory agent and median 2 prior therapies (n=193) PFS: 10.6 m. vs. 5.8 m.	Difference not statistically significant

bort = bortezomib, dex = dexamethasone, len = lenalidomide, mDOR = median duration of response,
m = months, MM = multiple myeloma, NE = not evaluable, ORR = overall response rate, pred = prednisone,
RCT = randomized controlled trial, TTP = time to progression, Δ = difference

3. CHEMISTRY MANUFACTURING AND CONTROLS (CMC): (This section was excerpted from the CMC reviews of Drs. Tura Camilli, Maria Jose Lopez Barragan, Laura Fontan, and Natalia Pripuzova. For details, see the reviews of these individuals.)

3.A. CMC Facilities: (The section was excerpted from the review of Dr. Laura Fontan. For details, see her review).

Daratumumab is a fully human immunoglobulin G1k monoclonal antibody that binds with high affinity and specificity to the extracellular domain of human CD38 and is a transmembrane glycoprotein. The DP is provided in two strengths, 400 mg/mL and 100 mg/mL.

The subject BLA proposes manufacture of daratumumab drug substance (DS) and drug product (DP) at the facilities listed below. The drug substance is manufactured at two facilities: (b) (4) at Janssen Biologics in Ringaskiddy, Cork County, Ireland (FEI: 3007029098). The drug product is filled

into vials at 100mg/ml and 400 mg/ml strengths. Both strengths are filled at (b) (4) . Additionally the 100 mg/vial strength is filled at Cilag A. G., Schaffhausen, Switzerland (FEI: 3002806695). Cell banking operations will occur at Janssen Biotech, Inc., Malvern PA (FEI: 3001610451). A complete list of facilities associated with Daratumumab manufacturing is provided below in Tables 3 and 4.

Table 3

Site Name	Address	FEI Number	Responsibilities
(b) (4)			
Janssen Biologics (Ireland)	Barnahely Ringaskiddy, Cork, Ireland	3007029098	-Daratumumab (b) (4) manufacture -Process (b) (4) testing -Release testing of drug substance
Janssen Biotech, Inc	200 Great Valley Parkway Malvern, PA	3001610451	-Manufacture of working cell bank -Biological and characterization assays -Release testing of bulk drug substance and drug product
Janssen Biologics B. V.	Einsteinweg 101 23333 CB Leiden Netherlands	3002806632	- Bulk DS stability testing - DP stability and release testing for all tests but CCIT -Mycoplasma and In Vitro Assay for Adventitious Agents
(b) (4)			-Mycoplasma and In Vitro Assay for Adventitious Agents
			-Mycoplasma and In Vitro Assay for Adventitious Agents

Table 4

Site Name	Address	FEI Number	Responsibilities
Cilag A G.	Hochstrasse 201 8200 Schaffhausen Switzerland	3002806695	-DP-100mg/ vial liquid -DP release and stability testing for CCIT -DP in process testing -DP labelling and packaging
(b) (4)			DP-100mg and 400mg/ vial liquid Endotoxin and sterility
Janssen Biologics (Ireland)	Barnahely Ringaskiddy, Cork, Ireland	3007029098	-DP release testing
Janssen Biotech, Inc	200 Great Valley Parkway Malvern, PA	3001610451	-Biological and characterization assays
Janssen Biologics B. V.	Einsteinweg 101 23333 CB Leiden Netherlands	3002806632	-DP release and stability testing for all test except CCIT
(b) (4)			

[redacted]	-DP labelling and packaging

The facilities for manufacture of daratumumab DS are adequately described above in Table 3. Compliance decisions are pending for the [redacted]/2015 inspection of the [redacted] DS manufacture, and the 10/5-9/2015 inspection of the Janssen Biologics site (FEI 3007029098) proposed for [redacted] DS manufacture. Both of these sites are currently in acceptable compliance standing. The compliance status of drug product sites, [redacted] Cilag A. G., Schaffhausen, Switzerland (FEI: 3002806695) are also acceptable compliance standing. Final recommendation for the proposed manufacturing and testing sites is pending final compliance decisions for the DS manufacturing facilities.

Regulatory Recommendation: Approval

3.B. Drug Substance (This section was excerpted in part from the review of Maria Jose Lopez Barragan, PhD. For details, see the review of that individual).

The facilities listed above in Table 4 are also involved in the manufacture, release testing, and stability testing of daramumab drug substance.

Daratumumab DS is manufactured in [redacted] steps including [redacted]. Two facilities are involved in the DS manufacture: [redacted] and Janssen Biologics in Cork, Ireland. Steps [redacted] to produce the formulated DS bulk. Manufactured DS is stored [redacted] at a recommended temperature of [redacted] °C.

All aspects of the manufacturing process were found to be satisfactory.

There is one post-marketing commitment:

Provide data demonstrating that the (b) (4) has the same microbial growth promotion properties than the daratumumab (b) (4). Sponsor has agreed to complete these studies by 06/30/2016.

Regulatory Recommendation: Approval

3.C. Drug Product Quality Microbiology Review: (This review is excerpted from the review of Dr. Natalia Pripuzova. For details, see her review).

BLA761036, Module 3, "Quality", was submitted in electronic format on 09-July- 2015 as a part of the rolling submission to license daratumumab for 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 (IMiD) or are double refractory to a PI and an IMiD.

Daratumumab (HuMax-CD38) is a monoclonal antibody which specifically binds an epitope of the CD38 molecule present on the extracellular surface. The concentrated (b) (4). The drug substance (DS) is manufactured in Cork, Ireland. The Drug Product (DP) is manufactured by Cilag A.G. in Schaffhausen, Switzerland (100mg/vial) and (b) (4)

The daratumumab DP is supplied as a sterile, 20 mg/mL liquid concentrate for infusion in two presentations: 100 mg/vial and 400 mg/vial. It is intended for administration by the intravenous (IV) route after dilution in commercially available 0.9% sodium chloride.

All aspects of the manufacturing of the DP that were reviewed by the FDA team were satisfactory.

Regulatory Recommendation: Approval

3.D. Product Quality Review (This section was excerpted from the review of Dr. Tura Camilli and Dr. Jee Chung. For details, see their reviews)

I. Primary Reviewer Summary Recommendation: We recommend approval of this BLA. The data submitted in this Biologics License Application support the conclusion that the manufacture of daratumumab is well controlled and leads to a product that is pure and potent. The product is free of endogenous and adventitious infectious agents sufficient to meet the parameters recommended by FDA. There will be a PMR concerning work to be done in the area of the development of an immunogenicity assay.

The conditions used in manufacturing have been sufficiently validated, and a consistent product has been manufactured from multiple production runs. It is recommended that daratumumab be approved for human use (under conditions specified in the package insert). We recommend an expiration dating period of (b) (4) months for daratumumab (b) (4) when stored at (b) (4)C. We recommend an expiration dating period of 18 months for daratumumab drug substance when stored at (b) (4)°C. We recommend an expiration dating period of 18 months for drug product when stored at 2-8°C protected from light.

