

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**761036Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

**PEDIATRIC PAGE**  
**(Complete for all filed original applications and efficacy supplements)**

NDA/BLA#: BLA 761036 Supplement Number: \_\_\_\_\_ NDA Supplement Type (e.g. SE5): \_\_\_\_\_

Division Name: Division of Hematology Products PDUFA Goal Date: March 9, 2016 Stamp Date: 7/9/2015

Proprietary Name: Darzalex

Established/Generic Name: daratumumab

Dosage Form: sterile liquid solution for infusion

Applicant/Sponsor: Janssen Biotech, Inc.

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

- (1) \_\_\_\_\_
- (2) \_\_\_\_\_
- (3) \_\_\_\_\_
- (4) \_\_\_\_\_

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Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1  
(Attach a completed Pediatric Page for each indication in current application.)

**Indication:** 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 an immunomodulatory agent

**Q1:** Is this application in response to a PREA PMR? Yes  Continue  
No  Please proceed to Question 2.

If Yes, NDA/BLA#: \_\_\_\_\_ Supplement #: \_\_\_\_\_ PMR #: \_\_\_\_\_

Does the division agree that this is a complete response to the PMR?

- Yes. Please proceed to Section D.
- No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

**Q2:** Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW  active ingredient(s) (includes new combination);  indication(s);  dosage form;  dosing regimen; or  route of administration?\*

(b)  No. PREA does not apply. **Skip to signature block.**

\* **Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

**Q3:** Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**
- No. Please proceed to the next question.

**Q4:** Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
- No: Please check all that apply:
- Partial Waiver for selected pediatric subpopulations (Complete Sections B)
  - Deferred for some or all pediatric subpopulations (Complete Sections C)
  - Completed for some or all pediatric subpopulations (Complete Sections D)
  - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
  - Extrapolation in One or More Pediatric Age Groups (Complete Section F)
- (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

**Section A: Fully Waived Studies (for all pediatric age groups)**

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- Necessary studies would be impossible or highly impracticable because:
- Disease/condition does not exist in children
  - Too few children with disease/condition to study
  - Other (e.g., patients geographically dispersed): \_\_\_\_\_
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

Justification attached.

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.*

**Section B: Partially Waived Studies (for selected pediatric subpopulations)**

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

*Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).*

		Reason (see below for further detail):					
		minimum	maximum	Not feasible <sup>#</sup>	Not meaningful therapeutic benefit <sup>*</sup>	Ineffective or unsafe <sup>†</sup>	Formulation failed <sup>Δ</sup>
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

Reason(s) for partial waiver (check reason corresponding to the category checked above, and attach a brief justification):

**#** Not feasible:

Necessary studies would be impossible or highly impracticable because:

- Disease/condition does not exist in children
- Too few children with disease/condition to study
- Other (e.g., patients geographically dispersed): \_\_\_\_\_

**\*** Not meaningful therapeutic benefit:

Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

**†** Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

**Δ** Formulation failed:

Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.*)

Justification attached.

*For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4)*

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL ([cderpms@fda.hhs.gov](mailto:cderpms@fda.hhs.gov)) OR AT 301-796-0700.

additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

**Section C: Deferred Studies (for selected pediatric subpopulations).**

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
Population	minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received	
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

\* Other Reason: \_\_\_\_\_

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

**Section D: Completed Studies (for some or all pediatric subpopulations).**

Pediatric subpopulation(s) in which studies have been completed (check below):

Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):**

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)**

*Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as*

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pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population	minimum	maximum	Extrapolated from:	
			Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.*

*If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.*

This page was completed by:

{See appended electronic signature page}

\_\_\_\_\_  
Regulatory Project Manager

(Revised: 6/2008)

**NOTE: If you have no other indications for this application, you may delete the attachments from this document.**

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

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*/s/*

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JESSICA L BOEHMER  
11/20/2015

November 20, 2015

The vial container labeling (submitted October 20, 2015) attached to the below approval letter was inadvertently blank.

A courtesy copy of this letter was e-mailed to the applicant but the official copy was not mailed. The communication function of this letter has been changed to Advice. The corrected approval letter was entered on November 19, 2015, and backdated to November 16, 2015, to maintain the original action date.



BLA 761036

**BLA ACCELERATED APPROVAL**

Janssen Biotech, Inc.  
c/o Janssen Research and Development, LLC  
Attention: Brian Maloney, RPh, MS  
Director, Regulatory Affairs  
920 Route 202, PO Box 300  
Raritan, NJ 08869

Dear Mr. Maloney:

Please refer to your Biologics License Application (BLA) dated July 9, 2015, received July 9, 2015, and your amendments, submitted under section 351 of the Public Health Service Act for Darzalex™ (daratumumab) injection, 100 mg/5 mL and 400 mg/20 mL.

**LICENSING**

We have approved your BLA for Darzalex™ (daratumumab) effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Darzalex™ under your existing Department of Health and Human Services U.S. License No. 1864. Darzalex™ is indicated for treatment of patients with multiple myeloma who have received at least 3 prior lines of therapy including a proteasome inhibitor and an immunomodulatory agent or are double refractory to a proteasome inhibitor and an immunomodulatory agent.

**MANUFACTURING LOCATIONS**

Under this license, you are approved to manufacture (b) (4). You are approved to manufacture daratumumab drug substance at Janssen Biologics, Cork, Ireland. The final formulated 100 mg/5 mL drug product will be manufactured, filled, labeled, and packaged at Cilag A.G., Schaffhausen, Switzerland and the 100 mg/5 mL and 400 mg/20 mL drug product will be manufactured, filled, and labeled at (b) (4). The 100 mg/5 mL and 400 mg/20 mL drug product may also be packaged at (b) (4). You may label your product with the proprietary name Darzalex and will market it in 100 mg/5 mL and 400 mg/20 mL injection in single-dose vials.

### **DATING PERIOD**

The dating period for Darzalex™ shall be 18 months from the date of manufacture when stored at 2°C - 8°C. The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product. The dating period for your drug substance shall be 18 months from the date of manufacture when stored at (b)(4)°C. The dating period for your (b)(4) shall be (b)(4) months from the date of manufacture when stored at (b)(4)°C. We have approved the stability protocols in your license application for the purpose of extending the expiration dating period of your drug substance and drug product under 21 CFR 601.12.

### **FDA LOT RELEASE**

You are not currently required to submit samples of future lots of Darzalex™ to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1, requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

Any changes in the manufacturing, testing, packaging, or labeling of Darzalex™, or in the manufacturing facilities, will require the submission of information to your biologics license application for our review and written approval, consistent with 21 CFR 601.12.

### **APPROVAL & LABELING**

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

### **CONTENT OF LABELING**

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>.

Content of labeling must be identical to the enclosed labeling (text for the package insert, text for the patient package insert). Information on submitting SPL files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

In addition, within 14 days of the date of this letter, amend any pending supplement that includes labeling changes for this BLA with content of labeling in SPL format to include the changes approved in this supplement.

## **CARTON AND IMMEDIATE CONTAINER LABELS**

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels, as soon as they are available, but no more than 30 days after they are printed.

### Container Labels

Use the container labels submitted October 2, 2015 for initial marketing.

Use the container labels submitted October 20, 2015 starting 6 weeks post launch.

### Carton Labeling

Use the carton labeling submitted October 20, 2015.

Please submit these labels electronically according to the guidance for industry titled “*Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)*.” Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**Final Printed Carton and Container Labels for approved BLA 761036.**” Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with final printed labeling (FPL) that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

## **ADVISORY COMMITTEE**

Your application for daratumumab was not referred to an FDA advisory committee because the application did not raise significant safety or efficacy issues.

## **ACCELERATED APPROVAL REQUIREMENTS**

Products approved under the accelerated approval regulations, 21 CFR 601.41, require further adequate and well-controlled clinical trials to verify and describe clinical benefit. You are required to conduct such clinical trials with due diligence. If postmarketing clinical trials fail to verify clinical benefit or are not conducted with due diligence, we may, following a hearing in accordance with 21 CFR 601.43(b), withdraw this approval. We remind you of your postmarketing requirement specified in your submission dated November 16, 2015. This requirement, along with required completion dates, is listed below.

- |            |  |
|------------|--|
| PMR 3000-1 | Conduct the analysis and 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.” |
|------------|--|

Trial Completion (primary endpoint): 04/2017  
Final Report Submission: 07/2017

PMR 3000-2 Conduct the analysis and 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.”

Trial Completion (primary endpoint): 02/2017  
Final Report Submission: 05/2017

Submit clinical protocols to your IND 100638 for this product. In addition, under 21 CFR 601.70 you should include a status summary of each requirement in your annual report to this BLA. The status summary should include expected trial completion and final report submission dates, any changes in plans since the last annual report, and number of patients entered into each trial.

Submit final reports to this BLA as a supplemental application. For administrative purposes, all submissions relating to this postmarketing requirement must be clearly designated “**Subpart E Postmarketing Requirement(s)**.”

### **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this biologic product for this indication has an orphan drug designation, you are exempt from this requirement.

### **POSTMARKETING REQUIREMENTS UNDER 505(o)**

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify unexpected serious risks of developing antibodies causing immunogenicity related adverse events, including hypersensitivity reactions and loss of product efficacy that can lead to increased mortality rate in treated patients; or to assess a signal of a serious risk of treatment emergent adverse events in patients with hepatic impairment treated with the product.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

- PMR 3000-3      Submit the final report of a study conducted to assess the anti-drug antibody (ADA) response to daratumumab with the validated assay developed under PMR 3000-4.

The timetable you submitted on November 16, 2015, states that you will conduct this study according to the following schedule:

Final Report Submission:      11/2018

- PMR 3000-4      Conduct a study to validate an assay for binding antibodies to daratumumab to assess the product's potential for immunogenic reactions in treated patients. Submit a validation report for the 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 expected in the serum or plasma at the time of patient sampling.

The timetable you submitted on November 16, 2015, states that you will conduct this study according to the following schedule:

Final Report Submission:      11/2018

- PMR 3000-5      Conduct a study to validate an assay for neutralizing antibodies to daratumumab to assess the potential for increased adverse outcome from loss of product effect in treated patients. Submit a validation report for the 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 in the serum or plasma at the time of patient sampling.

The timetable you submitted on November 16, 2015, states that you will conduct this study according to the following schedule:

Final Report Submission:      12/2015

PMR 3000-6 Collect, analyze, and submit additional safety data from ongoing clinical trials to characterize the safety of daratumumab in patients with baseline hepatic impairment.

The timetable you submitted on November 16, 2015, states that you will conduct this study according to the following schedule:

Study Completion:	04/2017
Final Report Submission:	07/2017

Submit the protocol(s) to your IND 100638, with a cross-reference letter to this BLA. Submit all final report(s) to your BLA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **“Required Postmarketing Protocol Under 505(o),” “Required Postmarketing Final Report Under 505(o),” “Required Postmarketing Correspondence Under 505(o).”**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 601.70 requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 601.70. We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

**POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B**

We remind you of your postmarketing commitments:

PMC 3000-7 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-shipment 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.

The timetable you submitted on November 16, 2015, states that you will conduct this study according to the following schedule:

Final Report Submission: 08/2016

PMC 3000-8 Provide quantitative extractables study data and a toxicological risk assessment for all compounds extracted from the [REDACTED] (b) (4) [REDACTED] and drug substance long term storage containers.

The timetable you submitted on November 16, 2015, states that you will conduct this study according to the following schedule:

Final Report Submission: 03/2016

PMC 3000-9 Re-evaluate [REDACTED] (b) (4) lot release and stability data after at least 30 lots have been manufactured using the commercial manufacturing process. Submit the corresponding data, the analytical and statistical plan used to evaluate the specifications, and any proposed changes to the specifications.

The timetable you submitted on November 16, 2015, states that you will conduct this study according to the following schedule:

Study Completion: 07/2016  
Final Report Submission: 09/2016

PMC 3000-10 Re-evaluate daratumumab drug substance lot release and stability data after at least 30 lots have been manufactured using the commercial manufacturing process. Submit the corresponding data, the analytical and statistical plan used to evaluate the specifications, and any proposed changes to the specifications.

The timetable you submitted on November 16, 2015, states that you will conduct this study according to the following schedule:

Study Completion: 07/2016  
Final Report Submission: 09/2016

PMC 3000-11 Re-evaluate daratumumab drug product lot release and stability data after at least 30 lots have been manufactured using the commercial manufacturing process. Submit the corresponding data, the analytical and statistical plan used to evaluate the specifications, and any proposed changes to the specifications.

The timetable you submitted on November 16, 2015, states that you will conduct this study according to the following schedule:

Study Completion: 07/2016  
Final Report Submission: 09/2016

PMC 3000-12 To determine the maximum hold times for all [REDACTED] (b) (4) [REDACTED] using a surrogate solution that supports microbial growth. Submit results in accordance with 21 CFR 601.12, in the Final Report.

The timetable you submitted on November 16, 2015, states that you will conduct this study according to the following schedule:

Final Report Submission: 06/2016

Submit clinical protocols to your IND 100638 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should include expected study completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled “**Postmarketing Commitment Protocol**,” “**Postmarketing Commitment Final Report**,” or “**Postmarketing Commitment Correspondence**.”

### **PROMOTIONAL MATERIALS**

Under 21 CFR 601.45, you are required to submit, during the application pre-approval review period, all promotional materials, including promotional labeling and advertisements, that you intend to use in the first 120 days following marketing approval (i.e., your launch campaign). If you have not already met this requirement, you must immediately contact the Office of Prescription Drug Promotion (OPDP) at (301) 796-1200. Please ask to speak to a regulatory project manager or the appropriate reviewer to discuss this issue.

As further required by 21 CFR 601.45, submit all promotional materials that you intend to use after the 120 days following marketing approval (i.e., your post-launch materials) at least 30 days before the intended time of initial dissemination of labeling or initial publication of the advertisement. We ask that each submission include a detailed cover letter together with three copies each of the promotional materials, annotated references, and approved package insert (PI)/Medication Guide/patient PI (as applicable).

Send each submission directly to:

OPDP Regulatory Project Manager  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotions (OPDP)  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Alternatively, you may submit promotional materials for accelerated approval products electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

## **REPORTING REQUIREMENTS**

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (21 CFR 600.80). You should submit postmarketing adverse experience reports to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Central Document Room  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Prominently identify all adverse experience reports as described in 21 CFR 600.80.

You must submit distribution reports under the distribution reporting requirements for licensed biological products (21 CFR 600.81).

You must submit reports of biological product deviations under 21 CFR 600.14. You should promptly identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA-3486 to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Compliance Risk Management and Surveillance  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Biological product deviations, sent by courier or overnight mail, should be addressed to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Compliance Risk Management and Surveillance  
10903 New Hampshire Avenue, Bldg. 51, Room 4206  
Silver Spring, MD 20903

### **MEDWATCH-TO-MANUFACTURER PROGRAM**

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at <http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm>.

### **POST APPROVAL FEEDBACK MEETING**

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

### **PDUFA V APPLICANT INTERVIEW**

FDA has contracted with Eastern Research Group, Inc. (ERG) to conduct an independent interim and final assessment of the Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs under PDUFA V ('the Program'). The PDUFA V Commitment Letter states that these assessments will include interviews with applicants following FDA action on applications reviewed in the Program. For this purpose, first-cycle actions include approvals, complete responses, and withdrawals after filing. The purpose of the interview is to better understand applicant experiences with the Program and its ability to improve transparency and communication during FDA review.

ERG will contact you to schedule a PDUFA V applicant interview and provide specifics about the interview process. Your responses during the interview will be confidential with respect to the FDA review team. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final assessments. Members of the FDA review team will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to these assessments.

If you have any questions, call Jessica Boehmer, Regulatory Project Manager, at (301) 796-5357.

Sincerely,

*{See appended electronic signature page}*

Richard Pazdur, MD  
Director  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

ENCLOSURES:

Content of Labeling  
Carton and Container Labeling

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/s/  
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RICHARD PAZDUR  
11/16/2015

## Boehmer, Jessica

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**From:** Boehmer, Jessica  
**Sent:** Tuesday, November 10, 2015 7:01 PM  
**To:** Maloney, Brian [JRDUJ]  
**Cc:** Boehmer, Jessica  
**Subject:** FDA Proposed edits to the PI - daratumumab, BLA 761036 - response requested by noon Thursday 11/12  
**Attachments:** DARZALEX USPI\_FDA\_10Nov2015.doc  
**Importance:** High

Dear Brian,

Please reference BLA 761036 for daratumumab.

Please see attached revised draft of the PI and PPI. Please review the Agency's minor format edits in the HL section and do the following to the same draft:

- Accept all changes that you agree with
- Edit over the ones that you do not agree with (do not reject any changes that the FDA proposed)

After you have made the changes, please send me the revised tracked changes document (Word version). If you agree with all the proposed edits you should provide a clean version and also formally submit to the BLA. Any additional edits you make should be in tracked changes.

Please provide the labeling to me via email by **12:00 PM Thursday, November 12, 2015**.

Please confirm receipt of this message. Please contact me if you have any questions.

Thank you,

Jessica

Jessica Boehmer, MBA  
Senior Regulatory Project Manager  
Division of Hematology Products (DHP)  
FDA/CDER/OND/OHOP  
(301) 796-5357 (phone)  
(301) 796-9845 (fax)

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/s/  
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JESSICA L BOEHMER  
11/10/2015

## Boehmer, Jessica

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**From:** Boehmer, Jessica  
**Sent:** Friday, November 06, 2015 5:13 PM  
**To:** Maloney, Brian [JRDUJ]  
**Cc:** Boehmer, Jessica  
**Subject:** FDA Proposed edits to the PI - daratumumab, BLA 761036 - response requested by 12PM Monday  
**Attachments:** DARZALEX USPI\_FDA\_Edits\_6Nov2015.doc  
**Importance:** High

Dear Brian,

Please reference BLA 761036 for daratumumab.

Please see attached revised draft of the PI and PPI. Please review the Agency's changes/comments and do the following to the same draft:

- Accept all changes that you agree with
- Edit over the ones that you do not agree with (do not reject any changes that the FDA proposed)
- Make revisions requested in the comments section

After you have made the changes, please send me the revised tracked changes document (Word version). Any additional edits you make should be in tracked changes.

Please provide the labeling to me via email by **12:00 PM, Monday, November 9, 2015**.

Please confirm receipt of this message. Please contact me if you have any questions.

Thank you,

Jessica

Jessica Boehmer, MBA  
Senior Regulatory Project Manager  
Division of Hematology Products (DHP)  
FDA/CDER/OND/OHOP  
(301) 796-5357 (phone)  
(301) 796-9845 (fax)

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/s/

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JESSICA L BOEHMER  
11/06/2015

## Boehmer, Jessica

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**From:** Boehmer, Jessica  
**Sent:** Wednesday, November 04, 2015 6:58 PM  
**To:** Maloney, Brian [JRDUS]  
**Cc:** Boehmer, Jessica  
**Subject:** Please respond: Agreement - PMRs/PMCs - daratumumab - BLA 761036 - response requested by 9AM Friday  
**Attachments:** BLA761036\_FINAL\_PMRsPMCs4Nov2015.docx  
**Importance:** High  
**Follow Up Flag:** Follow up  
**Flag Status:** Flagged  
**Categories:** Red Category

Dear Brian,

The Agency agrees with your proposed edit to PMR-4.

Upon mutual agreement, we ask you to submit a copy of the PMC and PMR studies description (attached) with a statement that you agree to perform the studies as described and within the timelines that you specify for the studies. Please send to me via email and formally submit to your BLA. Please respond by 9:00 AM Friday, November 6, 2015.

