

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761036Orig1s000

OTHER REVIEW(S)

Given the current validation data for the anti-drug antibody assay and the PK data from the clinical studies, it is not clear that the assay is capable of detection of anti-drug antibodies in serum samples that included drug at the higher end of the range identified. Immune-related reactions to daratumumab could include hypersensitivity reactions and is not limited to effects on efficacy alone. It is critical that immunogenicity data be obtained to more fully understand the safety profile of the drug. In addition, the assay should be available in the post-marketing environment to allow for the rapid evaluation of patient serum samples with adverse events that might be attributable to the presence of anti-drug antibodies. The study required under this PMR will provide assurance that anti-daratumumab binding antibodies can be detected in patient samples characterized by the level of daratumumab expected to be present at the time of sample collection.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Validation of a sensitive, accurate assay for the detection of anti-drug antibodies to daratumumab or submission of additional data from the current partially validated assay to demonstrate sufficient sensitivity of the current assay. This PMR is linked to PMR3 regarding testing of clinical samples.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
Validation of a sensitive and accurate assay for detection of anti-daratumumab binding antibodies
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

-
- Other
Clinical pharmacology study/Validation of an assay to assess immunogenicity
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

Validation of an assay capable of detecting neutralizing antibodies against daratumumab was not included in the submission. The presence of neutralizing antibodies would lead to a loss of efficacy, meaning that any patient who develops neutralizing antibodies would be subject to all the safety risks of the product with no chance of benefit from the product. These patients could still benefit from a different product, so there is additional risk from lack of treatment. The study required under this PMR will provide assurance that neutralizing antibodies directed against daratumumab can be detected in patient samples at the time of sample collection.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Validation of a sensitive, accurate assay for the detection of neutralizing antibodies to daratumumab. This validation study would be performed if PMR 3 leads to the identification of binding antibodies to daratumumab.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
Validation of a sensitive and accurate assay for detection of neutralizing antibodies to daratumumab.
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

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- Other
Clinical pharmacology study/Validation of an assay to assess immunogenicity
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
 - Are the objectives clear from the description of the PMR/PMC?
 - Has the applicant adequately justified the choice of schedule milestone dates?
 - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
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- The trial will emphasize risk minimization for participants as the protocol is developed

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(signature line for BLAs)

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

Shipping validation studies using commercial shipping conditions will be performed to evaluate the performance of the commercial shippers and to assess the impact of shipping on product quality.

5. To be completed by OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

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

5. To be completed by OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

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Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

Statistical analysis of release data acquired following manufacture and testing of additional commercial lots

5. To be completed by OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

Statistical analysis of release data acquired following manufacture and testing of additional commercial lots

5. To be completed by OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

Statistical analysis of release data acquired following manufacture and testing of additional commercial lots

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs only)

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/s/

JESSICA L BOEHMER
11/16/2015

JEE Y CHUNG
11/16/2015

PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

NDA/BLA # 761036
Product Name: Darzalex® (daratumumab)

PMC-12 Description: To determine the maximum hold times for all (b) (4) using a surrogate solution that supports microbial growth. Submit results in accordance with 21CFR601.12, in the Final Report.

PMC Schedule Milestones: Final Report Submission: 06/2016

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

Microbial quality attributes (bioburden and endotoxin) will be monitored at the end of all (b) (4) hours. In addition, the (b) (4) therefore, the risk of unacceptable bioburden levels (b) (4) deemed low.

2. Describe the particular review issue and the goal of the study.

The data submitted in the original BLA describe the use of a (b) (4) as a surrogate to demonstrate microbial control (b) (4) of daratumumab (b) (4). However, the (b) (4) used in the study was not demonstrated to be an adequate surrogate because its microbial growth promotion properties were not compared with those of daratumumab product (b) (4).
The goal of the study is to demonstrate the suitability of the (b) (4) as a surrogate for daratumumab product (b) (4).

3. [OMIT – for PMRs only]
4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

<p>The agreed-upon study will consist of a comparison at small scale of the microbial growth promoting properties of the surrogate (b) (4) and the daratumumab (b) (4)</p> <p>In the event that the (b) (4) shows worse growth promoting properties than the (b) (4), a second study should be conducted to demonstrate microbial control of the (b) (4) proposed by the applicant.</p>

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs only)

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/s/

JESSICA L BOEHMER
11/16/2015

PATRICIA F HUGHES TROOST
11/16/2015

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

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.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

Confirmatory clinical trial under 21CFR314 Subpart H

Agreed upon:

Quality study without a safety endpoint (e.g., manufacturing, stability)

Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E

Dose-response study or clinical trial performed for effectiveness

Nonclinical study, not safety-related (specify)

Other

5. Is the PMR/PMC clear, feasible, and appropriate?

Does the study/clinical trial meet criteria for PMRs or PMCs?

Are the objectives clear from the description of the PMR/PMC?

Has the applicant adequately justified the choice of schedule milestone dates?

Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

There is a significant question about the public health risks of an approved drug

There is not enough existing information to assess these risks

Information cannot be gained through a different kind of investigation

The trial will be appropriately designed to answer question about a drug's efficacy and safety, and

The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
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- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

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- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
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- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

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.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
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Continuation of Question 4

Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

Confirmatory clinical trial under 21CFR314 Subpart H

Agreed upon:

Quality study without a safety endpoint (e.g., manufacturing, stability)

Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E

Dose-response study or clinical trial performed for effectiveness

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5. Is the PMR/PMC clear, feasible, and appropriate?

Does the study/clinical trial meet criteria for PMRs or PMCs?

Are the objectives clear from the description of the PMR/PMC?

Has the applicant adequately justified the choice of schedule milestone dates?

Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

There is a significant question about the public health risks of an approved drug

There is not enough existing information to assess these risks

Information cannot be gained through a different kind of investigation

The trial will be appropriately designed to answer question about a drug's efficacy and safety, and

The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

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- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A study to assess the anti-drug antibody (ADA) response to daratumumab with the validated assay developed under PMR 4. The assay must be capable of sensitively detecting ADA responses in the presence of daratumumab levels that are expected to be present at the time of patient sampling.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
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- Dosing trials
- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
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- Other
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If so, does the clinical trial meet the following criteria?

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- There is not enough existing information to assess these risks
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- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Collect sufficient safety data from patients with baseline hepatic impairment, being enrolled in current clinical trials, to characterize the safety profile of daratumumab in patients with hepatic impairment

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
The safety profile of daratumumab in patients with baseline hepatic impairment will be characterized with additional data from patients enrolled in ongoing clinical trials.
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 Immunogenicity as a marker of safety
 Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 Dose-response study or clinical trial performed for effectiveness
 Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
 Are the objectives clear from the description of the PMR/PMC?
 Has the applicant adequately justified the choice of schedule milestone dates?
 Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
 There is not enough existing information to assess these risks
 Information cannot be gained through a different kind of investigation
 The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
 The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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/s/

JESSICA L BOEHMER
11/14/2015

DIANE V LEAMAN
11/16/2015
for Ann Farrell, MD



DEPARTMENT OF HEALTH & HUMAN SERVICES

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatric and Maternal Health Review

Date: October 22, 2015

From: Suchitra M. Balakrishnan, MD, PhD., Medical Officer, Maternal Health
Division of Pediatric and Maternal Health

Through: Tamara Johnson, MD, MS, Acting Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, OND, Division Director
Division of Pediatric and Maternal Health

To: Division of Hematology Products (DHP)

Drug: Darzalex (daratumumab)

BLA: 761036

Applicant: Genentech, Inc.

Subject: Pregnancy and Lactation Labeling

Indication: treatment of patients with multiple myeloma refractory to a proteasome inhibitor (PI) and immunomodulatory agent

Materials Reviewed:

- DPMH Consult request dated September 21, 2015
- Nonclinical review dated October 20, 2015 by Dr. Emily Place (DARRTs ID 3835974)
- Applicant's proposed labeling for daratumumab
- Applicant's assessment for embryo-fetal toxicity dated October 29, 2015

Consult Question:

Please review the Applicant's proposed PLLR and provide feedback.

INTRODUCTION

Janssen Biotech, Inc., has submitted a biologics license application (BLA) for Darzalex (daratumumab), a human anti-CD38 monoclonal antibody on July 9, 2015. The proposed indication is treatment of patients with multiple myeloma who have received at least three prior lines of therapy, including a proteasome inhibitor (PI) and an immunomodulatory agent, or who are double-refractory to a PI and immunomodulatory agent. The planned action date is November 17, 2015. Daratumumab was designated as a breakthrough therapy for the proposed indication and the applicant was granted rolling review on April 24, 2015.

DHP has consulted the Maternal Health Team (MHT) for review of the proposed labeling to ensure compliance with the Pregnancy and Lactation Labeling Rule (PLLR) format.

BACKGROUND

Daratumumab Drug Characteristics

Daratumumab is a first-in-class, human immunoglobulin G1 kappa (IgG1 κ) monoclonal antibody that binds to the cell surface molecule CD38. CD38 is a cell surface glycoprotein that has enzymatic activity as well as receptor functions¹. CD38 is highly expressed in human hematopoietic cells/tissues, and at a lower level in pancreas, Purkinje cells, pituitary, eye, kidney, prostate, smooth muscle cells, and bone². The main effect of daratumumab antibody binding to CD38+ myeloma cell lines is lysis and cell death either through complement dependent cytotoxicity [CDC], antibody dependent cell-mediated cytotoxicity [ADCC] or antibody-dependent cell phagocytosis [ADCP], or by direct apoptosis following crosslinking of the antibody molecules. The primary mechanism of action in patients with multiple myeloma is not fully elucidated.

The recommended dose of daratumumab is 16 mg/kg body weight as an intravenous infusion. The dosing regimen is one dose weekly on Weeks 1 to 8, every two weeks from Weeks 9 to 24, and every four weeks from Week 25 onwards.

The mean terminal half-life that can be expected upon complete saturation of target mediated clearance and repeat dosing of daratumumab was approximately 18 (SD= 9) days³.

Multiple Myeloma:

Multiple myeloma is a malignant disorder of the plasma cells, characterized by uncontrolled and progressive proliferation of a plasma cell clone. It is the third most common hematologic malignancy (after lymphoma and leukemia) in the United States and constituted approximately 1.4 percent of the estimated new cancer cases in 2014. Since 1975, overall myeloma incidence has increased nearly 1 percent annually⁴. The median age of patients at diagnosis is 69 years and the disease has a typical course characterized by a chronic phase lasting several years and an aggressive terminal phase⁵. Progress has been made over the last

1 Deaglio S, Aydin S, Vaisitti T, Bergui L, and Malavasi F. CD38 at the junction between prognostic marker and therapeutic target. Trends in Molecular Medicine 2008;14:210-218.

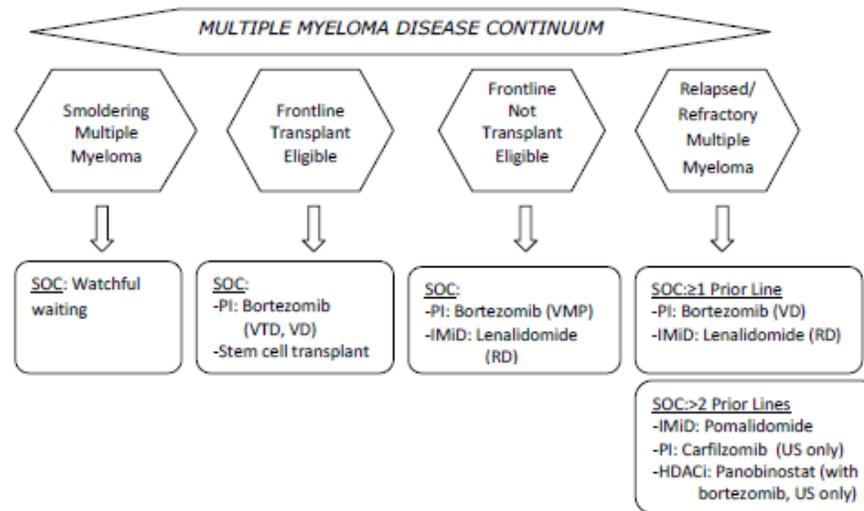
2 Non-clinical review dated October 20, 2015 by Dr. Emily Place, , BLA 761036, DARRTs ID 3835974

3 Clinical Pharmacology review by Dr. Jeanne Fourie Zirkelbach dated October 22, 2015, BLA 761036, DARRTs ID 3836843

4 <http://www.cancer.gov/research/progress/snapshots/myeloma>

5 Clinical overview, eCTD 2.5, BLA761036

15 years in the treatment of multiple myeloma, such that survival of patients with newly diagnosed multiple myeloma has increased from 33 months, with no improvement from the years 1985 to 1998⁷ to 6 to 10 years today, with a 5 year survival rate of 46.6%⁶. Treatment options for the disease continuum are broadly summarized below.



Note: Other treatment options include corticosteroids, alkylators, anthracyclines, nitrosoureas, high-dose chemotherapy
 IMiD=immunomodulatory agent; PI=proteasome inhibitor; RD=REVLIMiD (lenalidomide)/dexamethasone; SOC=Standard of Care; VD=VELCADE (bortezomib)/dexamethasone; VCD= bortezomib/cyclophosphamide/dexamethasone; VMP=bortezomib/melphalan/dexamethasone; VTD= bortezomib/thalidomide/dexamethasone

Source: Figure 1- Multiple Myeloma Disease Continuum: Standard of Care, Applicant's Clinical Overview, eCTD 2.5, July 9, 2015

Multiple Myeloma and Pregnancy:

About 2% of patients with multiple myeloma are younger than 40⁸. Therefore, the occurrence of multiple myeloma during pregnancy is rather exceptional. Physiological changes associated with pregnancy may facilitate the proliferation of multiple myeloma cells, constituting a suitable condition for disease relapse⁹. Estrogen and progesterone could also impact multiple myeloma cells; the temporary immune system impairment observed during pregnancy, characterized by the expansion of regulatory T-cells, may also facilitate a flare of plasma cell proliferation¹⁰. In addition, despite the expected toxicity of chemotherapy (around 30% of women older than 30 years suffered severe menopausal symptoms – three to four times more than expected after high-dose therapy)¹¹, fertility may be preserved, and

6 <http://seer.cancer.gov/statfacts/html/mulmy.html>

7 Kyle RA, Gertz MA, Witzig TE, et al. Review of 1027 patients with newly diagnosed multiple myeloma. Mayo Clin Proc 2003;78:21-33.

8 Palumbo A, Anderson K. Multiple myeloma. N Engl J Med 2011; 364:1046–1060.

9 Gargosky SE, Moyse KJ, Walton PE, et al. Circulating levels of insulin-like growth factors increase and molecular forms of their serum binding proteins change with human pregnancy. Biochem Biophys Res Commun 1990;170:1157–1163.

10 Bommert K, Bargou RC, Stuhmer T. Signaling and survival pathways in multiple myeloma. Eur J Cancer 2006;42:1574–1580.

11 Behringer K, Mueller H, Goergen H, et al. Gonadal function and fertility in survivors after Hodgkin lymphoma treatment within the German Hodgkin Study Group HD13 to HD15 trials. J Clin Oncol 2013;31:231–239

ovarian function may recover, in selected patients, even those receiving more than one autologous stem cell transplant (ASCT)¹².

Management of multiple myeloma during pregnancy is dependent on myeloma-related organ damage (hypercalcemia, renal impairment, anemia and bone lesions) and the time of diagnosis (either during the first trimester or after)¹³.

Based on review of case series describing management of patients with multiple myeloma during pregnancy^{14,15}, a “watch and wait” approach is generally used with asymptomatic myeloma. Dexamethasone was administered in the patients who require treatment due to clinical progression antepartum, for the purpose of stabilizing the disease. Symptomatic progressive disease necessitates specific anti-myeloma therapy (agents used include cyclophosphamide, vincristine, melphalan and prednisone [CMOP], doxorubicin, all-*trans* retinoic acid, interferon and urethane). Induction regimens with novel agents as proteasome inhibitors (e.g. bortezomib) or immunomodulatory agents (e.g. lenalidomide) are contraindicated during pregnancy.

In a case series of 32 women with multiple myeloma during pregnancy reported in the literature¹⁵ (see Appendix), 68.7% were diagnosed before the third trimester. Two patients diagnosed during the first trimester died at 38 weeks gestation; the status of the newborn was reported as healthy in one patient and not available for the other. Two other patients diagnosed in the third trimester delivered healthy newborns, but died within 1 year and 22 months post-partum (they did not receive anti-myeloma treatment during the pregnancy). Survival status at one year post-partum was reported as not available for one patient. Twenty-three of 26 infants were healthy (two had low birth weight and one an Apgar score of 5 at birth). No congenital abnormalities or neonatal death have been reported. Four women had abortions (not reported as spontaneous or elective) The status of the newborn was unknown in two patients. Sixteen of 30 pregnant women did not start treatment before partum. The newborns that were exposed to chemotherapy during pregnancy had no congenital anomalies reported. In general, information from these case reports are limited due to the small sample size, the rarity of this condition and lack of safety data regarding chemotherapy use during pregnancy.

Pregnancy and Nursing Mothers Labeling

On December 4, 2014, the Food and Drug Administration (FDA) announced the publication of the “*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*,”¹⁶ also known as the

12 Loren AW, Chow E, Jacobsohn DA, et al. Pregnancy after hematopoietic cell transplantation: a report from the late effects working committee of the Center for International Blood and Marrow Transplant Research (CIBMTR). *Biol Blood Marrow Transplant* 2011;17:157–166.

13 Brenner B, Avivi I, Lishner M. Haematological cancers in pregnancy. *Lancet* 2012;379:580–587.

14 Pregnancy and multiple myeloma are not antinomic; Gabriel Brisou, Fadhela Bouafia-Sauvy, Lionel Karlin, Laure Lebras, Gilles Salles, Bertrand Coiffier & Anne-Sophie Michallet. *Leukemia & Lymphoma*, December 2013; 54(12): 2738–2741

15 Management multiple myeloma during pregnancy: a case report and review, Valentin Cabañas-Perianes *et al*, *Hematol Oncol* 2014, Published online in Wiley Online Library (wileyonlinelibrary.com) DOI: 10.1002/hon.2184

Pregnancy and Lactation Labeling Rule (PLLR). The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation and create a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) are being removed from all prescription drug and biological product labeling and a new format is required for all products that are subject to the 2006 Physicians Labeling Rule¹⁷ format to include information about the risks and benefits of using these products during pregnancy and lactation.

DISCUSSION

Nonclinical Experience

Standard genotoxicity studies are not generally applicable to biotechnology-derived pharmaceuticals (per ICH S6) and were not needed. No reproductive and developmental toxicology studies were conducted for daratumumab. The considerations that led to this decision included the lack of a pharmacologically relevant species for testing (aside from the chimpanzee wherein these studies are not feasible); and that these studies are not warranted to support marketing of pharmaceuticals intended for the treatment of patients with advanced cancer (per ICH S9). The reader is referred to the Pharmacology-toxicology review for further details².

The nonclinical team has communicated the following information request to the applicant¹⁸: “Please provide a risk assessment of the potential for reproductive and developmental toxicity 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”

The applicant’s risk assessment was received electronically on October 29th 2015, and the conclusions reported were as follows:

“There are no human or animal data on the developmental or reproductive toxicity of daratumumab. CD38 expression, potential embryo/fetal exposure, knockout mouse data, and effects of other monoclonal antibodies that affect leukocyte populations were considered in evaluating the potential for daratumumab to effect development or reproduction. The fetus and neonate, but not the embryo, are likely to be exposed to daratumumab via placental transfer. This exposure may deplete CD38 positive immune cells and may result in an increased susceptibility to certain infections during the early postnatal period. Bone density in the neonate may also be reduced. Both of these effects would most likely be reversed as daratumumab exposure decreases. Female reproduction is unlikely to be affected. Male fertility could be affected by changes in seminal fluid from the prostate, but this is considered to be unlikely as CD38 KO mice reproduce normally.”

Reviewer’s Comment:

¹⁶ *Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling* (79 FR 72063, December 4, 2014).

¹⁷ *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, published in the Federal Register (71 FR 3922; January 24, 2006).

¹⁸ Late Cycle meeting Communication dated October 21, 2015, DARRTs ID 3836588

The applicant's risk assessment was discussed with the non-clinical team. Based on available information, potential risks to a fetus exposed to daratumumab in utero appear to be limited to myeloid/ lymphoid cell depletion and decreased bone mineral density.

Clinical Experience

Daratumumab and Pregnancy:

The applicant did not conduct studies with daratumumab in pregnant women. A search of published literature for available human pregnancy data was performed to update the Pregnancy subsection of labeling for this BLA, and no studies were found.

Based on information provided in the applicants risk assessment (*see non-clinical experience*), CD 38 expression varies significantly with age and during pregnancy¹⁹. CD38 expression is extremely high in T cells up until 2 years of age and decreases thereafter. CD38 expression in cord blood B cells is also high, but very low numbers of CD38+ B cells are seen in adults. Unlike adults, there is no expression of CD38 in the prostate of fetuses or 9 month old infants²⁰. During pregnancy there is a significant increase in the percentage of CD38, CD8, HLA-class II lymphocytes. These populations of lymphocytes peak during the third trimester and decreases to normal levels 1 month after delivery.