II. List of Deficiencies To Be Communicated: None

III. List Of Post-Marketing Commitments/Requirements:

PMR 1: Submit a validation report for a validated, sensitive, and accurate assay for the detection of binding antibodies to daratumumab, including procedures for the accurate detection of binding antibodies to daratumumab in the presence of daratumumab levels that are expected to be present in the serum or plasma at the time of patient sampling.

PMR 2: Conduct an assessment of the anti-drug antibody (ADA) response to daratumumab with the validated assay developed under PMR 1 capable of sensitively detecting ADA responses in the presence of daratumumab levels that are expected to be present at the time of patient sampling.

PMR 3: Submit a validation report for a validated, sensitive, and accurate assay for the detection of neutralizing antibodies to daratumumab, including procedures for the accurate detection of neutralizing antibodies to daratumumab in the presence of daratumumab levels that are expected to be present in the serum or plasma at the time of patient sampling.

PMC 1: Perform a shipping study to confirm validation of the commercial daratumumab drug product shipping conditions. The study will include monitoring of temperature during the shipment, testing of pre- and post-shipping samples for product quality (purity by SEC, cSDS reduced and non-reduced, cIEF, sub-visible particles, and potency of daratumumab), and 7 confirmation that the commercial shipping configuration minimizes physical damage to drug product containers.

PMC 2: Provide quantitative extractables study data and a toxicological risk assessment for all compounds extracted from the (b) (4) and drug substance long term storage containers.

PMC 3: Re-evaluate (b) (4) lot release and stability data after 30 lots have been manufactured using the commercial manufacturing process and tested using the commercial specification methods. Janssen will submit the corresponding data, the analytical and statistical plan used to evaluate the specifications, and any proposed changes to the specifications.

PMC 4: Re-evaluate daratumumab drug substance lot release and stability data after 30 lots have been manufactured using the commercial manufacturing process and tested using the commercial specification methods. Janssen will submit the corresponding data, the analytical and statistical plan used to evaluate the specifications, and any proposed changes to the specifications.

PMC 5: Re-evaluate daratumumab drug product lot release and stability data after 30 lots have been manufactured using the commercial manufacturing process. Janssen will submit the corresponding data, the analytical and statistical plan used to evaluate the specifications, and any proposed changes to the specifications.

PMC 6: Provide data to demonstrate that the (b) (4) validation studies of (b) (4) has the same microbial growth promotion properties as daratumumab (b) (4). These studies are needed to demonstrate that (b) (4) daratumumab product (b) (4) are adequate to support microbial quality.

IV. Review Of Common Technical Document-Quality Module 1: Environmental Assessment or Claim of Categorical Exclusion as specified in 21 CFR 25.15(d), Janssen states that this Biologic License Application qualifies for a categorical exclusion to the environmental assessment requirement under 21CFR 25.31(c), based on consideration of its effects when exposed to the environment. Daratumumab is considered to be a nonhazardous, biodegradable product. The environmental impact in terms of use and disposal is considered to be negligible and, therefore, does not require the preparation of an environmental assessment. The claim of categorical exclusion is acceptable.

Regulatory Recommendation: Approval.

Regulatory Recommendation of the Entire CMC Division: Approval.

4. PHARMACOLOGY/TOXICOLOGY: (This section was derived in part from the reviews of Christopher Sheth, PhD and Emily Place, PhD. For details, see the primary reviews of these individuals.)

According to the Applicant, daratumumab is designed to target CD38 positive plasma cells and cause depletion of these cells via several effector-based mechanisms. CD38 is a 45 kDa type II transmembrane glycoprotein that has been described as both a receptor and a multifunctional enzyme involved in the production of nucleotide metabolites. CD38 is expressed in human hematopoietic cells/tissues, and at a lower level in pancreas, Purkinje cells, pituitary, eye, kidney, prostate, smooth muscle cells, and bone. Daratumumab (HuMax-CD38) bound to human and chimpanzee CD38, but it did not bind to CD38 from the mouse, rat, rabbit, pig, and cynomolgus and rhesus monkey. Another anti-CD38 mAb, HuMab-CD38 or HuMab- 3003-003, that binds human and cynomolgus monkey CD38 was also characterized and used in some exploratory studies.

In vitro pharmacology studies were generally conducted with one or more antibodies including daratumumab, HuMab-CD38, and/or the human isotype (negative) control antibody (HuMab-KLH). 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 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 Cmax 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:

a. 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).

b. 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.

c. Spinal cord and nervous system (monkey only): Spinal cord myelitis and inflammatory cell infiltrates found in spinal cord and sciatic nerves in recovery animals.

d. 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.

Regulatory Recommendation: The nonclinical studies submitted to this BLA provide sufficient information to support the use of Darzalex 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.

5. CLINICAL PHARMACOLOGY: (This section was derived in part from the review of Dr. Jeanne Fourie Zirchelbach, PhD. For details, see the primary review of Dr. Fourie Zirchelbach.)

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 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 ($C_{pre\text{-}infusion,\ max}$) $\geq$ 270 µg/mL. Furthermore, the median progression free survival (PFS) appears shorter in patients with daratumumab $C_{pre\text{-}infusion,\ max}$ < 270 µg/mL (1.9 month) and longer (6.6 months) in those with daratumumab concentrations $\geq$ 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 true 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 $\geq$ grade 3 treatment emergent adverse events (TEAE), treatment discontinuation due to TEAE and death due to TEAE, compared to patients with normal hepatic function. There are no safety data in patients with moderate and severe hepatic impairment. 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 was issued to conduct a study to evaluate the safety of daratumumab in patients with baseline hepatic impairment.

Data from three monotherapy trials (trials GEN501, MMY2002 and MMY 2001), in patients with relapsed or refractory multiple myeloma, were included in the pharmacokinetic analyses (N=232). Following the Part 1 dose-escalation portion of trial GEN501, the other trials were conducted at 8 mg/kg and 16 mg/kg daratumumab.

Trial GEN501:
Trial GEN501 is entitled "Daratumumab safety study in multiple myeloma – Open-label, dose-escalation followed by open-label, single-arm study". In Part 1, the first full infusion was followed by a 3-week resting period, and the subsequent 6 full infusions were given at weekly intervals. In Part 2 of trial GEN501, the 8 mg/kg and 16 mg/kg doses were further evaluated. Subjects received the first full infusion with a 3-week resting period, followed by weekly dosing for 7 weeks and then biweekly dosing for 14 additional weeks, and once every four week dosing thereafter for up to 72 weeks until disease progression.