Kind regards,

Jessica

Jessica Boehmer, MBA  
Senior Regulatory Project Manager  
Division of Hematology Products (DHP)  
FDA/CDER/OND/OHOP  
(301) 796-5357 (phone)  
(301) 796-9845 (fax)

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**From:** Maloney, Brian [JRDUS] [<mailto:BMalone1@ITS.JNJ.COM>]  
**Sent:** Tuesday, November 03, 2015 2:06 PM  
**To:** Boehmer, Jessica  
**Subject:** RE: Please respond: FDA proposed edits to PMRs/PMCs - daratumumab - BLA 761036

Dear Jessica,

Attached please find Janssen's response to the PMRs/PMCs. We have accepted all the proposed changes, but have suggested 1 change (tracked) for the submission date for PMR #4 to coincide with the with the date for PMR #3.

Please confirm receipt and let me know if you have any questions.

Thank you and kind regards  
Brian

PMR/PMC Description:  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.	
PMR Schedule Milestones:		
	Trial Completion (primary endpoint):	04/2017
	Final Report Submission:	07/2017
PMR/PMC Description:  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.	
PMR Schedule Milestones:		
	Trial Completion (primary endpoint):	02/2017
	Final Report Submission:	05/2017
PMR/PMC Description:  PMR-3	Submit the final report of a study conducted to assess the anti-drug antibody (ADA) response to daratumumab with the validated assay developed under PMR 4.	
PMR Schedule Milestones:	Final Protocol Submission:	N/A
	Study/Trial Completion:	N/A
	Final Report Submission:	11/2018
PMR/PMC Description:  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 expected in the serum or plasma at the time of patient sampling.	
PMR Schedule Milestones:	Final Protocol Submission:	N/A
	Study/Trial Completion:	N/A

	Final Report Submission:	11/2018
PMR/PMC Description:  PMR-5	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 in the serum or plasma at the time of patient sampling.	
PMR Schedule Milestones:	Final Protocol Submission:	N/A
	Study/Trial Completion:	N/A
	Final Report Submission:	12/2015
PMR/PMC Description:  PMR-6	Collect and submit additional safety (b) (4) data from ongoing clinical trials to characterize the safety of daratumumab in patients with baseline hepatic impairment.	
PMR Schedule Milestones:	Final Protocol Submission:	N/A
	Study/Trial Completion:	04/2017
	Final Report Submission:	07/2017
PMR/PMC Description:  PMC-7	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-shipment 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.	
PMC Schedule Milestones:	Final Protocol Submission:	N/A
	Study/Trial Completion:	N/A
	Final Report Submission:	08/31/2016
PMR/PMC Description:  PMC-8	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 Schedule Milestones:	Final Protocol Submission:	N/A
	Study/Trial Completion:	N/A
	Final Report Submission:	03/31/2016
PMR/PMC Description: PMC-9	Re-evaluate (b) (4) lot release and stability data after at least 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 Schedule Milestones:	Final Protocol Submission:	N/A
	Study/Trial Completion:	07/29/2016
	Final Report Submission:	09/30/2016
PMR/PMC Description: PMC-10	Re-evaluate daratumumab drug substance lot release and stability data after at least 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 Schedule Milestones:	Final Protocol Submission:	N/A
	Study/Trial Completion:	07/29/2016
	Final Report Submission:	09/30/2016
PMR/PMC Description: PMC-11	Re-evaluate daratumumab drug product lot release and stability data after at least 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 Schedule Milestones:	Final Protocol Submission:	N/A
	Study/Trial Completion:	07/29/2016
	Final Report Submission:	09/30/2016
PMC-12 Description:	Provide data that demonstrate the (b) (4)	

	<p>(b) (4) validation studies for (b) (4)  has the same or better microbial growth promotion properties than  the daratumumab (b) (4).</p> <p>Validation report should be reported per 21CFR601.12 by 06/30/2016.</p>	
PMC Schedule Milestones:	Final Protocol Submission:	N/A
	Study/Trial Completion:	N/A
	Final Report Submission:	06/30/2016

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/s/  
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JESSICA L BOEHMER  
11/04/2015

## Boehmer, Jessica

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**From:** Boehmer, Jessica  
**Sent:** Wednesday, November 04, 2015 6:44 PM  
**To:** Maloney, Brian [JRDUJ]  
**Cc:** Boehmer, Jessica  
**Subject:** FDA Proposed edits to the PI - daratumumab, BLA 761036 - response requested by 9AM Friday  
**Attachments:** DARZALEX USPI\_FDA\_edits\_4Nov2015.doc  
**Importance:** High  
**Follow Up Flag:** Follow up  
**Flag Status:** Flagged  
**Categories:** Red Category

Dear Brian,

Please reference BLA 761036 for daratumumab.

Please see attached revised draft of the PI and PPI. Please review the Agency's changes/comments and do the following to the same draft:

- Accept all changes that you agree with
- Edit over the ones that you do not agree with (do not reject any changes that the FDA proposed)
- Make revisions requested in the comments section

After you have made the changes, please send me the revised tracked changes document (Word version). If you agree with all the proposed edits you should provide a clean version and also formally submit to the BLA. Any additional edits you make should be in tracked changes.

Please provide the labeling to me via email by **9:00 AM Friday, November 6, 2015**.

Please confirm receipt of this message. Please contact me if you have any questions.

Thank you,

Jessica

Jessica Boehmer, MBA  
Senior Regulatory Project Manager  
Division of Hematology Products (DHP)  
FDA/CDER/OND/OHOP  
(301) 796-5357 (phone)  
(301) 796-9845 (fax)

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JESSICA L BOEHMER  
11/04/2015

## Boehmer, Jessica

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**From:** Boehmer, Jessica  
**Sent:** Monday, November 02, 2015 5:22 PM  
**To:** Maloney, Brian [JRDU5]  
**Cc:** Boehmer, Jessica  
**Subject:** FDA Proposed edits to the PI - daratumumab, BLA 761036 - response requested by tomorrow:  
**Attachments:** DARZALEX\_USPI\_FDA\_edits\_2Nov2015.doc; PPI\_FDA\_edits\_2Nov2015.doc

Dear Brian,

Please reference BLA 761036 for daratumumab.

Please see attached revised draft of the PI and PPI. Please review the Agency's changes/comments and do the following to the same draft:

- Accept all changes that you agree with
- Edit over the ones that you do not agree with (do not reject any changes that the FDA proposed)
- Make revisions requested in the comments section

After you have made the changes, please send me the revised tracked changes document (Word version). If you agree with all the proposed edits you should provide a clean version. Any additional edits you make should be in tracked changes.

Please provide the labeling to me via email by **3:00 PM tomorrow, November 3, 2015**.

Please confirm receipt of this message. Please contact me if you have any questions. Additional comments from the Agency may be forthcoming.

Thank you,

Jessica

Jessica Boehmer, MBA  
Senior Regulatory Project Manager  
Division of Hematology Products (DHP)  
FDA/CDER/OND/OHOP  
(301) 796-5357 (phone)  
(301) 796-9845 (fax)

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JESSICA L BOEHMER  
11/02/2015

## Boehmer, Jessica

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**From:** Boehmer, Jessica  
**Sent:** Monday, November 02, 2015 4:56 PM  
**To:** Maloney, Brian [JRDUS] (BMalone1@ITS.JNJ.COM)  
**Cc:** Boehmer, Jessica  
**Subject:** Please respond: FDA proposed edits to PMRs/PMCs - daratumumab - BLA 761036  
**Attachments:** BLA761036\_FDA\_edits\_PMRsPMCs2Nov2015.docx

**Importance:** High

**Follow Up Flag:** Follow up  
**Flag Status:** Flagged

**Categories:** Red Category

Dear Brian,

The Agency has received your October 30, 2015 email correspondence with proposed edits and milestone dates for the proposed PMRs and PMCs for daratumumab, BLA 761036.

Please see the attached FDA responses and edits. Accept all the tracked changes edits that FDA has proposed with which you agree. Use track changes to show any additional edits. Please respond to me via email by 3:00 PM tomorrow, November 3, 2015.

Kindly confirm receipt.

Kind regards,

Jessica

Jessica Boehmer, MBA  
Senior Regulatory Project Manager  
Division of Hematology Products (DHP)  
FDA/CDER/OND/OHOP  
(301) 796-5357 (phone)  
(301) 796-9845 (fax)

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/s/  
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JESSICA L BOEHMER  
11/02/2015

## Boehmer, Jessica

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**From:** Boehmer, Jessica  
**Sent:** Thursday, October 29, 2015 3:44 PM  
**To:** Maloney, Brian [JRDU5] (BMalone1@ITS.JNJ.COM)  
**Cc:** Boehmer, Jessica  
**Subject:** PMR and PMCs for BLA 761036 - daratumumab - Please respond by tomorrow at 4:00PM

**Importance:** High

Dear Brian,

Please reference BLA 761036 for daratumumab. Please provide a response by **4:00 PM Friday, October 30, 2015**.

As we continue our review of your application, our normal policy is to consider post-marketing studies and labeling at this time, in order to gain agreement in advance of an action date. We have determined that the following studies are necessary as post-marketing commitments (PMCs) or post-marketing requirements (PMRs), based on the data available to date. We may have additional PMRs/PMCs later. These brief descriptions of the necessary studies are intended to describe the main objective and study characteristics of interest. Please provide edits and comments in clarifying mutually acceptable descriptions of the key elements. It is also necessary for you to provide schedule milestone dates as indicated. Most milestones only require the applicant to provide the month and year for completion of each category (however, PREA milestones require month, day, and year). For milestone calculation purposes only, assume that an approval occurs on the PDUFA action date. We are available to discuss by teleconference, if needed.

Upon mutual agreement, we ask you to submit both by email and officially a copy of the PMC and PMR studies description to us with a statement that you agree to perform the studies as described and within the timelines that you specify for the studies.

Final PMC and PMR designation numbers will be assigned later.

Some things you can do to expedite this process:

1. For PMR/PMCs, reply to our drafts as soon as possible, and be sure to send the RPM a courtesy copy by email. Reply with your edits in a WORD document submitted by email as well as to the document room. Use track changes to show YOUR edits. ACCEPT all the track changes edits that FDA has proposed with which you agree.
2. Assuming and following a favorable action, you will then be submitting protocols intended to address the objectives of the PMCs and PMRs agreed upon. We ask the following:
  - a. For any new study to address a PMR /PMC, it is necessary to submit the protocol for DHP review and concurrence prior to initiating the study. Note that the "Final Protocol Submission" date is the date by which you HAVE submitted a complete protocol and DHP has advised you that the protocol is judged acceptable to address the PMR/PMC. A fulfillment decision requires review.

- b. Send the RPM an email courtesy copy of the draft version of the protocol, in WORD, as well as to the EDR officially. Again, for iterations, accept track changes sent to you by FDA that you agree with, and only return to us YOUR edits in track changes.
- c. It is critical that you advise, prominently, both with the email and cover letter to the EDR that the protocol you are sending is to address a SPECIFIC POST MARKETING REQUIREMENT OR COMMITMENT (WITH THE PMR/PMC NUMBER). This helps the document room and DHP to code the submission properly. All protocol submissions are made to the IND.

PMR/PMC Description: 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.						
PMR Schedule Milestones:	<table> <tr> <td>Final Protocol Submission:</td> <td>MM/DD/YYYY</td> </tr> <tr> <td>Study/Trial Completion:</td> <td>MM/DD/YYYY</td> </tr> <tr> <td>Final Report Submission:</td> <td>MM/DD/YYYY</td> </tr> </table>	Final Protocol Submission:	MM/DD/YYYY	Study/Trial Completion:	MM/DD/YYYY	Final Report Submission:	MM/DD/YYYY
Final Protocol Submission:	MM/DD/YYYY						
Study/Trial Completion:	MM/DD/YYYY						
Final Report Submission:	MM/DD/YYYY						

PMR/PMC Description: 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.						
PMR Schedule Milestones:	<table> <tr> <td>Final Protocol Submission:</td> <td>MM/DD/YYYY</td> </tr> <tr> <td>Study/Trial Completion:</td> <td>MM/DD/YYYY</td> </tr> <tr> <td>Final Report Submission:</td> <td>MM/DD/YYYY</td> </tr> </table>	Final Protocol Submission:	MM/DD/YYYY	Study/Trial Completion:	MM/DD/YYYY	Final Report Submission:	MM/DD/YYYY
Final Protocol Submission:	MM/DD/YYYY						
Study/Trial Completion:	MM/DD/YYYY						
Final Report Submission:	MM/DD/YYYY						

PMR/PMC Description: PMR-3	Submit the final report of a study conducted to assess the anti-drug antibody (ADA) response to daratumumab with the validated assay developed under PMR 4. <span style="float: right;">(b) (4)</span>						
PMR Schedule Milestones:	<table> <tr> <td>Final Protocol Submission:</td> <td>MM/DD/YYYY</td> </tr> <tr> <td>Study/Trial Completion:</td> <td>MM/DD/YYYY</td> </tr> <tr> <td>Final Report Submission:</td> <td>MM/DD/YYYY</td> </tr> </table>	Final Protocol Submission:	MM/DD/YYYY	Study/Trial Completion:	MM/DD/YYYY	Final Report Submission:	MM/DD/YYYY
Final Protocol Submission:	MM/DD/YYYY						
Study/Trial Completion:	MM/DD/YYYY						
Final Report Submission:	MM/DD/YYYY						

PMR/PMC Description: 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.						
PMR Schedule Milestones:	<table> <tr> <td>Final Protocol Submission:</td> <td>MM/DD/YYYY</td> </tr> <tr> <td>Study/Trial Completion:</td> <td>MM/DD/YYYY</td> </tr> <tr> <td>Final Report Submission:</td> <td>MM/DD/YYYY</td> </tr> </table>	Final Protocol Submission:	MM/DD/YYYY	Study/Trial Completion:	MM/DD/YYYY	Final Report Submission:	MM/DD/YYYY
Final Protocol Submission:	MM/DD/YYYY						
Study/Trial Completion:	MM/DD/YYYY						
Final Report Submission:	MM/DD/YYYY						

PMR/PMC Description: PMR-5	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.
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PMR Schedule Milestones:	Final Protocol Submission:	MM/DD/YYYY
	Study/Trial Completion:	MM/DD/YYYY
	Final Report Submission:	MM/DD/YYYY
PMR/PMC Description: PMR-6	Collect additional data from ongoing clinical trials to characterize the safety of daratumumab in patients with baseline hepatic impairment.	
PMR Schedule Milestones:	Final Protocol Submission:	MM/DD/YYYY
	Study/Trial Completion:	MM/DD/YYYY
	Final Report Submission:	MM/DD/YYYY
PMR/PMC Description: PMC-7	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-shipment 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.	
PMC Schedule Milestones:	Final Protocol Submission:	MM/DD/YYYY
	Study/Trial Completion:	MM/DD/YYYY
	Final Report Submission:	MM/DD/YYYY
PMR/PMC Description: PMC-8	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 Schedule Milestones:	Final Protocol Submission:	MM/DD/YYYY
	Study/Trial Completion:	MM/DD/YYYY
	Final Report Submission:	MM/DD/YYYY
PMR/PMC Description: PMC-9	Re-evaluate (b) (4) 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 Schedule Milestones:	Final Protocol Submission:	MM/DD/YYYY
	Study/Trial Completion:	MM/DD/YYYY
	Final Report Submission:	MM/DD/YYYY
PMR/PMC Description: PMC-10	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.	
PMC Schedule Milestones:	Final Protocol Submission:	MM/DD/YYYY
	Study/Trial Completion:	MM/DD/YYYY
	Final Report Submission:	MM/DD/YYYY

PMR/PMC Description: 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 Schedule Milestones: Final Protocol Submission: MM/DD/YYYY  
Study/Trial Completion: MM/DD/YYYY  
Final Report Submission: MM/DD/YYYY

PMC-12 Description: To provide data to demonstrate that the (b) (4) validation studies of (b) (4) has the same or better microbial growth promotion properties than the daratumumab (b) (4). In the event that the data fail to demonstrate the adequacy of the (b) (4) additional studies will be performed to support the proposed (b) (4). Validation report should be submitted per 21CFR601.12 by 06/30/2016.

PMC Schedule Milestones: Final Protocol Submission: MM/DD/YYYY  
Study/Trial Completion: MM/DD/YYYY  
Final Report Submission: 06/30/2016

Please respond to me via email and officially submit your response to the BLA.

Please confirm receipt of this email.

Kind regards,

Jessica

Jessica Boehmer, MBA  
Senior Regulatory Project Manager  
Division of Hematology Products (DHP)  
FDA/CDER/OND/OHOP  
(301) 796-5357 (phone)  
(301) 796-9845 (fax)

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/s/  
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JESSICA L BOEHMER  
10/29/2015



BLA 761036

**GENERAL ADVICE**

Janssen Biotech, Inc.  
c/o Janssen Research and Development, LLC  
Attention: Brian Maloney, RPh, MS  
Director, Regulatory Affairs  
920 Route 202, PO Box 300  
Raritan, NJ 08869

Dear Dr. Maloney:

Please refer to your Biological License Application submitted under section 356(a) of the Public Health Service Act for daratumumab injection 100 and 400 mg/vial.

On October 16, 2015 at 1:59 pm an email sent to Janssen titled *RE: Daratumumab BLA 761036 Information Request* relating to your facilities inadvertently included an email address for another sponsor. At 3:56 pm that day, the recipient of the information contacted the Office of Program and Regulatory Operations to let us know he received the information in error and stated that he had not opened the attachment and would delete the email.

On October 19, 2015, the Office of Program and Regulatory Operations asked the recipient to confirm that he had deleted the email and that he would not use the information in the email. The Office of Program and Regulatory Operations will inform the recipient that we notified you of the inadvertent disclosure of this information.

We apologize for the inadvertent disclosure of your information. CDER takes its disclosure responsibilities very seriously and we make every effort to ensure that information is disclosed only in accordance with applicable laws and regulations.

If you have any questions, please contact Anita Brown at 301-796-2066 or [Anita.Brown@fda.hhs.gov](mailto:Anita.Brown@fda.hhs.gov).

Sincerely,

*{See appended electronic signature page}*

Tanya D Clayton, MPH  
Division Director (Acting), Regulatory and  
Business Process Management I  
Office of Program and Regulatory Operations  
Center for Drug Evaluation and Research  
Food and Drug Administration

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/s/  
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TANYA D CLAYTON  
10/23/2015

## Boehmer, Jessica

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**From:** Boehmer, Jessica  
**Sent:** Friday, October 23, 2015 11:16 AM  
**To:** Maloney, Brian [JRDU] (BMalone1@ITS.JNJ.COM)  
**Cc:** Boehmer, Jessica  
**Subject:** FDA Proposed edits to the PI - daratumumab, BLA 761036 - response requested by 10/28  
**Attachments:** FDA\_edits\_PI\_PPI\_FDA\_proposed\_edits\_23Oct2015\_.doc  
**Importance:** High

Dear Brian,

Please reference BLA 761036 for daratumumab.

Please see attached revised draft of the PI and PPI. Please review the Agency's changes/comments and do the following to the same draft:

- Accept all changes that you agree with
- Edit over the ones that you do not agree with (do not reject any changes that the FDA proposed)
- Make revisions requested in the comments section

After you have made the changes, please send me the revised tracked changes document (Word version). If you agree with all the proposed edits you should provide a clean version. Any additional edits you make should be in tracked changes.

Please provide the labeling to me via email by **9:00 AM, Wednesday, October 28, 2015**.

Please confirm receipt of this message. Please contact me if you have any questions. Additional comments from the Agency may be forthcoming.