Monoclonal antibodies, such as daratumumab, appear to be transported across the placenta with a continuous linear rise in fetal IgG starting as early as 13 weeks gestation (start of the second trimester of pregnancy). One study (Malek, *et al.*) demonstrated that there is a continuous rise in the level of IgG observed between 17 and 41 weeks gestation. Fetal levels of IgG were 5-10% of the maternal level between 17 and 22 weeks gestation, but exceeded the maternal level by three-fold at term. It's possible that this is also due to increased fetal production and not maternal transport across the placenta alone²¹. In another study (Garty, *et al.*), the blood from 34 fetuses was obtained by percutaneous umbilical blood sampling via amniocentesis and peripheral venous blood was drawn from the mothers at the time of the procedure. The authors showed that although all IgG subclasses cross the human placenta, their transport is not uniform. IgG1 and IgG4 are transported more efficiently than IgG2 and IgG3. Fetal IgG subclass concentrations are similar to maternal concentrations at 38 weeks gestation and on occasion, IgG concentrations may be higher than maternal concentrations at delivery.²² Therefore, since monoclonal antibodies, such as daratumumab, appear to cross the placenta in increasing amounts as pregnancy proceeds, it is possible that the effects of daratumumab may be greater during the second and third trimester of pregnancy.

The Applicant-proposed labeling indicates that there are no human or animal data to inform daratumumab use in pregnancy. DPMH agrees that there is insufficient information to make a clear assessment of risk since there are no data regarding daratumumab use in pregnant

19 Malvasi F, et al.; 2008. Evolution and Function in the ADP Ribosyl Cyclase/CD38 Gene Family in Physiology and Pathology. *Physiol Rev* 88:841-886

20 Kramer G, et al.; 1995. High Expression of a CD38-like Molecule in Normal Prostatic Epithelium and its Differential Loss in Benign and Malignant Disease. *The Journal of Urology* 154:1636-1641

21 Malek, et al. *Ex vivo* human placenta models: transport of immunoglobulin G and its subclasses. *Vaccine* 2003;21:3362-4

22 Garty *et al.* Placental Transfer of Immunoglobulin G Subclass. *Clinical and Diagnostic Laboratory Immunology*. 1994; 1 (6): 667-669.

women. However, there are clinical considerations since Immunoglobulin G1 (IgG1) monoclonal antibodies are transferred across the placenta. Based on its mechanism of action, daratumumab may cause fetal/neonatal myeloid or lymphoid-cell depletion and this should be reflected in the labeling.

Lactation

A search of published literature in the Drugs and Lactation Database (LactMed)²³ and PubMed for available human lactation data was performed to update the Lactation subsection of labeling for this application. There is no information on the clinical use of daratumumab during lactation in published literature, which includes the presence in human milk, the effects on the breastfed infant, or the effects on milk production.

In general, IgG is present in human breast milk in small amounts; therefore, there is a hypothetical likelihood that daratumumab, an IgG1 antibody, will be present in breast milk. Since daratumumab is a large protein molecule with a molecular weight of about 148 kDa and Volume of distribution of 4.7 (1.3) L³, the amount in milk is likely to be low and absorption is likely to be minimal because denaturation generally occurs in the infant's gastrointestinal tract²⁴.

However, the effects of local gastrointestinal and potential for systemic exposure to daratumumab are unknown.

DPMH and the DHP nonclinical team agree that breastfeeding should not be contraindicated during drug therapy with daratumumab, and the Lactation Risk Summary should include the following risk and benefit statement:

“The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for DARZALEX and any potential adverse effects on the breastfed (b) (4) from DARZALEX or from the underlying maternal condition.”

DPMH also notes that a clinical lactation study to obtain more data is not possible, given the expected age of the population at risk.

Daratumumab and Females/Males of Reproductive Potential:

As discussed earlier, no nonclinical genotoxicity, reproductive and developmental toxicity studies have not been conducted for daratumumab.

The applicant includes a statement in the label advising women of reproductive potential to use effective contraception during and up to 3months after cessation of daratumumab treatment. DPMH agrees with this statement, given the potential for myeloid and lymphoid cell depletion.

²³The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides any available information on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants, if known, as well as alternative drugs that can be considered. The database also includes the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.
<http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>

²⁴ Nice, F and Luo, Amy. Medications and breast-feeding: Current Concepts. Journal of the American Pharmacists Association. 2012; 51 (1): 86-94

The applicant also includes a statement

(b) (4)

DPMH recommends deleting this statement, since actual daratumumab are unknown and the sponsor did not provide any data to support this statement.

(b) (4)

CONCLUSIONS

Darzalex (daratumumab) labeling has been updated to comply with the PLLR. A review of the published literature revealed no information with daratumumab use in pregnant or lactating women. DPMH has the following recommendations for daratumumab labeling:

- **Pregnancy, Section 8.1**

- The “Pregnancy” subsection of daratumumab labeling was formatted in the PLLR format to include a “Risk Summary” and “Clinical Considerations,” subsections²⁵.

- **Lactation, Section 8.2**

- The “Lactation” subsection of daratumumab labeling was formatted in the PLLR format to include the “Risk Summary” subsection²⁶.

- **Females and Males of Reproductive Potential, Section 8.3**

- The “Females and Males of Reproductive Potential” subsection of daratumumab labeling was formatted in the PLLR format to include “Contraception” to advise females of reproductive potential to use effective contraception during treatment and for 6 half-lives following completion of therapy because of the potential for adverse fetal and infant effects from maternal exposure. This subsection is consistent with the PLLR for drugs with a likelihood of embryofetal toxicity²⁷

- **Patient Counseling Information, Section 17**

- The “Patient Counseling Information” section of Darzalex (daratumumab) labeling was updated to correspond with changes made to sections 8.1, 8.2 and 8.3 of labeling.

RECOMMENDATIONS

- 1.) DPMH revised subsections 8.1 and 8.2 and section deleted 8.3 in Darzalex (daratumumab) labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling.

²⁵ Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format. December 2014. Part IV Specific Subsection A-8.1 Pregnancy, 2-Risk Summary.

²⁶ Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format. December 2014. Part IV Specific Subsection, B- 8.2 Lactation, 1- Risk Summary.

²⁷ Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format. December 2014. Part IV Specific Subsection, C-8.3 Females and Males of Reproductive Potential.

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no human data to inform a risk with use of DARZALEX during pregnancy. Animal (b) (4) studies have not been conducted. However, there are clinical considerations [see *Clinical Considerations*]. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations:

Fetal/Neonatal Adverse Reactions

Immunoglobulin G1 (IgG1) monoclonal antibodies are transferred across the placenta. Based on its mechanism of action, DARZALEX may cause fetal myeloid or lymphoid-cell depletion and decrease bone density [see *Clinical Pharmacology (12.1)*]. Defer administering live vaccines to neonates and infants exposed to DARZALEX in utero until a hematology evaluation is completed.

8.2 Lactation

Risk Summary

There is no information regarding the presence of daratumumab in human milk, the effects on the breastfed infant, or the effects on milk production. Human IgG is known to be present in human milk. Published data suggest that antibodies in breast milk do not enter the neonatal and infant circulations in substantial amounts. (b) (4)

The developmental and health benefits of breast-feeding should be considered along with the mother's clinical need for DARZALEX and any potential adverse effects on the breast-fed (b) (4) from DARZALEX or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Contraception

To avoid exposure to the fetus, women of reproductive potential should use effective contraception during and up to 3 months after cessation of DARZALEX treatment

17 PATIENT COUNSELING INFORMATION

(b) (4)

(b) (4)



Table 1. Multiple myeloma and pregnancy. Clinical cases

#	Reference	Age at diagnosis	Trimester at diagnosis	MM subtype	Durie & Salmon ISS	Cytogenetic	Time at ending of pregnancy (week)	Caesarian (Yes/No)	Survival from diagnosis to 1 year post-partum	Mother Status at partum or after pregnancy?	Anti-MM Treatment: During pregnancy?	MM Treatment	Response to therapy
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Source: Table 1, Multiple myeloma and pregnancy. Clinical cases, Valentin Cabañas-Perianes et al, Hematol Oncol 2014, Published online in Wiley Online Library (wileyonlinelibrary.com) DOI: 10.1002/hon.2184

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/s/

SUCHITRA M BALAKRISHNAN
11/04/2015

TAMARA N JOHNSON
11/05/2015

LYNNE P YAO
11/06/2015

Division of Hematology Products (DHP) Labeling Review

BLA Number	761036
Supporting Document Number	New BLA (1)
Proprietary Name (nonproprietary name)	Darzalex Daratumumab
Receipt Date	06/05/2015
PDUFA Goal Date (Internal Goal Date)	02/05/2016 (8 mos.) 11/17/2015 (5 mos)
Review Classification	Priority (expedited)
Proposed Indication (or current indication if unchanged)	For the treatment of patients with multiple myeloma who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent (IMiD) or are double refractory to a PI and an IMiD.
Dosing Regimen	16 mg/kg body weight weekly for weeks 1- 8, then every 2 weeks for weeks 9-24, and every 4 weeks for week 25 onwards until PD. Pre-and post-infusion medications are required.
From	Virginia Kwitkowski, MS, ACNP-BC Associate Director for Labeling, DHP

Background of Application:

The BLA for Darzalex (daratumumab) was submitted to FDA on June 5, 2015. Daratumumab (DARZALEX) is a human CD38-directed monoclonal antibody indicated for the treatment of patients with multiple myeloma who have received at least three prior lines of therapy including a proteasome inhibitor and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent.

The proposed indication is based upon the results of a single arm trial evaluating daratumumab monotherapy in patients with relapsed or refractory MM who had received at least 3 prior therapies including a proteasome inhibitor and an immunomodulatory agent or who were double-refractory to a proteasome inhibitor and an immunomodulatory agent. In 106 patients, DARZALEX 16 mg/kg was administered with pre- and post-infusion medication. Treatment continued until unacceptable toxicity or disease progression. The overall response rate in this trial was 29.2%. A second, supportive study was

conducted as a dose-escalation trial also evaluating daratumumab monotherapy in patients with relapsed or refractory multiple myeloma who had received at least 2 different cytoreductive therapies. In 42 patients, DARZALEX 16 mg/kg was administered with pre- and post-infusion medication. Treatment continued until unacceptable toxicity or disease progression. The ORR in this trial was 36%.

In this review, I propose labeling recommendations and edits in the DARZALEX labeling to ensure that the prescribing information is a useful communication tool for healthcare providers and uses clear, concise language; is based on regulations and guidances; and conveys the essential scientific information needed for the safe and effective use of DARZALEX.

The following pages contain my recommended edits for the DARZALEX PI and comments (identified as 'VK1' through 'VK8'). Given that the scientific review of the labeling is ongoing, my labeling recommendations in this review should be considered preliminary and may not represent DHP's final recommendations for the DARZALEX labeling.

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

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/s/

VIRGINIA E KWITKOWSKI
11/04/2015

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: October 28, 2015

To: Ann Farrell, MD
Director
Division of Hematology Products (DHP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Rowell Medina, PharmD
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Kathleen Davis, RN
Team Leader
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): DARZALEX (daratumumab)

Dosage Form and Route: injection, for intravenous use

Application Type/Number: BLA 761036

Applicant: Janssen Biotech, Inc.

1 INTRODUCTION

On June 5, 2015, Janssen Biotech, Inc. submitted for the Agency's review the third and final part of a rolling submission for Biologics License Application (BLA) 761036 for DARZALEX (daratumumab) injection, for intravenous use, with the proposed indication 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 collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Hematology Products (DHP) on September 8, 2015, and September 1, 2015, respectively, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for DARZALEX (daratumumab) injection, for intravenous use.

2 MATERIAL REVIEWED

- Draft DARZALEX (daratumumab) injection, for intravenous use PPI received on June 5, 2015, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on October 16, 2015.
- Draft DARZALEX (daratumumab) injection, for intravenous use Prescribing Information (PI) received on June 5, 2015, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on October 16, 2015.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI, the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)

- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

ROWELL MEDINA
10/28/2015

KATHLEEN T DAVIS
10/28/2015

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10/28/2015



Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Biotechnology Products

FINAL LABEL AND LABELING REVIEW

Date:	October 27 2015
Reviewer:	Jibril Abdus-Samad, PharmD, Labeling Reviewer Office of Biotechnology Products Jibril Abdus-samad - S <small>Digitally signed by Jibril Abdus-samad - S DN: cn=Jibril Abdus-samad - S, ou=FDA, ou=People, o=U.S. Government, ou=HHS, ou=FDA, c=US, email=j.abdusamad@fda.hhs.gov Date: 2015.10.27 13:59:23 -0400</small>
Through:	Tura Camilli, PhD, Quality Reviewer Division of Biotechnology Review and Research I Tura C. Camilli - S <small>Digitally signed by Tura C. Camilli - S DN: cn=Tura C. Camilli - S, ou=FDA, ou=People, o=U.S. Government, ou=HHS, ou=FDA, c=US, email=t.camilli@fda.hhs.gov Date: 2015.10.27 14:36:56 -0400</small>
Application:	761036/0
Product:	Darzalex™ (daratumumab)
Applicant:	Janssen Biotech, Inc.
Submission Dates:	July 9; October 2, 9, 20 2015

Executive Summary:

The container labels and carton labeling for Darzalex™ (daratumumab) were reviewed and found to comply with the following regulations: 21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57, 21 CFR 201.100 and United States Pharmacopeia (USP), USP 38/NF 33 [August 1, 2015 to November 30, 2015]. Labeling deficiencies were identified and resolved. The container labels and carton labeling submitted on October 20 2015 are acceptable. However, the Applicant can use the container labels submitted on October 2 2015 for initial product launch then approximately 4 to 6 weeks later, replace these labels with the container labels submitted October 20 2015.

Background and Summary Description:

The Applicant submitted BLA 761036/0 Darzalex™ (daratumumab) on July 9 2015 as a rolling BLA. Table 1 lists the proposed characteristics of Darzalex™ (daratumumab).

Table 1: Proposed Product Characteristics of Darzalex™ (daratumumab).

Proprietary Name:	Darzalex™
Proper 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 (IMiD) or who are double-refractory to a PI and IMiD
Dose:	16 mg/kg body weight administered as an intravenous infusion weekly (Weeks 1 to 8, every 2 weeks (weeks 9 to 24), and every 4 weeks (Week 25 onwards until disease progression))
Route of Administration:	Intravenous infusion
Dosage Form:	Injection
Strength and Container-Closure:	100 mg/5 mL or 400 mg/20 mL in single-dose vials
Storage and Handling:	Store in a refrigerator at 2°C to 8°C (36°F to 46°F). Do not freeze or shake. Protect from light. This product contains no preservative.

Materials Reviewed:

Container Labels
Carton Labeling

Start of Sponsor Material

Container Label, 100 mg/5 mL



Container Label, 400 mg/20 mL



End of Sponsor Material

Subpart G-Labeling Standards
Subpart A-General Labeling Provisions

I. Container

A. 21 CFR 610.60 Container Label

(a) Full label. The following items shall appear on the label affixed to each container of a product capable of bearing a full label:

- (1) The proper name of the product [see 21 CFR 600.3 (k) and section 351 of the PHS Act]; *conforms*.
- (2) The name, address, and license number of manufacturer; *conforms*.
- (3) The lot number or other lot identification; *conforms*.
- (4) The expiration date; *conforms*.
- (5) The recommended individual dose, for multiple dose containers; *not applicable*.
- (6) The statement: "Rx only" for prescription biologicals; *does not conform*.

OBP Request: Add "Rx Only" to the top right of the principal display panel (PDP) across from the NDC.
Applicant revised as requested.

(7) If a Medication Guide is required under part 208 of the chapter, the statement required under §208.24(d) of this chapter instructing the authorized dispenser to provide a Medication Guide to each patient to whom the drug is dispensed and stating how the Medication Guide is provided, except where the container label is too small, the required statement may be placed on the package label. *Not applicable.*

(b) Package label information. If the container is not enclosed in a package, all the items required for a package label shall appear on the container label. *Not applicable.*

(c) Partial label. If the container is capable of bearing only a partial label, the container shall show as a minimum the name (expressed either as the proper or common name), the lot number or other lot identification and the name of the manufacturer; in addition, for multiple dose containers, the recommended individual dose. Containers bearing partial labels shall be placed in a package which bears all the items required for a package label. *Not applicable.*

(d) No container label. If the container is incapable of bearing any label, the items required for a container label may be omitted, provided the container is placed in a package which bears all the items required for a package label. *Not applicable.*

(e) Visual inspection. When the label has been affixed to the container, a sufficient area of the container shall remain uncovered for its full length or circumference to permit inspection of the contents; *does not conform.*

OBP Request: Indicate how the label is affixed to the vial and where the visual area of inspection is located per 21 CFR 610.60(e).

Applicant's October 2 2015 submission: The label is affixed to the vial [REDACTED] (b) (4) Due to the design of the label, it is confirmed that after the label has been affixed to the vial a sufficient area of the vial surface remains uncovered to permit visual inspection of the contents of the drug product solution.
Applicant's response is acceptable.

B. 21 CFR 201.2 Drugs and devices; National Drug Code numbers – The National Drug Code (NDC) number is located at the top of the label. [See 21 CFR 207.35]; *conforms. Additionally, we concur with the Division of Medication Error Prevention and Analysis (DMEPA) recommendation to revise the middle digits of the NDC code.*

C. 21 CFR 201.5 Drugs; adequate directions for use; *conforms.*

D. 21 CFR 201.6 Drugs; misleading statements; *conforms.*

E. 21CFR 201.10 Drugs; statement of ingredients; placement and prominence. *Does not conform.*

OBP Request: Delete the lines above and below the proper name as this is intervening matter per 21 CFR 210.10. *Applicant revised as requested.*

F. 21 CFR 201.15 Drugs; prominence of required label statements; *does not conform.*

OBP Requests:
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)

Applicant revised as requested.

Bold "[REDACTED] (b) (4). 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. *Applicant revised as requested.*

G. 21 CFR 201.17 Drugs; location of expiration date; *conforms.*

- H. 21 CFR [REDACTED] ^{(b) (4)} *conforms.*
- I. 21 CFR 201.50 Statement of identity; *conforms.*
- J. 21 CFR 201.51 Declaration of net quantity of contents; *conforms.*
- K. 21 CFR 201.55 Statement of dosage; *conforms.*
- L. 21 CFR 201.100 Prescription drugs for human use; *does not conform.*

OBP Request: Add "Rx Only" to the top right of the principal display panel. *Applicant revised as requested.*

Start of Sponsor Material
Carton labeling, 100 mg/5 mL

(b) (4)



Carton labeling, 400 mg/20 mL

(b) (4)



End of Sponsor Material

II. Carton

A. 21 CFR 610.61 Package Label:

- a) The proper name of the product; [see 21 CFR 600.3 (k) and section 351 of the PHS Act]; *conforms.*

- b) The name, addresses, and license number of manufacturer; *does not conform.*

OBP Request: 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.

Applicant revised as requested.

- c) The lot number or other lot identification; *conforms.*
- d) The expiration date; *conforms.*
- e) The preservative used and its concentration, if no preservative is used and the absence of a preservative is a safety factor, the words "no preservative"; *conforms.*
- f) The number of containers, if more than one; *not applicable.*
- g) The amount of product in the container expressed as (1) the number of doses, (2) the volume, (3) units of potency, (4) weight, (5) equivalent volume (for dried product to be reconstituted), or (6) such combination of the foregoing as needed for an accurate description of the contents, whichever is applicable; *conforms.*
- h) The recommended storage temperature; *conforms.*
- i) The words "Do not Freeze" or the equivalent, as well as other instructions, when indicated by the character of the product; *conforms.*
- j) The recommended individual dose if the enclosed container(s) is a multiple-dose container; *not applicable.*
- k) The route of administration recommended, or reference to such directions in and enclosed circular; *conforms.*
- l) Known sensitizing substances, or reference to enclosed circular containing appropriate information; *not applicable.*

- m) The type and calculated amount of antibiotics added during manufacture; *not applicable*.
- n) The inactive ingredients when a safety factor, or reference to enclosed circular containing appropriate information; *not applicable*.
- o) The adjuvant, if present; *not applicable*.
- p) The source of the product when a factor in safe administration; *not applicable*.
- q) The identity of each microorganism used in manufacture, and, where applicable, the production medium and the method of inactivation, or reference to an enclosed circular containing appropriate information; *not applicable*.
- r) Minimum potency of product expressed in terms of official standard of potency or, if potency is a factor and no U.S. standard of potency has been prescribed, the words "No U.S. standard of potency"; *conforms*.
- s) The statement "Rx only" for prescription biologicals; *conforms*.
- Note: If product has a medication guide, a statement is required on the package label if it is not on the container label (see above). It is recommended on both labels; *not applicable*.