Trial MMY2002:
Trial MMY2002 entitled "An open-label, multicenter, phase 2 trial investigating the efficacy and safety of daratumumab in subjects with multiple myeloma who have received at least 3 prior lines of therapy (including a PI and IMiD) or are double refractory to a PI and an IMiD" was conducted in the current proposed patient population. In Study MMY2002, a total of 33 subjects (2 [11%] in the 8 mg/kg group and 31 [29%] in the 16 mg/kg group) out of 124 treated subjects had a PR or better response.

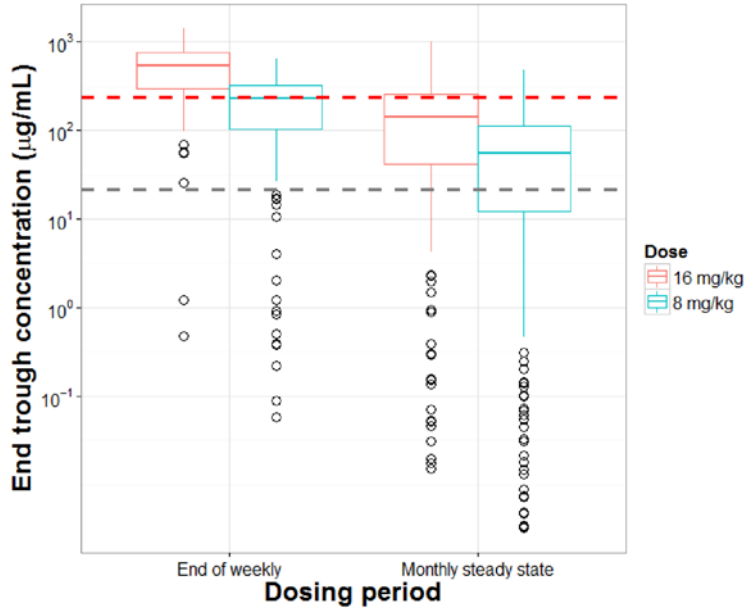
Part 1 patients were randomized to receive 8 mg/kg datatumumub once every 4 weeks, continuously or 16 mg/kg daratumumab with the final recommended dosing schedule. The ORR was 11% and 32% at the 8 mg/kg and 16 mg/kg doses, respectively. In Part 2, a total of 106 patients were treated at 16 mg/kg dose with the recommended dosing schedule (daratumumab weekly for 8 weeks, biweekly for 16 weeks and then once every 4 weeks thereafter until disease progression.

In Study MMY2002, a total of 33 subjects (2 [11%] in the 8 mg/kg group and 31 [29%] in the 16 mg/kg group) out of 124 treated subjects had a PR or better response. Of the 12 subjects in the higher dose groups (≥4 mg/kg daratumumab) in Part 1 of GEN501, 4 subjects (33.3%) had a PR. In Part 2 of Study GEN501, 3 subjects in the 8 mg/kg group (out of 30 subjects; 10%) had a PR, while for subjects in 16 mg/kg groups, 15 out of 42 subjects (36%) had a PR or better response. Positive association was consistently observed between daratumumab exposure and efficacy endpoints tested (ORR, PFS).

There was no apparent exposure-response relationship between the predicted first C_{max} and infusion related reactions (IRR), and the predicted maximal end-of-infusion concentration ($C_{post-infusion,max}$) and thrombocytopenia, anemia, neutropenia, and lymphopenia based on either the data from the pooled analysis of Studies MMY2002 and GEN501 or Study MMY2002 alone. In general, a slightly lower incidence of Grade 3+ AEs was observed in subjects in the high-exposure quartiles (Q3 and Q4) than in subjects in the low-exposure quartiles (Q1 and Q2). Although the event rate of infection appeared to numerically increase with drug exposure, this trend was not observed for Grade 3+ infections. Further analysis demonstrated that there was no significant difference in the rate of infections/infestations between IgG and non-IgG multiple myeloma subjects, although higher exposure was observed in non-IgG multiple myeloma subjects.

Daratumumab exhibits target-mediated drug disposition. Simulations based on the final model further suggested that the 16 mg/kg dose was the lowest tested dose that achieved the EC_{99}^{TAR} in the majority of the study subjects (>80%) at the end of weekly dosing (see Figure 1 below). Furthermore, this is also supported by *in vitro* data from binding of daratumumab to human CD38 cells, as the estimated EC_{90}^{TAR} and EC_{99}^{TAR} *in vivo* are much higher than the *in vitro* EC_{99}^{TAR} (~1 µg/mL) to human CD38 cells.

Figure 1. Box Plot for the Predicted Pre-infusion (Trough) Concentrations at the End of Weekly (QW) and Every 4 Week (Q4W) Steady State Dosing at Dose Levels of 16 mg/kg and 8 mg/kg Daratumumab.

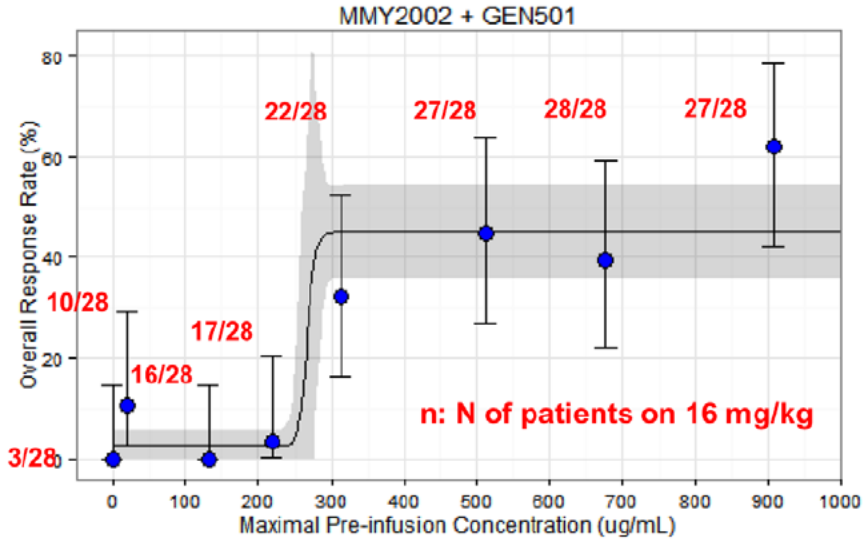


Note: EC_{99}^{TAR} was obtained by solving $\frac{EC_{99}^{TAR}}{K_m+EC_{99}^{TAR}} = 99\%$ and EC_{90}^{TAR} was obtained by solving $\frac{EC_{90}^{TAR}}{K_m+EC_{90}^{TAR}} = 90\%$. The percentages of subjects who achieved >99% target saturation at the end of weekly dosing at 16 mg/kg and 8 mg/kg were 83% and 48%, respectively. The percentages of subjects who achieved >90% target saturation at end Q4W dosing for 16 mg/kg and 8 mg/kg were 82% and 67%, respectively.