Thank you,

Jessica

Jessica Boehmer, MBA  
Senior Regulatory Project Manager  
Division of Hematology Products (DHP)  
FDA/CDER/OND/OHOP  
(301) 796-5357 (phone)  
(301) 796-9845 (fax)

19 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/  
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JESSICA L BOEHMER  
10/23/2015

## Boehmer, Jessica

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**From:** Boehmer, Jessica  
**Sent:** Friday, October 16, 2015 4:42 PM  
**To:** Maloney, Brian [JRDUS] (BMalone1@ITS.JNJ.COM)  
**Cc:** Rothschild, Melanie [JRDUS] (MRothsch@ITS.JNJ.COM); Boehmer, Jessica  
**Subject:** Response needed: Carton/Container - Information Requests - BLA 761036 - daratumumab - response due October 21

**Importance:** High

Dear Brian:

Please refer to BLA 761036 for daratumumab, submitted and received July 9, 2015. Please respond to the following information requests by the requested due date.

### [Information Request:](#)

#### Container Labels and Carton Labeling Comments

We have the following comments regarding your draft container labels and carton labeling submitted on October 2 and October 10 2015. Please respond by COB October 21 2015.

#### Container Labels

Provide a timeline for your plan to use the container labels (submitted October 2 2015) with the (b) (4) on the principal display panel for the initial product launch and then replace them with post-launch container labels (submitted October 10 2015).

#### Container Labels and Carton Labeling

Revise the term (b) (4) to "Single-Dose". "Single-Dose" is the appropriate package term for a container designed for use with a single patient as a single injection or infusion per USP General Chapters: <7> Packaging and Storage Requirements.

Please respond to me via email by **October 21, 2015**, and also formally submit to your BLA. Kindly confirm receipt.

Thank you,

Jessica

Jessica Boehmer, MBA  
Senior Regulatory Project Manager  
Division of Hematology Products (DHP)  
FDA/CDER/OND/OHOP  
(301) 796-5357 (phone)  
(301) 796-9845 (fax)

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/s/  
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JESSICA L BOEHMER  
10/16/2015

## Boehmer, Jessica

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**From:** Boehmer, Jessica  
**Sent:** Tuesday, October 13, 2015 10:13 AM  
**To:** Maloney, Brian [JRDU5] (BMalone1@ITS.JNJ.COM)  
**Cc:** Boehmer, Jessica  
**Subject:** Response needed: Clinical Pharmacology Information Request - BLA 761036 - daratumumab - response due Oct 14

**Importance:** High

Dear Brian:

Please refer to BLA 761036 for daratumumab, submitted and received July 9, 2015. Please respond to the following information to me via email **by noon tomorrow October 14, 2015**, and formally submit the information to your BLA.

### [Clinical Pharmacology Information Request:](#)

Safety data included in the current submission indicate that the rates of serious treatment emergent adverse events (TEAE), grade 3 or higher TEAE, treatment discontinuation due to TEAE and death due to TEAE are higher in patients with mild hepatic impairment compared to patients with normal hepatic function at the 16 mg/kg dose level of daratumumab. Please provide a comparative analysis to address whether the increased incidence of adverse events in patients with mild hepatic impairment may be associated with a difference in the distribution of any other baseline risk factors. Also provide summary of comparative liver function data (normal vs. mild hepatic impairment) in graphical and tabular format.

Please respond to me via email and also formally submit to your BLA.

Thank you,

Jessica

Jessica Boehmer, MBA  
Senior Regulatory Project Manager  
Division of Hematology Products (DHP)  
FDA/CDER/OND/OHOP  
(301) 796-5357 (phone)  
(301) 796-9845 (fax)

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/s/

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JESSICA L BOEHMER  
10/13/2015

## Boehmer, Jessica

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**From:** Boehmer, Jessica  
**Sent:** Wednesday, October 07, 2015 4:35 PM  
**To:** Maloney, Brian [JRDU5] (BMalone1@ITS.JNJ.COM)  
**Cc:** Boehmer, Jessica  
**Subject:** Response needed: Clinical Pharmacology Information Request - BLA 761036 - daratumumab - response due Oct 8

**Importance:** High

Dear Brian:

Please refer to BLA 761036 for daratumumab, submitted and received July 9, 2015. Please respond to the following information to me via email **by tomorrow October 8, 2015**, and formally submit the information to your BLA.

[Clinical Pharmacology Information Request:](#)

The population PK analysis indicates that patients with mild hepatic impairment have 30% lower daratumumab exposure, compared to patients with normal hepatic function. Could you please comment on a possible mechanism for this?

Please respond to me via email and also formally submit to your BLA.

Thank you,

Jessica

Jessica Boehmer, MBA  
Senior Regulatory Project Manager  
Division of Hematology Products (DHP)  
FDA/CDER/OND/OHOP  
(301) 796-5357 (phone)  
(301) 796-9845 (fax)

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/s/  
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JESSICA L BOEHMER  
10/07/2015

## Boehmer, Jessica

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**From:** Boehmer, Jessica  
**Sent:** Wednesday, October 07, 2015 4:37 PM  
**To:** Maloney, Brian [JRDU5] (BMalone1@ITS.JNJ.COM)  
**Cc:** Boehmer, Jessica  
**Subject:** RE: Response needed: Clinical Pharmacology Information Request - BLA 761036 - daratumumab - response due Oct 9

**Importance:** High

Dear Brian:

Please refer to BLA 761036 for daratumumab, submitted and received July 9, 2015. Please respond to the following information to me via email **by tomorrow October 9, 2015**, and formally submit the information to your BLA.

[Clinical Pharmacology Information Request:](#)

Data from trial GEN501, part 2, show a statistically significant increase in QTcF, however the proposed draft label does not contain any information describing this change. Please propose labeling language for Section 12.2 of the proposed package insert, briefly describing the patient subset, exposure and magnitude of the effect observed.

Please respond to me via email and also formally submit to your BLA.

Thank you,

Jessica

Jessica Boehmer, MBA  
Senior Regulatory Project Manager  
Division of Hematology Products (DHP)  
FDA/CDER/OND/OHOP  
(301) 796-5357 (phone)  
(301) 796-9845 (fax)

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/s/

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JESSICA L BOEHMER  
10/07/2015

## Boehmer, Jessica

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**From:** Boehmer, Jessica  
**Sent:** Tuesday, October 06, 2015 4:32 PM  
**To:** Maloney, Brian [JRDU5] (BMalone1@ITS.JNJ.COM)  
**Cc:** Boehmer, Jessica  
**Subject:** Response needed: Carton/Container - Information Requests - BLA 761036 - daratumumab - response due October 12

**Importance:** High

Dear Brian:

Please refer to BLA 761036 for daratumumab, submitted and received July 9, 2015. Please respond to the following information requests by the requested due date. Please send the response to me via email and formally submit the information to your BLA.

### Container Labels and Carton Labeling Comments

We have the following comments regarding your draft container labels and carton labeling submitted on October 2, 2015. Please respond by COB October 12, 2015.

#### Carton Labeling

Revise the statements "[REDACTED] (b) (4)" to read "Store vial in original carton to protect from light."

#### Container Label

Remove the [REDACTED] (b) (4) from the principal display panel. It competes with the prominence of the critical information on the label. If you wish to include this [REDACTED] (b) (4) consider placing it on the carton labeling on the side or back panel, away from the required [REDACTED] (b) (4) and in a size that does not compete with or distract from the presentation of other required or recommended information on the label.<sup>[1]</sup>

<sup>[1]</sup> Guidance for Industry, Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (Draft Guidance) April 2013, page 20. Available from:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>

Please respond to me via email by **October 12, 2015**, and also formally submit to your BLA.

Thank you,

Jessica

Jessica Boehmer, MBA  
Senior Regulatory Project Manager  
Division of Hematology Products (DHP)  
FDA/CDER/OND/OHOP  
(301) 796-5357 (phone)  
(301) 796-9845 (fax)

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<sup>[1]</sup> Guidance for Industry, Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (Draft Guidance) April 2013, page 20. Available from:  
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>

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/s/  
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JESSICA L BOEHMER  
10/06/2015

## Boehmer, Jessica

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**From:** Boehmer, Jessica  
**Sent:** Monday, October 05, 2015 11:20 AM  
**To:** Maloney, Brian [JRDU] (BMalone1@ITS.JNJ.COM)  
**Cc:** Boehmer, Jessica  
**Subject:** Response needed: Clinical Pharmacology Information Request - BLA 761036 - daratumumab - response due Oct 6

**Importance:** High

Dear Brian:

Please refer to BLA 761036 for daratumumab, submitted and received July 9, 2015. Please respond to the following information to me via email **by tomorrow October 6, 2015**, and formally submit the information to your BLA.

[Clinical Pharmacology Information Request:](#)

Could you please clarify why patients with moderate and severe hepatic impairment were not enrolled in trial MMY2002?

Was there an inclusion/exclusion criterion that would have limited enrollment only to patients with normal and mild hepatic impairment?

Please respond to me via email and also formally submit to your BLA.

Thank you,

Jessica

Jessica Boehmer, MBA  
Senior Regulatory Project Manager  
Division of Hematology Products (DHP)  
FDA/CDER/OND/OHOP  
(301) 796-5357 (phone)  
(301) 796-9845 (fax)

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JESSICA L BOEHMER  
10/05/2015

## Boehmer, Jessica

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**From:** Boehmer, Jessica  
**Sent:** Monday, October 05, 2015 4:39 PM  
**To:** Maloney, Brian [JRDUJ] (BMalone1@ITS.JNJ.COM)  
**Cc:** Boehmer, Jessica  
**Subject:** Response needed: Clinical Pharmacology Information Request - BLA 761036 - daratumumab - response due Oct 6

**Importance:** High

Dear Brian:

Please refer to BLA 761036 for daratumumab, submitted and received July 9, 2015. Please respond to the following information to me via email **by tomorrow October 6, 2015**, and formally submit the information to your BLA.

[Clinical Pharmacology Information Request:](#)

For trial MMY2002, please provide a listing of the protocol specified time points at which blood samples were drawn for analysis of ADA to daratumumab.

For Trial MMY2002, please provide a dataset showing the actual times at which blood samples were drawn for analysis of ADA to daratumumab so that these can be compared to the protocol specified time points.

Please respond to me via email and also formally submit to your BLA.

Thank you,

Jessica

Jessica Boehmer, MBA  
Senior Regulatory Project Manager  
Division of Hematology Products (DHP)  
FDA/CDER/OND/OHOP  
(301) 796-5357 (phone)  
(301) 796-9845 (fax)

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/s/  
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JESSICA L BOEHMER  
10/05/2015

## Jones, Jacquin

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**From:** Jones, Jacquin  
**Sent:** Friday, October 02, 2015 5:43 PM  
**To:** 'Maloney, Brian [JRDUS]'  
**Cc:** Boehmer, Jessica  
**Subject:** Response needed: Clinical Information Requests - BLA 761036 - daratumumab - response due Oct 6

Good evening Mr. Maloney,

Sent on behalf of Jessica Boehmer.

Please refer to BLA 761036 for daratumumab, submitted and received July 9, 2015. Please respond to the following information requests by the requested due date. Please send the response to Jessica Boehmer via email **no later than COB, October 6, 2015.**

Clinical Information Request:

We are unable to confirm the incidence of treatment emergent adverse events that you present in proposed prescribing information. There are differences in incidence of TEAEs in the SCS, the PI, and our analyses. We note that using both flagged and unflagged AEs in the ADAE dataset result in #'s similar to those in your PI. Please explain how you used the treatment emergent flag in generating the adverse reaction table.

Thank you,

Jackie

Jacquin L. Jones, MS, BSN  
CDR, U.S. Public Health Service  
Regulatory Health Project Manager  
Division of Hematology Products  
Food and Drug Administration  
WO Bldg 22, Rm 2222  
10903 New Hampshire Ave.  
Silver Spring, MD 20903  
Tel: 240-402-4590, Fax: 301-796-9909

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JACQUIN L JONES  
10/02/2015

## Boehmer, Jessica

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**From:** Boehmer, Jessica  
**Sent:** Wednesday, September 30, 2015 10:29 AM  
**To:** Maloney, Brian [JRDU] (BMalone1@ITS.JNJ.COM)  
**Cc:** Boehmer, Jessica  
**Subject:** Response needed: Clinical Information Requests - BLA 761036 - daratumumab - response due Oct 2 and 7

**Importance:** High

Dear Brian:

Please refer to BLA 761036 for daratumumab, submitted and received July 9, 2015. Please respond to the following information requests by the requested due date. Please send the response to me via email **by October 7, 2015 for item 1 and by October 2, 2015 for item 2**, and formally submit the information to your BLA.

### Clinical Information Request:

1. Given that IMWG criteria for determination of CR or sCR require negative M-protein by SPEP/UPEP or IFE and that daratumumab can interfere with SPEP and IFE assays, what is your plan for informing prescribers of this problem? Please provide proposed text for inclusion in the PI Section 7, which allows for a description of interactions of an agent with diagnostic tests. Please also provide proposed text to add to Section 5; include measures the prescriber should take to determine their patient's response to daratumumab.
2. Regarding validation of your DIRA, [REDACTED] (b) (4) [REDACTED] for the purposes of the reflex assay?

Please respond to me via email (do not send revised labeling for item 1, but proposed text), and also formally submit to your BLA.

Thank you,

Jessica

Jessica Boehmer, MBA  
Senior Regulatory Project Manager  
Division of Hematology Products (DHP)  
FDA/CDER/OND/OHOP  
(301) 796-5357 (phone)  
(301) 796-9845 (fax)

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JESSICA L BOEHMER  
09/30/2015

## Boehmer, Jessica

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**From:** Boehmer, Jessica  
**Sent:** Friday, September 25, 2015 1:52 PM  
**To:** Maloney, Brian [JRDU] (BMalone1@ITS.JNJ.COM)  
**Cc:** Boehmer, Jessica  
**Subject:** Response needed: Carton/Container - Information Requests - BLA 761036 - daratumumab - response due October 5

**Importance:** High

Dear Brian:

Please refer to BLA 761036 for daratumumab, submitted and received July 9, 2015. Please respond to the following information requests by the requested due date. Please send the response to me via email and formally submit the information to your BLA.

### Information Request:

#### Container Labels and Carton Labeling Comments

We have the following comments regarding your proposed container labels and carton labeling submitted on July 9, 2015. Please respond by COB October 5, 2015.

#### A. General Comments

1. Confirm there is no text on top of the [REDACTED] (b)(4) of the vials to comply with United States Pharmacopeia (USP) General Chapters: <7> Labeling, Labels and Labeling for Injectable Products, [REDACTED] (b)(4).
2. Indicate how the label is affixed to the vial and where the visual area of inspection is located per 21 CFR 610.60(e).
3. Consider using a different font color for the proper name to provide greater contrast between the background and the proper name. As currently presented, it lacks adequate visibility due to the use of [REDACTED] (b)(4) font and thus, lacks contrast with the white background.
4. Revise the middle digits of the NDC product code. As currently presented, the product code in the NDC number of the 100 mg/5 mL size (-502-) is the same as the product code in the NDC number for the 400 mg/20 mL volume size (-502-). This can lead to wrong strength errors because barcode scanners may only read the first 8 digits of the NDC code (i.e. "57894-502") and pharmacists may rely on the middle portion as a manual check. Therefore, we recommend revising the product code in the NDC numbers to ensure that the middle 3 digits (502) are different between strengths or volume sizes.<sup>[1]</sup>

#### B. Carton Labeling



1. Relocate the graphic  where it appears before the proprietary name, ‘Darzalex’ as users may interpret the letter as an “A”, “Z”, or “X”.<sup>[2]</sup>
2. Delete the <sup>(b)(4)</sup> the proper name as this is intervening matter per 21 CFR <sup>(b)(4)</sup>.
3. Bold the route of administration statement “For Intravenous Infusion Only” where it appears on the carton labeling.
4. Add the statement “Dilute Before Use” to the principal display panel (PDP).
5. Relocate “<sup>(b)(4)</sup>. Discard Unused Portion” from the top of the labeling to appear below the “Dilute Prior to Use”. Thus, the PDP should appear as:

Darzalex  
(daratumumab)  
Injection  
100 mg/5 mL  
(20 mg/mL)  
For Intravenous Infusion  
Dilute Before Use  
<sup>(b)(4)</sup> Only. Discard Unused Portion

6. Decrease the prominence of the “Rx Only” by removing bold font and relocating to the top right of the PDP.
7. Revise the manufacturer information to comply with 21 CFR 610.61(b). The Applicant/licensed manufacturer should appear as “Manufactured by”.

Manufactured by:  
Janssen Biotech, Inc.  
Horsham, PA 19044  
U.S. License Number 1864

If you want to display additional manufacturer information, cite regulation that you are attempting to fulfill.

8. Revise the labeling of ingredients to appear as:

Each 5 mL vial contains daratumumab 100 mg, glacial acetate acid (x mg), mannitol (x mg), polysorbate 20 (x mg), sodium acetate trihydrate (x mg), sodium chloride (x mg) and water for injection.

Use this format for the 400 mg/20 mL vial.

9. Add the finished dosage form to the diluent <sup>(b)(4)</sup>” on the side panel to read “0.9% Sodium Chloride Injection, USP”.
10. Delete <sup>(b)(4)</sup>” that appears on the side panel. This product will be used only in clinical settings.

### C. Vial Container Label

1. Delete the (b) (4) the proper name as this is intervening matter per 21 CFR (b) (4).
2. Remove bolding from the strength per mL so that the strength per total volume is the primary and prominent expression of strength per USP General Chapters: <1> Injections, Labels and Labeling, Strength and Total Volume for Single- and Multiple-Dose Injectable Drug Products. Thus, the strength expression should appear as:

**100 mg/5 mL**  
(20 mg/mL)

3. Bold “Single-Use Only. Discard Unused Portion” and “Must dilute before intravenous infusion” statements on the side panel of the container label in order to ensure safe handling and appropriate use of the product.
4. Add “Rx Only” to the top right of the PDP across from the NDC to comply with 21 CFR 201.100.

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<sup>1</sup> Guidance for Industry, Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (Draft Guidance) April 2013, page 14. Available from:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>

<sup>2</sup> Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (Draft Guidance). April 2013. Available from:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>. “We recommend not superimposing text over images or logos or placing a logo immediately before or after the proprietary name, because the logo can often look like an additional letter in the proprietary name.”

Please respond to me via email by **October 5, 2015**, and also formally submit to your BLA.

Thank you,

Jessica

Jessica Boehmer, MBA  
Senior Regulatory Project Manager  
Division of Hematology Products (DHP)  
FDA/CDER/OND/OHOP  
(301) 796-5357 (phone)  
(301) 796-9845 (fax)

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<sup>[1]</sup> Guidance for Industry, Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (Draft Guidance) April 2013, page 14. Available from:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>

<sup>[2]</sup> Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (Draft Guidance). April 2013. Available from:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>. "We recommend not superimposing text over images or logos or placing a logo immediately before or after the proprietary name, because the logo can often look like an additional letter in the proprietary name."

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/s/  
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JESSICA L BOEHMER  
09/25/2015



BLA 761036

**MID-CYCLE COMMUNICATION**

Janssen Biotech, Inc.  
c/o Janssen Research and Development, LLC  
Attention: Brian Maloney, RPh, MS  
Director, Regulatory Affairs  
920 Route 202, PO Box 300  
Raritan, NJ 08869

Dear Mr. Maloney:

Please refer to your Biologic License Application (BLA) submitted under section 351(a) of the Public Health Service Act for daratumumab injection, 100 and 400 mg/vial.

We also refer to the teleconference between representatives of your firm and the FDA on September 24, 2015. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call Jessica Boehmer, Regulatory Project Manager at (301) 796-5357.