B. 21 CFR 610.62 Proper name; package label; legible type [Note: Per 21 CFR 601.2(c)(1), certain regulation including 21 CFR 610.62 do not apply to the four categories of "specified" biological products listed in 21 CFR 601.2(a)]. *Exempt. Darzalex (daratumumab) is a monoclonal antibody; therefore it is a "specified" biological product.*

C. 21 CFR 610.63 Divided manufacturing responsibility to be shown; *not applicable*.

D. 21 CFR 610.64 Name and address of distributor; *not applicable*

The name and address of the distributor of a product may appear on the label provided that the name, address, and license number of the manufacturer also appears on the label and the name of the distributor is qualified by one of the following phrases:

"Manufactured for _____". "Distributed by _____", "Manufactured by _____ for _____", "Manufactured for _____ by _____", "Distributor: _____", or "Marketed by _____". The qualifying phrases may be abbreviated.

E. 21 CFR 610.67 Bar code label requirements: *conforms. See our comments below regarding the 2 dimensional barcode on the PDP.*

Biological products must comply with the bar code requirements at §201.25 of this chapter;

F. 21 CFR 201.2 Drugs and devices; National Drug Code numbers – The National Drug Code (NDC) number is located on top of the label [See 21 CFR 207.35]; *conforms. Additionally, we concur with DMEPA's recommendation to revise the middle digits of the NDC code.*

G. 21 CFR 201.5 Drugs; adequate directions for use; *conforms.*

H. 21 CFR 201.6 Drugs; misleading statements; *conforms.*

I. 21 CFR 201.10 Drugs; statement of ingredients [Placement and Prominence]; *does not conform.*

OBP Request: Delete the lines above and below the proper name as this is intervening matter per 21 CFR 210.10. *Applicant revised as requested.*

J. 21 CFR 201.15 Drugs; prominence of required label statements; *does not conform.*

OBP Requests:

We concur with DMEPA's recommendation to relocate the graphic

 where it appears before the proprietary name, 'Darzalex' as users may interpret the letter as an "A", "Z", or "X". *Applicant revised as requested.*

Bold the route of administration statement "For Intravenous Infusion Only" where it appears on the carton labeling. *Applicant revised as requested.*

Add the statement "Dilute Before Use" to the principal display panel (PDP). *Applicant revised as requested.*

Relocate "[REDACTED] (b) (4) 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

[REDACTED] (b) (4) Discard Unused Portion
Applicant revised as requested.

Decrease the prominence of the "Rx Only" by removing bold font and relocating to the top right of the PDP. *Applicant revised as requested.*

- K. 21 CFR 201.17 Drugs; location of expiration date; *conforms.*
- L. 21 CFR 201.25 Bar code label requirements; *conforms.*
- M. 21 CFR 201.50 Statement of identity; *conforms.*
- N. 21 CFR 201.51 Declaration of net quantity of contents; *conforms.*
- O. 21 CFR 201.55 Statement of dosage; *conforms.*
- P. 21 CFR 201.100 Prescription drugs for human use; *conforms.*
However, we recommend changing to the recommended format.

OBP Request: 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.

CDER Labeling Recommendations

This section describes additional recommendations provided to the Applicant that address CDER Labeling preferences. The Applicant's response to these recommendations was acceptable.

A. General Comments

1. Confirm there is no text on the [REDACTED] (b) (4) of the vials to comply with USP General Chapters: <7> Labeling, Labels and Labeling for Injectable Products, [REDACTED] (b) (4)

B. Carton Labeling

1. Add the dosage form to the diluent "[REDACTED] (b) (4)" to read "0.9% Sodium Chloride Injection, USP".
2. Delete [REDACTED] (b) (4) that appears on the side panel. This product will be used only in clinical settings.

Discussion of Applicant's Proposals





Conclusions

The container labels and carton labeling for Darzalex™ (daratumumab) were reviewed and found to comply with the following regulations: 21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57, 21 CFR 201.100 and United States Pharmacopeia (USP), USP 38/NF 33 [August 1, 2015 to November 30, 2015]. Labeling deficiencies were identified and resolved. The container labels and carton labeling submitted on October 20 2015 are acceptable. However, the Applicant can use the container labels submitted on October 2 2015 for initial product launch then approximately 4 to 6 weeks later, replace these labels with the container labels submitted October 20 2015 (see next page).

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**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

******Pre-decisional Agency Information******

Memorandum

Date: October 21, 2015

To: Jessica Boehmer, Regulatory Project Manager
Division of Hematology Products (DHP)

From: Nisha Patel, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Kathleen Davis, Team II Leader, OPDP

Subject: Comments on draft labeling (Package Insert) for Darzalex (daratumumab) injection, for intravenous use BLA 761036

In response to your consult dated September 1, 2015, we have reviewed the draft Package Insert (PI) for Darzalex (daratumumab) injection, for intravenous use (Darzalex) and offer the following comments. Please note that OPDP has made these comments using the version e-mailed to OPDP on October 16, 2015.

Section	Statement from draft	Comment
Highlights, Indications and Usage	DARZALEX is a human CD38-directed monoclonal antibody indicated for the treatment of patients with multiple myeloma who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent.	In draft promotional materials, the sponsor is currently positioning [REDACTED] (b) (4). If this is a concern, please consider revising the Indications and Usage section.
Indications and Usage	DARZALEX is indicated for the treatment of patients with multiple myeloma who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are	

Section	Statement from draft	Comment
	<p>double-refractory to a PI and an immunomodulatory agent.</p>	
2 Dosage and Administration	<p>Consider incremental escalation of the infusion rate only if the previous infusion of DARZALEX (b) (4) as defined in Table 2.</p> <p>^a Escalate only if (b) (4) no Grade 1 (mild) or greater infusion reactions during the first 3 hours.</p> <p>^b Escalate only if (b) (4) no Grade 1 (mild) or greater infusion reactions during a final infusion rate of ≥ 100 mL/hr (b) (4)</p>	<p>The bolded term is promotional in tone and could be used to minimize the risks of Darzalex. Please consider revising or deleting this term.</p>
12 Clinical Pharmacology	<p>Daratumumab is an IgG1κ human monoclonal antibody (mAb) that binds to the CD38 (b) (4)</p> <p>(b) (4)</p>	<p>Is the bolded language needed? It could be used promotionally to imply efficacy in various hematological malignancies beyond multiple myeloma.</p>
12 Clinical Pharmacology	<p>NK cells (b) (4) express (b) (4) CD38 and are susceptible to daratumumab mediated cell lysis. Decreases in absolute counts and percentages of total NK cells (CD16+CD56+) and activated (CD16+CD56^{dim}) NK cells in peripheral whole blood and bone marrow were observed with DARZALEX treatment. (b) (4)</p> <p>(b) (4)</p> <p>T cells (CD3+, CD4+, and CD8+) are also known to express CD38 depending on the stage of development and the level of activation. (b) (4)</p> <p>(b) (4) T cell absolute counts, (b) (4) percentages of lymphocytes, (b) (4) with DARZALEX treatment (b) (4) peripheral (b) (4) blood and bone marrow. (b) (4)</p> <p>(b) (4)</p>	<p>Are the bolded terms and statements needed? They could be used promotionally to overstate the efficacy of Darzalex.</p>

Section	Statement from draft	Comment
	(b) (4)	
12 Clinical Pharmacology	DARZALEX as a large (b) (4) protein has a low likelihood of direct ion channel interactions (b) (4)	Is Darzalex a “large (b) (4)” protein? If these terms are not necessary, please consider deleting as they are vague and could be used promotionally to indicate the drug is more narrowly (b) (4) than it is.
14 Clinical Studies	Study 2 was an open-label dose escalation trial evaluating DARZALEX monotherapy in patients with relapsed or refractory multiple myeloma who had received at least 2 different cytoreductive therapies . . . Overall response rate was 36% with (b) (4) VGPR. The median time to response was 1 month (range: 0.5 to 3.2 months). The median duration of response was not (b) (4)	We note that comment [BJ44] states, “Requires further review.” Has overall response rate and very good partial response based on an open-label dose escalation trial (Study 2) been adequately demonstrated? The sponsor will most likely use these efficacy results in promotional materials.

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/s/

NISHA PATEL
10/21/2015

**Interdisciplinary Review Team for QT Studies Consultation:
Thorough QT Study Review**

BLA	761036
Brand Name	DARZALEX
Generic Name	JNJ-54767414 (Daratumumab)
Sponsor	Janssen Research & Development, LLC
Indication	Treatment of patients with multiple myeloma who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent (IMiD) or are double refractory to a PI and an IMiD.
Dosage Form	Injection
Drug Class	Human anti-CD38 monoclonal antibody
Therapeutic Dosing Regimen	16 mg/kg
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	No maximum tolerated dose was established in human
Submission Number and Date	001 6/5/2015
Review Division	DHP

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

This study was comprised of two-parts: Part 1 was a dose-escalation phase; Part 2 was a single-arm phase with multiple cohorts, based on the dose levels established in Part 1. In Part 1, 32 subjects received 10 dose levels of daratumumab were sequentially evaluated: 0.005, 0.05, 0.10, 0.50, 1, 2, 4, 8, 16, and 24 mg/kg. In Part 2, 72 subjects received daratumumab 8 mg/kg (Cohorts A, B and C) and daratumumab 16 mg/kg (Cohorts D and E). No positive control (moxifloxacin) arms included, therefore, no assay sensitivity was established.

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

2 PROPOSED LABEL

The sponsor did not provide any QT related labeling language.

QT-IRT's proposed labeling language is a suggestion only. We defer final labeling decisions to the Division.

12.2 Pharmacodynamics

Cardiac Electrophysiology

DARZALEX as a large targeted protein has a low likelihood of direct ion channel interactions. There is no evidence from nonclinical or clinical data to suggest that DARZALEX has the potential to delay ventricular repolarization.

3 BACKGROUND

3.1 PRODUCT INFORMATION

Daratumumab is a human anti-CD38 monoclonal antibody indicated for the treatment of patients with multiple myeloma who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent (IMiD) or who are double-refractory to a PI and IMiD.

3.2 MARKET APPROVAL STATUS

Daratumumab is not approved for marketing in any country.

3.3 PRECLINICAL INFORMATION

See Appendix 6.1.

3.4 PREVIOUS CLINICAL EXPERIENCE

See Appendix 6.1.

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of daratumumab's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT did not review the protocol prior to conducting this study under IND 100638. The sponsor submitted the study report GEN501 including electronic datasets and most of the waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

Daratumumab (HuMax-CD38) Safety Study in Multiple Myeloma - Open-label, Dose-Escalation Followed by Open-Label, Single-Arm Study

4.2.2 Protocol Number

GEN501

4.2.3 Study Dates

First subject visit date : 26 March 2008

Clinical cutoff date : 09 January 2015.

4.2.4 Objectives

Primary objective: To establish the safety profile of daratumumab when given as monotherapy in subjects with multiple myeloma relapsed from or refractory to at least 2 different cytoreductive therapies and without further established treatment options.

Secondary objectives:

- To establish the pharmacokinetic profile of daratumumab after single and multiple infusions for both the Phase 2 and Phase 3 drug products;
- To evaluate the efficacy of daratumumab when given as monotherapy in the proposed subject population;
- To establish safe dose levels for future studies with daratumumab;
- To optimize pre-infusion medication and infusion parameters for daratumumab;
- To evaluate the immunogenicity of daratumumab; and
- To evaluate biomarkers of daratumumab's mechanism of action, infusion reactions, and clinical response.

4.2.5 Study Description

4.2.5.1 Design

This was a Phase 1/2, open-label, safety study divided into 2 parts. Part 1 was a dose-escalation phase; Part 2 was a single-arm phase with multiple cohorts, based on the dose levels established in Part 1. In Part 1, 10 dose levels of daratumumab were sequentially evaluated: 0.005, 0.05, 0.10, 0.50, 1, 2, 4, 8, 16, and 24 mg/kg.

In Part 1, the 10 dose levels of daratumumab were sequentially evaluated: 0.005, 0.05, 0.10, 0.50, 1, 2, 4, 8, 16, and 24 mg/kg. The 2 lowest dose cohorts were allocated 1 (+3) subject(s) each, and a standard 3 (+3) subject allocation was applied to the remaining 8 dose cohorts. Subjects received 7 full infusions, with the first and

second infusions separated by a 3-week washout. Total treatment period for subjects in Part 1 of the study was 8 weeks. Part 1 included a follow-up period of 44 weeks.

In Part 2, Cohorts A, B, C received 8 mg/kg of daratumumab weekly for 8 weeks, then once every 2 weeks for 16 weeks, followed by once every 4 weeks. Cohorts D and E received the first full infusion, with a 3 week resting period, followed by weekly dosing for 7 weeks, then every 2 weeks for 14 additional weeks, followed by once every 4 weeks.

Possible duration of treatment for subjects in Part 2 was 96 weeks, or until disease progression or unacceptable toxicity. In Part 2, survival follow-up was to continue until death, lost to follow-up, consent withdrawal for study participation, or study end, whichever occurred first.

4.2.5.2 Controls

No placebo and positive (moxifloxacin) controls included in this study.

4.2.5.3 Blinding

Treatment from Part 1 and Part 2 are conducted in an open-label.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

Part 1:

In Part 1, the patients received 7 full infusions of daratumumab. To prevent cytokine release syndrome, the first 2 infusions were preceded by a predose infusion the day before the full infusion. The predose infusion was 10% of the full dose - though never more than 10 mg in total dose. Ten doses levels of daratumumab were sequentially evaluated: 0.005, 0.05, 0.10, 0.50, 1, 2, 4, 8, 16, and 24 mg/kg.

Part 2:

- Cohorts A, B, C received 8 mg/kg of daratumumab weekly for 8 weeks, then once every 2 weeks for 16 weeks, followed by once every 4 weeks.
- Cohorts D and E received 16 mg/kg of daratumumab the first full infusion, with a 3 week resting period, followed by weekly dosing for 7 weeks, then every 2 weeks for 14 additional weeks, followed by once every 4 weeks.

4.2.6.2 Sponsor's Justification for Doses

As this was the first study of daratumumab in humans, the minimal anticipated biological effect level (MABEL) was used to establish a starting dose in Part 1. The MABEL was estimated to be 0.005 mg/kg and this was chosen as the starting dose in Part 1. The following dose levels were planned in Part 1: 0.005, 0.05, 0.1, 0.5, 1, 2, 4, 8,

16, and 24 mg/kg daratumumab. Up to 2 intermediate dose levels were possible between any of the planned dose levels, if deemed necessary by the Sponsor, based on an IDMC recommendation.

Initiation of Part 2 was based on the IDMC's recommendation. Based on results from Part 1 of the study, the IDMC recommended continuing into Part 2 with doses of 8 mg/kg or higher. The dose regimen that maximally saturated the target (ie, CD38) was selected using the principles of target-mediated drug disposition. At lower doses, the majority of daratumumab is bound to CD38 receptors in the body, and the complex with daratumumab is rapidly cleared. As the dose is increased, CD38 becomes saturated and the impact of target binding clearance on serum daratumumab concentrations is minimized. At a target saturating dose, the clearance of daratumumab approximates the clearance of endogenous IgG1. The 8 mg/kg dose was initially chosen as the dose to go forward into Part 2. However, during Part 2 based on emerging data, it was determined that a dose of 8 mg/kg did not saturate a majority of the target throughout dosing, as indicated by the high inter-subject variability in pharmacokinetic parameters. When pharmacokinetic variability and heterogeneity in target expression on the tumor were taken into account, a dose of 16 mg/kg every week \times 7 weeks; 16 mg/kg every 2 weeks \times 14 weeks; and 16 mg/kg every 4 weeks was selected as the maximal target saturating dosing regimen. It was expected this dose would result in complete saturation of the target for all time points in a majority of subjects. It was determined that the 24 mg/kg dose offered no additional efficacy benefit over the 16 mg/kg dose based on the Part 1 pharmacokinetic and efficacy data.

Reviewer's Comment: Acceptable. The studied 16 mg/kg regimen in Part 2 is the proposed therapeutic dose.

4.2.6.3 Instructions with Regard to Meals

Reviewer's Comment: As the route of administration is IV, this appears reasonable.

4.2.6.4 ECG and PK Assessments

Part 1

The protocol was initially designed with site supplied ECG equipment and ECG analysis. Following protocol amendment 6 on 15 Dec 2010 for consistent handling (after the first 23 patients), ECG equipment were provided and digital ECGs were transmitted to a central provider, (b) (4) who performed central reading for analysis purposes. ECGs were performed according to the schedule described in the following table.

Table 1: ECG Collection Schedule (Part 1)

<u>Visit</u>	<u>Visit ID in EG SDTM Dataset</u>	<u>ECGs Collected</u>
V1	Screening	Single ECG
V2 (D0 – pre-dose infusion)	Visit 1	triplicate ECGs before infusion; single ECGs 0 and 6 hours post infusion
V3 (D1- full dose infusion)	Visit 2	triplicate ECGs before infusion; single ECGs 0 and 6 hours post infusion
V4 (D2)	Visit 3	24 hours post infusion
V6 (D8)	Visit 5	single ECG
V7 (D15)	Visit 6	single ECG
V8 (D21 – pre-dose infusion)	Visit 7	triplicate ECGs before infusion; single ECGs 0 and 6 hours post infusion
V9 (D22 – full dose infusion)	Visit 8	triplicate ECGs before infusion; single ECGs 0 and 6 hours post infusion
V10 (D29 – full dose infusion)	Visit 9	triplicate ECGs before infusion; single ECGs 0 and 2-6 hours post infusion
V11 (D36 – full dose infusion)	Visit 10	triplicate ECGs before infusion; single ECGs 0 and 2-6 hours post infusion
V12 (D43 – full dose infusion)	Visit 11	triplicate ECGs before infusion; single ECGs 0 and 2-5 hours post infusion
V13 (D50 – full dose infusion)	Visit 12	triplicate ECGs before infusion; single ECGs 0 and 2-6 hours post infusion
V14 (D57 – full dose infusion)	Visit 13	triplicate ECGs before infusion; single ECGs 0 and 2-6 hours post infusion
V15 (D58)	Visit 14	24 hour post infusion

Source: GEN501 clinical study report page 240.

Blood samples were collected for analysis of daratumumab serum concentration on the days of scheduled ECG collections according to the following schedule:

Table 2: PK Collection Schedule (Part 1)

<u>Visit ID in CRF</u>	<u>Visit ID in PC SDTM dataset</u>	<u>Timing of PK Collections</u>
V2 (D0 – pre-dose infusion)	Visit 1	Before infusion; EOI
V3 (D1- full dose infusion)	Visit 2	Before infusion, EOI, 2, 5 and 24 hours post EOI
V6 (D8)	Visit 5	During clinic visit
V7 (D15)	Visit 6	During clinic visit
V8 (D21 – pre-dose infusion)	Visit 7	pre-dose
V9 (D22 – full dose infusion)	Visit 8	pre-dose
V10 (D29 – full dose infusion)	Visit 9	pre-dose
V11 (D36 – full dose infusion)	Visit 10	pre-dose
V12 (D43 – full dose infusion)	Visit 11	pre-dose
V13 (D50 – full dose infusion)	Visit 12	pre-dose
V14 (D57 – full dose infusion)	Visit 13	pre-dose, EOI, 2, 5 and 24 hours post EOI

Source: GEN501 clinical study report page 242.

Part 2

ECGs were performed according to the schedule described in the following table.

Table 3: ECG Collection Schedule (Part 2)

<u>Visit ID in CRF</u>	<u>Visit ID in EG SDTM Dataset</u>	<u>ECGs Collected Cohorts A, B, C</u>	<u>ECGs Collected Cohorts D, E</u>
Screening	Visit 0	Triplicate ECGs	Triplicate ECGs
Visit 1	Visit 1 (Schedules A & B)	Single ECG before and after infusion	
Visit 2	Visit 2	Triplicate ECGs before and after infusion	Triplicate ECGs before and after infusion
Visit 3/Visit 4	Visit 3-4	Single ECG before and after infusion	
Visit 5	Visit 5	triplicate ECGs before and after infusion	
Visit 6	Visit 6	Single ECG before and after infusion	
Visit 7	Visit 7	Single ECG before and after infusion	Triplicate ECGs before and after infusion
Visit 8-21	Visit 8-21	Single ECG before and after infusion	
End of Study	End of Trial	Single ECG	Single ECG

Source: GEN501 clinical study report page 1045.

Blood samples were collected for analysis of daratumumab serum concentration on the days of scheduled ECG collections according to the following schedule:

Table 4: PK Collection Schedule (Part 2)

Visit	Day/Week	Cohorts A-C	Cohort D	Cohort E
0	-	N/A	N/A	N/A
2	D1	Before Infusion End of Infusion 2 hours post End of Infusion	Before Infusion End of Infusion 2 hours post End of Infusion	Before Infusion End of Infusion 2 hours post End of Infusion 5 hours post End of Infusion (optional)
NS	D2			24 hours post End of Infusion
NS	D4			Timing Not Specified
3, 4	Week 1, 2	Timing Not Specified	Timing Not Specified	Timing Not Specified
5-9	Week 3-7	Before Infusion End of Infusion		Before Infusion End of Infusion
9D	Week 8			Before Infusion End of Infusion
10	Week 9	Before Infusion End of Infusion	Before Infusion End of Infusion	Before Infusion End of Infusion
12, 14	Week 13, 17	Before Infusion End of Infusion		
13, 16	Week 15, 21	Before Infusion End of Infusion	Before Infusion End of Infusion	Before Infusion End of Infusion
18-36	Week 27-99	Before Infusion End of Infusion		
End of Trial		Timing Not Specified	Timing Not Specified	Timing Not Specified

Source: GEN501 clinical study report page 1046.