The applicant conducted the exposure-response analyses based on pooled data from trials MMY2002 and GEN501, which show that ORR significantly increased with daratumumab exposure, and there was an E_{max} relationship between exposure ($C_{pre\text{-}infusion,max}$) and ORR (see Figure 2.

Therefore, limited additional benefit in ORR is expected with $C_{pre\text{-}infusion,max}$ higher than the predicted EC_{90}^{ORR}*=274 µg/mL*. At an individual level, 70% (104/150) of patients after weekly administration of 16 mg/kg achieved $C_{pre\text{-}infusion,max}$ over the estimated EC_{90}^{ORR} and reached the plateau part of the exposure-response curve.

Figure 2. Logistic Regression Analysis between Overall Response Rate and Predicted Maximal Pre-infusion (Trough) Concentration Using an E_{max} Model.



Key: Solid blue dots represent the proportion of responders grouped by 8-quantile of maximal pre-infusion concentration and plotted at the geometric mean for each group. The bar represents the 95% confidence interval for the proportion in each group. Centered curves and shaded areas represent predicted values and 95% confidence intervals of model-predicted response rate, respectively.

Furthermore, with respect to the proposed dosing regimen, the population PK analyses suggest that the total clearance of daratumumab decreased over time, most likely due to the saturation of the target (CD38). The intensive weekly dosing at the beginning of the treatment was selected to overcome the high clearance initially, and establish efficacious concentrations in a timely manner.

Exposure-response analyses for efficacy and safety were conducted using data from trials GEN501 and MMY2002. The exposure-efficacy analysis showed that ORR increases with increasing daratumumab concentration, with a plateau achieved at daratumumab maximal pre-infusion concentrations ($C_{pre\text{-}infusion,\ max}$) > 270 µg/mL.

Furthermore, the median progression free survival (PFS) appears shorter in patients with daratumumab $C_{pre\text{-}infusion,\ max}$ < 270 µg/mL(1.9 month) and longer (6.6 months) in those with daratumumab concentrations of > 270 µg/mL.

However, this analysis was confounded by baseline risk factors such as disease severity. Patients with lower exposure who did not respond well 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 true contribution of exposure from other baseline risk factors on efficacy. As such, we recommend sponsor to evaluate the possibility of dose optimization in these patients with lower exposure when more data is available from the controlled ongoing 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 trial

MMY2002 and GEN501.

At the 16 mg/kg dose level, data suggest that patients with baseline mild hepatic impairment have increased incidences of ≥ grade 3 treatment emergent adverse events (TEAEs), treatment discontinuation due to TEAE and death due to TEAE, compared to patients with normal hepatic function. There are no safety data in patients with moderate and severe hepatic impairment. A PMR was issued to conduct a study to evaluate the safety of daratumumab in patients with baseline hepatic impairment.

Population pharmacokinetic analyses indicated that the central volume of distribution and clearance of daratumumab increase with increasing body weight, supporting the body weight-based dosing regimen. Other intrinsic factors, including age, gender, mild to severe renal impairment and mild hepatic impairment do not have clinically important effect on the pharmacokinetics of daratumumab.

Relationship between Renal Impairment and Exposure: Based on the pharmacometrics reviewer's analysis of the applicant population PK dataset described above, no dose adjustments are needed for patients with mild, moderate and severe renal impairment. The CrCL was calculated by the Cockcroft and Gault equation, and the CL was estimated for each individual in the PK data set, i.e. normal renal function (CrCL ≥ 90 mL/min, N=71), mild renal impairment (CrCL <90 and ≥60 mL/min; n=78), moderate renal impairment (CrCL <60 and ≥30 mL/min; n=68) and severe renal impairment (CrCL <30 mL/min and ≥ 15 mL/min; n=5). CrCL was not a significant covariate on daratumumab clearance, and there is no need for dose adjustment in patients with renal impairment (see Appendix 4.1, Pharmacometrics Review). This is consistent with renal elimination not being a significant clearance pathway of daratumumab. The potential effect of end-stage renal disease on daratumumab pharmacokinetics cannot be determined as clinical and pharmacokinetic data are available from only one patient.

Relationship between Hepatic Impairment and Exposure: Based on the pharmacometrics reviewer's analysis of the applicant population PK dataset described above, no dose adjustments are needed for patients with mild hepatic impairment. There were no available PK data to assess the effect of moderate or severe hepatic impairment on daratumumab PK.

The effect of hepatic impairment on the clearance of daratumumab was evaluated in subjects who had mild hepatic impairment (total bilirubin 1.0× to 1.5× upper limit of normal [ULN] or AST >ULN as defined using the National Cancer Institute - Organ Dysfunction Working Group (NCI-ODWG) criteria; n=34) compared with subjects who had normal hepatic function (total bilirubin and AST ≤ULN; n=189) in the population pharmacokinetic analysis. Mild hepatic impairment was not a significant covariate based on the model-based covariate analysis. No clinically important differences in the exposure to daratumumab were observed between subjects with mild hepatic impairment and those with normal hepatic function. Daratumumab has not been studied in subjects with moderate (total bilirubin >1.5× to 3× ULN and any AST) or severe (total bilirubin >3× ULN and any AST) hepatic impairment.

Relationship between Renal Impairment and Exposure: Based on the pharmacometrics reviewer's analysis of the applicant population PK dataset described above, no dose adjustments are needed for patients with mild, moderate and severe renal impairment. The CrCL was

calculated by the Cockcroft and Gault equation, and the CL was estimated for each individual in the PK data set, i.e. normal renal function (CrCL ≥ 90 mL/min, N=71), mild renal impairment (CrCL <90 and ≥60 mL/min; n=78), moderate renal impairment (CrCL <60 and ≥30 mL/min; n=68) and severe renal impairment (CrCL <30 mL/min and ≥ 15 mL/min; n=5). CrCL was not a significant covariate on daratumumab clearance, and there is no need for dose adjustment in patients with renal impairment. This is consistent with renal elimination not being a significant clearance pathway of daratumumab. The potential effect of end-stage renal disease on daratumumab pharmacokinetics cannot be determined as clinical and pharmacokinetic data are available from only one patient.

Relationship between Hepatic Impairment and Exposure: Based on the pharmacometrics reviewer's analysis of the applicant population PK dataset described above, no dose adjustments are needed for patients with mild hepatic impairment. There were no available PK data to assess the effect of moderate or severe hepatic impairment on daratumumab PK.

The effect of hepatic impairment on the clearance of daratumumab was evaluated in subjects who had mild hepatic impairment (total bilirubin 1.0× to 1.5× upper limit of normal [ULN] or AST >ULN as defined using the National Cancer Institute - Organ Dysfunction Working Group (NCI-ODWG) criteria; n=34) compared with subjects who had normal hepatic function (total bilirubin and AST ≤ULN; n=189) in the population pharmacokinetic analysis. Mild hepatic impairment was not a significant covariate based on the model-based covariate analysis. No clinically important differences in the exposure to daratumumab were observed between subjects with mild hepatic impairment and those with normal hepatic function. Daratumumab has not been studied in subjects with moderate (total bilirubin >1.5× to 3× ULN and any AST) or severe (total bilirubin >3× ULN and any AST) hepatic impairment.