Sincerely,

*{See appended electronic signature page}*

Albert Deisseroth, MD, PhD  
Clinical Team Leader  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

Enclosure:  
Mid-Cycle Communication



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MID-CYCLE COMMUNICATION**

**Meeting Date and Time:** September 24, 2015; 1:00 PM – 2:00 PM

**Application Number:** BLA 761036  
**Product Name:** daratumumab  
**Indication:** 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 are double refractory to a proteasome inhibitor and an immunomodulatory agent.

**Applicant Name:** Janssen Biotech, Inc.

**Meeting Chair:** Albert Deisseroth, MD, PhD, CDTL  
**Meeting Recorder:** Jessica Boehmer, MBA, Senior Regulatory Project Manager

**FDA ATTENDEES**

Office of Hematology and Oncology Products (OHOP)

Richard Pazdur, MD, Director

Division of Hematology Products (DHP)

Ann Farrell, MD, Director

Albert Deisseroth, MD, PhD, Clinical Team Leader, Cross-Discipline Team Leader

Barry Miller, MS, CRNP, Senior Clinical Analyst

Theresa Carioti, MPH, Chief, Project Management Staff

Jessica Boehmer, MBA, Senior Regulatory Project Manager

Office of Clinical Pharmacology (OCP)

Jeanne Fourie Zirkelbach, PhD, Clinical Pharmacology Reviewer

Office of Pharmaceutical Quality (OPQ)

Jee Chung, PhD, Product Quality Team Leader

Office of Surveillance and Epidemiology (OSE), Office of Medication Error Prevention and Risk Management (OMEPRM), Division of Risk Management (DRISK)

Joyce Weaver, PharmD, BCPS, Senior Drug Risk Management Analyst

Office of Surveillance and Epidemiology (OSE), Division of Pharmacovigilance II (DPV)

Shaily Arora, PharmD, DPV Safety Evaluator

Office of Medical Policy Initiatives (OMPI), Division of Medical Policy Programs (DMPP)  
Rowe Medina, PharmD, Patient Labeling Reviewer

**EASTERN RESEARCH GROUP ATTENDEES**

Christopher Sese, Independent Assessor

**APPLICANT ATTENDEES**

Janssen Attendees:

Joanita Aguiar, PhD, Global Labeling Product Leader  
Tahamtan Ahmadi, MD, PhD, Sr. Director, Clinical Leader  
Sudhir Burman, PhD, Associate Director, CMC  
Pamela Clemens, PhD, Associate Director, Clinical Pharmacology  
Timothy Coogan, PhD, VP, Head of Biologics Toxicology  
Adam Dinerman, PhD, Scientific Director, CMC Team Leader  
Huaibao Feng, PhD, Manager, Biostatistics  
Todd Gibson, Associate Director, Technical Integration  
Latonya Harris, Principal Scientist  
Tom Hogan, MS, Senior Director, CMC Regulatory Affairs  
Mary Houchin, Principal Scientist  
Richard Jansson, PhD, Senior Director, Compound Team Leader  
Imran Khan, MD, PhD, Director, Clinical Development  
Barbara Kolb, MBA, Senior Director, North America Therapeutic Area Leader, Regulatory Affairs  
Thomas Lin, MD, PhD, Senior Director, Medical Oncology  
Baolian Liu, MD, PhD, Director, Global Medical Safety Oncology  
Kevin Liu, PhD, Director, Biostatistics  
Ying Liu, Manager, CMC Regulatory Affairs  
Tony Lubiniecki, ScD, Senior Scientific Director, CMC Strategy  
Reshma Patel, Senior Director, Global Regulatory Leader  
Ming Qi, MD, PhD, Senior Director, Clinical Leader  
Sandra Rattray, PhD, VP, Regulatory Affairs Oncology  
Melanie Rothschild, MBA, Manager, Regulatory Affairs  
Kate Sasser, PhD, Senior Scientific Director, Translational Research  
Judith Shuster, PhD, Senior Director, CMC Regulatory Affairs  
Craig Tendler, MD, VP, Medical Affairs and Late Development  
Clarissa Uhlar, PhD, Associate Director, Clinical Project Scientist  
Jon Ukropec, PhD, Global Medical Affairs Scientific Advisor  
Kevin Wanczyk, Director, CMC Regulatory Affairs  
Jim Wang, PhD, Associate Director, Biostatistics  
Sen Hong Zhuang, MD, PhD, VP, Clinical Research Development

Genmab Attendee:

Michael Karl Bauer, PhD, Clinical Development Head



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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## 1.0 INTRODUCTION

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

## 2.0 SIGNIFICANT ISSUES

No significant issues have been identified to date.

## 3.0 INFORMATION REQUESTS

1. At the Applicant Orientation meeting, the following statements were made during the remarks made by Janssen personnel:

*“Although CD38 is present on T cells, B cells and NK cells, and the administration of Daratumumab is accompanied by decreases in the levels of the circulating NK cell mass, no significant decreases in the levels of B or T cell lymphocytes are seen following the administration of Daratumumab. Please provide a summary of data that led to that conclusion.”*

What data has Janssen developed that explains this disparate effect of Daratumumab on NK cells vs Lymphocytes?

2. We anticipate additional information requests from Product Quality.

## 4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

The Agency would like to follow up on the information request dated September 17, 2015, that read:

“Provide a specific plan for distribution of your materials describing daratumumab interference with serological testing.”

Janssen indicated they plan to provide a response to the Agency by close-of-business September 25, 2015. The response will include their plan for education to blood banks and other hematologists/oncologists.

There are no major safety concerns identified at this time and there is currently no need for a REMS.

#### **5.0 ADVISORY COMMITTEE MEETING**

There are no plans at this time for an AC meeting.

#### **6.0 LATE-CYCLE MEETING /OTHER PROJECTED MILESTONES**

Late-Cycle Meeting date: October 19, 2015, 3:00 PM

As we indicated during the Mid-Cycle Communication, we plan to act early on this application under an expedited review. The Late-Cycle Meeting between you and the review team is currently scheduled for October 19, 2015. We intend to send the briefing package to you approximately 4 days in advance of the meeting. If these timelines change, we will communicate updates to you during the course of review.

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/s/  
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ALBERT B DEISSEROTH  
09/25/2015

## Boehmer, Jessica

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**From:** Boehmer, Jessica  
**Sent:** Thursday, September 17, 2015 11:18 AM  
**To:** Maloney, Brian [JRDU] (BMalone1@ITS.JNJ.COM)  
**Cc:** Boehmer, Jessica  
**Subject:** Response needed: Clinical and Clinical Pharmacology Information Requests - BLA 761036 - daratumumab - response due Sept 23

**Importance:** High

Dear Brian:

Please refer to BLA 761036 for daratumumab, submitted and received July 9, 2015. Please respond to the following information requests by the requested due date. Please send the response to me via email and formally submit the information to your BLA.

### Clinical Information Request:

Provide a specific plan for distribution of your materials describing daratumumab interference with serological testing.

### Clinical Pharmacology Information Request:

For Study GEN501 Part 2:

1. Please update dataset adeg.xpt to have other ECG parameters PR, QRS, RR and QT available. As QTCB, QTCF and HRMEAN in the dataset, please have baseline and change values available for all of the requested parameters.
2. Please clarify/confirm that exposure response analysis for part 2 was based on dataset adegpk.xpt.

Furthermore, please submit all ECG waveforms related to this study report to the ECG warehouse at: [www.ecgwarehouse.com](http://www.ecgwarehouse.com).

Please respond to me via email by **10:00 AM September 23, 2015**, and also formally submit to your BLA.

Thank you,

Jessica

Jessica Boehmer, MBA  
Senior Regulatory Project Manager  
Division of Hematology Products (DHP)  
FDA/CDER/OND/OHOP  
(301) 796-5357 (phone)  
(301) 796-9845 (fax)

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/s/  
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JESSICA L BOEHMER  
09/17/2015

## Boehmer, Jessica

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**From:** Boehmer, Jessica  
**Sent:** Tuesday, September 15, 2015 2:11 PM  
**To:** Maloney, Brian [JRDU5] (BMalone1@ITS.JNJ.COM)  
**Cc:** Boehmer, Jessica  
**Subject:** Clin Pharm - QT/IRT Information Request: BLA 761036: daratumumab - due Sept 24  
**Attachments:** Highlights\_ClinPharm\_and\_Cardiac\_Safety.doc

**Importance:** High

Dear Brian:

Please refer to BLA 761036 for daratumumab, submitted and received July 9, 2015. Please respond to the attached information request by the requested due date. Please send the response to me via email and formally submit the information to your BLA.

[Clinical Pharmacology – QT/IRT Information Request:](#)

Please complete the attached Clinical Pharmacology and Cardiac Safety Table and send it back to me via email as soon as possible.

Please respond to me via email as soon as possible, and no later than **September 24, 2015**, and also formally submit to your BLA. Kindly confirm receipt of this email.

Thank you,

Jessica

Jessica Boehmer, MBA  
Senior Regulatory Project Manager  
Division of Hematology Products (DHP)  
FDA/CDER/OND/OHOP  
(301) 796-5357 (phone)  
(301) 796-9845 (fax)

**Table 1. Highlights of Clinical Pharmacology and Cardiac Safety**

Therapeutic dose	Include maximum proposed clinical dosing regimen	
Maximum tolerated dose	Include if studied or NOAEL dose	
Principal adverse events	Include most common adverse events; dose limiting adverse events	
Maximum dose tested	Single Dose	Specify dose
	Multiple Dose	Specify dosing interval and duration
Exposures Achieved at Maximum Tested Dose	Single Dose	Mean (%CV) Cmax and AUC
	Multiple Dose	Mean (%CV) Cmax and AUC
Range of linear PK	Specify dosing regimen	
Accumulation at steady state	Mean (%CV); specify dosing regimen	
Metabolites	Include listing of all metabolites and activity	
Absorption	Absolute/Relative Bioavailability	Mean (%CV)
	Tmax	<ul style="list-style-type: none"> <li>• Median (range) for parent</li> <li>• Median (range) for metabolites</li> </ul>
Distribution	Vd/F or Vd	Mean (%CV)
	% bound	Mean (%CV)
Elimination	Route	<ul style="list-style-type: none"> <li>• Primary route; percent dose eliminated</li> <li>• Other routes</li> </ul>
	Terminal t½	<ul style="list-style-type: none"> <li>• Mean (%CV) for parent</li> <li>• Mean (%CV) for metabolites</li> </ul>
	CL/F or CL	Mean (%CV)
Intrinsic Factors	Age	Specify mean changes in Cmax and AUC
	Sex	Specify mean changes in Cmax and AUC
	Race	Specify mean changes in Cmax and AUC
	Hepatic & Renal Impairment	Specify mean changes in Cmax and AUC
Extrinsic Factors	Drug interactions	Include listing of studied DDI studies with mean changes in Cmax and AUC
	Food Effects	Specify mean changes in Cmax and AUC and meal type (i.e., high-fat, standard, low-fat)
Expected High Clinical Exposure Scenario	Describe worst case scenario and expected fold-change in Cmax and AUC. The increase in exposure should be covered by the supra-therapeutic dose.	
Preclinical Cardiac Safety	Summarize <i>in vitro</i> and <i>in vivo</i> results per S7B guidance.	
Clinical Cardiac Safety	Describe total number of clinical trials and number of subjects at different drug exposure levels. Summarize cardiac safety events per ICH E14 guidance (e.g., QT prolongation, syncope, seizures, ventricular arrhythmias, ventricular tachycardia, ventricular fibrillation, flutter, torsade de pointes, or sudden deaths).	

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/s/  
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JESSICA L BOEHMER  
09/15/2015

## Boehmer, Jessica

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**From:** Boehmer, Jessica  
**Sent:** Monday, September 14, 2015 9:36 AM  
**To:** Maloney, Brian [JRDU] (BMalone1@ITS.JNJ.COM)  
**Cc:** Boehmer, Jessica  
**Subject:** Response needed: Clinical Pharmacology Information Request - BLA 761036 - daratumumab - response due by tomorrow

**Importance:** High

Dear Brian:

Please refer to BLA 761036 for daratumumab, submitted and received July 9, 2015. Please also refer to your presubmission dated June 5, 2015. Please respond to the following information request by the requested due date. Please send the response to me via email and formally submit the information to your BLA.

[Clinical Pharmacology Information Request:](#)

For the submission dated 6/5/15 (SDN 1), please provide the PK dataset used to obtain plots on page 267 – 271 of the final clinical study report for protocol GEN501.

Please respond to me via email by **10:00 AM tomorrow, September 15, 2015**, and also formally submit to your BLA.

Thank you,

Jessica

Jessica Boehmer, MBA  
Senior Regulatory Project Manager  
Division of Hematology Products (DHP)  
FDA/CDER/OND/OHOP  
(301) 796-5357 (phone)  
(301) 796-9845 (fax)

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/s/  
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JESSICA L BOEHMER  
09/14/2015



BLA 761036

**FILING COMMUNICATION -  
FILING REVIEW ISSUES IDENTIFIED**

Janssen Biotech, Inc.  
c/o Janssen Research and Development, LLC  
Attention: Brian Maloney, RPh, MS  
Director, Regulatory Affairs  
920 Route 202, PO Box 300  
Raritan, NJ 08869

Dear Mr. Maloney:

Please refer to your Biologics License Application (BLA) dated July 9, 2015, received July 9, 2015, submitted under section 351(a) of the Public Health Service Act for daratumumab injection, 100 and 400 mg/vial.

We also refer to your amendments dated June 5 and 15; July 9 and 15; and August 7, 11, 14, and 20, 2015.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 601.2(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. Therefore, the user fee goal date is March 9, 2016. This application is also subject to the provisions of “the Program” under the Prescription Drug User Fee Act (PDUFA) V (refer to:

<http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>.

However, we plan to act early on this application under an expedited review, provided that no significant application deficiencies or unexpected shifts in work priorities or team staffing prevent an early action.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: *Good Review Management Principles and Practices for PDUFA Products*. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by

February 17, 2016. This date conforms to the 21<sup>st</sup> Century Review timeline for your application. If our review continues on an expedited timeline, we may communicate revised dates for labeling and postmarketing requirement/commitment requests.

In addition, the planned date for our internal mid-cycle review meeting is September 16, 2015. We are not currently planning to hold an advisory committee meeting to discuss this application.

During our filing review of your application, we identified the following potential review issues:

#### Drug Product Microbiology

1. Provide the worst-case (b) (4) process parameters validated with CCIT in comparison to the parameters used for routine production (Section 3.2.P.2.5). Indicate which CCIT method was used to qualify (b) (4) process parameters.
2. Provide the sample volume for the bioburden test performed for DS (b) (4) sterile filtration (3.2.P.3.4). Clarify, if the bioburden samples are taken (b) (4).
3. Submit the (b) (4) validation data and information for Cilag and (b) (4) Drug Product processes (in section 3.2.P.3.5).
4. Shipping validation studies should be provided in section 3.2.P.3.5.
5. The current acceptance criterion for endotoxin is set at (b) (4) (3.2.P.5.6). This is based on the maximum endotoxin limit of (b) (4) and the maximum proposed dose of Drug Product (DP) of 24 mg/kg. However, the daratumumab DP is intended for administration by the intravenous (IV) route after dilution in commercially available 0.9% sodium chloride. No (b) (4) contribution was considered during the endotoxin specification limit calculation (Section 3.2.P.5.6). A (b) (4) safety factor is recommended for the commercial endotoxin release specification. Taking into account that the endotoxin levels at release and during stability of DP at (b) (4) (Section 3.2.P.5.6) the adjustment of the limit appears to be possible. Please re-adjust the endotoxin limits for both in-process limits (Section P.3.4, Control of Critical Steps and Intermediates) and release specification (Section 3.2.P.5.6) for DP. Alternatively, provide justification for the proposed specification.

#### Drug Substance Microbiology

6. With respect to the Description of the Manufacturing Process and Process Controls (Section 3.2.S.2.2)
  - a. Bioburden and endotoxin at the (b) (4) for each cycle at the end of hold should be monitored. Implement a microbial monitoring program for the (b) (4).

- 
7. Regarding Section 3.2.S.2.5, Process Validation and/or Evaluation
    - a. Indicate if microbial quality attributes (bioburden and endotoxin) are monitored during the validation (b) (4) lifetime studies at scale.
    - b. Provide data to support microbial control during maximum hold times. Validation of maximum hold time for microbial quality should be performed at manufacturing scale in three independent runs unless a valid justification is provided.
    - c. Shipping validation studies for drug substance should be submitted under section 3.2.S.2.5 instead of 3.2.S.6 (Container Closure System).
  8. The endotoxin specifications for daratumumab drug substance should be lowered for alignment with the drug product specifications (section 3.2.S.4.1).
  9. Describe bioburden and endotoxin methods used for (b) (4) release samples (Section 3.2.S.4.2).
  10. Provide a detailed description of the bioburden method validation including the preparation of negative and positive controls and test samples (Section 3.2.S.4.3).
  11. Regarding the Container Closure System – Shipping Qualification (Section 3.2.S.6),
    - a. Clarify the temperature (ambient temperature profile) used to qualify shipping systems (b) (4).

- b. Indicate how many shippers were evaluated for each configuration tested and how many times (runs) each validation test was performed for each shipping system.
- c. Provide shipping qualification reports, indicating ambient and internal shipping temperatures registered during the studies.
- d. Provide a diagram to show where the position of the (b) (4) within the shippers during shipping validation and during routine shipping.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

We request that you submit the following information:

#### CMC Information Requests

1. Form 356h and sections 3.2.S.2.1 and 3.2.P.3.1 do not clearly distinguish the specific functions of each facility, e.g., sites that perform release and stability testing for the drug substance and drug product are not clearly stated and clarity regarding which tests are performed is only provided on the 356h and only for some sites. Update the BLA with the following information regarding the manufacturing and testing sites for daratumumab:
  - a. Identification of the specific tests to be performed at each site. For each site and assay, data demonstrating adequate transfer between the sites should be provided.
  - b. Identification of storage/maintenance sites for the cell bank vials (Working Cell Bank and Master Cell Bank, if appropriate) that will be used to manufacture daratumumab. The cell bank(s) should be stored under GMP conditions (see ICH Q7 Table 1).
2. Per 21 CFR 610.14, an identity test must be performed on products after all labeling operations have been completed. Section 3.2.P.3.3.3.5 states that visual identification and verification of batch number on the (b) (4) and vial label of each filled batch is performed after all labeling operations have been completed. Clarify if the seal and batch number are added to the vial before samples are pulled for release testing.
3. The executed batch record for (b) (4) batch 14C0903 was duplicated and included in (b) (4) the executed batch record (b) (4). Therefore, we are unable to review the information for (b) (4). Submit the executed batch record for (b) (4) for batch 14C0903.
4. In the summary paragraph of Section 3.2.A.2- Adventitious Agents Safety Evaluation- Non-Viral Adventitious Agents, you state that (b) (4),” and section 3.2.S.2.3 is referenced. The use of (b) (4)

(b) (4) is not described in section 3.2.S.2.3 or in Section 3.2.A.2- Adventitious Agents Safety Evaluation – Viral Adventitious Agents. Please clarify at what stage (b) (4) was used in the manufacturing of daratumumab and provide a risk evaluation for the use of this material.