Reviewer's Comment: Acceptable. ECG/PK monitoring was collected at baseline, after first dose, and at steady state around T_{max} for daratumumab.

4.2.6.5 Baseline

The sponsor used the time-averaged pre-dose QTc values as baselines.

4.2.7 ECG Collection

Intensive 12-Lead Holter monitoring will be used to obtain digital ECGs. Standard 12-Lead ECGs will be obtained while subjects are recumbent.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

Part 1:

Thirty-two subjects received at least 1 dose of study medication. Of the 32 subjects, 15 subjects completed the study, receiving 7 full infusions of daratumumab. The remaining 17 (53%) discontinued treatment with aratumumab, 12 (38%) due to progressive disease and 5 (16%) due to adverse events.

Following a protocol amendment, the ECGs of the final 11 patients dosed during Part 1 were recorded digitally and were evaluated by a centralized ECG core lab. The ECG data of these 11 patients who had centralized ECG analysis of digitally recorded ECGs were the basis for the cardiac central ECG report.

Part 2: Seventy-two subjects received at least 1 dose of study medication.

- Cohort A [16 subjects] received 8 mg/kg of daratumumab
- Cohort B [8 subjects] received 8 mg/kg of daratumumab
- Cohort C [6 subjects] received 8 mg/kg of daratumumab
- Cohort D [20 subjects] received 16 mg/kg of daratumumab
- Cohort E [22 subjects] received 16 mg/kg of daratumumab

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

The primary objective for Part 1 and Part 2 was safety; no formal statistical hypothesis testing was planned. The results as a mean change from baseline and new outliers from baseline for the daratumumab dose groups are presented below.

Table 5: Time-Averaged Mean Change from Baseline and New Outliers by Dose Group for ECGs (Part 1)

	Daratumumab 4.0 mg/kg	Daratumumab 8.0 mg/kg	Daratumumab 16.0 mg/kg	Daratumumab 24.0 mg/kg	Daratumumab pooled doses
Total N	2	3	3	3	11
Heart Rate in bpm (mean change from baseline)	-1.1	6.1	9.2	-1.3	3.6
Heart Rate Bradycardic Outliers n (%)	0	0	0	1 (33%)	1 (9%)
Heart Rate Tachycardic Outliers n (%)	0	0	2 (67%)	0	2 (18%)
PR in ms (mean change from baseline)	-5.6	-4.4	-2.3	2.6	-2.1
PR Outliers n (%)	0	0	0	0	0
QRS in ms (mean change from baseline)	-0.4	-1.3	0.8	4.8	1.1
QRS Outliers n (%)	0	0	0	0	0
QT in ms (mean change from baseline)	6.3	-9.9	-2.6	7.7	-0.2
QT new >500 ms n (%)	0	0	0	0	0
QTcF in ms (mean change from baseline)	2.8	2.9	10.1	5.5	5.5
QTcF new >500 ms n (%)	0	0	0	0	0
QTcF new >480 ms n (%)	0	1 (33%)	0	0	1 (9%)
QTcF 30-60 ms n (%)	1 (50%)	2 (67%)	0	1 (33%)	4 (36%)
QTcF >60 ms n (%)	0	0	0	0	0
QTcB in ms (mean change from baseline)	1.1	9.7	17.9	4.4	8.9
QTcB new >500 ms n (%)	0	1 (33%)	0	0	1 (9%)
QTcB new >480 ms n (%)	0	1 (33%)	0	0	1 (9%)
QTcB 30-60 ms n (%)	1 (50%)	3 (100%)	3 (100%)	1 (33%)	8 (73%)
QTcB >60 ms n (%)	0	0	0	0	0
New abnormal U waves n (%)	0	0	0	0	0
New ST segment depression changes n (%)	0	0	0	0	0
New ST segment elevation changes n (%)	0	0	0	0	0
New T wave inverted n (%)	1 (50%)	0	0	0	1 (9%)
New 2nd and 3rd Degree Heart Block n (%)	0	0	0	0	0
New AF n (%)	0	0	0	0	0
New Complete RBBB n (%)	0	0	0	1 (33%)	1 (9%)

Source: GEN501 clinical study report page 251.

Table 6: Time-Averaged Mean Change from Baseline and New Outliers by Dose Group for ECGs (Part 2)

	Schedule A Daratumumab 8 mg/kg	Schedule B Daratumumab 8 mg/kg	Schedule C Daratumumab 8 mg/kg	Schedule D Daratumumab 16 mg/kg	Schedule E Daratumumab 16 mg/kg	Daratumumab 8 mg/kg pooled	Daratumumab 16 mg/kg pooled	Daratumumab All Doses Pooled
Total N	16	8	6	20	22	30	42	72
Heart Rate in bpm (mean change from baseline)	6.3	2.4	5.9	2.5	1.4	5.2	1.9	3.3
Heart Rate Bradycardic Outliers n (%)	0	0	0	0	0	0	0	0
Heart Rate Tachycardic Outliers n (%)	7 (44%)	1 (13%)	0	0	2 (9%)	8 (27%)	2 (5%)	10 (14%)
PR in ms (mean change from baseline)	-2.0	-3.0	-4.7	1.6	-0.3	-2.8	0.6	-0.8
PR Outliers n (%)	0	0	0	0	0	0	0	0
QRS in ms (mean change from baseline)	-0.5	0.7	1.9	-0.2	0.7	0.3	0.3	0.3
QRS Outliers n (%)	0	0	0	0	0	0	0	0
QT in ms (mean change from baseline)	-6.8	1.4	-6.3	-0.2	1.6	-4.5	0.7	-1.4
QT new >500 ms n (%)	0	0	0	0	0	0	0	0
QTcF in ms (mean change from baseline)	3.5	6.0	4.5	4.0	4.6	4.4	4.3	4.4
QTcF new >500 ms n (%)	0	0	0	0	0	0	0	0
QTcF new >480 ms n (%)	0	0	0	0	0	0	0	0
QTcF 30-60 ms n (%)	4 (25%)	1 (13%)	1 (17%)	1 (5%)	3 (14%)	6 (20%)	4 (10%)	10 (14%)
QTcF >60 ms n (%)	0	0	0	0	0	0	0	0
QTcB in ms (mean change from baseline)	9.4	8.4	10.2	6.5	6.3	9.3	6.4	7.6
QTcB new >500 ms n (%)	0	0	0	0	0	0	0	0
QTcB new >480 ms n (%)	1 (6%)	0	0	0	1 (5%)	1 (3%)	1 (2%)	2 (3%)
QTcB 30-60 ms n (%)	8 (50%)	3 (38%)	4 (67%)	6 (30%)	5 (23%)	15 (50%)	11 (26%)	26 (36%)
QTcB >60 ms n (%)	1 (6%)	0	0	0	0	1 (3%)	0	1 (1%)
New abnormal U waves n (%)	0	0	0	0	0	0	0	0
New ST segment depression changes n (%)	1 (6%)	0	0	0	2 (9%)	1 (3%)	2 (5%)	3 (4%)
New ST segment elevation changes n (%)	0	0	0	0	0	0	0	0
New T wave inverted n (%)	3 (19%)	0	0	2 (10%)	1 (5%)	3 (10%)	3 (7%)	6 (8%)
New 2nd and 3rd Degree Heart Block n (%)	0	0	0	0	0	0	0	0
New AF n (%)	0	0	0	0	0	0	0	0
New Complete RBBB n (%)	0	0	0	0	1 (5%)	0	1 (2%)	1 (1%)
New Complete LBBB n (%)	0	0	0	0	0	0	0	0
New MI n (%)	0	0	0	0	0	0	0	0

bpm= beats per minute; ms= milliseconds; QTcB: Bazett correction; QTcF= Fridericia correction; RBBB= right bundle branch block; LBBB= left bundle branch block; AF= atrial fibrillation/flutter "new" means not present at baseline, and only seen post-dose, Source: Selected data from Tables 14.2.3.1 through 14.2.3.17 in an appendix. Daratumumab pooled dose group includes all dosing schedules.

Source: GEN501 clinical study report page 1055.

Reviewer's Comments: We will provide our independent analysis results in Section 5.2.

4.2.8.2.2 Assay Sensitivity

No positive control arm included, therefore, no assay sensitivity established.

4.2.8.2.3 Categorical Analysis

In Part 2, 72 patients enrolled in 8 mg/kg and 16 mg/kg dose cohorts showed median changes from baseline of < 30 ms for QTcF, and no patient had a QTcF > 500 ms or a > 60 ms change from baseline in QTcF.

4.2.8.3 Safety Analysis

Part 1:

Doses of daratumumab from 0.005 mg/kg up to and including 24 mg/kg were studied without reaching a maximum tolerated dose (MTD). Two subjects had dose-limiting toxicities; 1 subject in the 0.1 mg/kg group with Grade 3 anemia, and 1 subject in the 1.0 mg/kg group with Grade 3 abnormal hepatic function (isolated AST elevated).

In the All-Treated Part 1 population, 31 subjects (97%) experienced a TEAE. The most frequently reported TEAEs across all dose groups were proteinuria (47%), pyrexia (34%), cough (19%), ECG QT prolonged (16%), and free hemoglobin present (16%). Influenza-like illness, nausea, anemia, and hypertension also were reported for 13% of subjects each.

The 5 subjects with ECG QT prolongation reported as an AE were described below.

Subject ID	Age/ Sex	Treatment Group	Cardiac-Related Medical History	Concomitant Medication	Study Day of TEAE	Serious/ Toxicity Grade	Action Taken With Study Drug	Baseline QTc (msec)	Maximum QTc (msec)	Change from Baseline (ms)
501003	76/ M	0.1 mg/kg	History of atrial fibrillation; baseline ECG showed left side anterior fascicular block	Glucosamine, zopiclone	23	N/1 ^{a,c}	None	QTcF: 391-418	QTcF: 461	<60
501008	65/ M	0.1 mg/kg	Baseline ECG showed right bundle branch block	Acetylsalicylic acid	31	N/3 ^{a,c}	None	QTcF 430-453	QTcF: 502	<60
501009	69/ M	0.5 mg/kg	None reported	Morphine sulphate, pamidronate disodium	21	N/2 ^{b,c}	None	QTcF 423-425	QTcF: 455	<30
501012	61/ F	1.0 mg/kg	Hypertension	Acetylsalicylic acid, amitriptyline, amlodipine, ciprofloxacin, fentanyl, gabapentin, pamidronate disodium, pantoprazole, potassium chloride, hypromellose	22	N/1 ^{b,c}	None	QTcF: ~440	QTcF: 470	<60
501014	44/ F	1.0 mg/kg	Hypertension, myxoedema	Acyclovir, gabapentin, levothyroxine sodium, omeprazole, oxycodone hydrochloride, pamidronate disodium, paracetamol, bendroflumethiazide, zolpidem, vitamins NOS, calcium, magnesium oxide	22	N/2 ^{b,c}	Drug interrupted	QTcB: 440	QTcB: 483	<60
					31	N/2 ^{a,c}	None	QTcB: 440	QTcB: 483	<60
					32	N/1 ^{a,c}	None	QTcB: 440	QTcB: 483	<60
					38	N/2 ^{a,c}	None	QTcB: 440	QTcB: 483	<60
					45	N/2 ^{a,c}	None	QTcB: 440	QTcB: 483	<60
					52	N/2 ^{a,c}	None	QTcB: 440	QTcB: 483	<60

Relationship to study drug according to investigator:

^aPossible/probable

^bNot related

Adverse event outcome:

^cResolved

Source: GEN501 clinical study report page 1055.

Part 2:

Daratumumab as monotherapy is well-tolerated with a favorable safety profile with clinically manageable side effects.

- In the 16 mg/kg group, the most frequently reported TEAEs included fatigue (41%), allergic rhinitis (24%), nasopharyngitis (24%), back pain (24%), cough (21%), and nausea (21%).
- Fourteen subjects (33%) in the 16 mg/kg group experienced a serious TEAE. The most commonly reported serious TEAEs were pneumonia (3 subjects; 7%), crossmatch incompatible (3 subjects; 7%), and pyrexia (2 subjects; 5%). None of the 3 subjects who had a serious TEAE of crossmatch incompatible experienced a transfusion-related reaction after transfusion of red blood cells. In the 16 mg/kg group, 11 subjects (26%) experienced a Grade 3/4 TEAE.
- The most common were leukopenia, neutropenia, and pneumonia, with 2 subjects (5%) each. One subject, in the 16 mg/kg group, had a TEAE (pneumonia, unrelated to study drug) that led to treatment discontinuation and, subsequently, to death. No subject died due to a daratumumab-related TEAE. Grade 3/4 infections were reported in 2 subjects (5%) in the 16 mg/kg group. The incidence of infections (any grade) did not increase over time.
- No AE of febrile neutropenia (any grade) was reported.

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

The PK results of daratumumab at first dose and at steady state (in Part 1 and Part 2) are presented in the following tables and figures. The steady state C_{max} at the 16 mg/kg dosing regimen is ~1000 µg/mL.

Table 18: Summary of Daratumumab Pharmacokinetic Parameters for the First Full Infusion: Pharmacokinetic Analysis Set (Study GEN501 Part 1)

	0.1 mg/kg N = 6	0.5 mg/kg N = 3	1 mg/kg N = 6	2 mg/kg N = 3	4 mg/kg N = 3	8 mg/kg N = 3	16 mg/kg N = 3	24 mg/kg N = 3
C_{trough} (µg/mL)								
n	6	3	6	3	3	3	3	3
Mean	0.000	0.000	0.000	0.000	0.596	3.733	7.023	0.000
SD	0.0000	0.0000	0.0000	0.0000	1.0329	6.4663	12.1636	0.0000
CV (%)					173.2	173.2	173.2	
C_{max} (µg/mL)								
n	6	3	6	3	3	3	3	3
Mean	0.297	4.764	20.279	38.139	83.403	153.611	405.754	500.104
SD	0.2721	3.6521	5.8662	7.3573	15.9857	40.8315	72.5004	80.4271
CV (%)	91.7	76.7	28.9	19.3	19.2	26.6	17.9	16.1
T_{max} (h)								
n	4	3	6	3	3	3	3	3
Median	5.833	8.083	6.017	9.667	9.583	9.933	8.000	10.000
Range	5.83 – 6.00	6.08 – 21.92	5.67 – 8.00	8.42 – 11.00	7.58 – 9.92	9.50 – 11.60	8.00 – 12.17	8.33 – 10.72
AUC(0-t) (µg·h/mL)								
n	6	3	6	3	3	3	3	3
Mean	1.126	110.061	715.885	1853.260	6575.376	15615.308	34319.272	48778.049
SD	1.5648	153.8467	673.3481	420.8798	3574.4199	6208.0563	6665.3957	13192.1517
CV (%)	138.9	139.8	94.1	22.7	54.4	39.8	19.4	27.0
AUC(0-inf) (µg·h/mL)								
n	0	1	5	3	3	3	3	3
Mean		313.276	977.236	1927.138	10062.880	27916.416	56893.559	97175.647
SD			758.0958	373.2869	6886.0158	16155.6804	22030.4204	39899.8745
CV (%)			77.6	19.4	68.4	57.9	38.7	41.1
AUC(0-7day) (µg·h/mL)								
n	1	3	6	3	3	3	3	3
Mean	6.482	118.694	762.755	1936.018	6354.139	14899.574	35613.298	47678.061
SD		161.1607	656.7838	302.4440	3400.8875	5256.1083	7686.8697	14396.5478
CV (%)		135.8	86.1	15.6	53.5	35.3	21.6	30.2
T (1/2) (h)								
n	0	1	5	3	3	3	3	3
Mean		20.011	28.273	25.615	91.492	131.776	109.900	154.651
SD			17.8534	5.6050	59.8914	68.1924	42.0480	36.4843
CV (%)			63.1	21.9	65.5	51.7	38.3	23.6

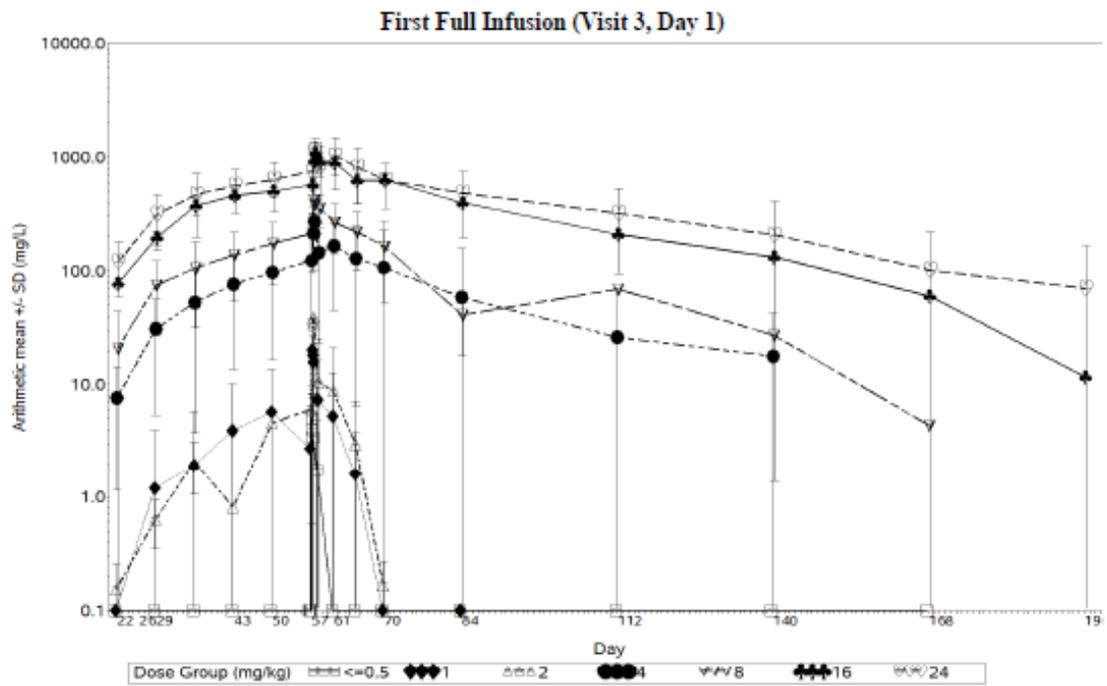
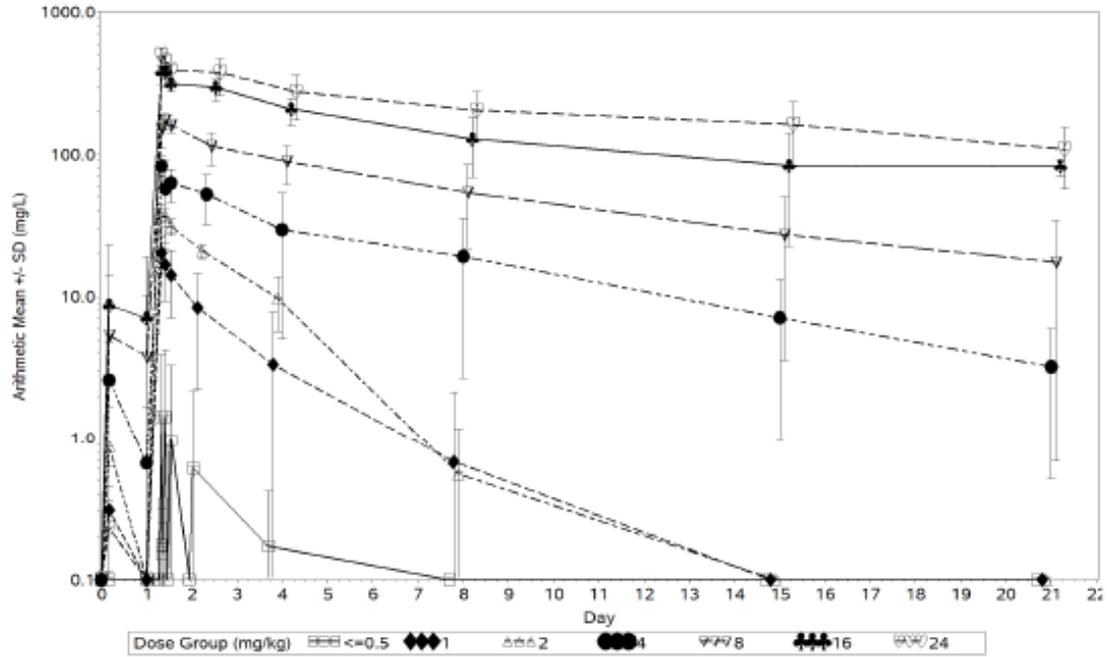
Source: GEN501 clinical study report page 99.