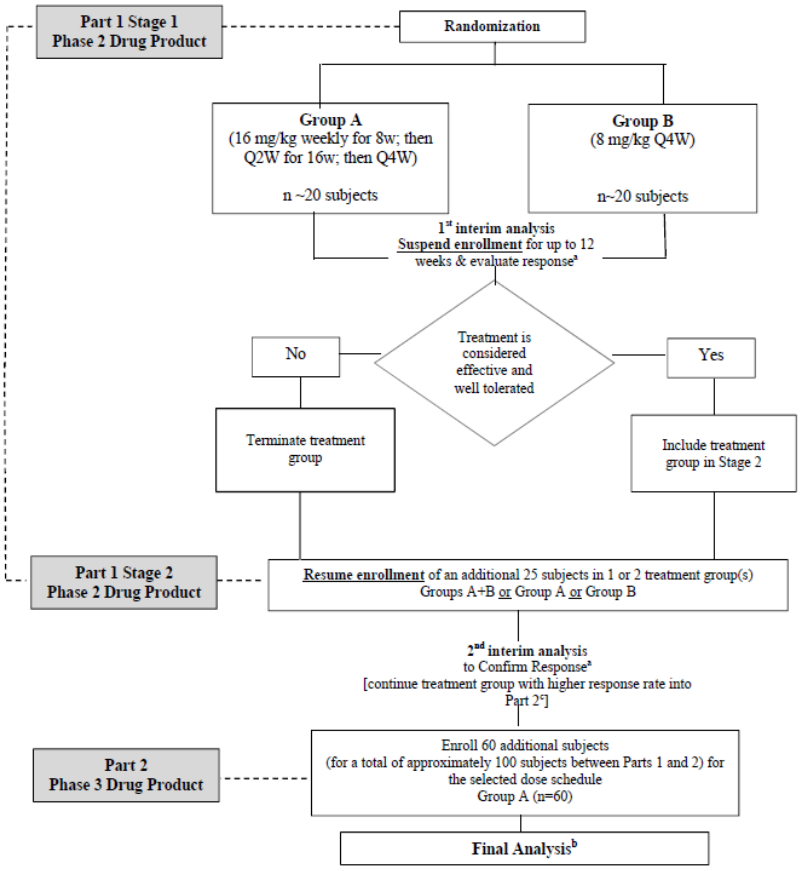
Regulatory Recommendation of Clinical Pharmacology Team: Approval

6. EFFICACY: (This section is excerpted from the reviews of Dr. Yaping Wang and Barry Miller. For details, please see the primary review of these individuals)

Trial MMY2002: Trial MMY2002 is an open-label, multicenter, phase 2, two-part trial of daratumumab in patients with relapsed and refractory with multiple myeloma. The trial included dose and schedule randomization and expansion cohorts using the early and final drug products. The primary objective of Part 1 was to select the optimal dose and schedule; for Part 2, overall response rate (ORR) was the primary efficacy endpoint. The secondary objectives were to evaluate: safety and tolerability of daratumumab, duration of response, TTR, TTP, PFS, OS, exploration of biomarkers, and predictive of response to daratumumab.

Trial Design: The key eligibility criteria was for up to 150 patients with multiple myeloma who had received at least 3 prior lines of therapy, including a proteasome inhibitor and an immunomodulating agent, or whose disease was double refractory to agents in both of these classes. Refractory disease was defined as nonresponse while on therapy or progression of disease within 60 days of stopping therapy for patients who achieved a minimal response (MR)

or better. After the screening period (a maximum 21 days), treatment started and was continued until disease progression, for unacceptable toxicity, or for other reasons listed in the protocol. After treatment, follow-up was to continue until death, consent withdrawal, loss of contact/lost to follow-up, or the end of study. The planned study design (from the protocol) is shown in 3. Patients were centrally randomized to Group A or B. Group A received the dose regimen of 16mg/kg weekly for 8 weeks, 16mg/kg every 2 weeks for 16 weeks, then 16mg/kg every 4 weeks. This dose was selected as it appeared to maximally saturate the target of CD38 for all time points in a majority of patients. Patients in Group B received 8mg/kg every 4 weeks. This dose was selected to better determine the dose response relationship while maintaining near complete CD38 suppression.



[a] Response will be assessed by the Sponsor based on available data (eg, pharmacodynamics, efficacy, safety, biomarkers).
[b] Confirmation of response by the IRC is required.
[c] If only 1 treatment group proceeded to Part 1 Stage 2, this will be the dose that is used in Part 2 of the study.
Q2W=every 2 weeks; Q4W=every 4 weeks; w=week(s)

Figure 3 Trial MMY2002 Schematic

Eligibility: Diagnostic criteria and the definition of need for treatment included in the eligibility criteria are consistent with the target population in the U.S. Patients were required to have documented multiple myeloma as defined by the criteria below and evidence of disease progression on the most recent prior treatment regimen based on IMWG criteria:

- Prior documentation of monoclonal plasma cells in the bone marrow ≥10% or presence of a biopsy-proven plasmacytoma.
- Presence of measurable disease at baseline as defined by any of the following:
    - Serum M-protein level ≥1.0 g/dL or urine M-protein level ≥200 mg/24 hours; or
    - IgA multiple myeloma: Serum M-protein level ≥0.5 g/dL or urine M-protein level ≥200 mg/24 hours; or
    - Light chain multiple myeloma: Serum immunoglobulin free light chain (FLC) ≥10 mg/dL and abnormal serum immunoglobulin kappa lambda FLC ratio.
- Evidence of response (i.e., achieved ≥25% reduction in M-protein for ≥6 weeks [MR]) to at least 1 of their prior treatment regimens.

The expectations for prior treatments received are also consistent with contemporary treatment of multiple myeloma in the U.S. Patients were required to have received an alkylating agent (≥2 cycles or 2 months) either alone or in combination with other myeloma treatments. One course of an alkylating agent for autologous stem cell transplantation alone or in combination was acceptable. Patients must have also:

- Received at least 3 prior lines of therapy including a PI (≥2 cycles or 2 months of treatment) and an IA (≥2 cycles or 2 months of treatment) in any order during the course of treatment (except for subjects who discontinued either of these treatments due to a severe allergic reaction within the first 2 cycles/months).

OR

- Disease was double refractory to a PI and an IA. For subjects who received more than 1 type of PI, their disease was to be refractory to the most recent one. Similarly, for those who received more than 1 type of IA, their disease was to be refractory to the most recent one.