5. Regarding the reference material (RM):
  - a. Limited information is provided regarding the potency testing and potency acceptance criteria for qualification of new RM. To control for drift in the quality of the marketed product, the approach(s) and criteria used for RM qualification should ensure minimal drift in potency of new RM that are implemented. Provide a more comprehensive description of the approach used for RM qualification (e.g., the number of independent determinations of the potency of the new RM, the statistical analysis), and provide a justification of the proposed acceptance criteria.
  - b. Provide all available stability data for the current primary and working RM.
6. Provide the validation protocols for the manufacturing scale reprocessing of the concentrated (b) (4)
7. Section 3.2.S.2.2 (b) (4)  
The protocol(s) should include the testing plan and acceptance criterion for each parameter evaluated and the target number of cycles.
8. Provide the protocol for manufacturing and qualification of new Working Cell Banks (WCB). The protocol should include (b) (4) cell growth parameters and DS product quality testing to ensure that the DS manufactured using the new WCB is comparable to DS manufactured using the established (current) WCB.
9. In section 3.2.S.2.2, the viability a (b) (4)  
The proposed limit for viability should be supported by manufacturing data.
10. The CoA for the Master Cell Bank indicates that the cell bank was tested for contamination by (b) (4). Confirm that this testing meets the 9 CFR requirements.

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [PLLR Requirements for Prescribing Information](#) websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances, and
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

### **PROMOTIONAL MATERIAL**

We will review this application under the provisions of 21 CFR 601 Subpart E – *Accelerated Approval of Biological Products for Serious or Life-Threatening Illnesses*. Unless we otherwise inform you, as required by 21 CFR 601.45, you must submit during the preapproval review period copies of all promotional materials, including promotional labeling and advertisements, intended for dissemination or publication within 120 days following marketing approval (i.e., your launch campaign). During the preapproval review period, please submit, in triplicate, a detailed cover letter (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), and patient PI (as applicable). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

OPDP Regulatory Project Manager  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion (OPDP)  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Alternatively, you may submit promotional materials for accelerated approval products electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and patient PI (as applicable), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

You submitted establishment information that is not required as part of a BLA for specified products. Please refer to the *Guidance for Industry For the Submission of Chemistry, Manufacturing, and Controls Information for a Therapeutic Recombinant DNA-Derived Product or a Monoclonal Antibody Product for In Vivo Use* for the information you should include in your application. We will assess this information during the pre-license inspection of your establishment, but not as part of your application. Its inclusion in the file does not constitute approval.

#### **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because the biological product for this indication has orphan drug designation, you are exempt from this requirement.

If you have any questions, call Jessica Boehmer, Regulatory Project Manager, at (301) 796-5357.

Sincerely,

*{See appended electronic signature page}*

Ann T. Farrell, MD  
Director  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

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/s/  
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ANN T FARRELL  
09/04/2015



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration  
Silver Spring, MD 20993

BLA 761036

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Janssen Biotech, Inc.  
920 Route 202  
P.O. Box 300  
Raritan, NJ 08869

ATTENTION: Brian Maloney, R.Ph., MS  
Regulatory Affairs, Director

Dear Mr. Maloney:

Please refer to your Biologics License Application (BLA) dated and received July 9, 2015, submitted under section 351(a) of the Public Health Service Act for Daratumumab, 20 mg/mL.

We also refer to your correspondence dated and received July 15, 2015, requesting review of your proposed proprietary name, Darzalex.

We have completed our review of the proposed proprietary name, Darzalex, and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your July 15, 2015, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names  
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,  
(<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Kevin Wright, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3621. For any other information regarding this application, contact Jessica Boehmer, Regulatory Project Manager in the Office of New Drugs, at (301) 796-5357.

Sincerely,

*{See appended electronic signature page}*

Todd Bridges, RPh  
Director  
Division of Medication Error Prevention and Analysis  
Office of Medication Error Prevention and Risk Management  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

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/s/  
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TODD D BRIDGES  
09/04/2015

## Boehmer, Jessica

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**From:** Boehmer, Jessica  
**Sent:** Monday, August 17, 2015 12:00 PM  
**To:** Maloney, Brian [JRDUS] (BMalone1@ITS.JNJ.COM); Rothschild, Melanie [JRDUS] (MRothsch@ITS.JNJ.COM)  
**Subject:** Response needed: Clinical Pharmacology Information Request - BLA 761036 - daratumumab - response due by Aug 21st  
**Importance:** High

Dear Brian and Melanie:

Please refer to BLA 761036 for daratumumab, submitted and received July 9, 2015. Please respond to the following information request by the requested due date. Please send the response to me via email and formally submit the information to your BLA.

[Clinical Pharmacology Information Request:](#)

Submit the simulation code for simulated dataset EX1\_QWTR.csv (ex1-qwtr-csv.xpt) in Module 5.3.3.5. Also submit the simulation code and dataset associated with Figure 17 in your Summary of Clinical Pharmacology Studies. If already submitted in the BLA, please point us to the correct location.

Please respond to me via email by **4:00 PM August 21, 2015**, and also formally submit to your BLA.

Thank you,

Jessica

Jessica Boehmer, MBA  
Senior Regulatory Project Manager  
Division of Hematology Products (DHP)  
FDA/CDER/OND/OHOP  
(301) 796-5357 (phone)  
(301) 796-9845 (fax)

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/s/  
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JESSICA L BOEHMER  
08/17/2015



IND 100638

**MEETING MINUTES**

Janssen Research & Development, LLC  
Attention: Brian J. Maloney, R.Ph., M.S.  
Director, Regulatory Affairs  
1400 McKean Road, P.O. Box 776  
Spring House, PA 19477

Dear Mr. Maloney:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for daratumumab.

We also refer to the meeting between representatives of your firm and the FDA on July 31, 2013. The purpose of the meeting was to discuss a comprehensive overview of the planned development program for daratumumab, including planned clinical studies and Phase 3 Chemistry Manufacturing and Controls (CMC) plans for the development of daratumumab and the proposed comparability strategy between Phase 1/2 and Phase 3 clinical/commercial material.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Jessica Boehmer, Regulatory Project Manager at (301) 796-5357.

Sincerely,

*{See appended electronic signature page}*

Virginia Kwitkowski, M.S., R.N., A.C.N.P.-B.C.  
Lead Clinical Analyst  
Clinical Team Leader  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

Enclosure:  
Meeting Minutes



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** Type B  
**Meeting Category:** Breakthrough Therapy

**Meeting Date and Time:** July 31, 2013, 11:00 AM – 12:00 PM, ET  
**Meeting Location:** 10903 New Hampshire Avenue  
White Oak Building 22, Conference Room: 1415  
Silver Spring, Maryland 20903

**Application Number:** IND 100638  
**Product Name:** Daratumumab (HuMax<sup>®</sup>-CD38, JNJ-54767414)  
**Indication:** Treatment of patients with multiple myeloma who have received at least 3 prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent (IMiD) or are double refractory to a PI and an IMiD.

**Sponsor/Applicant Name:** Janssen Research & Development, LLC

**Meeting Chair:** Virginia Kwitkowski  
**Meeting Recorder:** Jessica Boehmer

**FDA ATTENDEES**

Office of Hematology and Oncology Products (OHOP)  
Anthony Murgo, M.D., Associate Director

Division of Hematology Products (DHP)  
Edvardas Kaminskas, M.D., Deputy Division Director  
Virginia Kwitkowski, M.S., RN, ACNP-BC, Lead Clinical Analyst, Clinical Team Leader  
Barry Miller, M.S., C.R.N.P., Clinical Reviewer  
Alexandria Schwarsin, M.D., Clinical Reviewer  
Kris Kolibab, Ph.D., Regulatory Project Manager  
Jessica Boehmer, M.B.A., Regulatory Project Manager

Office of Biotechnology Products (OBP) /Division of Monoclonal Antibodies (DMA)  
Sarah Kennett, Ph.D., Review Chief  
Michele Dougherty, Ph.D., Product Quality Team Leader  
Tura Camilli, Ph.D., Product Quality Reviewer

Meeting Minutes  
Breakthrough Therapy

Office of Biostatistics (OB), Division of Biometrics (DB)

Lei Nie, Ph.D., Statistical Team Leader  
Yun Wang, Ph.D., Statistical Reviewer

Office of Clinical Pharmacology (OCP)

Bahru Habtemariam, Pharm.D., Clinical Pharmacology Reviewer

Office of Manufacturing and Product Quality (OMPQ)

Patricia Hughes, Ph.D., Team Leader  
Kalavati Suvarna, Ph.D., Reviewer

**SPONSOR ATTENDEES**

Genmab

Christian Cimander, Ph.D., Associate Director, CMC  
Nikolai Constantin Brun, M.D., Ph.D., Medical Head

Janssen R&D

Sudhir Burman, Ph.D., CMC Analytical Technical Integrator  
Andrew Cakana, M.D., F.R.C.Path., Clinical Leader  
Adam Dinerman, Ph.D., CMC Team Leader  
Yusri Elsayed, M.D., M.H.Sc., Ph.D., Disease Area Stronghold Leader, Hematology  
Richard Jansson, Ph.D., Compound Development Team Leader  
Vinaya Kapoor, Ph.D., Global Regulatory Affairs – CMC  
Kevin Liu, Ph.D., Biostatistics Leader  
Tony Lubinecki, Sc.D., CMC Strategy  
Brian Maloney, R.Ph., M.S., North American Regulatory Affairs  
Reshma Patel, Global Regulatory Leader  
Thomas Puchalski, Pharm.D., Clinical Pharmacology Leader  
Kate Sasser, Ph.D., Oncology Biomarker Leader

Meeting Minutes  
Breakthrough Therapy

## 1.0 BACKGROUND

Janssen R&D, LLC (the Sponsor) requested this meeting as a follow-up to the Food and Drug Administration's (FDA's) granting of Breakthrough Therapy Designation of daratumumab (May 1, 2013) for the treatment of patients with multiple myeloma who have received at least 3 prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent (IMiD) or are double refractory to a PI and an IMiD. The purpose of the meeting is for the Sponsor to provide FDA with a comprehensive overview of the planned daratumumab development program, including planned clinical studies.

In addition, the Sponsor proposes to discuss Phase 3 Chemistry Manufacturing and Controls (CMC) plans for the development of daratumumab and the proposed comparability strategy between Phase 1/2 and Phase 3 clinical/commercial material. Recognizing the principles for assessing the pre- and post-change products as described in the International Conference on Harmonization [ICH] Guideline Q5E, Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process (ICH Q5E), the Sponsor wishes to begin discussion with the Agency to guide future daratumumab development. These discussions are viewed by the Sponsor as important in obtaining alignment on critical path activities for the development of daratumumab.

## 2. DISCUSSION

### 2.1. Comparability

#### **CMC Comparability Strategy – Phase 1/2 Manufacturing Process to Phase 3/Commercial Manufacturing Process:**

##### **Question 1:**

***Does the Agency agree with the proposed analytical testing plan, which includes a comprehensive panel of biochemical, biophysical and biological tests, that will be used to demonstrate comparability?***

##### **FDA Response to Question 1:**

Overall, we agree with the panel of tests that are proposed to be used in the comparability exercise. FDA notes only one method is proposed to be used to assess charge variants. The use of an orthogonal method to detect the presence of charge variants is recommended.

##### **Discussion:**

**FDA agrees that the peptide map method is sufficient to capture information on charge variants to establish comparability.**

Meeting Minutes  
Breakthrough Therapy**Question 2:**

***Does the Agency agree with the proposed comparability approach which includes development batch comparability, followed by full-scale Phase 3 clinical batch comparability of post-change material (DP manufactured from [REDACTED]<sup>(b) (4)</sup>) and pre-change material (DP manufactured from [REDACTED]<sup>(b) (4)</sup>)?***

**FDA Response to Question 2:**

Adequate information is not provided in the meeting package to agree to the acceptability of the comparability approach. The information in the meeting package does not make clear how comparability acceptance criteria will be established. Comparability acceptance criteria should be based on historical data and should be tighter than the lot release acceptance criteria. Development batch comparability data would be considered supportive of comparability between the Phase 1/2 clinical process and the Phase 3 manufacturing process. Development batch data should be supported by a comparison of manufacturing parameters that could impact quality attributes of daratumumab between the development scale and the Phase 3 scale process and the rationale for any differences in parameter settings between the two scales. Conclusions as to the comparability of the Phase 1/2 clinical and Phase 3 manufacturing processes will be made following review of the clinical batch comparability. FDA notes the proposed comparability approach includes comparison to one lot manufactured by the Phase 3 manufacturing process. FDA recommends including additional lots of drug product manufactured by the Phase 3 process in the comparability assessment. If the comparability approach described in the meeting package is maintained and no additional lots of Phase 3 drug product are included in the comparability study, appropriate characterization of the additional Phase 3 batches included in the BLA will be necessary to establish that all lots manufactured by the Phase 3 manufacturing process are representative of daratumumab used in the clinical studies intended to support licensure. The appropriateness of the characterization studies will be a BLA review issue. FDA has the following additional comments regarding the comparability approach:

- a. Comparison to historical ranges should be provided in place of “report results” as acceptance criteria for the testing performed as part of the development batch comparability study.

**Discussion:**

**FDA stated that historical data with Phase 1 lots should be used to inform comparability acceptance criteria. Attribute knowledge and scientific justification should be provided to support the acceptance criteria.**

Meeting Minutes  
Breakthrough Therapy

- b. FDA notes that the proposed comparability testing plan does not clearly describe stability studies intended to support comparability of the two processes. Include accelerated or stressed stability data as part of the comparability study.

**Discussion:**

**The stability approach presented by the Sponsor appears to be acceptable (see attached slides). The FDA requested multiple timepoints be submitted for the stressed and accelerated stability studies.**

**Question 3:**

***Does the Agency agree that Phase 3 clinical batch comparability results can be submitted via an amendment to the IND? Further, assuming acceptable results, does the Agency agree that a written response of acknowledgement would be provided by the Agency?***

**FDA Response to Question 3:**

Yes, the clinical batch comparability results can be submitted as an amendment to the IND. FDA notes Janssen's plan to submit the clinical comparability amendment in 3Q2013-1Q2014 and to use drug product manufactured by the (b)(4) manufacturing process in the clinic beginning in 1/2Q2014. FDA recommends including a request for expedited review of the amendment in the cover letter. FDA agrees to provide a written response when review of the comparability amendment is complete; however, FDA cannot, at this time, provide a definitive time frame for the written response.

**Discussion:**

No discussion occurred.

## 2.2. Clinical Plans

### **Clinical Plans Using DP Manufactured From Post-Change (Proposed Phase 3) Process:**

**Question 4:**

***Assuming biochemical, biophysical, and in vitro biological comparability is demonstrated, does the Agency agree that the proposed comparability plan would support dosing of new subjects enrolled in all ongoing studies, including Study MMY2002 (Part 2), GEN503, and all new studies with clinical material manufactured from the proposed Phase 3 process, and not require additional clinical studies?***

Meeting Minutes  
Breakthrough Therapy**FDA Response to Question 4:**

The clinical (PK, PD and safety) comparability evaluation of your drug products in Study MMY2002 should be completed before using the Phase 3 Drug Product in Phase 3 studies. Whether additional clinical studies will be needed will depend on the review of the comparability data from Study MMY2002.

**Discussion:**

**The Agency reiterated the necessity to conduct PK/PD comparability of the existing and new Phase 3 DPs before introducing the Phase 3 DP into new studies. The Sponsor proposed to conduct PK/PD comparability as a run-in for the Phase 3 trial. The sample size will depend upon the variability between patients and not statistically powered. The PK evaluations would be compared to historical data from the pre-change product.**

**Question 5:**

***Does the Agency agree that the clinical data from subjects dosed with both DPs could be included in the first BLA submission to support approval in the Breakthrough Therapy Designation population based on biochemical, biophysical, and in vitro biological comparability and on PK, PD, and safety data of the Phase 1/2 and Phase 3/commercial DP in subjects in the MMY2002 study?***

**FDA Response to Question 5:**

This will depend on the comparability results of MMY2002. See responses to Questions 2 and 4.

**Discussion:**

**No discussion occurred.**

**Question 6:**

***Further, does the FDA agree that proposed number of subjects listed in Table 20 provides sufficient exposure data with the post-change Phase 3 DP from planned clinical studies to support the first BLA and commercial registration of the proposed Phase 3 process?***

**FDA Response to Question 6:**

This will be a review issue based upon the comparability of the Drug Products.

Meeting Minutes  
Breakthrough Therapy

**Discussion:**

No discussion occurred.

**2.3. CMC Data for a BLA Submission**

**Stability Data Package for the BLA Submission:**

**Question 7a:**

*Does the Agency agree that the (b) (4) DS stability package including 3 commercially representative Phase 3 clinical batches, 1 representative development batch, and 2 supportive Phase 1/2 clinical batches, and assuming comparability is established, provides sufficient stability data for the BLA submission?*

**FDA Response to Question 7a:**

Provided that comparability is established and no manufacturing changes are made prior to the BLA submission, the proposed stability package appears to be acceptable. Stability data from the development lot would be considered supportive, rather than representative stability data. The impact of manufacturing changes on Drug Substance stability profiles should be assessed as part of the comparability exercise. The outcome of the comparability assessment will influence whether Phase 1/2 clinical batch data can be considered supportive stability data.

**Discussion:**

**FDA clarified that sufficient data should be presented to demonstrate that the development batch is representative of product manufactured by the Phase 3/commercial process. Conclusions as to the representativeness of the data will be a review issue. If the data are sufficient to demonstrate that the development batch is representative of the Phase 3 manufacturing process, development batch stability data can be considered representative.**

**Question 7b:**

*Does the Agency agree that the DP stability package including 3 commercially representative Phase 3 clinical batches, 1 representative development batch and 4 supportive Phase 1/2 clinical batches, and assuming comparability is established, provides sufficient stability data for the BLA submission?*

Meeting Minutes  
Breakthrough Therapy**FDA Response to Question 7b:**

FDA notes that Phase 3 drug product will be filled at Janssen-Cilag and (b) (4) and commercial drug product will be manufactured at (b) (4). Comparability of the Phase 3 drug product manufactured at the two sites should be established and should include an assessment of any impact of different fill technologies on product quality and stability profiles. Provided that comparability is established and no manufacturing changes are made prior to the BLA submission, the proposed stability package appears to be acceptable. The outcome of the comparability assessment will influence whether Phase 1/2 clinical batch data can be considered supportive stability data.

**Discussion:**

**If comparability of the Phase 1/2 is established, the proposal appears acceptable. The shelf life is a review issue. For the DP the discussion pertains to the 100 mg vial presentation (see attached slides).**

**Question 7c:**

*Further, given the minor formulation and process improvement changes between Phase 1/2 and Phase 3/commercial DP, and assuming comparability is established, does the Agency agree that the Phase 1/2 clinical stability batches be considered supportive stability data for the BLA submission?*

**FDA Response to Question 7c:**

Refer to responses to Questions 7a and 7b above.

**Discussion:**

No discussion occurred.

**BLA Specifications Approach:****Question 8:**

*Does the Agency agree that the proposed approach for setting commercial specifications that utilizes a combination of Janssen mAb process experience, daratumumab clinical batch experience and product knowledge, and the results of available structure- function studies is sufficient to support the BLA submission?*

Meeting Minutes  
Breakthrough Therapy**FDA Response to Question 8:**

Commercial specifications are based on lots used in clinical studies, manufacturing consistency, and stability data. Knowledge of critical quality attributes for daratumumab can support establishing specifications for licensure. FDA acknowledges limited data may be available at the time of licensure and would support re-evaluating specifications once sufficient commercial manufacturing experience is gained.

The (b) (4) test should be conducted on commercial material, if the commercial process is different from the phase 3 process.

**Discussion:**

No discussion occurred.