Table 19: Summary of Daratumumab Pharmacokinetic Parameters for the Last (7th) Full Infusion: Pharmacokinetic Analysis Set (Study GEN501 Part I)

	0.1 mg/kg N = 6	0.5 mg/kg N = 3	1 mg/kg N = 6	2 mg/kg N = 3	4 mg/kg N = 3	8 mg/kg N = 3	16 mg/kg N = 3	24 mg/kg N = 3
Ctrough (µg/mL)								
N	1	3	2	1	2	3	2	2
Mean	0.000	0.000	2.679	6.083	123.293	213.853	574.962	753.943
SD		0.0000	3.7880		86.0259	117.2155	94.6109	387.2286
CV (%)			141.4		69.8	54.8	16.5	51.4
Cmax (µg/mL)								
n	1	3	2	1	2	3	2	2
Mean	0.000	6.759	20.235	39.279	218.496	426.615	993.648	1163.338
SD		3.7585	11.9084		101.2563	176.5507	127.0395	333.9474
CV (%)		55.6	58.9		46.3	41.4	12.8	28.7
Tmax (h)								
n	0	3	2	1	2	3	2	2
Median		5.917	5.808	12.917	8.725	8.417	11.100	9.475
Range		5.75 - 6.00	5.67 - 5.95	12.92 - 12.92	7.53 - 9.92	7.78 - 22.80	9.95 - 12.25	9.42 - 9.53
AUC(0-t) (µg·h/mL)								
N	1	3	2	1	2	3	2	2
Mean	0.000	96.577	1194.031	3623.794	28495.376	51844.829	169590.533	180029.359
SD		82.2914	1441.2007		17598.3565	20030.0645	80851.4261	98543.2379
CV (%)		85.2	120.7		61.8	38.6	47.7	54.7
AUC(0-inf) (µg·h/mL)								
N	0	3	2	1	2	2	1	2
Mean		179.660	1345.216	4231.701	138149.094	186611.920	371159.322	1018233.501
SD		220.7550	1620.2447		163369.9648	90617.6371		1029108.3627
CV (%)		122.9	120.4		118.3	48.6		101.1
AUC(0-8day) (µg·h/mL)								
N	0	3	2	1	2	2	1	2
Mean		253.782	1226.337	3596.853	30832.564	66765.805	171652.702	185591.882
SD		338.7561	1394.0483		20789.3243	12571.4743		88439.3124
CV (%)		133.5	113.7		67.4	18.8		47.7
T (1/2) (h)								
N	0	3	2	1	2	2	1	2
Mean		12.682	35.684	72.140	396.487	289.499	215.329	586.564
SD		12.3041	37.5450		408.0819	121.8816		486.8880

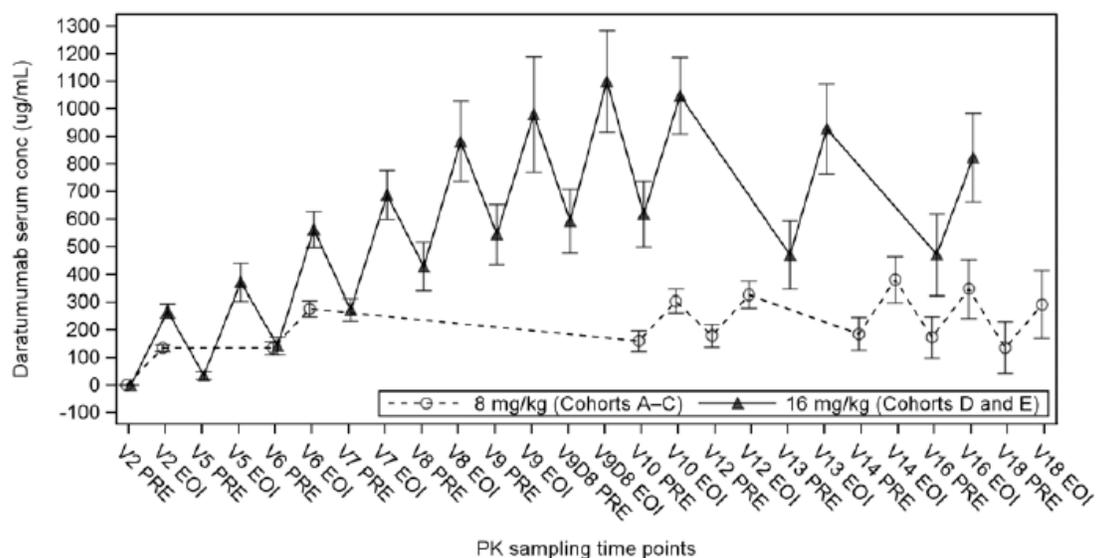
Source: GEN501 clinical study report page 101.

Figure 6 Mean Log Serum Daratumumab Concentrations vs. Nominal Time by Dose Group: Pharmacokinetic Analysis Set (Study GEN501 Part 1)



Source: GEN501 clinical study report page 98.

Figure 22: Mean Daratumumab Serum Peak and Trough Concentrations (ug/mL) for Full Infusions; Pharmacokinetics Analysis Set (Study GEN501 Part 2)

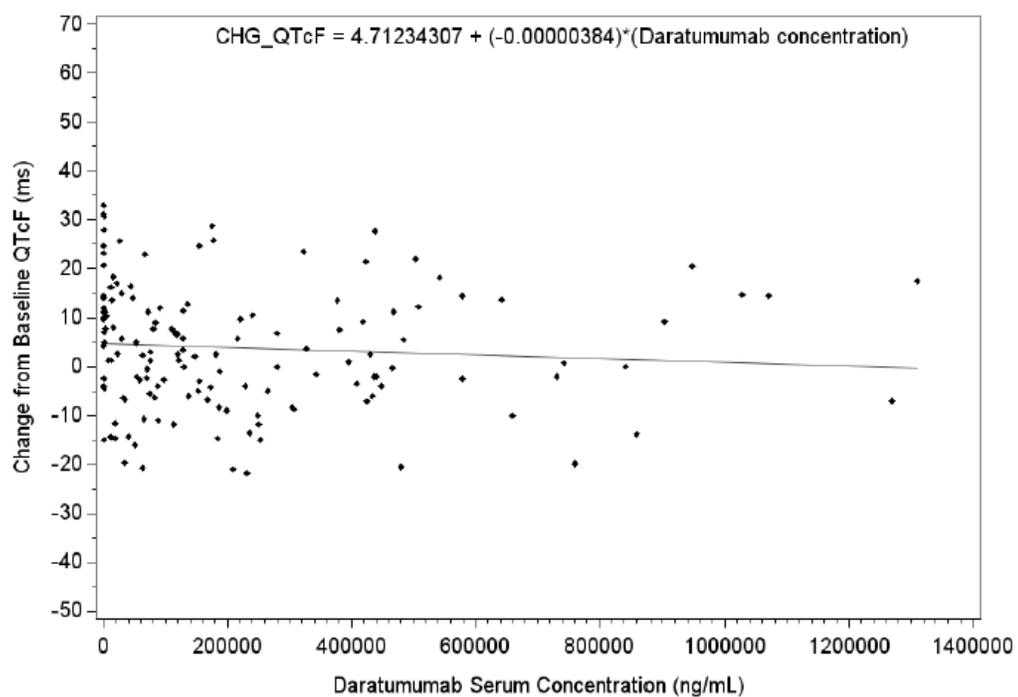


Source: GEN501 clinical study report page 180.

4.2.8.4.2 Exposure-Response Analysis

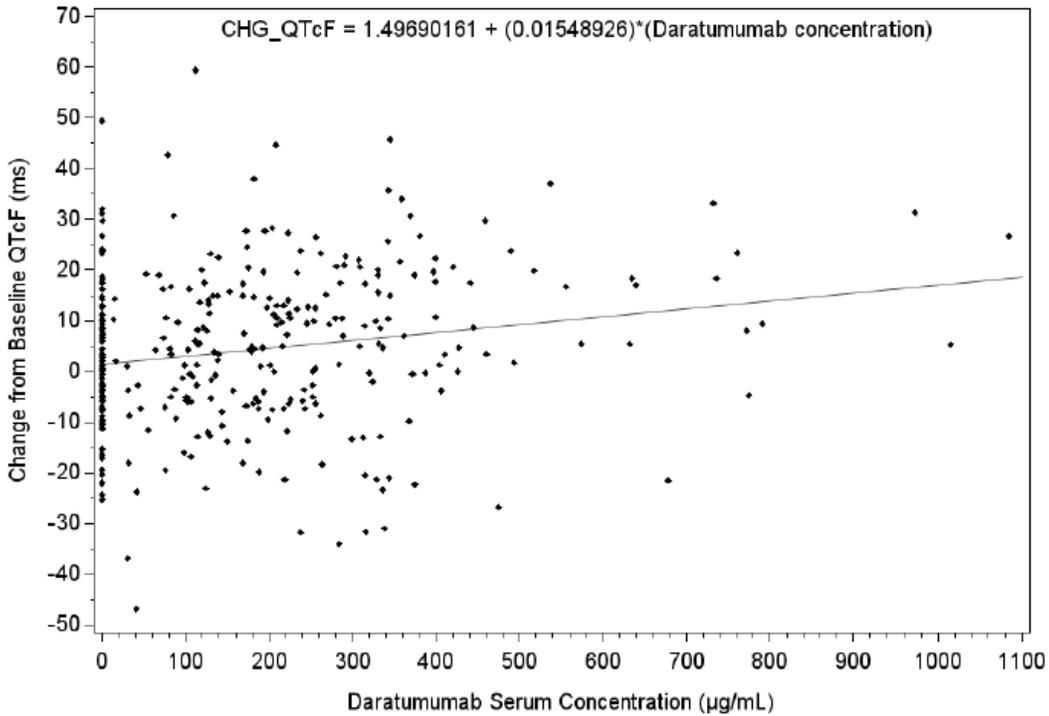
The relationship between the daratumumab concentration and QTc change from baseline was investigated by line mixed effect modeling with no evident relationship in Part 1 (Figure 1) and significantly positive relationship in Part 2 (Figure 2 and Table 7).

Figure 1: Δ QTcF vs. Daratumumab Concentration (Part 1, Sponsor's Analysis)



Source: GEN501 clinical study report page 261.

Figure 2: Δ QTcF vs. Daratumumab Concentration (Part 2, Sponsor’s Analysis)



Source: GEN501 clinical study report page 1068.

Table 7: QTc Change from Baseline versus the Daratumumab Concentration - Estimates from Linear Mixed Model (Part 2)

QT Parameter	Slope of Serum Conc. Effect on Δ QTc [1]	Standard Error of Slope of Serum Conc. Effect on Δ QTc [1]	p-value Slope pf Serum Conc. Effect on Δ QTc [1]	Overall Model Fit [1]	Overall Daratumumab Dose Levels	
					Predicted Δ QTc at Average Cmax 700 µg/mL	One-sided Upper 95% Confidence Bound of Predicted Δ QTc [2]
QTcF	0.01548926	0.00381245	<0.0001	<0.0001	12.34	16.37
QTcB	0.02730648	0.00455003	<0.0001	<0.0001	22.36	27.03

[1] Linear Mixed Model is fit for change from baseline versus the Daratumumab serum concentration. Subject random effects on the intercept are also included; concentration could not be included in the random effects. The Overall Model Fit p-value is based on the null likelihood ratio test using an estimation method of REML.

[2] Upper Bound = upper one-sided 95% linear mixed model based confidence limit.

Source: GEN501 clinical study report page 1067.

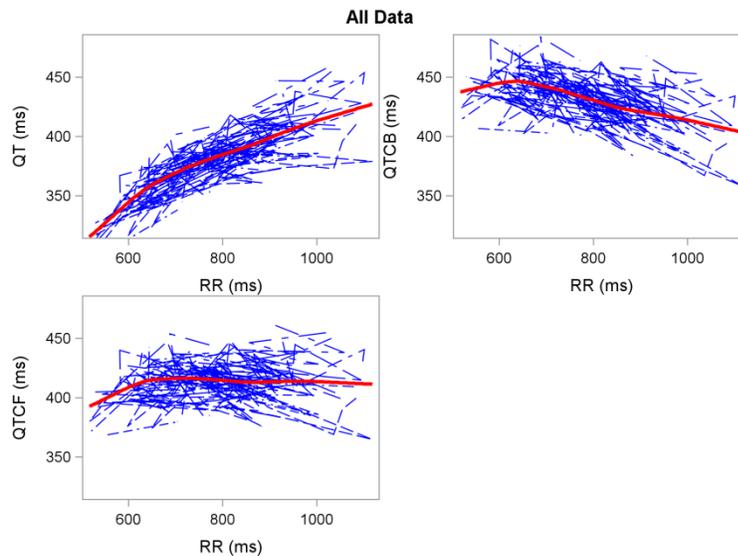
Reviewer's Analysis: The reviewer conducted an independent analysis. A plot of ΔQTc vs. drug concentrations is presented in Figure 5.

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

This review did not evaluate QT/RR correction method because the sponsor only provided QTcB and QTcF correction intervals. This reviewer chooses to present QTcF as the primary statistical analysis. The relationship between different correction methods and RR is presented in Figure 3.

Figure 3: QT, QTcB, and QTcF vs. RR (Each Subject's Data Points are Connected with a Line: in Part 2 with Triplicate ECG Measurements)



5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for daratumumab

The primary endpoint is the change from baseline of QTcF. The descriptive statistics are listed in Table 8 and Table 9.

Table 8: Analysis Results of Δ QTcF for Daratumumab Doses 4 mg/kg up to 24 mg/kg (Part 1, By Time)

Treatment	Time (H)	N	Mean	Std Dev	90% CI for Mean
G: 4 mg/kg	0	6	11.4	12.0	(1.5, 21.3)
	24	3	-5.8	18.8	(-37.6, 26.0)
H: 8 mg/kg	0	9	12.6	11.7	(5.3, 19.8)
	24	4	0.4	7.4	(-8.3, 9.0)
I: 16 mg/kg	0	7	16.8	10.8	(8.9, 24.7)
	24	5	3.2	9.2	(-5.6, 12.0)
J: 24 mg/kg	0	8	7.9	11.8	(-0.0, 15.8)
	24	6	-7.3	7.7	(-13.6, -0.9)

Table 9: Analysis Results of Δ QTcF for Daratumumab 8 mg/kg up and 16 mg/kg (Part 2, By Time)

Treatment	Time(H)	N	Mean	Std Dev	90% CI for Mean
Visit=2					
Schedule A - 8mg/kg - Dose Chosen By IDMC	Predose	16	8.5	14.0	(2.4, 14.7)
	0 to 1 hr	14	8.2	11.7	(2.7, 13.8)
Schedule B - 8mg/kg - 500 mL 1st Full Infusion	Predose	8	5.5	20.0	(-7.9, 18.9)
	0 to 1 hr	8	8.5	23.0	(-6.9, 23.9)
Schedule C - 8mg/kg - No Pre-dose 1000 mL 1st Full Infusion	Predose	4	3.2	14.1	(-13.4, 19.7)
	0 to 1 hr	6	3.5	8.9	(-3.9, 10.8)
Schedule D - 16mg/kg - Opt. Pre-dose 1000 mL 1st 2 Infusions	Predose	19	-0.8	14.9	(-6.7, 5.2)
	0 to 1 hr	20	8.9	12.9	(3.9, 13.9)
Schedule E - 16mg/kg - No Pre-dose 1000 mL 1st 2 Infusions	Predose	21	-0.7	12.0	(-5.2, 3.8)
	0 to 1 hr	22	9.1	14.9	(3.7, 14.6)
Visit=7					

Treatment	Time(H)	N	Mean	Std Dev	90% CI for Mean
Schedule E - 16mg/kg - No Pre-dose 1000 mL 1st 2 Infusions	Pre-dose	14	-5.8	19.4	(-15.0, 3.4)
	0 to 1 hr	19	12.1	16.9	(5.3, 18.8)

5.2.1.1 Assay Sensitivity Analysis

No assay sensitivity analysis performed in this study because no positive control arm included.

5.2.1.2 Categorical Analysis

The following tables list the number of subjects as well as the number of observations whose QTcF values are ≤ 450 ms, between 450 ms and 480 ms, between 480 ms and 500 ms; and changes from baseline QTc ≤ 30 ms, between 30 and 60 ms, and >60 ms. No subject's QTcF is above 480 ms (see Table 10 and Table 11). No subject's change from baseline is above 60 ms (see Table 12 and Table 13).

Table 10: Categorical Analysis for QTcF (Part 1)

TREAT	QTcF		
	Value \leq 450 ms	450 ms<Value \leq 480 ms	Total
H: 8 mg/kg	2	1	3
I: 16 mg/kg	3	0	3
J: 24 mg/kg	3	0	3
G: 4 mg/kg	2	0	2
Total	10	1	11

Table 11: Categorical Analysis for QTcF (Part 2)

TREAT	QTcF		
	Value \leq 450 ms	450 ms<Value \leq 480 ms	Total
Schedule E - 16mg/kg - No Pre-dose 1000 mL 1st 2 Infusions	19	3	22
Schedule D - 16mg/kg - Opt. Pre-dose 1000 mL 1st 2 Infusions	20	0	20
Schedule A - 8mg/kg - Dose Chosen By IDMC	16	0	16
Schedule B - 8mg/kg - 500 mL 1st Full Infusion	8	0	8
Schedule C - 8mg/kg - No Pre-dose 1000 mL 1st Full Infusion	6	0	6
Total	69	3	72

Table 12: Categorical Analysis for Δ QTcF (Part 1)

TREAT	QTcF_CFB		
	Value \leq 30 ms	30 ms<Value \leq 60 ms	Total
H: 8 mg/kg	2	1	3
I: 16 mg/kg	3	0	3
J: 24 mg/kg	2	1	3
G: 4 mg/kg	1	1	2
Total	8	3	11

Table 13: Categorical Analysis for Δ QTcF (Part 2)

TREAT	QTcF_CFB		
	Value \leq 30 ms	30 ms<Value \leq 60 ms	Total
Schedule E - 16mg/kg - No Pre-dose 1000 mL 1st 2 Infusions	19	3	22
Schedule D - 16mg/kg - Opt. Pre-dose 1000 mL 1st 2 Infusions	19	1	20
Schedule A - 8mg/kg - Dose Chosen By IDMC	13	3	16
Schedule B - 8mg/kg - 500 mL 1st Full Infusion	7	1	8
Schedule C - 8mg/kg - No Pre-dose 1000 mL 1st Full Infusion	6	0	6
Total	64	8	72

5.2.2 HR Analysis

This primary endpoint is the change from baseline of HR. The descriptive statistics are listed in Table 14 and Table 15.

Table 14: Analysis Results of Δ HR of Daratumumab Doses 4 mg/kg up to 24 mg/kg (Part 1, By Time)

Treatment	Time (H)	N	Mean	Std Dev	90% CI for Mean
G: 4 mg/kg	0	6	-1.7	10.1	(-10.1, 6.6)
	24	3	-0.6	11.8	(-20.5, 19.3)
H: 8 mg/kg	0	9	7.0	5.1	(3.8, 10.2)
	24	4	4.5	9.9	(-7.1, 16.1)
I: 16 mg/kg	0	7	15.4	8.8	(8.9, 21.8)
	24	5	10.8	5.3	(5.8, 15.8)
J: 24 mg/kg	0	8	-0.2	8.8	(-6.1, 5.7)
	24	6	3.1	6.6	(-2.3, 8.5)

Table 15: Analysis Results of Δ HR of Daratumumab Doses 8 mg/kg and 16 mg/kg (Part 2, By Time)

Treatment	Time(H)	N	Mean	Std Dev	90% CI for Mean
Visit=2					
Schedule A - 8mg/kg - Dose Chosen By IDMC	Predose	16	2.8	11.1	(-2.0, 7.7)
	0 to 1 hr	14	5.8	9.5	(1.3, 10.3)
Schedule B - 8mg/kg - 500 mL 1st Full Infusion	Predose	8	1.3	9.9	(-5.4, 8.0)
	0 to 1 hr	8	0.5	10.5	(-6.5, 7.5)
Schedule C - 8mg/kg - No Pre-dose 1000 mL 1st Full Infusion	Predose	4	-4.4	1.1	(-5.7, -3.1)
	0 to 1 hr	6	10.3	15.6	(-2.5, 23.1)
Schedule D - 16mg/kg - Opt. Pre-dose 1000 mL 1st 2 Infusions	Predose	19	-1.5	7.8	(-4.6, 1.6)
	0 to 1 hr	20	8.8	7.7	(5.8, 11.8)
Schedule E - 16mg/kg - No Pre-dose 1000 mL 1st 2 Infusions	Predose	21	-2.8	7.1	(-5.5, -0.2)
	0 to 1 hr	22	7.4	12.0	(3.0, 11.7)

Treatment	Time(H)	N	Mean	Std Dev	90% CI for Mean
Visit=7					
Schedule E - 16mg/kg - No Pre-dose 1000 mL 1st 2 Infusions	Predose	14	-3.0	9.4	(-7.4, 1.5)
	0 to 1 hr	19	3.1	10.4	(-1.0, 7.3)

The following tables present the categorical analysis of HR. No subject who experienced HR interval greater than 100 bpm is in daratumumab group in Part 1 (Table 16). Two subjects experienced HR interval greater than 100 bpm are in daratumumab groups in Part 2 (Table 17).