A single line of therapy could consist of 1 or more agents, and could include induction, hematopoietic stem cell transplantation, and maintenance therapy (specified in protocol). Radiotherapy, bisphosphonate, or a single short course of steroids (i.e., less than or equal to the equivalent of dexamethasone 40 mg/day for 4 days) would not be considered prior lines of therapy.

Only patients 18 years of age and older were allowed to enter the trial. This is appropriate as multiple myeloma does not occur in children and is rare in adults less than 30 years of age. An ECOG performance status of 0, 1, or 2 was required.

Key exclusion criteria were:

- Previous daratumumab or other anti-CD38 therapies
- Anti-myeloma treatment within 2 weeks before Cycle 1, Day 1
- Non-secretory multiple myeloma based upon standard M-component criteria (i.e., measurable serum/urine M-component) unless the baseline serum FLC level was elevated
- Allogeneic stem cell transplant or ASCT within 12 weeks before Cycle 1, Day 1
- Cumulative corticosteroids more than the equivalent of ≥140 mg of prednisone within the 2–week period before Cycle 1, Day 1
- History of other malignancy within 5 years before Cycle 1, Day 1 (exceptions were squamous and basal cell carcinomas of the skin and carcinoma in situ of the cervix, or

malignancy that in the opinion of the investigator, with concurrence with the sponsor's medical monitor, was considered cured with minimal risk of recurrence)
- Clinical signs of meningeal involvement of multiple myeloma

Excluded were patients with the following comorbidities:

- Chronic obstructive pulmonary disease
- Hepatitis B, hepatitis C, or HIV
- Clinically significant cardiac disease
    - Myocardial infarction within one year
    - Unstable or uncontrolled angina or heart failure NYHA Class III-IV
    - Arrhythmias requiring treatment or intervention
    - Prolonged QT interval at screening (QTcF >470msec)

Study Endpoints: The primary endpoint was ORR, defined as the proportion of patients who achieve a partial response (PR), very good partial response (VGPR), complete response (CR), and stringent complete response (sCR) based on the International Myeloma Workshop Consensus Panel 1 criteria (Rajkumar, Harousseau, et al. 2011) using results from a central laboratory. Investigator-determined response was made on an ongoing basis while the sponsor used a computerized algorithm to derive response and progressive disease assessment. An independent review committee (IRC) was established to review data and assess response of all patients on trial.

Secondary endpoints included:

- Clinical benefit rate, which included minimal response, PR, VGPR, CR, and sCR
- Time to disease progression defined as the number of days from the start of daratumumab to the date of progressive disease
- Progression-free survival defined as the time from the start of daratumumab to disease progression or death
- Time to response defined as the time from the start of daratumumab to response of PR or better
- Duration of response defined as the interval from an initial response of PR or better to disease progression
- Overall survival defined from the start of daratumumab to death
- Serum/urine M-protein or FLC reduction
- Change in the percentage of bone marrow plasma cells
- Overall safety of daratumumab by evaluation of the incidence of treatment emergent adverse events, death, laboratory results, vital signs, physical examination findings, and ECG results.

Efficacy Results – Primary Endpoint: The primary analysis population consisted of data from patients enrolled to part 1 and part 2 combined. The objective response rate (ORR) which included partial response or better, among all patients treated with 16 mg/kg was 29%, including 3 stringent complete responses and 10 very good partial responses (VGPR); i.e., VGPR or better was observed in 13 of 106 (12%) patients treated with 16 mg/kg. The ORR among patients treated with 8 mg/kg daratumumab was 11%, which did not meet the protocol specified criteria for continuation of this dose.

None of the complete responses in this trial were impacted with the interference of daratumumab on serum protein electrophoresis and immunofixation assays used. Two of the three patients with stringent complete responses had IgA myeloma disease and one had free light chain only disease; none had IgG kappa myeloma protein disease.

Patients on trial who had a best response of VGPR and persistent positive immunofixation or SPEP were tested using an assay under development by the Applicant. This assay has been validated for clinical trial use only. None of the other responses tested demonstrated interference with daratumumab, meaning VGPR was confirmed to be the best response.

Regulatory Recommendation: Approval.

7. SAFETY: (This section was derived in part from the review of Barry Miller. For details, please see his review).
Safety data were available for 331 patients treated with various doses and schedules of daratumumab. Data from the three monotherapy studies were pooled to provide an integrated safety data base of 237 patients. Of these, 156 patients received the proposed dose of 16mg/kg. Data from two studies of daratumumab with other agents were pooled for 94 patients; 84 of these patients received 16mg/kg (see Tables 5-7 below for additional information).

Table 5 Safety Population, Size and Denominators

Safety Database for the Study Drug[1] Individuals exposed to the study drug in this development program for the indication under review n=331			
Clinical Trial Groups	New Drug (n=331)	Active Control (n=0)	Placebo (n=0)
Normal Volunteers	0	0	0
Controlled trials conducted for this indication[2]	0	0	0
All other than controlled trials conducted for this indication[3]	237	0	0
Controlled trials conducted for other indications[4]	94	0	0

[1] *study drug* means the drug being considered for approval; do not include comparator arm drugs, placebo, or vehicle control in this table
[2] to be used in product's labeling
[3] if placebo arm patients switch to study drug in open label extension, the n should include their number; do not count twice patients who go into extension from randomized study drug arm

[4] include n in this column only if patients exposed to the study drug for indication(s) other than that in the marketing application have been included in the safety database under review. Consider n=0 in this column if no patients treated for other indication(s) were included in this safety database.

Table 6 Duration of Exposure

	All doses n=237		≤4 mg/kg n=23		8 mg/kg n=55		16 mg/kg n=156		24 mg/kg n=3	
Month(s)										
	n	%	n	%	n	%	n	%	N	%
<1	44	18.6	7	30.4	14	25.5	22	14.1	1	33.3
1 to <3	92	38.8	16	69.6	21	38.2	53	34.0	2	66.7
3 to <6	36	15.2	0	0	9	16.4	27	17.3	0	0
6 to <9	27	11.4	0	0	5	9.1	22	14.1	0	0
9 to <12	11	4.6	0	0	2	3.6	9	5.8	0	0
≥12	27	11.4	0	0	4	7.3	23	14.7	0	0
Total dose mg/kg										
Mean	158		7		77		209		144	
Median	141		4		70		177		170	
Range	0; 528		0; 30		8; 232		2; 528		81; 182	
Total infusions										
Mean	11.4		5		9		13		6	
Median	10		5		9		12		7	
Range	1; 33		1; 7		1; 26		1; 33		3; 7	