**Process Qualification (PQ) Timing (As Part of Process Validation [PV]):****Question 9a:**

*Does the Agency agree with the proposed timing and availability for PPQ batches with DS PPQ results included in the initial BLA submission?*

**FDA Response to Question 9a:**

The timing and availability of process performance qualification (PPQ) batches to support drug substance process validation appears to be acceptable. The proposed availability of stability data for the drug substance PPQ batches would be acceptable providing no manufacturing changes are made for the commercial drug substance manufacturing process.

Manufacturing operations should be on-going during the BLA review cycle for inspection purposes.

**Discussion:**

No discussion occurred.

**Question 9b:**

*Further, does the Agency agree that the DP PPQ results can be submitted within 60 days of the initial BLA submission?*

Meeting Minutes  
Breakthrough Therapy**FDA Response to Question 9b:**

No, data supporting drug product process validation is necessary to constitute a complete BLA submission. Per the PUDFA V legislation, limited components of a BLA submission may be submitted within 30 days of the BLA submission; FDA does not consider drug product process validation information to be a 'limited component' of the submission

The sterilization and (b) (4) process validation data and information should be included in the BLA at the time of initial submission.

**Discussion:**

**No discussion occurred.**

**Question 9c:**

***Further, does the Agency agree that available stability results for PPQ batches would be submitted to FDA with the Clinical Safety update during the BLA review period and subsequent updates in the BLA Annual Report for this product?***

**FDA Response to Question 9c:**

No, per the PDUFA V legislation, limited components of the BLA submission may be submitted within 30 days of the BLA submission. Any available stability data for the drug product PPQ batches should be submitted with the BLA submission. With respect to the submission of additional stability data to support a proposed expiry period, the FDA may request a 'simple stability update'. A simple stability update is defined as stability data and analyses performed under the same conditions and for the same drug product batches in the same container closure system(s) as described in the stability protocol provided in the original submission; it will use the same tabular presentation as in the original submission as well as the same mathematical or statistical analysis methods (if any) and will not contain any matrix or bracketing approaches that deviate from the stability protocol in the original BLA. If FDA requests this information, the simple stability update would need to be submitted within 7 months of the submission of the BLA, or if designated a priority review within 4 months of the submission of the BLA. A simple stability update submitted at the FDA's request within these timeframes may be reviewed and considered in shelf life determinations. With respect to the submission of subsequent stability updates following licensure, stability updates for the PPQ drug substance and drug product batches may be submitted to the annual report only if no manufacturing changes are made between the Phase 3 and commercial manufacturing processes.

Meeting Minutes  
Breakthrough Therapy

**Discussion:**

No discussion occurred.

**2.4. Clinical Pharmacology Plan**

**Question 10:**

*Does the Agency agree that the proposed clinical pharmacology plan is sufficient to support a BLA?*

**FDA Response to Question 10:**

Yes. Your clinical pharmacology plan appears acceptable. In addition, we encourage you to validate your analytical methods in a timely fashion. Your briefing package did not provide information regarding analytical method validation efforts.

**Discussion:**

No discussion occurred.

**2.5. Clinical Plan**

**VELCADE Dose and Schedule for Proposed Phase 3 Registration Study:**

**Question 11:**

*Does the Agency agree that the proposed VELCADE dose and schedule (1.3 mg/m<sup>2</sup> as a SC injection administered twice weekly for one 6 week cycle, followed by once weekly administrations for eight 6-week cycles) in the Phase 1b study is acceptable for use as a comparator in a future Phase 3 registration study for the treatment of frontline multiple myeloma?*

**FDA Response to Question 11:**

Yes.

**Discussion:**

No discussion occurred.

**Sufficiency of Proposed BLA Package:****Question 12:**

*Assuming that the two DP are comparable, and that Study MMY2002 has statistically persuasive results, does the Agency agree the data from Study MMY20002 could support a BLA for the Breakthrough Therapy Designation indication?*

**FDA Response to Question 12:**

When you have established the dose of the proposed Phase 3 product you are carrying forward, and have results with this dose, please request an End-of-Phase 2 Meeting.

**Discussion:**

**The Sponsor agrees to request a meeting with FDA upon selection of a Phase 3 dose.**

**Additional Statistical Comments:**

- For your proposed phase 3 study of DRD vs. RD, we discourage the proposed interim efficacy analysis of PFS as estimated effects will be less precise, the comparison will be weighted towards early events, and it may be difficult to evaluate the magnitude of PFS benefit. Stopping the trial when 23% of the subjects have an event will provide inadequate subject follow-up.
- Further statistical comments may arise when detailed study protocol and statistical analysis plan are submitted.

**Additional Chemistry, Manufacturing, and Controls Comments:**

1. The proposed changes to the [REDACTED] (b) (4) [REDACTED] could have an impact on the ability of the new process to clear viruses. As such, a viral clearance study for the post-change process should be included.
2. Levels of Polysorbate-20 need to be controlled [REDACTED] (b) (4) [REDACTED]. Testing with defined acceptance criteria for Polysorbate-20 levels should be included [REDACTED] (b) (4) [REDACTED].
3. FDA notes the plan to replace the enzyme immuno assay (EIA) binding assay currently used to assess potency of drug substance and drug product with the Time Resolved-Fluorescence Energy Transfer (TR-FRET) homogeneous antigen binding assay. Sufficient data should be provided to demonstrate that the TR-FRET assay has similar capabilities to control potency of daratumumab as the EIA binding assay. FDA recommends that the EIA binding assay be retained in the drug substance and

Meeting Minutes  
Breakthrough Therapy

drug product release and stability protocols through development to generate data supporting that lots used in clinical studies are representative of the Phase 3 manufacturing process.

**Discussion:**

**The Sponsor's approach appears to be acceptable (see attached slides). However, data will need to be submitted to the IND to demonstrate the capabilities of the TR-FRET assay in comparison to the EIA binding assay and this data should be used to inform the acceptance criteria for the TR-FRET assay.**

### **3.0 PREA REQUIREMENTS**

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP). The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email [pdit@fda.hhs.gov](mailto:pdit@fda.hhs.gov). For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

### **4.0 ISSUES REQUIRING FURTHER DISCUSSION**

None

### **5.0 ACTION ITEMS**

None

### **6.0 ATTACHMENTS AND HANDOUTS**

See attached Sponsor slides.

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/s/  
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VIRGINIA E KWITKOWSKI  
08/01/2013

## Boehmer, Jessica

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**From:** Boehmer, Jessica  
**Sent:** Friday, August 14, 2015 11:59 AM  
**To:** Maloney, Brian [JRDUS] (BMalone1@ITS.JNJ.COM); Rothschild, Melanie [JRDUS] (MRothsch@ITS.JNJ.COM)  
**Cc:** Boehmer, Jessica  
**Subject:** Response needed: Clinical Pharmacology Information Request - BLA 761036 - daratumumab - response due by Aug 20th

**Importance:** High

Dear Brian and Melanie:

Please refer to BLA 761036 for daratumumab, submitted and received July 9, 2015. Please respond to the following information request by the requested due date. Please send the response to me via email and formally submit the information to your BLA.

[Clinical Pharmacology Information Request:](#)

Please submit any datasets, codes and define files associated with your simulations. If already submitted in the BLA, please point us to the correct location.

Please respond to me via email by **4:00 PM August 20, 2015**, and also formally submit to your BLA.

Thank you,

Jessica

Jessica Boehmer, MBA  
Senior Regulatory Project Manager  
Division of Hematology Products (DHP)  
FDA/CDER/OND/OHOP  
(301) 796-5357 (phone)  
(301) 796-9845 (fax)

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/s/  
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JESSICA L BOEHMER  
08/14/2015



BLA 761036

**BLA ACKNOWLEDGMENT**

Janssen Biotech, Inc.  
c/o Janssen Research and Development, LLC  
Attention: Brian Maloney, RPh, MS  
Director, Regulatory Affairs  
920 Route 202, PO Box 300  
Raritan, NJ 08869

Dear Mr. Maloney:

We have received your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for the following:

Name of Biological Product: daratumumab  
sterile liquid solution for infusion, 100 mg/vial and 400 mg/vial

Date of Application: July 9, 2015

Date of Receipt: July 9, 2015

Our Reference Number: BLA 761036

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on September 7, 2015, in accordance with 21 CFR 601.2(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 601.14(b) in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action. The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The BLA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Hematology Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to [SecureEmail@fda.hhs.gov](mailto:SecureEmail@fda.hhs.gov). Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me at (301) 796-5357.

Sincerely,

*{See appended electronic signature page}*

Jessica Boehmer, MBA  
Senior Regulatory Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

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/s/  
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JESSICA L BOEHMER  
07/23/2015

## Wright, Kevin

---

**From:** Wright, Kevin  
**Sent:** Tuesday, June 30, 2015 3:01 PM  
**To:** 'Maloney, Brian [JRDUS]'  
**Cc:** Kang, Sue  
**Subject:** RE: BLA 761036 daratumumab: Request for Proprietary Name Review

Mr. Maloney,

Thank you for your response. Please proceed with your proprietary name submission as planned. Thanks again.

Best regards,

Kevin Wright, PharmD

Safety Regulatory Project Manager | OSE | CDER | FDA | 301.796.3621 [kevin.wright@fda.hhs.gov](mailto:kevin.wright@fda.hhs.gov)

 Thinking green when printing

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**From:** Maloney, Brian [JRDUS] [<mailto:BMalone1@ITS.JNJ.COM>]  
**Sent:** Monday, June 29, 2015 4:37 PM  
**To:** Wright, Kevin  
**Cc:** Kang, Sue  
**Subject:** RE: BLA 761036 daratumumab: Request for Proprietary Name Review

Dear Dr. Wright,

Received thank you!

We plan to re-submit the proposed trade name for daratumumab within a few days after submission of the final components of the BLA (Scheduled for 15 July 2015 at the latest, possibly sooner). We have received a "conditionally acceptable" correspondence (see attached) of the proposed trade name "DARZALEX" on 25 March 2015 (Submitted to IND 100,638 on 23 January 2015).

We very much appreciate your reminder to re-submit the proposed trade name.

Please let know if the planned submission timing is not adequate for your review so that we can plan an earlier alternate submission date.

Thank you and kind regards  
Brian

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**From:** Wright, Kevin [<mailto:Kevin.Wright@fda.hhs.gov>]  
**Sent:** Monday, June 29, 2015 3:10 PM  
**To:** Maloney, Brian [JRDUS]  
**Cc:** Kang, Sue  
**Subject:** BLA 761036 daratumumab: Request for Proprietary Name Review  
**Importance:** High

Hello Mr. Maloney,

This email is to notify you that the Division of Medication Error and Prevention Analysis (DMEPA) is requesting you submit a request for proprietary name review to BLA 761036, we recognize your BLA is being reviewed as a rolling submission.

As a reminder, the request for proprietary name review should include FDA Form 356h, and a cover letter stating "REQUEST FOR PROPRIETARY NAME", on the first page of the submission. Also, this submission should contain the proposed labels and labeling or a reference to the submission containing the labels and labeling.

A complete request for proprietary name review should include the primary proprietary name and where applicable the alternate proprietary name, intended pronunciation, derivation of proprietary name, and/or intended meaning of any modifiers (e.g. prefix, suffix) contained in the proprietary name.

Additionally, your request should include the following product characteristics: established name, prescription status, dosage form, product strength, proposed indication for use, route of administration, usual dosage, frequency of administration, dosing in specific populations, instructions for use, setting of use, storage requirements and the intended package configuration.

Attached for your convenience is a copy of the Guidance document outlining the information you need to submit when requesting review of a proprietary name.

If you have any questions or comments regarding this email, please contact me.

Best regards,

Kevin Wright, PharmD

Safety Regulatory Project Manager | OSE | CDER | FDA | 301.796.3621 | [kevin.wright@fda.hhs.gov](mailto:kevin.wright@fda.hhs.gov)

 Thinking green when printing

**THIS MESSAGE IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PREDECISIONAL, PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER LAW.**

**If you are not the named addressee, or if this message has been addressed to you in error, you are directed not to read, disclose, reproduce, disseminate, or otherwise use this transmission. If you have received this document in error, please immediately notify me by email or telephone.**

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/s/  
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KEVIN WRIGHT  
06/30/2015



BLA 761036

**ACKNOWLEDGE PRESUBMISSION**

Janssen Biotech, Inc.  
c/o Janssen Research and Development, LLC  
Attention: Brian Maloney, RPh, MS  
Director, Regulatory Affairs  
920 Route 202, Box 300  
Raritan, NJ 08869

Dear Mr. Maloney:

We have received the first section of your Biologics License Application (BLA) under the program for step-wise submission of sections of a marketing application under 351 of the Public Health Service Act for the following:

Name of Drug Product: daratumumab  
sterile liquid solution for infusion, 100 mg/vial and 400 mg/vial

Date of Submission: June 5, 2015

Date of Receipt: June 5, 2015

Our Reference Number: BLA 761036

We will review this presubmission as resources permit. Presubmissions are not subject to a review clock or to a filing decision by FDA until the application is complete.

Please cite the application number listed above at the top of the first page of any communications concerning this supplemental application. Unless you are using the FDA Electronic Submissions Gateway (ESG), send all submissions by overnight mail or courier to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Hematology Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to

set it up, send an email request to [SecureEmail@fda.hhs.gov](mailto:SecureEmail@fda.hhs.gov). Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me at (301) 796-5357.

Sincerely,

*{See appended electronic signature page}*

Jessica Boehmer, MBA  
Senior Regulatory Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

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/s/  
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JESSICA L BOEHMER  
06/23/2015



IND 100638

**MEETING MINUTES**

Janssen Research & Development, LLC  
Attention: Brian J. Maloney, RPh, MS  
Director, Regulatory Affairs  
1400 McKean Road, PO Box 776  
Spring House, PA 19477

Dear Mr. Maloney:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for daratumumab.

We also refer to the meeting between representatives of your firm and the FDA on March 31, 2015. The purpose of the meeting was to discuss the topline results from the MMY2002 study and additional content of the Biologics License Application (BLA).

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Jessica Boehmer, Regulatory Project Manager at (301) 796-5357.

Sincerely,

*{See appended electronic signature page}*

Albert Deisseroth, MD, PhD  
Clinical Team Leader  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

Enclosure:  
Meeting Minutes



**FOOD AND DRUG ADMINISTRATION**  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** Type B  
**Meeting Category:** Pre-BLA

**Meeting Date and Time:** March 31, 2015; 10:00 AM - 11:00 AM  
**Meeting Location:** 10903 New Hampshire Avenue  
White Oak Building 22, Conference Room: 1315  
Silver Spring, Maryland 20903

**Application Number:** IND 100638  
**Product Name:** Daratumumab  
**Indication:** Daratumumab is indicated for the treatment of patients with multiple myeloma (MM) who have received at least 3 prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or are double refractory to a PI and an immunomodulatory agent.

**Sponsor/Applicant Name:** Janssen Research & Development, LLC

**Meeting Chair:** Albert Deisseroth, MD, PhD  
**Meeting Recorder:** Jessica Boehmer, MBA

**FDA ATTENDEES**

Office of Hematology and Oncology Products (OHOP)  
Richard Pazdur, MD, Director

OHOP/Division of Hematology Products (DHP)  
Ann Farrell, MD, Director  
Albert Deisseroth, MD, PhD, Clinical Team Leader  
Barry Miller, MS, CRNP, Senior Clinical Analyst  
Amy Baird, Chief, Project Management Staff  
Tawanna Dabney, BA, Consumer Safety Technician  
Jessica Boehmer, MBA, Senior Regulatory Project Manager

OHOP/Division of Hematology, Oncology, Toxicology  
Pedro Del Valle, PhD, Acting Team Leader  
Emily Place, PhD, Nonclinical Reviewer

Office of Biostatistics/Division of Biometrics V

Yuan-Li Shen, PhD, Statistical Team Leader  
Xin (Cindy) Gao, PhD, Statistical Reviewer

Office of Clinical Pharmacology (OCP)/Division of Clinical Pharmacology V

Bahru Habtemariam, PharmD, Acting Clinical Pharmacology Team Leader

Office of Biotechnology Products (OBP)/Division of Biotechnology Review and Research I

Jee Chung, PhD, Product Quality Team Leader  
Tura Camilli, PhD, Product Quality Reviewer

Office of Process and Facility/Division of Microbiology Assessment Branch IV

Patricia Hughes, PhD, Team Leader

Center for Biologics Evaluation and Research (CBER) / Office of Cellular, Tissue, and Gene Therapies (OCTGT)

Chaohong Fan, MD, Medical Officer

**EASTERN RESEARCH GROUP ATTENDEES**

Christopher Sese, Analyst

**SPONSOR ATTENDEES**

Genmab

Michael Karl Bauer, PhD, MSc, Medical Head of Clinical Development

Janssen Research & Development, LLC

Tahamtan Ahmadi, MD, PhD, Clinical Leader  
Pamela Clemens, PhD, Associate Director, Clinical Pharmacology  
Adam Dinerman, PhD, CMC Team Leader  
Richard Jansson, PhD, Compound Development Team Leader  
Imran Khan, MD, PhD, Project Physician  
Huaibao Feng, PhD, Biostatistics  
Brian Maloney, RPh, MS, North America Regulatory Affairs  
Reshma Patel, MS, Global Regulatory Leader  
Kevin Wanczyk, Global Regulatory Affairs – CMC  
Sen Hong Zhuang, MD, PhD, VP, Clinical Research Development

**1.0 BACKGROUND**

The Sponsor submitted a Meeting Request, on October 31, 2014, for a Pre-Biologic License Application (pre-BLA) Meeting to discuss the topline results from the MMY2002 study and additional content of the BLA. The BLA to support the use of daratumumab for the treatment of patients with multiple myeloma is targeted for a submission in July 2015. The meeting was granted by the Agency on November 20, 2014.

Daratumumab is a human IgG1 $\kappa$  monoclonal antibody that targets CD38. Breakthrough Therapy Designation was granted May 1, 2013 for daratumumab for the treatment of patients with multiple myeloma who have received at least 3 prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or are double refractory to a PI and an immunomodulatory agent.

The Sponsor proposes an initial BLA to be based on data from the phase 2 trial MMY2002 and supported by the phase 1/2 trial GEN501. The Sponsor also plans to include safety data from the additional monotherapy trial MMY1002 and trials GEN503 and MMY1001, in which daratumumab is administered in combination with other therapies.

FDA sent Preliminary Comments to Janssen Research & Development, LLC on March 26, 2015.

## 2. DISCUSSION

### 2.1. Efficacy Data

#### Question 1:

**Based on the Study MMY2002 topline results (Appendix MMY2002 Topline Report) and the final SAP (Appendix MMY2002 SAP), does the Agency request any additional analyses that should be provided in the BLA?**

#### FDA Response to Question 1:

Provide an analysis of infusion reactions, which includes timing within infusion and by dose, which supports your plan for pre-medications and dose and infusion delays. Your product label will need to clearly characterize the clinical symptoms associated with the infusion reaction.

Please include a drug product flag in the clinical datasets so as to differentiate the different manufacturing processes used.

We note the absence, in the background materials, of one important identified risk presented in the daratumumab DSUR: laboratory interference for blood typing. If most patients develop positive antibody screen tests (indirect Coombs test) after infusion of daratumumab and complete blood typing may be compromised, how will you mitigate this risk to patients? Include a description and analysis of the problem, and provide a thorough plan to address it. Also include an analysis for hemolysis, including ‘subclinical’ and delayed manifestations. Explorations for elevations of haptoglobin or LDH in patients receiving daratumumab should be included.