Table 16: Categorical Analysis for HR (Part 1)

TREAT	HR	
	HR <= 100 bpm	Total
H: 8 mg/kg	3	3
I: 16 mg/kg	3	3
J: 24 mg/kg	3	3
G: 4 mg/kg	2	2
Total	11	11

Table 17: Categorical Analysis for HR (Part 2)

TREAT	HR		
	HR <= 100 bpm	HR >100 bpm	Total
Schedule E - 16mg/kg - No Pre-dose 1000 mL 1st 2 Infusions	21	1	22
Schedule D - 16mg/kg - Opt. Pre-dose 1000 mL 1st 2 Infusions	20	0	20
Schedule A - 8mg/kg - Dose Chosen By IDMC	15	1	16
Schedule B - 8mg/kg - 500 mL 1st Full Infusion	8	0	8
Schedule C - 8mg/kg - No Pre-dose 1000 mL 1st Full Infusion	6	0	6
Total	70	2	72

5.2.2 PR Analysis

This primary endpoint is the change from baseline of PR. The descriptive statistics are listed in Table 18 and Table 19.

Table 18: Analysis Results of Δ PR of Daratumumab Doses 4 mg/kg up to 24 mg/kg (Part 1, By Time)

Treatment	Time(H)	N	Mean	Std Dev	90% CI for Mean
G: 4 mg/kg	0	6	-8.1	10.5	(-16.7, 0.5)
	24	3	-9.4	1.7	(-12.2, -6.5)
H: 8 mg/kg	0	9	-9.8	16.7	(-20.1, 0.5)
	24	4	-12.9	2.2	(-15.5, -10.3)
I: 16 mg/kg	0	7	-0.2	15.1	(-11.3, 10.9)
	24	5	-7.5	6.5	(-13.6, -1.3)
J: 24 mg/kg	0	8	3.2	9.2	(-3.0, 9.4)
	24	6	-2.2	6.2	(-7.3, 2.9)

Table 19: Analysis Results of Δ PR of Daratumumab Doses of 8 mg/kg and 16 mg/kg (Part 2, By Time)

Treatment	Time(H)	N	Mean	Std Dev	90% CI for Mean
Visit=2					
Schedule A - 8mg/kg - Dose Chosen By IDMC	Predose	16	-0.0	9.9	(-4.4, 4.3)
	0 to 1 hr	14	-2.3	12.7	(-8.3, 3.7)
Schedule B - 8mg/kg - 500 mL 1st Full Infusion	Predose	8	0.8	12.9	(-7.8, 9.5)
	0 to 1 hr	8	-4.7	6.8	(-9.2, -0.1)
Schedule C - 8mg/kg - No Pre-dose 1000 mL 1st Full Infusion	Predose	4	0.3	6.7	(-7.6, 8.1)
	0 to 1 hr	6	-2.5	4.8	(-6.5, 1.4)
Schedule D - 16mg/kg - Opt. Pre-dose 1000 mL 1st 2 Infusions	Predose	19	1.5	9.6	(-2.3, 5.3)
	0 to 1 hr	20	2.6	13.6	(-2.7, 7.9)
Schedule E - 16mg/kg - No Pre-dose 1000 mL 1st 2 Infusions	Predose	21	1.0	11.7	(-3.5, 5.4)
	0 to 1 hr	22	2.3	8.2	(-0.7, 5.3)
Visit=7					
Schedule E - 16mg/kg - No Pre-dose 1000 mL 1st 2 Infusions	Predose	14	-3.5	10.5	(-8.5, 1.5)
	0 to 1 hr	19	-1.3	8.1	(-4.5, 2.0)

The following tables present the categorical analysis of PR. One subject who experienced PR interval greater than 200 ms is in daratumumab group in Part 1 (Table 20). Six subjects who experienced PR interval greater than 200 ms are in daratumumab groups in Part 2 (Table 21).

Table 20: Categorical Analysis for PR (Part 1)

TREAT	PR		
	PR <= 200 ms	PR >200 ms	Total
H: 8 mg/kg	2	1	3
I: 16 mg/kg	3	0	3
J: 24 mg/kg	3	0	3
G: 4 mg/kg	2	0	2
Total	10	1	11

Table 21: Categorical Analysis for PR (Part 2)

TREAT	PR		
	PR <= 200 ms	PR >200 ms	Total
Schedule E - 16mg/kg - No Pre-dose 1000 mL 1st 2 Infusions	21	1	22
Schedule D - 16mg/kg - Opt. Pre-dose 1000 mL 1st 2 Infusions	16	4	20
Schedule A - 8mg/kg - Dose Chosen By IDMC	16	0	16
Schedule B - 8mg/kg - 500 mL 1st Full Infusion	7	1	8
Schedule C - 8mg/kg - No Pre-dose 1000 mL 1st Full Infusion	6	0	6
Total	66	6	72

5.2.3 QRS Analysis

This primary endpoint is the change from baseline of QRS. The descriptive statistics are listed in Table 22 and Table 23.

Table 22: Analysis Results of Δ QRS of Daratumumab Doses 4 mg/kg up to 24 mg/kg (Part 1, By Time)

Treatment	Time(H)	N	Mean	Std Dev	90% CI for Mean
G: 4 mg/kg	0	6	-3.1	3.7	(-6.1, -0.0)
	24	3	-2.2	2.7	(-6.8, 2.4)
H: 8 mg/kg	0	9	-4.3	6.2	(-8.2, -0.5)
	24	4	1.8	10.0	(-10.0, 13.5)
I: 16 mg/kg	0	7	-0.3	4.3	(-3.5, 2.9)
	24	5	2.0	2.0	(0.1, 3.9)
J: 24 mg/kg	0	8	5.8	7.6	(0.7, 10.9)
	24	6	0.6	9.4	(-7.2, 8.3)

Table 23: Analysis Results of Δ QRS of Daratumumab Doses 8 mg/kg and 16 mg/kg (Part 2, By Time)

Treatment	Time(H)	N	Mean	Std Dev	90% CI for Mean
Visit=2					
Schedule A - 8mg/kg - Dose Chosen By IDMC	Predose	16	2.3	7.2	(-0.8, 5.5)
	0 to 1 hr	14	3.4	6.1	(0.5, 6.2)
Schedule B - 8mg/kg - 500 mL 1st Full Infusion	Predose	8	1.5	4.8	(-1.7, 4.7)
	0 to 1 hr	8	1.7	5.3	(-1.9, 5.2)
Schedule C - 8mg/kg - No Pre-dose 1000 mL 1st Full Infusion	Predose	4	3.7	2.8	(0.4, 7.0)
	0 to 1 hr	6	2.9	4.1	(-0.5, 6.3)
Schedule D - 16mg/kg - Opt. Pre-dose 1000 mL 1st 2 Infusions	Predose	19	-0.3	7.0	(-3.1, 2.5)
	0 to 1 hr	20	-1.0	6.3	(-3.5, 1.4)
Schedule E - 16mg/kg - No Pre-dose 1000 mL 1st 2 Infusions	Predose	21	-0.3	5.6	(-2.4, 1.8)
	0 to 1 hr	22	-0.2	5.5	(-2.3, 1.8)
Visit=7					
Schedule E - 16mg/kg - No Pre-dose 1000 mL 1st 2 Infusions	Predose	14	-1.3	4.2	(-3.3, 0.7)
	0 to 1 hr	19	1.7	7.8	(-1.3, 4.8)

The following tables present the categorical analysis of QRS. Two subjects who experienced QRS interval greater than 110 ms are in daratumumab groups in Part 1 (see Table 24). Four subjects who experienced QRS interval greater than 110 ms are in daratumumab groups in Part 2 (Table 25).

Table 24: Categorical Analysis for QRS (Part 1)

TREAT	QRS		
	QRS <= 110 ms	QRS > 110 ms	Total
H: 8 mg/kg	2	1	3
I: 16 mg/kg	3	0	3
J: 24 mg/kg	2	1	3
G: 4 mg/kg	2	0	2
Total	9	2	11

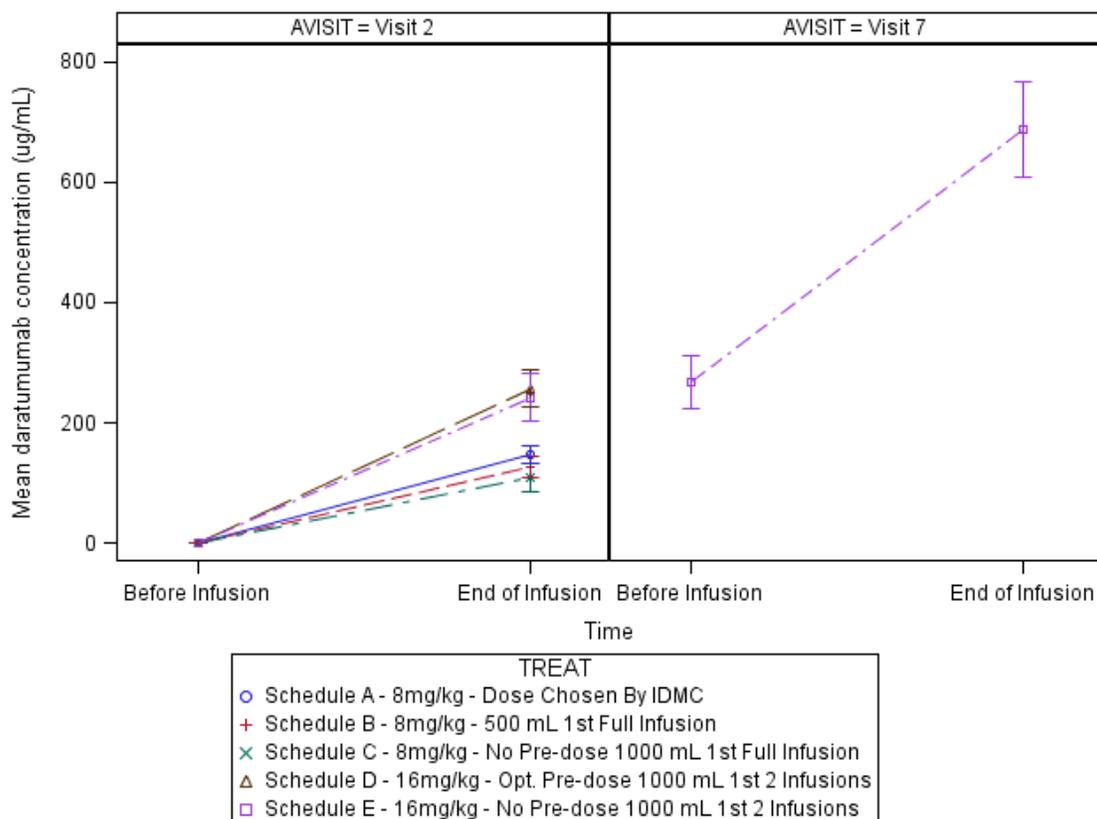
Table 25: Categorical Analysis for QRS (Part 2)

TREAT	QRS		
	QRS <= 110 ms	QRS > 110 ms	Total
Schedule E - 16mg/kg - No Pre-dose 1000 mL 1st 2 Infusions	21	1	22
Schedule D - 16mg/kg - Opt. Pre-dose 1000 mL 1st 2 Infusions	19	1	20
Schedule A - 8mg/kg - Dose Chosen By IDMC	15	1	16
Schedule B - 8mg/kg - 500 mL 1st Full Infusion	7	1	8
Schedule C - 8mg/kg - No Pre-dose 1000 mL 1st Full Infusion	6	0	6
Total	68	4	72

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

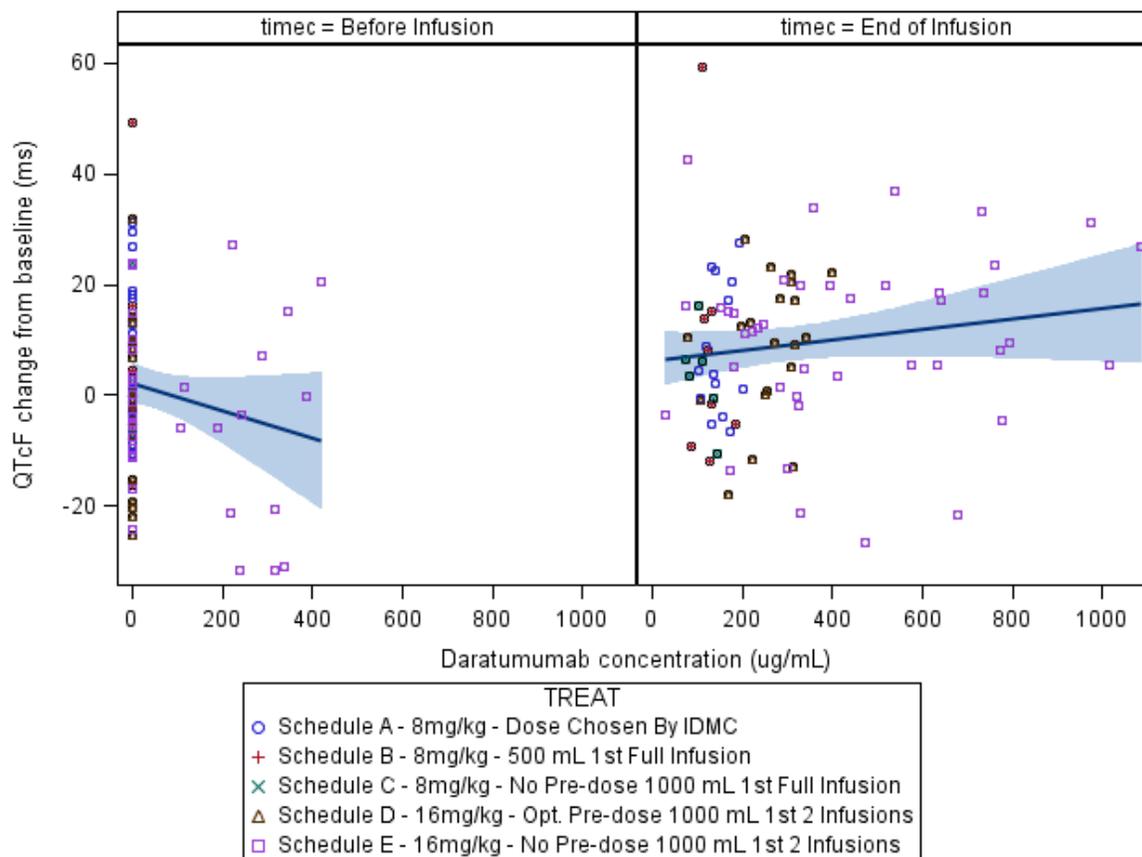
The mean daratumumab concentrations at pre-infusion and post-infusion at Visit 2 and Visit 7 in Part 2 are illustrated in Figure 4.

Figure 4: Mean Daratumumab Concentration-Time Observed in Part 2



The relationships between $\Delta QTcF$ and daratumumab concentrations by pre-infusion and post-infusion in Part 2 are visualized in Figure 5 with no evident exposure-response relationship (only ECG data with triplicate measurement in Part 2 were used). This analysis is inconsistent with the sponsor's concentration- QTc analysis. The sponsor did not include 'time' in their exposure-response model. Therefore, their significantly positive concentration- QTc relationship was confounded by the time effect. Including 'time' in the linear mixed effect model reduced the AIC value from 1394 to 1381 suggesting a significant improvement of the model. In the improved model, 'time' effect is significant, but the slope between the daratumumab concentration and $\Delta QTcF$ is flat (i.e., change from 0.0155 ms/(ug/mL) with the sponsor's model to 0.0046 ms/(ug/mL) with the improved model) and not significantly different from 0. With the improved model, the predicted $\Delta QTcF$ is less than 10 ms with upper bound less than 20 ms at the therapeutic C_{max} of 1000 ug/mL.

Figure 5: Δ QTcF vs. Daratumumab Concentration



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E 14 guidelines (i.e., syncope, seizure, significant ventricular arrhythmias or sudden cardiac death) occurred in this study.

5.4.2 ECG assessments

Overall ECG acquisition and interpretation in this study appears acceptable.

5.4.3 PR and QRS Interval

No clinically significant effects were seen on PR and QRS intervals.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose	16 mg/kg weekly for 8 weeks, every 2 weeks for 16 weeks, and then every 4 weeks thereafter.	
Maximum tolerated dose	In clinical studies no MTD has been identified; doses up to 24 mg/kg have been studied in clinical trials (Mod5.3.5.2/GEN501/Sec3.6.1)	
Principal adverse events	The following adverse drug reactions have been identified: infusion-related reaction (including but not limited to nasal congestion, cough, chills, allergic rhinitis, throat irritation, dyspnea, nausea, bronchospasm, hypertension, and hypoxia), fatigue, pyrexia, back pain, arthralgia, pain in extremity, musculoskeletal chest pain, upper respiratory tract infection, nasopharyngitis, nausea, diarrhea, constipation, anemia, neutropenia, thrombocytopenia, decreased appetite, hypercalcemia, pneumonia, and cough (Mod2.7.4/Sec2.6). For more information, see Mod2.7.4.	
Maximum dose tested	Single Dose	No single dose studies were performed.
	Multiple Dose	24 mg/kg weekly for 8 weeks, every 2 weeks for 16 weeks, and then every 4 weeks thereafter (Mod5.3.5.2/GEN501/Sec3.6.1)
Exposures Achieved at Maximum Tested Dose	Single (1 st) Dose	Mean C _{max} (%CV) - 500.10 µg/mL (16.1%) Mean AUC _{inf} (%CV) – 97,175.65 µg•h/mL (41.1%) (Mod5.3.5.2/GEN501/Tab18)
	Multiple (7 th) Dose	Mean C _{max} (%CV) - 1163.34 µg/mL (28.7%) Mean AUC _{inf} (%CV) – 1018233.50 µg•h/mL (101.1%) (Mod5.3.5.2/GEN501/Tab19)
Range of linear PK	Daratumumab elimination showed nonlinear characteristics; clearance is concentration and time dependent.	
Accumulation at steady state	Population Pharmacokinetic Evaluation: During the recommended dosing regimen of 16 mg/kg weekly for 8 weeks, every 2 weeks for 16 weeks, and then every 4 weeks thereafter, steady state is reached approximately 5 months into every 4 week dosing period. Mean (%CV) ratio of steady-state peak concentration to first dose peak concentration: 1.6 (31.3%)	
Metabolites	No metabolites of daratumumab have been identified and none are expected as an IgG-based monoclonal antibody.	
Absorption	Absolute Bioavailability	100% (administered as intravenous infusion)
	T _{max}	Median (range) 8 (8.00 to 12.17) h after start of first infusion (infusion duration is variable)
Distribution	V _d	Mean (%CV) population pharmacokinetic estimate of the central volume of distribution is 56.98 mL/kg (31.7% CV)
	% bound	0%; daratumumab is not bound in the systemic circulation
Elimination	Route	Elimination presumably follows the same catabolic pathway as endogenous IgG.
	Terminal t _{1/2}	The terminal half-life is concentration and time dependent. <ul style="list-style-type: none"> • Mean Terminal t_{1/2} (%CV) following the first dose of 16 mg/kg of daratumumab- 216.06 h [9.0 days] (48.2%) • Mean (%CV) model-derived linear elimination t_{1/2} (which can be expected upon complete saturation of target-mediated clearance and repeat dosing of daratumumab): 18 days (50%).