Table 7 Demographics of Safety Population

	All doses n=237		16mg/kg n=156	
	n	%	n	%
Sex				
Male	139	58.6	84	53.8
Female	98	41.4	72	46.2
Age				
Mean years (SD)	62.4 (9.33)		62.9 (9.50)	
Median (years)	63		63	
Min, max (years)	31, 84		31, 84	
Age Group				
18 - < 65 years	133	56.1	86	55.1
> 65 - < 75 years	84	35.4	54	34.6
≥ 75 years	20	8.4	16	10.3
Race				
White	180	75.9	119	76.3
Black or African American	17	7.2	16	10.3
Asian	13	5.5	9	5.8
Other, Unknown, or Not Reported	27	11.4	12	7.7
Ethnicity				
Hispanic or Latino	10	4.2	10	6.4
Not Hispanic or Latino	173	73.0	135	86.5
Unknown	54	22.8	11	7.1

Region				
United States	110	46.4	89	57.1
Canada	22	9.3	22	14.1
Europe	96	40.5	40	25.6
Japan	9	3.8	5	3.2
ECOG Performance Status				
0	74	31.2	46	29.5
1	149	62.9	100	64.1
2	14	5.9	10	6.4
Weight Groups				
<55 kg	24	23.2	20	12.8
55-100 kg	190	80.2	119	76.3
100 kg	23	9.7	17	10.9
Renal Dysfunction				
≥90 mL/min	71	30.0	44	28.2
60-<90 mL/min	86	36.3	51	32.7
30-<60 mL/min	73	30.8	56	35.9
15-<30 mL/min	6	2.5	4	2.6
<15 mL/min	1	0.4	1	0.6
Hepatic Dysfunction				
Normal	197	83.5	134	86.5
Mildly impaired[1]	39	16.5	21	13.5

[1] (total bilirubin ≤ULN and AST>ULN) or (total bilirubin 1-1.5xULN)

Deaths: Of the 237 patients treated with daratumumab in the development program, 56 (24%) died. Most deaths (41 patients, 17%) occurred more than 30 days after the last dose of daratumumab (see Table 8 below).

Table 8 Deaths

	All doses n=237		16mg/kg n=156	
	n	%	n	%
All	56	23.6	40	25.3
Within 30 days of last dose of daratumumab	15	6.3	14	9.0

Within 30 days of the last dose of daratumumab, 1 patient who received 8mg/kg died, and 14 patients who received 16mg/kg died. FDA reviewed all narratives to confirm the cause of deaths. FDA considered the cause of death to be the primary malignancy when supported by objective evidence of disease progression. The majority of deaths were due to multiple myeloma (11 patients, 5%).

Serious Adverse Events: An SAE occurring within 30 days of the last dose of daratumumab was reported for 74 (31%) of the 237 patients treated on all clinical trials of single-agent daratumumab. In the group of 156 patients treated with daratumumab 16mg/kg, 51 (33%) experienced a serious adverse event (see Table 9 below).

Table 9 Serious Adverse Events

	All doses n=237		16mg/kg n=156	
System Organ Class	n	%	n	%
Infections and infestations	25	10.55	20	12.82
General disorders and administration site conditions	13	5.49	13	8.33
Musculoskeletal and connective tissue disorders	8	3.38	6	3.85
Blood and lymphatic system disorders	7	2.95	3	1.92
Renal and urinary disorders	7	2.95	3	1.92
Gastrointestinal disorders	6	2.53	5	3.21
Investigations	6	2.53	4	2.56
Metabolism and nutrition disorders	6	2.53	6	3.85
Respiratory, thoracic and mediastinal disorders	6	2.53	4	2.56
Injury, poisoning and procedural complications	5	2.11	3	1.92
Nervous system disorders	5	2.11	3	1.92
Cardiac disorders	3	1.27	3	1.92
Psychiatric disorders	2	0.84	2	1.28
Vascular disorders	2	0.84	2	1.28
Hepatobiliary disorders	1	0.42	1	0.64
Immune system disorders	1	0.42	0	0
Neoplasms benign, malignant and unspecified	1	0.42	0	0
Reproductive system and breast disorders	1	0.42	0	0

There were 128 SAEs occurring on treatment or within 30 days of follow-up. SAEs considered at least possible related to daratumumab were reported for 21 (9%) patients in the group of all patients treated with single agent daratumumab.

There were 95 SAEs occurring in the subgroup of patients receiving daratumumab 16mg/kg. The most common (≥2%) were pneumonia (6%), general physical health deterioration (3%), pyrexia (3%), hypercalcemia (3%), crossmatch incompatible (2%), and herpes zoster (2%).

Of these, 15 (10%) were reported to be at least possible related to daratumumab. The most common (≥2%) related SAEs were pneumonia (3%), herpes zoster (2%), and crossmatch incompatible (2%).

Treatment Emergent Adverse Events and Adverse Reactions: Treatment emergent adverse events were assessed through 30 days after the last dose of daratumumab. The number of patients with a TEAE are shown in 10 by SOC in decreasing order of incidence in the entire safety population.

Table 10 Treatment Emergent Adverse Events by SOC

	All doses n=237		16mg/kg n=156	
System Organ Class	n	%	N	%
General disorders and administration site conditions	152	64.14	106	67.95
Respiratory, thoracic and mediastinal disorders	136	57.38	96	61.54
Musculoskeletal and connective tissue disorders	126	53.16	95	60.9
Infections and infestations	124	52.32	91	58.33
Gastrointestinal disorders	122	51.48	87	55.77
Blood and lymphatic system disorders	106	44.73	80	51.28
Metabolism and nutrition disorders	82	34.6	65	41.67
Nervous system disorders	81	34.18	56	35.9
Skin and subcutaneous tissue disorders	54	22.78	37	23.72
Renal and urinary disorders	52	21.94	26	16.67
Vascular disorders	48	20.25	29	18.59
Investigations	37	15.61	22	14.1
Psychiatric disorders	37	15.61	29	18.59
Injury, poisoning and procedural complications	32	13.5	29	18.59
Eye disorders	24	10.13	17	10.9
Cardiac disorders	17	7.17	13	8.33
Hepatobiliary disorders	13	5.49	8	5.13
Neoplasms benign, malignant and unspecified	10	4.22	9	5.77
Ear and labyrinth disorders	8	3.38	6	3.85
Immune system disorders	8	3.38	3	1.92
Reproductive system and breast disorders	8	3.38	5	3.21
Congenital, familial and genetic disorders	1	0.42	1	0.64

A TEAE was reported in 155 patients who received daratumumab at 16mg/kg. The numbers of patients with common (≥10%) TEAE are shown in Table 11 below.