#### Discussion:

***The Agency and the Sponsor engaged in a detailed discussion of the consequences of the presence of low levels of CD38 on hematopoietic lineage specific cells. The Sponsor***

*promised to provide the Agency with results from their analysis on RBC typing, infusion reactions, and presence of CD38 on neutrophil and platelet precursors.*

## **2.2. Risk Evaluation and Mitigation Strategy (REMS)**

### **Question 2:**

**Does the Agency agree that based on the preliminary review of the data and the Sponsor's rationale that a REMS is not warranted for this indication?**

### **FDA Response to Question 2:**

We agree that it appears that a REMS will not be warranted; however, final determination will be made during review of the Application.

### **Discussion:**

*No discussion occurred.*

## **2.3. Daratumumab Early Access**

### **Question 3:**

**Does the Agency agree that the draft protocol is appropriate and implementation of an early access program is warranted for daratumumab?**

### **FDA Response to Question 3:**

Yes, please submit the treatment protocol to the IND for review.

### **Discussion:**

*No discussion occurred.*

## **2.4. Toxicology Study for Subcutaneous Administration**

### **Question 4:**

**Does the Agency agree that submission of the data from the subcutaneous local tolerance study in rabbits is not required to be included in the original BLA for daratumumab in potential breakthrough therapy indication?**

### **FDA Response to Question 4:**

We agree the subcutaneous local tolerance study is not required for this submission.

**Discussion:**

*No discussion occurred.*

**Additional Comment:**

Please provide an update on the status of your confirmatory trial to include current enrollment, duration of treatment, and length of follow-up. When do you expect interim analyses?

**Discussion:**

*The two proposed Phase 3 confirmatory trials were described in detail with respect to the identity of PFS endpoints in each trial. In addition, other Phase 3 studies that have been launched in frontline patients were described for the Agency.*

*The Agency and the Sponsor discussed the provisions that have been made for comprehensive characterization of the responses in all projected Phase 3 trials. Janssen described the use of DNA sequencing as a method for determination of MRD status.*

### 3.0 OTHER IMPORTANT INFORMATION

#### **DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION**

- The content of a complete application was discussed.

There may be stability updates submitted, upon request of the CMC review team (if more than 30 days following receipt of the BLA) and the 4 month safety update will be submitted early as well.

All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- A preliminary discussion on the need for a REMS was held and it was concluded that at this time there is no need to submit a REMS proposal with the BLA.
- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. We agreed that the following minor application components may be submitted within 30 calendar days after the submission of the original application: There may be stability updates submitted, upon request of the CMC review team (if more than 30 days following receipt of the BLA) and the 4 month safety update will be submitted early as well.

Prominently identify each submission containing your late component(s) with the following wording in bold capital letters at the top of the first page of the submission:

**BLA NUMBER: LATE COMPONENT - BIOMETRICS**  
**BLA NUMBER: LATE COMPONENT - CLINICAL**  
**BLA NUMBER: LATE COMPONENT - CLINICAL PHARMACOLOGY**  
**BLA NUMBER: LATE COMPONENT - NONCLINICAL**  
**BLA NUMBER: LATE COMPONENT - QUALITY**

In addition, we note that a chemistry pre-submission meeting was held on December 12, 2015. We refer you to the minutes of that meeting for any additional agreements that may have been reached.

### **PREA REQUIREMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

### **PRESCRIBING INFORMATION**

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#) including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [PLLR Requirements for Prescribing Information](#) websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential in the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

**MANUFACTURING FACILITIES**

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, “Product name, NDA/BLA 012345, Establishment Information for Form 356h.”

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

**Office of Scientific Investigations (OSI) Requests**

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

**I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).**

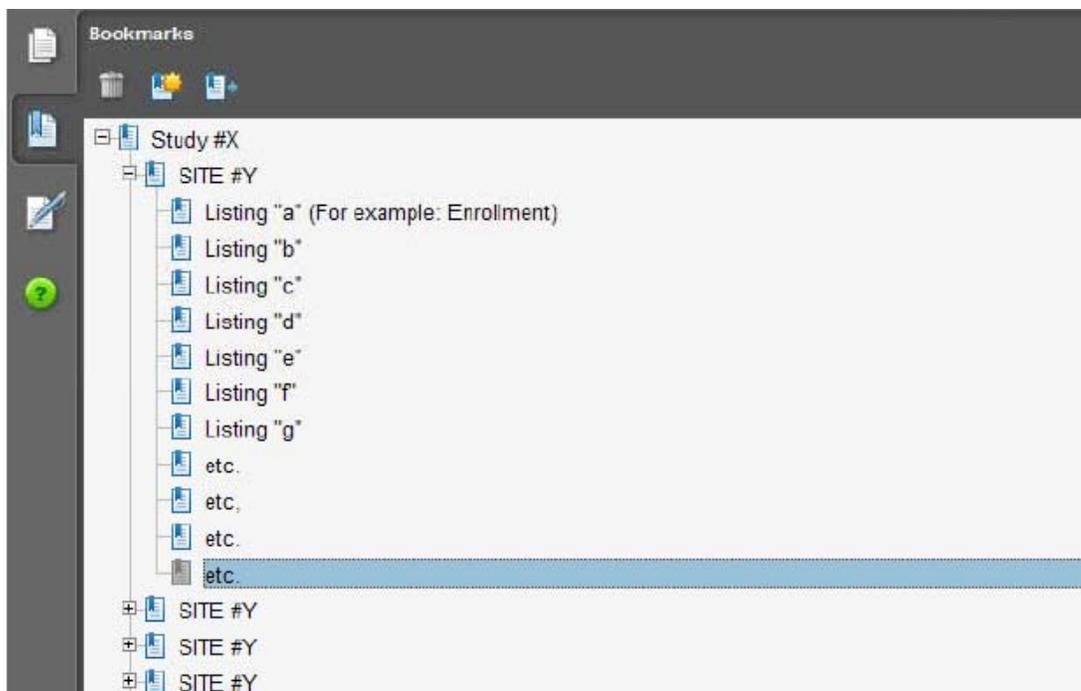
1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
  - a. Site number
  - b. Principal investigator
  - c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
  - d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.
2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
  - a. Number of subjects screened at each site
  - b. Number of subjects randomized at each site
  - c. Number of subjects treated who prematurely discontinued for each site by site
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
  - a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection.
  - b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
  - c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is

maintained. As above, this is the actual physical site where documents would be available for inspection.

4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments (or identify the location and/or provide a link if provided elsewhere in the submission).

## **II. Request for Subject Level Data Listings by Site**

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as “line listings”). For each site, provide line listings for:
  - a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated.
  - b. Subject listing for treatment assignment (randomization).
  - c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued.
  - d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol.
  - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
  - f. By subject listing, of AEs, SAEs, deaths and dates.
  - g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation.
  - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
  - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials).
  - j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



### III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft *“Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning”* (available at the following link <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>) for the structure and format of this data set.

#### 4.0 ISSUES REQUIRING FURTHER DISCUSSION

None

#### 5.0 ACTION ITEMS

The Sponsor will submit a request for Rolling Review.

#### 6.0 ATTACHMENTS AND HANDOUTS

See attached Sponsor’s slides.

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/s/  
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ALBERT B DEISSEROTH  
04/01/2015



IND 100638

**GRANT –  
BREAKTHROUGH THERAPY DESIGNATION**

Janssen Research & Development, LLC.  
Attention: Brian J. Maloney, R.Ph., M.S.  
Director, Regulatory Affairs  
1400 McKean Road  
PO Box 776  
Spring House, PA 19477

Dear Mr. Maloney:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Daratumumab (HuMax – CD38).

We also refer to your March 8, 2013, request for Breakthrough Therapy designation. We have reviewed your request and have determined that Daratumumab (HuMax – CD38) for treatment of patients with multiple myeloma who have received at least 3 prior lines of therapy including a proteasome inhibitor and an immunomodulatory agent or are double refractory to a proteasome inhibitor and an immunomodulatory agent meets the criteria for Breakthrough Therapy designation. Therefore, we are granting your request for Breakthrough Therapy designation. Please note that if the clinical development program does not continue to meet the criteria for Breakthrough Therapy designation, we may rescind the designation.

FDA will work closely with you to provide guidance on subsequent development of Daratumumab (HuMax – CD38) for treatment of patients with multiple myeloma who have received at least 3 prior lines of therapy including a proteasome inhibitor and an immunomodulatory agent or are double refractory to a proteasome inhibitor and an immunomodulatory agent, including providing advice on generating evidence needed to support approval of the drug in an efficient manner. For further information regarding Breakthrough Therapy designation and FDA actions to expedite development of a designated product, please refer to section 902 of the Food and Drug Administration Safety and Innovation Act (FDASIA). A guidance document is currently under development.

In terms of next steps, please submit a Type B meeting request. This meeting will be for a multidisciplinary comprehensive discussion of your development program, including planned clinical trials and plans for expediting the manufacturing development strategy. Please refer to

the *Guidance for Industry: Formal Meetings between FDA or Sponsors and Applicants*<sup>1</sup> for procedures on requesting a meeting.

If you have any questions, contact Jessica Boehmer, Regulatory Project Manager, at (301) 796-5357.

Sincerely,

*{See appended electronic signature page}*

Ann T. Farrell, M.D.  
Division Director  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

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<sup>1</sup> <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>

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/s/  
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ANN T FARRELL  
05/01/2013

Clinical Analyst Briefing Document  
Breakthrough Therapy for IND 100638  
Division of Hematology Products  
Office of Hematology and Oncology Products  
April 2, 2013

### **1. Executive Summary**

Janssen Research and Development has submitted a request for Breakthrough Therapy designation for daratumumab, a monoclonal antibody, 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 are double refractory to a proteasome inhibitor and an immunomodulatory agent. This reviewer concludes that the Sponsor has met the two key requirements (FDASIA § 902) for Breakthrough Therapy designation:

- The disease is serious and life-threatening
- Preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development.

### **2. Rationale for the use of daratumumab for treatment of multiple myeloma**

Daratumumab is a fully human IgG1κ monoclonal antibody that binds to CD38 on target cells resulting in immune mediated killing of tumor cells.

- CD38 is a glycoprotein ectoenzyme that functions in cell adhesion, signaling and regulation of intracellular calcium. CD38 is expressed by a variety of normal hematopoietic cells. It is highly expressed on the surface of multiple myeloma cells and is thought to be an activation marker for T and B cells.
- The mechanism of action of daratumumab appears to be due to signaling blockade and activation of cytotoxic immune effector functions, i.e., complement dependent cytotoxicity, antibody dependent cellular cytotoxicity, and by macrophages via antibody dependent cellular phagocytosis.

### **3. Multiple Myeloma (MM)**

In 2012, there were 21,700 estimated new U.S. cases and 10,700 deaths.<sup>1</sup> The median age at diagnosis in 2009 was 69 and the estimated prevalence was approximately 71,000 people. Five year overall relative survival is 41%.

MM is a systemic malignancy of plasma cells that accumulate in the bone marrow resulting in marrow failure and bone destruction. Visceral organ dysfunction can also occur from neoplastic plasma cell infiltration or deposition of abnormal immunoglobulin. The results of marrow destruction are thrombocytopenia, anemia, and neutropenia. The results of visceral organ deposition are hypercalcemia, renal failure, and cardiac dysfunction. Common symptoms of bone marrow destruction are bone pain, fatigue, weakness, and infection.

Treatment of MM is aimed at decreasing the clonal plasma cell population to restore the function of normal blood marrow cell lines.<sup>2</sup> The initial treatment regimen is based on disease stage and the patient's age and performance status. Combination chemotherapy followed by myeloablative therapy with autologous hematopoietic stem cell transplantation is typically employed for the

younger, healthier patient. Various two or three agent combinations, usually with a corticosteroid, are given. Though dexamethasone is approved for the treatment of hematologic diseases, single-agent dexamethasone is no longer considered an appropriate treatment for MM.

Because aggressive chemotherapy regimens are not tolerated by older patients and those with end organ impairment or other comorbidities, they typically receive a less aggressive regimen such as melphalan and prednisone with or without an immunomodulating agent or a proteasome inhibitor. No treatments approved for MM have been shown to be curative. Patients with MM tend to relapse after treatment and will frequently require multiple regimens in a lifetime.

Approved agents for MM are listed in the table below.

<i>Class</i>	<i>Drug</i>	<i>Approval</i>
Alkylating agent	melphalan	Regular
	cyclophosphamide	Regular
Anthracycline	liposomal doxorubicin	Regular
Nitrosurea	carmustine	Regular
Immunomodulating agent	thalidomide	Accelerated
	lenalidomide	Regular
	pomalidomide	Accelerated
Proteasome Inhibitors	bortezomib	Regular
	carfilzomib	Accelerated

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 pulse corticosteroids, proteasome inhibitors, immunomodulating agents, and stem cell transplants has further extended median survival to 45 to 60 months.

Treatment for relapsed and/or refractory MM 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, second stem cell transplant, or clinical trial therapy are all options for patients with relapsed or refractory MM. In one series, the ORR ( $\geq$ PR) to the first therapy after relapse is 58%, decreasing to 45% to 2<sup>nd</sup> regimen, 30% to the 3<sup>rd</sup>, and 15% to the 4<sup>th</sup>.<sup>3</sup> In patients who are refractory or relapsed to both an immunomodulating agent and the proteasome inhibitor bortezomib, ORR ( $\geq$ PR) ranged from 24% to the first therapy to 6% after the 5<sup>th</sup> regimen. The median overall survival of patients with multiple myeloma who have received multiple salvage therapies is 9 months.<sup>4</sup>

#### **4. Clinical trial experience with daratumumab**

- Trial GEN501

Trial GEN501 is a Phase 1/2, open-label trial of single-agent daratumumab in patients with multiple myeloma that has relapsed or is refractory to at least two prior therapies. In Part 1, 32 patients were enrolled and received drug using a 3+3 dose escalation design at doses ranging from 0.005 to 24 mg/kg given in 7 full-dose and 2 pre-dose infusions during a 9 week period. Most patients were heavily pre-treated prior to enrolling, with the median number of 6 treatments ranging from 3 to 12 in the  $\geq$ 4mg/kg cohorts.

Summary of Part 1 Baseline Characteristics (Source: Sponsor table)

Cohort (mg/kg)	# of subjects	Age	# of prior treatments	Len	Thal	Bor	Dex/ Pred	Chemo	ASCT
≤1	17	63(42-76)	5(2-8)	15	12	17	15/7	17	11
2	3	64(60-71)	8(6-10)	3	3	3	3/3	3	3
4	3	64(62-66)	6(3-6)	3	1	3	3/1	3	2
8	3	60(56-68)	11(5-12)	3	2	3	3/2	3	3
16	3	55(54-59)	7(4-8)	2	2	3	3/1	3	3
24	3	58(50-69)	5(4-6)	3	2	3	3/1	3	2

Len=lenalidomide; Thal=thalidomide; Bor=bortezomib; Dex=dexamethasone; Pred=prednisolone; Chemo=vincristine, doxorubicin, cyclophosphamide, melphalan, others; ASCT=autologous stem cell transplant

Preliminary efficacy information is provided for 12 patients in 4 cohorts receiving doses of 4-24 mg/kg. The median number of prior treatments is 6 ranging from 3-12. PRs were attained by 42% of patients receiving daratumumab. Of the 8 patients who had ≥5% tumor plasma cells in the bone marrow at baseline, 6 achieved a maximal reduction ≥75%. Of the 7 patients who had ≥10% tumor plasma cells in the marrow, 5 had normalization of the percentage of plasma cells (<5%). Other therapies approved for MM have not demonstrated this effect. Of 11 patients who had measurable paraprotein, 4 had a ≥50% maximal reduction. The median follow-up is 3.8 months. All 5 patients with PR remained in remission at last evaluation ranging from 5 to 23 weeks.

Maximum reduction in any response evaluation variable (Source: Modified from Sponsor Table)

Cohort (mg/kg)	N	Max. reduction in M-component (%)		Max. reduction in difference between involved and uninvolved FLC (%)	Max. reduction in plasma cells in BM smear (%) (baseline value [(%)])	Response according to IMWG <sup>5</sup>
		Serum	Urine			
4	3	49	*	*	80(12.5)	<del>MR</del> SD**
		100	87	96	89(23)	PR
		64	*	*	97(19)	PR
8	3	4	*	*	-29(14)	SD
		39	*	*	93(7.5)	<del>MR</del> SD**
		*	*	*	--	NE
16	3	-3	*	-12	--	PD
		50 <sup>b</sup>	*	88	100 (31.5)	PR
		*	-12	55	100 (2)	SD
24	3	*	*	80 <sup>b</sup>	51(18.5)	PR
		29	*	*	17(3)	<del>MR</del> SD**
		68 <sup>b</sup>	89	94	91(17)	PR

BM=bone marrow; FLC=free light chain; IMWG=International Myeloma Working Group; MR=Minimal Response;; NE=not evaluable; PD=progressive disease; PR=partial response, SD=stable disease.

Notes:\*= disease not measurable at baseline; -- =data not available; b=Follow-up still ongoing.

Cut-off date: 15 January 2013; response evaluation performed by Genmab algorithm.

\*\*Table edited by changing MR (which is not included in the IMWG criteria) to SD as best response.

In the ongoing Part 2 of the trial, 15 of 77 patients enrolled in a dose expansion phase of 8 infusions of drug at 8 mg/kg at weekly intervals followed by every other week infusions for 16 weeks, followed by monthly infusions for 72 weeks. No further safety or efficacy data were provided.

- Trial GEN503

Trial GEN503 is a Phase 1/2, open-label, multicenter trial of daratumumab in combination with lenalidomide and dexamethasone in patients with relapsed or refractory multiple myeloma. Three patients have been enrolled and given 2 mg/kg daratumumab. No DLTs were reported. Drug was discontinued in one patient prior to the 14<sup>th</sup> infusion due to prolonged QTc. All 3 achieved a PR.

- Safety of daratumumab in MM

Information was provided for the 32 patients in Part 1 of Trial GEN501. MTD was not reached. Two DLTs were reported in the lower dose cohorts: Grade 3 anemia and Grade 4 thrombocytopenia. No DLTs were reported in the 2 to 24 mg/kg cohorts. Treatment emergent SAEs were experienced by 47% of patients; the most common were infections (16%). The most common Grade 3 and higher AEs were lymphopenia (28%) and thrombocytopenia (22%). Forty-seven% of patients experienced infusion related AEs.

## 5. Regulatory Considerations

Multiple myeloma is a serious and life-threatening condition. The sponsor has shown that daratumumab has nonclinical and preliminary clinical evidence of activity that may represent a substantial improvement over existing therapies for patients with multiply relapsed and refractory MM. Although there are other monoclonal antibodies under investigation in MM, there are none approved for MM. Administration of daratumumab as a single agent has resulted in an ORR of 42%. The reduction of paraprotein and bone marrow tumor plasma cells, provides important evidence of activity in heavily pretreated patients with MM. In contrast, an ORR of <24% would be expected using existing approved therapies in the same patient population. The safety profile of daratumumab in patients with relapsed/refractory MM is acceptable.

- Drug development plan

The Sponsor has two planned clinical trials for MM, a Phase 2 trial of single agent daratumumab and a Phase 1/2 clinical trial of daratumumab combined with bortezomib, melphalan, and prednisone. Additional safety and efficacy trials are planned for 2014. (b) (4)

- Recommendation

DHP recommends that daratumumab be granted Breakthrough Therapy designation for the treatment of patients with multiple myeloma who have received at least 3 prior lines of therapy including a proteasome inhibitor and an immunomodulatory agent or are double refractory to a proteasome inhibitor and an immunomodulatory agent.