	CL/F or CL	<p>The clearance is concentration and time dependent.</p> <ul style="list-style-type: none"> • Following the first dose of daratumumab 16 mg/kg: Mean clearance (%CV) - 0.42 mL/h/kg (100.6%) • The mean (%CV) model-derived non-specific linear clearance (which can be expected upon complete saturation of –mediated clearance and repeat dosing of daratumumab) 0.13 mL/h/kg (66.3%)
Intrinsic Factors	Age	<p>Examined using population pharmacokinetic analysis, no clinically relevant difference in pharmacokinetics. Mean (95%CI) predicted maximal pre-infusion concentration (trough at the end of weekly dosing period) by age subgroups:</p> <ul style="list-style-type: none"> • Age <65 years: 414.52 (354.59, 484.58) µg/mL • Age ≥65 years: 441.54 (368.95, 528.41) µg/mL
	Sex	<p>Examined using population pharmacokinetic analysis, no clinically relevant difference in pharmacokinetics. Mean (95%CI) predicted maximal pre-infusion concentration (trough at the end of weekly dosing period) by sex subgroups:</p> <ul style="list-style-type: none"> • Male: 400.83 (344.05, 466.98) µg/mL • Female: 465.20 (387.03, 559.16) µg/mL
	Race	<p>Examined using population pharmacokinetic analysis, no clinically relevant difference in pharmacokinetics. Mean (95%CI) predicted maximal pre-infusion concentration (trough at the end of weekly dosing period) by race subgroups:</p> <ul style="list-style-type: none"> • White: 419.61 (370.18, 475.63) µg/mL • Non-white: 477.17 (337.95, 673.75) µg/mL
	Hepatic & Renal Impairment	<p>Examined using population pharmacokinetic analysis, no clinically relevant difference in pharmacokinetics. Mean (95%CI) predicted maximal pre-infusion concentration (trough at the end of weekly dosing period) by hepatic function subgroups:</p> <ul style="list-style-type: none"> • Normal: 448.95 (395.47, 509.66) µg/mL • Mild: 317.95 (235.77, 428.78) µg/mL <p>Mean (95%CI) predicted maximal pre-infusion concentration (trough at the end of weekly dosing period) by renal function subgroups:</p> <ul style="list-style-type: none"> • Normal: 410.27 (332.84, 505.70) µg/mL • Mild: 472.69 (387.18, 577.07) µg/mL • Moderate: 394.26 (318.40, 488.19) µg/mL • Severe: 411.80 (200.56, 845.53) µg/mL
Extrinsic Factors	Drug interactions	No formal drug interaction studies have been performed and no drug interactions are expected
	Food Effects	Not applicable since daratumumab is administered intravenously
Expected High Clinical Exposure Scenario	<p>Following the recommended 16 mg/kg dose & scheduled, highest clinical exposure expected at the end of weekly dosing; mean (%CV) end of infusion concentration is 914.86 µg/mL (44.9%), approximately 2.9-fold higher than following the first infusion.</p> <p>Following the last (7th) administered dose of 24 mg/kg weekly, which was the maximum tested dose, mean C_{max} (%CV) was 1163.34 µg/mL (28.7%) and</p>	

	mean AUC _{inf} (%CV) was 1018233.50 µg•h/mL (101.1%).
Preclinical Cardiac Safety	Traditional in vitro hERG assays were not performed for daratumumab as monoclonal antibodies are too large to access the channel. A standalone cardiovascular (CV) safety study was not conducted with daratumumab. Safety pharmacology endpoints were incorporated into the 6-week IV repeat-dose toxicology study in chimpanzees as suggested for biologics in ICH S6(R1). CV system evaluations were performed once pre-study, on the days of dosing (30 mins. and 24 h postdose), and on 6 occasions during the recovery period, and included assessment of electrocardiograms (ECGs; leads I, II, III, aVR, aVL, and aVF), blood pressure, and pulse rate. There were no treatment-related adverse effects on CV function at doses ≤25 mg/kg/week.
Clinical Cardiac Safety	<p>In 3 daratumumab monotherapy studies (GEN501, MMY2002 and MMY1002), of 237 subjects treated with daratumumab, a total of 6 subjects (2.5%) reported an AE of QT prolongation (Table TSFAE01F). The majority of these events, 5/6 occurred in the first subjects treated with daratumumab in part 1 of Study GEN501 and occurred in the lowest dose groups (0.005 mg/kg to 1 mg/kg group) (details are described in the CSR). Only 1 subject (100065) in Study MMY2002 in the 16 mg/kg group had a Grade 1 TEAE of QT prolongation on Study Day 22. On the same day, the subject also experienced Grade 1 non-serious TEAEs of dyspnea and musculoskeletal chest wall pain. All TEAEs were considered by the investigator to be doubtfully related to study drug. The subject had a history of hypomagnesemia and was receiving magnesium replacement throughout the study, with magnesium levels ranging from 1.5-1.8 mg/dL on the study (normal range 1.8-2.5 mg/dL). The subject also received ciprofloxacin on the day prior to the AE of QT prolongation for fever. The subject continued treatment and received 13 additional daratumumab infusions. The TEAEs of dyspnea and musculoskeletal chest wall pain resolved on the same day, and the TEAE of QT prolongation resolved the next day. Subsequent ECG assessments were normal. There was no dose dependent finding for QT prolongation.</p> <p>A search for cardiac safety events associated with QT prolongation per ICH E14 guidance (e.g., syncope, seizures, ventricular arrhythmias, ventricular tachycardia, ventricular fibrillation, flutter, torsade de pointes, or sudden deaths), identified 2 subjects, both with syncope in Study MMY2002. One subject (100007) with medical history of syncope had an episode of Grade 3 syncope (an SAE) at Cycle 1, Day 8 after a blood draw and lost consciousness. The subject was admitted for observation and evaluation and the event resolved on the same day. An ECG demonstrated normal sinus rhythm. The syncopal episode was most likely suggestive of vasovagal syncope or hypovolemic syncope and was considered not related to daratumumab by the investigator. Another subject with syncope (100094) had no medical history of cardiovascular disease but had abnormal ECGs (not clinically significant) reported at baseline and at all timepoints during treatment. This subject had one episode of Grade 3 syncope (not an SAE) at Cycle 4, Day 1 which resolved the same day and the subject continued additional 10 doses of daratumumab prior to discontinuation due to disease progression. This event was considered not related to daratumumab by the investigator.</p> <p>In summary, daratumumab does not induce the pro-arrhythmic risk associated with QT prolongation.</p>

	Treatment-Emergent Cardiac Events During the Study: All Treated Analysis Set (Studies: MMY2002, GEN501 and MMY1002)										
	0.005 mg/kg	0.05 mg/kg	0.1 mg/kg	0.5 mg/kg	1 mg/kg	2 mg/kg	4 mg/kg	8 mg/kg	16 mg/kg	24 mg/kg	Total
Analysis set: all treated	1	1	6	3	6	3	3	55	156	3	237
Total number of subjects with treatment-emergent cardiac events ^a	0	0	2 (33.3%)	1 (33.3%)	2 (33.3%)	0	0	1 (1.8%)	2 (1.3%)	0	8 (3.4%)
MedDRA system organ class / Preferred term											
Investigations	0	0	2 (33.3%)	1 (33.3%)	2 (33.3%)	0	0	0	1 (0.6%)	0	6 (2.5%)
Electrocardiogram QT prolonged	0	0	2 (33.3%)	1 (33.3%)	2 (33.3%)	0	0	0	1 (0.6%)	0	6 (2.5%)
Nervous system disorders	0	0	0	0	0	0	0	1 (1.8%)	1 (0.6%)	0	2 (0.8%)
Syncope	0	0	0	0	0	0	0	1 (1.8%)	1 (0.6%)	0	2 (0.8%)

^a Cardiac events include QT prolongation, syncope, seizures, ventricular arrhythmias, ventricular tachycardia, ventricular fibrillation, flutter, torsade de pointes, or sudden deaths.

Adverse events are reported using MedDRA version 17.0.

Percentages are calculated with the number of subjects in each group as denominator.

[TSFAE01F.rtf] [JNJ-54767414\Z_SCS\DBR_SCS_2014\RE_SCS_2014\tsfae01f.sas] 17SEP2015, 17:14

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/s/

JIANG LIU
10/19/2015

MOH JEE NG
10/19/2015

QIANYU DANG
10/19/2015

MICHAEL Y LI
10/19/2015

NORMAN L STOCKBRIDGE
10/19/2015

Consult
MEMORANDUM

Department of Health and Human Services
Public Health Service
Food and Drug Administration



DATE: October 16, 2015

RECEIVED: September 28, 2015

TO: Barry Miller and Jessica Boehmer, CDER/OHOP/DHP

FROM: Jennifer Dickey, CDRH/OIR/DMGP

THROUGH: Donna Roscoe and Reena Philip, CDRH/OIR/DMGP

SUBJECT: CDER consult request for BLA 761036

CDRH ICC Tracking Number: ICC1500525

Protocol Title MMY2002

Drug Sponsor Janssen Pharmaceuticals

Drug Name Daratumumab

Analyte Detected Daratumumab

Device Sponsor Janssen R&D

I. BACKGROUND

This consult is to review the analytical validation report for the daratumumab-specific immunofixation reflex assay (DIRA) to confirm daratumumab interference in serum IFE testing. This assay is designed to allow clinical assessment of CR or sCR following daratumumab treatment. The reflex assay is needed because the drug product may interfere with standard serum protein electrophoresis/immunofixation (SPE/IFE) assessments.

In this BLA, 2 subjects were designated CR on the basis of DIRA negative test results.

II. ANALYTICAL VALIDATION REPORT

1. **Materials:** Both daratumumab (dara) and the anti-idiotypic HuMax-CD38 (anti-dara) were provided to the clinical laboratory by the drug sponsor. It is unknown how and if the sponsor (b) (4)

. This was the subject of an information request by the sponsor.

Note to CDER: We recommend that the sponsor be encouraged to develop for marketing the DIRA assay so that daratumumab response levels may be accurately categorized post-approval.

2. Sensitivity:

- i. In development, purchased serum from 10 MM donors were spiked with clinically relevant levels of dara (250, 500, and 1000 $\mu\text{g/mL}$) plus or minus the anti-dara at a 1:1 ratio. In 2 out of 10 samples there was no detectable endogenous M-protein. The M-protein co-migrated with the dara complex in 7 out of the remaining 8 samples. In all samples dara was observed and a shift was observed at the 250 $\mu\text{g/mL}$ level. This concentration is below the expected serum levels of dara after 4 doses.
- ii. The LoD was further investigated using 10 purchased MM serum samples and 10 purchased normal serum samples. These samples were spiked with dara at 0, 100, 200, 250, and 500 $\mu\text{g/mL}$ plus or minus the anti-dara at a 1:1 ratio. For the MM sera dara could be detected in 9/10 samples at 100 $\mu\text{g/mL}$ and in all 10 samples at 200 $\mu\text{g/mL}$. For the normal samples dara could be detected in 8/10 samples at 100 $\mu\text{g/mL}$ and in all 10 samples at 200 $\mu\text{g/mL}$.
- iii. The sponsor concludes LoD is 200 $\mu\text{g/mL}$ (below the expected trough drug concentration).

Note to CDER: These studies are not reflective of appropriately designed LoD studies for serum analytes. While acceptable for the purposes of clinical studies, we would recommend a more extensive understanding of assay LoD in a marketed test.

3. Reproducibility:

- i. **Inter-assay reproducibility:** Reproducibility was evaluating using 10 clinical trial samples from dara treated subjects with clinical response $>$ PR and SPEP <0.5 g/dL. The samples were run 3 times and scored by 2 reviewers twice (6 runs per sample read by 2 reviewers for a total of 60 runs and 120 reads). In 10/10 samples the results were identical across the runs and reviewers. In 2 out of 10 samples an additional trace band was observed in the baseline serum samples spiked with anti-dara which is believed to be the interaction of the anti-dara with the endogenous M-protein. However the migration of dara was observed in these samples and the endogenous M-proteins did not shift. **These results indicate the need**

to always run control lanes to aid in assay interpretation.

(b) (4)

- ii. **Inter-day and inter-operator reproducibility:** Inter-day and inter-operator reproducibility was evaluated using 3 purchased MM samples on 3 days with 2 operators. Both 1:1 and 2:1 anti-dara:dara ratios were tested. In 2/3 samples there was no variability observed. In 1 sample residual dara was found using kappa antisera at the 1:1 ratio. The sponsor states that these residual levels cannot be misinterpreted for the M-band, thereby not influencing the final outcome of the assay.
- iii. The sponsor concludes that the assay is highly reproducible. This study design is acceptable for an assay used in clinical studies.

4. **Specificity:**

- i. **Specificity of anti-dara for dara:** Purchased MM samples (n=16) were spiked with dara plus or minus anti-dara at a 1:1 ratio at 500 µg/mL and 1000 µg/mL. The samples were run and assessed by 2 reviewers. For all samples and conditions the endogenous M-proteins were still present indicating the anti-dara only reacts with dara.

Next another 35 purchased MM samples were spiked with 1:1 and 2:1 of anti-dara + dara at 500 µg/mL dara. For all 51 total samples the M-protein band was detectable in all conditions. However when only the anti-dara was spiked in the serum, in 4/51 cases (7.8%) the immunofixation patterns were altered (shifted slightly). The sponsor states that this signal was very weak and cannot be misinterpreted for M-protein.

To date, out of 29 clinical samples tested in DIRA, 16 were DIRA positive (indicating residual M-protein) and 13 were DIRA negative (no remaining protein). Samples with endogenous M-protein showed no interaction of anti-dara with the M-spike. **Thus the anti-dara is somewhat specific but may have limited interactions with endogenous M-proteins which are not expected to impact assay results. This will be further investigated using relevant samples from the control arm of the clinical studies as samples become available.**

- ii. **False positive rates of DIRA:** Samples are being collected to investigate the assay false positive rate. Results of this study will be provided as an addendum in the BLA.
 - iii. **False negative rates of DIRA:** Samples are being collected to investigate the assay false negative rate. Results of this study will be provided as an addendum in the BLA.
 - iv. **Specificity of DIRA using excess anti-dara (DIRA Plus assay):** This testing was designed to determine if 1000 µg/mL anti-dara would be sufficient in all cases of suspected dara interference, specifically in patients with \geq PR and in whom the residual dara concentration might be higher. This assay is proposed to be used in cases where it is unclear if an incomplete shift of dara occurs due to lack of sufficient anti-dara or overlap of remaining M-protein. The effect of 2000 and 4000 µg/mL anti-dara on endogenous M-protein was evaluated in 14 samples from ongoing clinical studies. The results indicate that anti-dara up to 1000 µg/mL do not interfere with interpretation and are sufficient to shift all dara. However higher levels of anti-dara (4000 µg/mL) generated faint signals in the IgG antisera and therefore this concentration will not be recommended. Since serum levels of dara should only reach 500-1000 µg/mL, a fixed 1000 µg/mL anti-dara concentration should be sufficient. This will be evaluated further in the false positive/false negative studies.
5. **Evaluation of 2 lots of anti-dara:** MM serum was purchased for these studies and 8 samples were spiked separately with each lot of anti-dara and compared at 500 and 1000 µg/mL. The anti-dara always showed migration of the dara/anti-dara complex. No cases were observed in which the anti-dara altered the pattern of the M-proteins. However for some samples (2/8) a weak signal could be identified as residual dara after addition of the anti-dara in a 1:1 ratio. However this observation was not lot dependent.
6. **Stability:**
- i. **Sample stability:** Testing used 10 purchased MM samples spiked with 500 µg/mL dara. DIRA was performed on day 0 and then samples were frozen and subjected to 3 overnight freeze/thaw cycles. Assay performance on samples after 3 freeze/thaw cycles was consistent with day 0 testing. One sample had a residual band on the second cycle that did not appear in the third freeze/thaw indicating interference. In addition samples were stored at -80°C for 1, 2, and 3 month stability. **The results**

of storage sample stability studies will be provided in an addendum to this report.

- ii. **Reagent stability:** Aliquots of anti-dara were prepared and stored at different temperature prior to running in the assay. The assay assessed both 500 and 1000 µg/mL dara and anti-dara at a 1:1 ratio. Stability of anti-dara was evaluated at 4C for 10 weeks and at -80C for 2 months and after 3 freeze/thaw cycles. All time points passed stability testing. **Additional stability testing at 12 months and 3 years is planned and results will be reported in an addendum to this report.**

- 7. **Assay development plans:** The sponsor states that while DIRA has been validated for its purpose, the assay has limitations. Specifically DIRA is a qualitative assay and dara specific (b) (4)


III. ADVICE TO SPONSOR

- 1. The assay validation report appears to be sufficient for use in clinical trials. However, in light of the importance of this assay in the clinical management of patients being treated with daratumumab, we recommend that the DIRA assay be developed for marketing so that daratumumab response levels may be accurately categorized post-approval.
- 2. The analytical validation data provided to date indicate that there may be some lack of specificity of the anti-daratumumab antibody. Binding observed in the M-protein lanes lacking daratumumab may complicate assay interpretation. A full set of control lanes should always be used in patient sample assessment, and this binding activity should be further explored in the upcoming studies to assess false positive and false negative rates.

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/s/

JENNIFER S DICKEY
10/16/2015

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: September 28, 2015

TO: Jessica Boehmer, M.B.A., Regulatory Project Manager
Barry Miller, M.Sc., C.R.N.P., Clinical Analyst
Albert Deisseroth, M.D., Ph.D., Cross Discipline Team Leader
Division of Hematology Products (DHP)

FROM: Anthony Orenca, M.D., F.A.C.P.
Medical Officer, GCP Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

THROUGH: Susan D. Thompson, M.D.
Team Leader, GCP Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

Kassa Ayalew, M.D., M.P.H.
Branch Chief, GCP Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

BLA: 761036

APPLICANT: Janssen Research & Development, LLC

DRUG: daratumumab

NME: Yes

THERAPEUTIC CLASSIFICATION/REVIEW: Breakthrough Review

INDICATIONS: Treatment of resistant (b) (4) multiple myeloma

CONSULTATION REQUEST DATE (signed): February 10, 2015

INSPECTION SUMMARY GOAL DATE (original): August 31, 2015
INSPECTION SUMMARY GOAL DATE (revised): September 29, 2015
DIVISION ACTION GOAL DATE: October 15, 2015
PDUFA DATE: February 09, 2016

I. BACKGROUND:

Daratumumab is a human IgG1 κ monoclonal antibody that binds to an epitope on CD38, a transmembrane glycoprotein. This proposed immunotherapy attacks tumor cells that overexpress CD38 in multiple myeloma tumor cells. Daratumumab induces lysis of CD38-expressing tumor cells via mechanisms such as complement-dependent cytotoxicity (CDC), antibody-dependent cell-mediated cytotoxicity (ADCC), and antibody-dependent cellular phagocytosis (ADCP) through activation of complement proteins, natural killer (NK) cells, and macrophages.

Treatment options for subjects with primary resistant or relapsed multiple myeloma may include combination therapies with glucocorticoids and cytotoxic chemotherapeutic agents, more recently combined with autologous stem transplantation (ASCT).

A single adequate Phase 1 and a single Phase 2 open-label clinical trial were submitted in support of the applicant's BLA. For this NME BLA under the PDUFA V program review with breakthrough therapy designation, CDER DHP requested three domestic sites for inspection. The sites enrolled large numbers of patients, and according to the sponsor showed good response to treatment.

Study 54767414MMY2002

Study 54767414MMY2002 was an open-label, multicenter, Phase 2 clinical study of daratumumab for the treatment of subjects with multiple myeloma who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent (IMiD) or whose disease is double refractory to both these therapeutic agents. Subjects were stratified by the International Staging System (I, II, or III) and refractory status (none, refractory to either a PI or IMiD, or refractory to both a PI and IMiD). The primary objective was to determine the efficacy of two treatment regimens of daratumumab, as measured by the overall response rate (ORR) (complete response [CR] + partial response [PR]) in these subjects. The primary efficacy endpoint was tumor response and disease progression in accordance with the International Myeloma Working Group response criteria.

JNJ54767414GEN501 (Part 2)

Study GEN501 (Part 2) was an open-label, single-arm design at the Part 1 dose that was determined to be safe by the Independent Data Monitoring Committee (IDMC) based on safety, pharmacologic, and therapeutic effect data from Part 1. The doses chosen for Part 2 were 8 mg/kg and 16 mg/kg. The primary objective of the study was to establish the safety profile of daratumumab, as monotherapy in patients with multiple myeloma relapsed from or refractory to at least two different cyto-reductive therapies and without further established treatment options. During Study GEN501 (Part 2), study subjects received daratumumab for up to 96 weeks or until they experienced unacceptable toxicity or disease progression whichever came first. The primary study endpoint was safety, principally non-serious adverse event Grade 3 or higher, and serious adverse event assessment.

II. RESULTS:

Name of CI Location	Study Site/Protocol /Number of Subjects Enrolled (n)	Inspection Date	Classification*
Jacob Laubach, M.D. Dana Farber Cancer Institute 450 Brookline Ave. Boston, MA 02215	Site #50125 Protocol JNJ54767414GEN501 (Part 2) Subjects=20	July 13-21, 2015	Preliminary: VAI
Saad Usmani, M.D. Carolinas Medical Center 6940 Columbia Gateway Dr.Suite 110 Charlotte, NC 21046	Site #US10782 Protocol 54767414MMY2002 Subjects=9	July 13-15, 2015	Preliminary: NAI
Brendan Weiss, M.D. Abramson Cancer Center of the University of Pennsylvania 3624 Market Street, Suite 301 S Philadelphia, PA 19104	Site #US10555 Protocol 54767414MMY2002 Subjects=9	August 31 - September 4, 2015	Preliminary: NAI
Sponsor: Janssen Research & Development, LLC 1400 McKean Road PO Box 776 Spring House, PA 19477	Protocol JNJ54767414GEN501& Protocol 54767414MMY2002	August 17-19, 2015	Preliminary: NAI

***Key to Classifications**

NAI = No deviation from regulations. Data acceptable.

VAI-No Response Requested = Deviations(s) from regulations. Data acceptable.

OAI = Significant deviations from regulations. Data unreliable/critical findings may affect data integrity.

Preliminary=The Establishment Inspection Report (EIR) has not been received, findings are based on preliminary communication with the field at the Office of Regulatory Affairs (ORA), or final review of the EIR is pending. Once a final letter is issued by CDER to the inspected entity and the case file is closed, the preliminary designation is converted to a final regulatory classification.

CLINICAL STUDY SITE INVESTIGATOR

1. Jacob Laubach, M.D., Site #50125, Protocol JNJ54767414GEN501 (Part 2)
Boston, MA

a. What was inspected:

The inspection was conducted from July 13 to 21, 2015.