Table 11 Treatment Emergent Adverse Events by PT

	16mg/kg n=156			
	All Grade		Grade 3-4	
Preferred Term	n	%	N	%
Fatigue	61	39.10	3	1.92
Anemia	42	26.92	27	17.31
Nausea	42	26.92	0	0.00
Back pain	36	23.08	3	1.92
Neutropenia	35	22.44	19	12.18
Pyrexia	33	21.15	2	1.28
Cough	33	21.15	0	0.00
Thrombocytopenia	31	19.87	22	14.10
Upper respiratory tract infection	31	19.87	1	0.64
Arthralgia	26	16.67	0	0.00
Nasal congestion	26	16.67	0	0.00
Diarrhea	25	16.03	1	0.64
Nasopharyngitis	24	15.38	0	0.00
Dyspnea	24	15.38	1	0.64
Constipation	23	14.74	0	0.00
Decreased appetite	23	14.74	1	0.64
Pain in extremity	23	14.74	1	0.64
Vomiting	21	13.46	0	0.00
Musculoskeletal chest pain	19	12.18	2	1.28
Headache	19	12.18	2	1.28
Hypercalcemia	18	11.54	5	3.21
Pneumonia[1]	17	10.90	9	5.77
Chills	16	10.26	0	0.00

[1] Pneumonia included the Preferred Terms: Lobar pneumonia, Pneumonia, Pneumonia streptococcal

Laboratory Findings: Approximately 3% of the results were not graded by the applicant. There was insufficient information to apply grades to the missing test results (see Table 12 below).

Table 12 Maximum Laboratory Abnormalities

	16mg/kg n=156			
	All Grade		Grade 3-4	
Preferred Term	n	%	n	%
Hematology				
Lymphopenia	112	71.79	61	39.10
Neutropenia	93	59.62	31	19.87
Leukopenia	89	57.05	29	18.59
Thrombocytopenia	75	48.08	28	17.95
Anemia	70	44.87	30	19.23
Lymphocytes increased	5	3.21	1	0.64
Chemistry				
Hypoalbuminemia	62	39.74	5	3.21
Hypercalcemia	49	31.41	11	7.05
Hypocalcemia	48	30.77	0	0.00
Hyponatremia	45	28.85	6	3.85
Creatinine increased	33	21.15	3	1.92
Aspartate aminotransferase (AST) increased	32	20.51	2	1.28
Hypokalemia	30	19.23	5	3.21
Hyperuricemia	26	16.67	6	3.85
Alanine aminotransferase (ALT) increased	23	14.74	1	0.64
Alkaline phosphatase increased	20	12.82	1	0.64
Hypoglycemia	19	12.18	1	0.64
Hypomagnesemia	17	10.90	0	0.00
Hypophosphatemia	17	10.90	6	3.85
Hyperkalemia	13	8.33	4	2.56
Hypoalbuminemia	12	7.69	0	0.00
Bilirubin increased	11	7.05	1	0.64
Hyperglycemia	9	5.77	0	0.00
Hypernatremia	8	5.13	0	0.00
Creatine phosphokinase (CPK) increased	6	3.85	2	1.28
Hypermagnesemia	5	3.21	1	0.64
Cholesterol increased	3	1.92	0	0.00
Hypertriglyceridemia	1	0.64	0	0.00

Regulatory Recommendation for Safety: Approval.

8. ADVISORY COMMITTEE MEETING: No Advisory Committee meeting.

9. POSTMARKETING REQUIREMENTS:

Clinical PMR 1: Submit the complete final report and data showing clinical efficacy and safety from trial MMY3003, a Phase 3, 2-arm, randomized, parallel-group trial of lenalidomide and dexamethasone with or without daratumumab in patients with previously treated multiple myeloma.

Clinical PMR 2: Submit the complete final report and data showing clinical efficacy and safety from trial MMY3004, a Phase 3, 2-arm, randomized, parallel-group trial of bortezomib and dexamethasone with or without daratumumab in patients with previously treated multiple myeloma.

Clinical Pharmacology PMR 3: Conduct a study to evaluate the safety of daratumumab in patients with baseline hepatic impairment.

Immunogenicity PMR 4: Submit a validation report for a validated, sensitive, and accurate assay for the detection of binding antibodies to daratumumab, including procedures for the accurate detection of binding antibodies to daratumumab in the presence of daratumumab levels that are expected to be present in the serum or plasma at the time of patient sampling.

Immunogenicity PMR 5: Conduct an assessment of the anti-drug antibody (ADA) response to daratumumab with the validated assay developed under PMR 4 capable of sensitively detecting ADA responses in the presence of daratumumab levels that are expected to be present at the time of patient sampling.

Immunogenicity PMR 6: Submit a validation report for a validated, sensitive, and accurate assay for the detection of neutralizing antibodies to daratumumab, including procedures for the accurate detection of neutralizing antibodies to daratumumab in the presence of daratumumab levels that are expected to be present in the serum or plasma at the time of patient sampling.

10. POSTMARKETING COMMITMENTS:

Product Quality PMC 1: Perform a shipping study to confirm validation of the commercial daratumumab drug product shipping conditions. The study will include monitoring of temperature during the shipment, testing of pre- and post-shipping samples for product quality (purity by SEC, cSDS reduced and non-reduced, cIEF, sub-visible particles, and potency of daratumumab), and confirmation that the commercial shipping configuration minimizes physical damage to drug product containers.

Product Quality PMC 2: Provide quantitative extractables study data and a toxicological risk assessment for all compounds extracted from the [redacted] and drug substance long term storage containers.

Product Quality PMC 3: Re-evaluate [redacted] lot release and stability data after 30 lots have been manufactured using the commercial manufacturing process. Janssen will submit the corresponding data, the analytical and statistical plan used to evaluate the specifications, and any proposed changes to the specifications.

Product Quality PMC 4: Re-evaluate daratumumab drug substance lot release and stability data after 30 lots have been manufactured using the commercial manufacturing process. Janssen will submit the corresponding data, the analytical and statistical plan used to evaluate the specifications, and any proposed changes to the specifications.

Product Quality PMC 5: Re-evaluate daratumumab drug product lot release and stability data after 30 lots have been manufactured using the commercial manufacturing process. Janssen will submit the corresponding data, the analytical and statistical plan used to evaluate the specifications, and any proposed changes to the specifications.

Product Quality PMC 6: Provide data to demonstrate that the [redacted] validation studies of [redacted] has the same microbial growth promotion properties as daratumumab [redacted]. These studies are needed to demonstrate that [redacted] daratumumab product [redacted] are adequate to support microbial quality.

11. OTHER REGULATORY ISSUES:

11.A. Labelling: Under negotiation between the Agency and the Applicant.

11.B. Addition of Information about Interference with Blood Testing and with Determination of Complete Response to Patient Counseling Information and Patient Information: Review of materials and educational plan developed by Applicant about interference by daratumumab with ascertainment of Complete Response and with Blood Testing has been deemed satisfactory by the clinical reviewer, Barry Miller.

11.C. REMS: DRISK review has established that there is no need for a REMS.

12. REGULATORY RECOMMENDATION OF THE CDTL REVIEWER: Approval.

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

/s/

ALBERT B DEISSEROTH
10/26/2015