## References

<sup>1</sup> Howlader N, Noone AM, Krapcho M, Neyman N, Aminou R, Altekruse SF, Kosary CL, Ruhl J, Tatalovich Z, Cho H, Mariotto A, Eisner MP, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). *SEER Cancer Statistics Review, 1975-2009 (Vintage 2009 Populations)*, National Cancer Institute. Bethesda, MD, [http://seer.cancer.gov/csr/1975\\_2009\\_pops09/](http://seer.cancer.gov/csr/1975_2009_pops09/), based on November 2011 SEER data submission, posted to the SEER web site, 2012.

<sup>2</sup> National Comprehensive Cancer Network. Multiple Myeloma, Version 2.2013. Available at: [http://www.nccn.org/professionals/physician\\_gls/pdf/mm.pdf](http://www.nccn.org/professionals/physician_gls/pdf/mm.pdf). Accessed 03/22/2013.

<sup>3</sup> Durie BG, Moreau P, Sonneveld P, et al. Regional differences in the treatment approaches for relapsed multiple myeloma: An IMF study. *J Clin Oncol* 30, 2012 (suppl; abstr 8095).

<sup>4</sup> Kumar SK, Lee, JH, Jahuerta, JJ, et al. Risk of progression and survival in multiple myeloma relapsing after therapy with IMiDs and bortezomib: A multicenter international myeloma working group study. *Leukemia*. 2012;26:149-157.

<sup>5</sup> Rajkumar S, Harousseau J-L, Durie B, et al. Consensus recommendations from the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. *Blood*. 2011;117:4691-4695.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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BARRY W MILLER  
04/26/2013

VIRGINIA E KWITKOWSKI  
04/26/2013

**LATE-CYCLE COMMUNICATION**  
**DOCUMENTS**



BLA 761036

**LATE-CYCLE MEETING MINUTES**

Janssen Biotech, Inc.  
c/o Janssen Research and Development, LLC  
Attention: Brian Maloney, RPh, MS  
Director, Regulatory Affairs  
920 Route 202, PO Box 300  
Raritan, NJ 08869

Dear Mr. Maloney:

Please refer to your Biologic License Application (BLA) submitted under section 351 of the Public Health Service Act for daratumumab injection, 100 and 400 mg/vial.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on October 19, 2015.

A copy of the official minutes of the LCM is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Jessica Boehmer, Regulatory Project Manager, at (301) 796-5357.

Sincerely,

*{See appended electronic signature page}*

Albert Deisseroth, MD, PhD  
Clinical Team Leader  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

Enclosure:  
Late Cycle Meeting Minutes



**FOOD AND DRUG ADMINISTRATION**  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MEMORANDUM OF LATE-CYCLE MEETING MINUTES**

**Meeting Date and Time:** October 19, 2015; 3:00 PM – 4:00 PM ET  
**Meeting Location:** Teleconference

**Application Number:** BLA 761036  
**Product Name:** Daratumumab  
**Sponsor/Applicant Name:** Janssen Biotech, Inc.

**Meeting Chair:** Albert Deisseroth, MD, PhD  
**Meeting Recorder:** Jessica Boehmer, MBA

**FDA ATTENDEES**

Office of Hematology and Oncology Products (OHOP)  
Richard Pazdur, MD, Director

OHOP, Division of Hematology Products (DHP)  
Ann Farrell, MD, Director  
Edvardas Kaminskas, MD, Deputy Director  
Albert Deisseroth, MD, PhD, Clinical Team Leader, Cross-Discipline Team Leader  
Barry Miller, MS, CRNP, Senior Clinical Analyst  
Aviva Krauss, MD, Medical Officer  
Theresa Carioti, MPH, Chief, Project Management Staff  
Qin Ryan, MD, MPH, Safety Medical Officer  
Diane Leaman, BS, Safety Regulatory Project Manager  
Jessica Boehmer, MBA, Senior Regulatory Project Manager

OHOP, Division of Hematology Oncology Toxicology (DHOT)  
Christopher Sheth, PhD, Supervisory Pharmacologist  
Emily Place, PhD, MPH, Pharmacologist

Office of Clinical Pharmacology (OCP), Division of Clinical Pharmacology V (DCP V)  
Bahru Habtemariam, PharmD, Clinical Pharmacology Team Leader  
Jeanne Fourie Zirkelbach, PhD, Clinical Pharmacology Reviewer

Office of Biostatistics (OB), Division of Biometrics V (DB)  
Thomas Gwise, PhD, Deputy Director  
Yuan-Li Shen, PhD, Statistical Team Leader  
Yaping Wang, PhD, Statistical Reviewer

Office of Pharmaceutical Quality (OPQ), Office of Biotechnology Products

Sarah Kennett, PhD, Review Chief  
Jee Chung, PhD, Product Quality Team Leader  
Tura Camilli, PhD, Product Quality Reviewer  
Jibril Abdus-Samad, PharmD, Labeling Reviewer  
Laura Fontan, Consumer Safety Officer, Division of Inspectional Assessment Branch I  
Anita N. Brown, Regulatory Business Process Manager

Office of Surveillance and Epidemiology (OSE), Office of Medication Error Prevention and Risk Management (OMEPRM), Division of Risk Management (DRISK)

Joyce Weaver, PharmD, BCPS, Senior Drug Risk Management Analyst

OSE, Office of Pharmacovigilance and Epidemiology (OPE), Division of Pharmacovigilance II (DPVII)

Regina Lee, PharmD, Safety Evaluator

OSE, OPE, Division of Epidemiology -1 (DEPI-1)

Kate Gelperin, MD, MPH, Medical Officer

Center for Devices and Radiological Health (CDRH), Office of In Vitro Diagnostics and Radiological Health (OIR)

Donna Roscoe, PhD, Branch Chief  
Jennifer Dickey, PhD, RAC, Reviewer

**EASTERN RESEARCH GROUP ATTENDEES**

Christopher A. Sese, Independent Assessor

**APPLICANT ATTENDEES**

Joanita Aguiar, PhD, Global Labeling Product Leader  
Tahamtan Ahmadi, MD, PhD, Sr. Director, Clinical Leader  
Sudhir Burman, PhD, Associate Director, CMC  
Christopher Chiu, Principal Scientist, Translational Research  
Pamela Clemens, PhD, Associate Director, Clinical Pharmacology  
Adam Dinerman, PhD, Scientific Director, CMC Team Leader  
Huaibao Feng, PhD, Manager, Biostatistics  
Todd Gibson, PhD, Associate Director, Parenterals  
George Gunn, PhD, Associate Scientific Director  
Tom Hogan, MS, Sr. Director, CMC Regulatory Affairs  
Mary Houchin, Principal Scientist  
Richard Jansson, PhD, Sr. Director, Compound Team Leader  
Imran Khan, MD, PhD, Director, Clinical Development  
Barbara Kolb, MBA, Sr. Director, North America Therapeutic Area Leader, Regulatory Affairs  
Stephanie Laidig, Associate Director, API  
Baolian Liu, MD, PhD, Director, Global Medical Safety Oncology

Kevin Liu, PhD, Director, Biostatistics  
Ying Liu, Manager, CMC Regulatory Affairs  
Tony Lubiniecki, ScD, Sr. Scientific Director, CMC Strategy  
Brian Maloney, RPh, MS, Director, Regulatory Affairs  
Pauline Martin, PhD, Sr. Scientific Director, Biologics Toxicology  
Reshma Patel, Sr. Director, Global Regulatory Leader  
Ming Qi, MD, PhD, Sr. Director, Clinical Leader  
Mary Radwanski, Associate Director, CMC Regulatory Affairs  
Sandra Rattray, PhD, VP, Regulatory Affairs Oncology  
Melanie Rothschild, MBA, Manager, Regulatory Affairs  
Kate Sasser, PhD, Sr. Scientific Director, Translational Research  
Eugene Schaeffer, Sr. Scientific Director  
Judith Shuster, PhD, Sr. Director, CMC Regulatory Affairs  
Craig Tendler, MD, VP, Clinical Development, Global Medical Affairs  
Clarissa Uhlar, PhD, Associate Director, Clinical Project Scientist  
Kevin Wanczyk, Director, CMC Regulatory Affairs  
Jim Wang, PhD, Associate Director, Biostatistics  
Huimin Yuan, Sr. Director, Product Quality Management  
Sen Hong Zhuang, MD, PhD, VP, Clinical Research Development

## 1.0 BACKGROUND

BLA 761036 was submitted on July 9, 2015 for daratumumab.

Proposed indication(s): 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 are double refractory to a PI and an immunomodulatory agent.

PDUFA goal date: March 9, 2016

FDA issued a Background Package in preparation for this meeting on October 16, 2015.

## 2.0 DISCUSSION

### 1. Introductory Comments

#### **Discussion:**

#### **Welcome, Introductions, Ground rules, Objectives of the meeting:**

**The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and**

**therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.**

## 2. Discussion of Substantive Review Issues

### Clinical Pharmacology

#### Hepatic impairment:

Safety data included in the current submission indicate that the rates of serious treatment emergent adverse events (TEAE), grade 3 or higher TEAE, treatment discontinuations due to TEAE, and deaths due to TEAE are higher in patients with mild hepatic impairment compared to patients with normal hepatic function at the 16 mg/kg dose level of daratumumab.

Recent literature data suggest that CD38 may play roles in normal hepatic function and the liver disease as follows:

- CD38-mediated Ca<sup>2+</sup> signaling contributes to glucagon-induced hepatic gluconeogenesis [PMID: 26038839].
- Infiltration of inflammatory cells expressing mitochondrial proteins (including CD79a, CD38, CD138 IgM-positive and/or IgG positive plasma cells) may be involved in the pathogenesis of primary biliary cirrhosis [PMID: 24407434].

Based on the data submitted in the current submission to suggest an increased incidence TEAEs in patients with mild hepatic impairment, and the recent literature above, there may be unknown CD38-dependent mechanisms leading to enhanced toxicity to daratumumab in patients with multiple myeloma and baseline hepatic impairment.

Daratumumab has not been administered to patients with moderate to severe hepatic impairment in clinical trials. You should provide a strategy to further assess the safety of daratumumab in patients with pre-existing hepatic impairment. Please provide a comparative analysis to determine whether the increased incidence of adverse events with mild hepatic impairment may be associated with a difference in the distribution of any other baseline risk factors. You should also provide summary of comparative liver function data (normal vs. mild hepatic impairment) in graphical and tabular format.

### **Discussion:**

**The FDA reiterated the potential safety signal in patients with baseline hepatic impairment, and acknowledged that this is not due to differences in daratumumab exposure. The Applicant agreed to conduct additional evaluations in ongoing randomized trials.**

### Product Quality

Human-derived material ( (b)(4) ) used during cell line development

### **Discussion:**

**The Applicant has confirmed that the media containing the human derived material was not used during the development of the daratumumab cell line.**

Product Quality  
Immunogenicity

**Discussion:**

**The Agency reiterated to the Applicant that they should attempt to develop a new method for detecting ADAs and that information regarding the development process could be submitted as part of a response to the PMR.**

3. Discussion of Minor Review Issues

Nonclinical  
Potential Repro-tox risks:

Please provide a risk assessment of the potential for reproductive and developmental toxicity resulting from exposure to Darzalex using non product specific information. Since daratumumab can cross the placental barrier, also include in the assessment any information related to potential effects binding to CD38 may have on the developing fetus.

**Discussion:**

**The Applicant agreed to update the DART assessment.**

4. Additional Applicant Data

**Discussion:**

**The Applicant indicated they will submit their response to the carton and container Information Request on October 21, 2015.**

5. Information Requests (IR)

Product Quality  
There is a CMC IR pending a response (communicated on October 14, 2015).

**Discussion:**

**The Applicant and Agency confirmed a response to the October 14 2015 Information Requests was received on October 16, 2015.**

**The Applicant indicated their response to the 2 Information Requests from the Agency on October 16, 2015, will be sent via email on October 19, 2015. They will formally submit these to the BLA on October 20, 2015.**

**The Applicant confirmed the requested revisions to BLA modules (requested October 16, 2015) will be updated on October 21, 2015.**

6. REMS or Other Risk Management Actions

Interference with (1) serological testing and (2) interference with determination of response will need to be sufficiently described in the Prescribing Information (PI) so that risks to patients are minimized. Information sufficient for prescribers, transfusion medicine staff, and other providers will need to be included in the PI. Your risk mitigation plans to address interference with serologic testing and interference with determination of response are under review.

**Discussion:**

**Assuming additional information (see agenda item 8, below) is added to the label, your risk mitigation plans submitted to the BLA appear acceptable.**

7. Postmarketing Requirements/Postmarketing Commitments

Draft 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.

Draft 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.

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

Draft 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.

Draft Immunogenicity PMR 5: Conduct an assessment of the anti-drug antibody (ADA) response to daratumumab with the validated assay developed under PMR 4 (b) (4)

Draft 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.

Draft 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-shipment 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.

Draft Product Quality 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.

Draft Product Quality PMC 3: Re-evaluate (b) (4) 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.

Draft 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.

Draft 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.

**Discussion:**

**The Applicant indicated they will submit a report in response to PMR 6, following action on the application.**

8. Major Labeling Issues

Interference with serological testing and interference with determination of response will need to be sufficiently described in Sections 5, 7, 17 and in the Patient Information document.

Determination of Complete Responses identified using your investigational assay will not be included in the label. As there is no currently available method to assess interference of response with your product, best responses for these patients will be considered VGPR. The incidence of treatment-emergent laboratory abnormalities is under-represented in the adverse reaction table and should be presented in a separate table in Section 6.

**Discussion:**

**The Applicant has prepared responses and will provide this information by email on October 21, 2015.**

9. Review Plans

FDA plans to send proposed labeling edits and PMRs to the Applicant by October 25, 2015.

**Discussion:**

**No discussion occurred.**

10. Wrap-up and Action Items

This application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, this meeting did not address the final regulatory decision for the application.

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/s/  
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ALBERT B DEISSEROTH  
10/21/2015



BLA 761036

**LATE CYCLE MEETING  
BACKGROUND PACKAGE**

Janssen Biotech, Inc.  
c/o Janssen Research and Development, LLC  
Attention: Brian Maloney, RPh, MS  
Director, Regulatory Affairs  
920 Route 202, PO Box 300  
Raritan, NJ 08869

Dear Mr. Maloney:

Please refer to your Biologic License Application (BLA) submitted under the Public Health Service Act for daratumumab injection, 100 and 400 mg/vial.

We also refer to the Late-Cycle Meeting Package dated October 15, 2015. This document is an updated version and replaces that document for the Late-Cycle Meeting (LCM) scheduled for October 19, 2015. Attached is our background package, including our agenda, for this meeting.

If you have any questions, call Jessica Boehmer, Regulatory Project Manager, at (301) 796-5357.

Sincerely,

*{See appended electronic signature page}*

Albert Deisseroth, MD, PhD  
Clinical Team Leader  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

ENCLOSURE:  
Late-Cycle Meeting Background Package

## LATE-CYCLE MEETING BACKGROUND PACKAGE

**Meeting Date and Time:** October 19, 2015; 3:00 PM – 4:00 PM  
**Meeting Location:** 10903 New Hampshire Avenue  
White Oak Building 22, Conference Room: 1421  
Silver Spring, Maryland 20903

**Application Number:** BLA 761036  
**Product Name:** Daratumumab  
**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 or are double refractory to a PI and an immunomodulatory agent.  
**Sponsor/Applicant Name:** Janssen Biotech, Inc.

### INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

### BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

#### 1. Discipline Review Letters

No Discipline Review letters have been issued to date.

#### 2. Substantive Review Issues

The following substantive review issues have been identified to date:

#### Hepatic impairment:

Safety data included in the current submission indicate that the rates of serious treatment emergent adverse events (TEAE), grade 3 or higher TEAE, treatment discontinuations due to TEAE, and deaths due to TEAE are higher in patients with mild hepatic impairment compared to patients with normal hepatic function at the 16 mg/kg dose level of daratumumab.

Recent literature data suggest that CD38 may play roles in normal hepatic function and the liver disease as follows:

- CD38-mediated  $\text{Ca}^{2+}$  signaling contributes to glucagon-induced hepatic gluconeogenesis [PMID: 26038839].
- Infiltration of inflammatory cells expressing mitochondrial proteins (including CD79a, CD38, CD138 IgM-positive and/or IgG positive plasma cells) may be involved in the pathogenesis of primary biliary cirrhosis [PMID: 24407434].

Based on the data submitted in the current submission to suggest an increased incidence TEAEs in patients with mild hepatic impairment, and the recent literature above, there may be unknown CD38-dependent mechanisms leading to enhanced toxicity to daratumumab in patients with multiple myeloma and baseline hepatic impairment.

Daratumumab has not been administered to patients with moderate to severe hepatic impairment in clinical trials. You should provide a strategy to further assess the safety of daratumumab in patients with pre-existing hepatic impairment. Please provide a comparative analysis to determine whether the increased incidence of adverse events with mild hepatic impairment may be associated with a difference in the distribution of any other baseline risk factors. You should also provide summary of comparative liver function data (normal vs. mild hepatic impairment) in graphical and tabular format.

#### **ADVISORY COMMITTEE MEETING**

An Advisory Committee meeting is not planned.

#### **REMS OR OTHER RISK MANAGEMENT ACTIONS**

Interference with (1) serological testing and (2) interference with determination of response will need to be sufficiently described in the Prescribing Information so that risks to patients are minimized. Information sufficient for prescribers, transfusion medicine staff, and other providers will need to be included in the PI. Your risk mitigation plans to address interference with serologic testing and interference with determination of response are under review.

#### **LCM AGENDA**

1. Introductory Comments – 5 minutes (RPM/CDTL)

Welcome, Introductions, Ground rules, Objectives of the meeting

2. Discussion of Substantive Review Issues – 15 minutes

Each issue will be introduced by FDA and followed by discussion.

Clinical Pharmacology

Hepatic impairment

Product Quality

Human-derived material ( (b)(4) ) used during cell line development

Immunogenicity

3. Discussion of Minor Review Issues – 5 minutes

Nonclinical

Potential Repro-tox risks:

Please provide a risk assessment of the potential for reproductive and developmental toxicity resulting from exposure to Darzalex using non product specific information. Since daratumumab can cross the placental barrier, also include in the assessment any information related to potential effects binding to CD38 may have on the developing fetus.

4. Additional Applicant Data – 5 minutes (Applicant)

5. Information Request – 3 minutes

Product Quality

There is a CMC IR pending a response (communicated on October 14, 2015).

6. REMS or Other Risk Management Actions – 5 minutes

(1) serological testing and (2) interference with determination of response

7. Post-marketing Requirements/Post-marketing Commitments – 10 minutes

Draft 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.

Draft 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.

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

Draft 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.

Draft Immunogenicity PMR 5: Conduct an assessment of the anti-drug antibody (ADA) response to daratumumab with the validated assay developed under PMR 4 (b) (4)

Draft 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.

Draft 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-shipment 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.

Draft Product Quality 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.

Draft Product Quality PMC 3: Re-evaluate (b) (4) 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.

Draft 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.

Draft 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.

8. Major labeling issues – 5 minutes

Interference with serological testing and interference with determination of response will need to be sufficiently described in Sections 5, 7, 17 and in the Patient Information document.

Determination of Complete Responses identified using your investigational assay will not be included in the label. As there is no currently available method to assess interference of response with your product, best responses for these patients will be considered VGPR.

The incidence of treatment-emergent laboratory abnormalities is under-represented in the adverse reaction table and should be presented in a separate table in Section 6.

9. Review Plans – 2 minutes

FDA plans to send proposed labeling edits and PMRs to Applicant by October 25, 2015.

10. Wrap-up and Action Items – 5 minutes

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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ALBERT B DEISSEROTH  
10/16/2015