A total of 27 subjects were screened and 20 subjects were enrolled. Thirteen subjects discontinued due to progressive disease. Seven subjects completed the study. An audit of 20 enrolled subjects' records was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

b. General observations/commentary:

Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and BLA subject line listings. Source documents for the raw data used to assess the primary study endpoint (i.e., safety) were verifiable at the study site. No under-reporting of serious adverse events was noted. There were no limitations during conduct of the clinical site inspection.

A Form FDA 483 (Inspectional Observations) was issued at the end of the inspection. Specifically, the study was not conducted according to the investigational plan. For example:

- (a) Six out of 20 subjects enrolled were not delivered the full dose of study drug during their initial study drug infusion.
- (b) Subject #10 received 3 medications (Tobradex, Timolol, and Alphagan P) on 8/1/2013 to treat an adverse event of left eye swelling that were not reported as concomitant medications.

OSI Comment:

Subjects did not receive the full dose of daratumumab due to a significant infusion reaction requiring a pause in the infusion before the infusion could be restarted at half the previous rate. The infusion was then discontinued at the end of the treatment day prior to close of the infusion room to allow for the post-infusion observation period. As this was a Phase 1 open-label safety study, the study site adequately monitored subjects for infusion-related reactions (pre-infusion and post-infusion medications were administered to minimize potential reactions). Patients were not discontinued and the reduced dosing scheme was duly reported to the BLA.

Dr. Laubach responded adequately in a letter dated August 5, 2015.

c. Assessment of data integrity:

Despite the above minor regulatory deficiencies, data submitted by this clinical site appear acceptable in support of this specific indication.

2. Saad Usmani, M.D., Site # US10782, Protocol 54767414MMY2002
Charlotte, NC

a. What was inspected:

The inspection was conducted from July 13 to 15, 2015.

A total of 13 subjects were screened, and nine subjects were enrolled and randomized. Six subjects completed the treatment period phase of the study (all developed progressive disease). An audit of nine enrolled subjects' records was conducted.

OSI participation for a portion of the clinical site audit was also undertaken as part of its outreach. Dr. Usmani was considered a high risk clinical investigator, given his previous clinical trial oversight deficiencies at his prior institution at the University of Arkansas Medical School for a separate DHP BLA.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

b. General observations/commentary:

Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and BLA subject line listings. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of serious adverse events was noted. There were no limitations during conduct of the clinical site inspection.

Dr. Usmani's study site was under the regulatory oversight of the Levine Cancer Institute, as well as further administrative close supervision by the Carolinas HealthCare System Research Regulatory Affairs and Quality group.

A Form FDA 483 (Inspectional Observations) was not issued at the end of the inspection.

c. Assessment of data integrity:

In general, data submitted by this clinical site appear acceptable in support of this specific indication.

3. Brendan Weiss, M.D./ Site # US10555, Protocol 54767414MMY2002
Philadelphia, PA 19104

a. What was inspected:

The inspection was conducted from August 31 to September 4, 2015.

A total of ten subjects were screened and nine subjects enrolled. Nine subjects completed the treatment period phase of the study (all subjects developed progressive disease). An audit of nine enrolled subjects' records was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

b. General observations/commentary:

Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and BLA subject line listings. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of serious adverse events was noted. There were no limitations during conduct of the clinical site inspection.

A Form FDA 483 (Inspectional Observations) was not issued at the end of the inspection.

c. Assessment of data integrity:

Data submitted by this clinical site appear acceptable in support of this specific indication.

SPONSOR

4. Janssen Research & Development, LLC

Spring House, PA 19477

a. What was inspected:

The inspection was conducted from August 17 to 19, 2015. The inspection evaluated the following: documents related to study monitoring visits and correspondence, Institutional Review Board (IRB) approvals, completed Form FDA 1572s, monitoring reports, drug accountability, and training of staff and site monitors.

b. General observations/commentary:

Monitoring deficiencies, in terms of initiating interim monitoring visits within a timely manner, were identified. Noncompliant sites were not noted. There was no evidence of under-reporting of adverse events.

A Form FDA 483 was not issued at the end of the sponsor inspection.

c. Assessment of data integrity:

Data submitted by this sponsor appear acceptable in support of the requested indication.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Two clinical studies, Study JNJ54767414GEN501 and 54767414MMY2002, respectively, were inspected for this BLA. Three domestic clinical study sites covering three clinical investigators (Jacob Laubach, M.D., M.D., Saad Usmani, M.D. and Brendan Weiss, M.D.) were inspected. The sponsor (Janssen) was also audited.

The preliminary regulatory classification for Drs. Usmani and Weiss is No Action Indicated (NAI). The preliminary regulatory classification for Dr. Laubach is Voluntary Action Indicated (VAI). The sponsor regulatory classification is No Action Indicated (NAI).

In summary, OSI considers that data from the above three clinical and sponsor sites are acceptable in support of the BLA.

Note: The inspectional observations for the sponsor and the clinical study investigators are based on preliminary communications with the field investigator. A clinical inspection summary addendum will be generated if conclusions on the current inspection report change significantly, upon receipt and review of the Establishment Inspection Report (EIR). The CDER OSI classification of inspection is finalized when written correspondence is issued to the inspected entity.

{See appended electronic signature page}

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/s/

ANTHONY J ORENCIA
09/28/2015

SUSAN D THOMPSON
09/29/2015

KASSA AYALEW
09/29/2015

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review: September 24, 2015
Requesting Office or Division: Division of Hematology Products (DHP)
Application Type and Number: BLA 761036
Product Name and Strength: Darzalex (Daratumumab)
Injection
100 mg/5mL and 400 mg/20mL (20 mg/mL)
Product Type: Single-ingredient Product
Rx or OTC: Rx
Applicant/Sponsor Name: Janssen Research and Development, LLC
Submission Date: July 9, 2015
OSE RCM #: 2015-1325
DMEPA Primary Reviewer: Cathy A. Miller, BSN, MPH
DMEPA Team Leader: Yelena Maslov, PharmD

1 REASON FOR REVIEW

This review evaluates the container label, carton labeling and full prescribing information (PI) for Darzalex (daratumumab), BLA 761036, submitted on July 9, 2015. The Division of Hematology (DHP) requested that DMEPA review the labels and labeling for areas of vulnerability that may lead to medication errors. Darzalex is a first-in-class human immunoglobulin G1 kappa (IgG1k) mAb that binds with high affinity to CD38 and is not currently licensed anywhere in the world.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	B – N/A
Previous DMEPA Reviews	C – N/A
Human Factors Study	D – N/A
ISMP Newsletters	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

DMEPA reviewed the proposed labels and labeling to determine whether there are any areas of needed improvement which could lead to medication errors. The proprietary name and proper name on the principal display panel (PDP) of the container labels and on the PDP and side panels of carton labeling are difficult to read due to the font presentation and the use of a graphic that appears in front of the proprietary name. Additionally, the proprietary name font color is not differentiated from the font color of the product strength, which could lead to wrong strength errors as users may associate the proprietary name font color with a specific strength. The prominence of important product use information, which appears on container labels and carton labeling can also be improved to ensure safe use of the product and minimize confusion that could lead to medication errors. Additionally, we note that the middle digits of the NDC product codes for the 100 mg/5 mL and 400 mg/20 mL sizes are the same (-‘502’-), which may lead to wrong strength errors.

Lastly, we noted that the container label lacks the required statement “Rx only”.

Prescribing Information

Our review of the draft prescribing information for Darzalex found that improvements can be made to increase the clarity of important administration and infusion information in the Full Prescribing Section 2 Dosage and Administration. Additionally, we note that the presentations of the 100 mg/5 mL and 400 mg/20 mL volumes in Section 3: Dosage Forms and Strengths of the Highlights of Prescribing Information and Full Prescribing Information do not include the product strength per milliliter (20 mg/mL).

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed labels and labeling can be improved to increase the readability and prominence of important information, promote the safe use of the product, and mitigate any confusion. We provide recommendations for consideration to the Division of Hematology for proposed revisions to the prescribing information in Section 4.1 and revisions to the container labels and carton labeling in Section 4.2.

If you have further questions or need clarifications, please contact Kevin Wright, OSE Project Manager, at 301-796-3621.

4.1 RECOMMENDATIONS FOR THE DIVISION OF HEMATOLOGY PRODUCTS (DHP)

DMEPA provides the following comments for consideration by the review Division prior to the approval of this BLA:

1. In Section 2.1, consider whether to use actual body weight versus ideal body weight for recommended dose.
2. Section 2.2 contains the use of the abbreviation ‘IV’. To avoid confusion that could lead to wrong route of administration errors, consider revising with the full spelling ‘intravenously¹’.
3. Section 2.3 contains the use of the abbreviation ‘≥’. To avoid confusion that could lead to misinterpretation of this symbol, consider spelling out ‘greater than or equal to’.
4. Currently, Table 2: Infusion Rates for Darzalex administration, which provides infusion rate information for first and subsequent infusions, appears under section 2.1 Recommended Doses and Schedule. Because Section 2.5 Administration describes specific administration information for the healthcare professional, consider cross-referencing Table 2 in Section 2.5.
5. The presentations of the 100 mg/5 mL and 400 mg/20 mL volumes in Section 3: Dosage Forms and Strengths of the Highlights of Prescribing Information and Full Prescribing Information do not include the product strength (20 mg/mL). In order to minimize confusion that may lead to wrong strength during the preparation or administration of the product, we recommended adding the product strength per mL, ‘20 mg/mL’.

¹ ISMP’s List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2013 [cited 2013 Sep 16]. Available from: <http://www.ismp.org/tools/errorproneabbreviations.pdf>.

4.2 RECOMMENDATIONS FOR JANSEN PHARMACEUTICALS

We recommend the following revisions be implemented prior to approval of this BLA:

A. Container Label:

1. Increase the prominence, using bold font, of the “Single Use Only”, “Discard unused portion” and “Must dilute before intravenous infusion” statements on the side panel of the container label in order to label to ensure safe handling and appropriate use of the product.
2. 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 gray font and thus, lacks contrast with the white background.
3. Revise the statement “ (b) (4) ” to “For intravenous Infusion Only After Dilution” to minimize the risk of administering the drug as an intravenous bolus without dilution.
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 sizes².

B. Carton Labeling

1. Relocate the graphic  where it appears before the proprietary name, ‘Darzalex’ as users may interpret the letter as a “A” ,“Z” , or “X”.³
2. Relocate the “Single Use Only”, “Discard unused portion” and “ (b) (4) dilute before (b) (4) ” statements that currently appear at the top left corner of the PDP of the carton labeling to a more prominent location below the product strength and total volume, in order to ensure safe handling and appropriate use of the product.
3. Delete the “ (b) (4) ” statement that appears on the side panel since this product is only used in the clinical setting.
4. Bold the route of administration statement “For Intravenous Infusion only” where it appears on the carton labeling.
5. Refer to comment A2 through A4 above and revise carton labeling accordingly.

² FDA Guidance for Industry, Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (Draft Guidance) April 2013,page 14.

³ See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. 2013 Apr [cited 2014 Jun 12]. 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.”

APPEARS THIS WAY ON ORIGINAL

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Darzalex that Janssen submitted on July 9, 2015 (eCTD Sequence No. 002).

Table 2. Relevant Product Information for Portrazza	
Initial Approval Date	N/A
Active Ingredient	Daratumumab
Indication	A human anti-CD38 monoclonal antibody indicated for the treatment of patients with multiple myeloma who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent (IMiD) or who are double-refractory to a PI and IMiD.
Route of Administration	Intravenous infusion
Dosage Form	Injection for intravenous infusion
Strength	100 mg/5 mL (20 mg/mL) and 400 mg/20 mL (20 mg/mL)
Dose and Frequency	<p>Pre-medication with corticosteroids, antipyretics and antihistamines to prevent delayed infusion-related reactions (IRRs)</p> <p>Recommended dose is 16 mg/kg body weight:</p> <ul style="list-style-type: none">• Weekly: Weeks 1 to 8• Every two weeks: Weeks 9 to 24• Every four weeks: Week 25 onwards until disease progression. <p>Post-infusion medication with oral corticosteroid to prevent delayed IRRs to patients the first and second day after all infusions.</p>
How Supplied	100 mg/5mL and 400 mg/20 mL Single-use glass vials
Storage	Store refrigerated at 2°C to 8°C (36°F to 46°F)

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

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

/s/

CATHY A MILLER
09/24/2015

YELENA L MASLOV
09/24/2015

REGULATORY PROJECT MANAGER PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: BLA 761036

Application Type: New BLA

Name of Drug/Dosage Form: DARZALEX (daratumumab), sterile liquid solution for infusion, 100 mg/vial and 400 mg/vial

Applicant: Janssen Biotech, Inc.

Receipt Date: July 9, 2015

Goal Date: March 9, 2016 (Priority)

1. Regulatory History and Applicant's Main Proposals

Daratumumab is a human IgG1 κ mAb that binds with high affinity to a unique epitope on CD38. It is a targeted immunotherapy that binds to tumor cells that overexpress CD38, a transmembrane glycoprotein. Plasma cells from patients with multiple myeloma express high levels of CD38. This target is distinct from those of other approved agents for multiple myeloma therapy.

On April 1, 2013, daratumumab was granted Fast Track 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.

On May 1, 2013 daratumumab was granted Breakthrough Therapy Designation for the proposed 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.

On May 8, 2013, daratumumab was granted Orphan Drug Designation.

The Applicant is seeking accelerated approval for this indication under Subpart E.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3. Conclusions/Recommendations

No SRPI format deficiencies were identified in the review of this PI.

Selected Requirements of Prescribing Information

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

- YES** 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.

Comment:

- YES** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

- YES** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment:

- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment:

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

- YES** 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required

Selected Requirements of Prescribing Information

• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a BOXED WARNING is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state “None.”)
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: “**HIGHLIGHTS OF PRESCRIBING INFORMATION**”.

Comment:

Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: “**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**” The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

- YES** 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

- N/A** 12. All text in the BW must be **bolded**.

Comment:

- N/A** 13. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and

Selected Requirements of Prescribing Information

other words to identify the subject of the warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”). The BW heading should be centered.

Comment:

- N/A** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

- N/A** 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “*See full prescribing information for complete boxed warning.*”).

Comment:

Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.

Comment:

- N/A** 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

- YES** 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment:

Dosage Forms and Strengths in Highlights

- YES** 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Selected Requirements of Prescribing Information

Contraindications in Highlights

- YES** 21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

- YES** 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement in Highlights

- YES** 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**”

Comment:

Revision Date in Highlights

- YES** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

Comment:

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

YES 25. The TOC should be in a two-column format.

Comment:

YES 26. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”. This heading should be in all UPPER CASE letters and **bolded**.

Comment:

N/A 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

YES 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

YES 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].

Comment:

YES 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

YES 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”

Comment:

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment: 8.2 and 8.3 are updated per PLLR.

- YES** 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[*see Warnings and Precautions (5.2)*]” or “[*see Warnings and Precautions (5.2)*]”.

Comment:

N/A

Selected Requirements of Prescribing Information

34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES** 35. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- N/A** 36. In the BW, all text should be **bolded**.

Comment:

- N/A** 37. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”).

Comment:

CONTRAINDICATIONS Section in the FPI

- YES** 38. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

- YES** 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

Comment:

- N/A** 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

- YES** 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and

Selected Requirements of Prescribing Information

include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

- YES** 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Selected Requirements of Prescribing Information

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]

See full prescribing information for complete boxed warning.

- [text]
- [text]

RECENT MAJOR CHANGES

[section (X.X)] [m/year]
[section (X.X)] [m/year]

INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

DOSAGE AND ADMINISTRATION

- [text]
- [text]

DOSAGE FORMS AND STRENGTHS

[text]

CONTRAINDICATIONS

- [text]
- [text]

WARNINGS AND PRECAUTIONS

- [text]
- [text]

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- [text]
- [text]

USE IN SPECIFIC POPULATIONS

- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: [SUBJECT OF WARNING]

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 [text]

2.2 [text]

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 [text]

5.2 [text]

6 ADVERSE REACTIONS

6.1 [text]

6.2 [text]

7 DRUG INTERACTIONS

7.1 [text]

7.2 [text]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Labor and Delivery

8.3 Nursing Mothers

8.4 Pediatric Use

8.5 Geriatric Use

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

14.1 [text]

14.2 [text]

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

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

/s/

JESSICA L BOEHMER
09/01/2015

PATRICIA N GARVEY
09/02/2015

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
BLA# 761036	NDA Supplement #: N/A BLA Supplement #: N/A	Efficacy Supplement Category: N/A <input type="checkbox"/> New Indication (SE1) <input type="checkbox"/> New Dosing Regimen (SE2) <input type="checkbox"/> New Route Of Administration (SE3) <input type="checkbox"/> Comparative Efficacy Claim (SE4) <input type="checkbox"/> New Patient Population (SE5) <input type="checkbox"/> Rx To OTC Switch (SE6) <input type="checkbox"/> Accelerated Approval Confirmatory Study (SE7) <input type="checkbox"/> Labeling Change With Clinical Data (SE8) <input type="checkbox"/> Manufacturing Change With Clinical Data (SE9) <input type="checkbox"/> Animal Rule Confirmatory Study (SE10)
Proprietary Name: DARZALEX (pending, under review) Established/Proper Name: daratumumab Dosage Form: sterile liquid solution for infusion Strengths: 100 mg/vial and 400 mg/vial		
Applicant: Janssen Biotech, Inc. Agent for Applicant (if applicable): Janssen Research & Development, LLC		
Date of Application: July 9, 2015 Date of Receipt: July 9, 2015 Date clock started after UN: N/A		
PDUFA Goal Date: March 9, 2016		Action Goal Date (if different): November 17, 2015
Filing Date: September 7, 2015		Date of Filing Meeting: August 14, 2015
Chemical Classification (original NDAs only) : <input type="checkbox"/> Type 1- New Molecular Entity (NME); NME and New Combination <input type="checkbox"/> Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination <input type="checkbox"/> Type 3- New Dosage Form; New Dosage Form and New Combination <input type="checkbox"/> Type 4- New Combination <input type="checkbox"/> Type 5- New Formulation or New Manufacturer <input type="checkbox"/> Type 7- Drug Already Marketed without Approved NDA <input type="checkbox"/> Type 8- Partial Rx to OTC Switch		
Proposed 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.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		N/A N/A
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499		

Type of BLA	<input checked="" type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)
<i>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</i>	
Review Classification:	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority
<i>The application will be a priority review if:</i>	
<ul style="list-style-type: none"> <i>A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)</i> <i>The product is a Qualified Infectious Disease Product (QIDP)</i> <i>A Tropical Disease Priority Review Voucher was submitted</i> <i>A Pediatric Rare Disease Priority Review Voucher was submitted</i> 	<input type="checkbox"/> Pediatric WR <input type="checkbox"/> QIDP <input type="checkbox"/> Tropical Disease Priority Review Voucher <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)
<i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	

<input checked="" type="checkbox"/> Fast Track Designation <input checked="" type="checkbox"/> Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> <input checked="" type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies (FDCA Section 505B) <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
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Collaborative Review Division (if OTC product): N/A

List referenced IND Number(s): IND 100638

Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA/BsUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are the established/proper and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<i>to the supporting IND(s) if not already entered into tracking system.</i>				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i> http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm <i>If yes, explain in comment column.</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If affected by AIP, has OC been notified of the submission? If yes, date notified:	<input type="checkbox"/>	<input type="checkbox"/>		
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		Included in June 5, 2015 rolling submission
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>	Payment for this application (<i>check daily email from UserFeeAR@fda.hhs.gov</i>): <input type="checkbox"/> Paid <input checked="" type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>	Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<u>User Fee Bundling Policy</u> <i>Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:</i> http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf	Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i> <input checked="" type="checkbox"/> N/A <input type="checkbox"/> Yes <input type="checkbox"/> No			
505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment
Is the application a 505(b)(2) NDA? (<i>Check the 356h form,</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		

cover letter, and annotated labeling). If yes , answer the bulleted questions below:							
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?				<input type="checkbox"/>	<input type="checkbox"/>		N/A
• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].				<input type="checkbox"/>	<input type="checkbox"/>		N/A
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?				<input type="checkbox"/>	<input type="checkbox"/>		N/A
<i>If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.</i>							
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?				<input type="checkbox"/>	<input type="checkbox"/>		N/A
Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm							
If yes , please list below:							
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration				
<i>If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i>							
Exclusivity	YES	NO	NA	Comment			
Does another product (same active moiety) have orphan exclusivity for the same indication? Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm	<input type="checkbox"/>	<input checked="" type="checkbox"/>					
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>				
<i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>							
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>				
If yes , # years requested:							
<i>Note: An applicant can receive exclusivity without requesting it;</i>							

<i>therefore, requesting exclusivity is not required.</i>				
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? <i>If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager</i> <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Marlene has been notified.

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?	N/A			
Overall Format/Content	YES	NO	NA	Comment
If electronic submission, does it follow the eCTD guidance? ¹ If not, explain (e.g., waiver granted).	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Index: Does the submission contain an accurate comprehensive index?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		Is coded in DARRTS with "Form 3674"
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				

<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i> <i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Signed by Janssen Research & Development, LLC
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i> <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? <i>If yes, date consult sent to the Controlled Substance Staff:</i> <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff :</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		Orphan Designation

2

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829.htm>

Version: 7/10/2015

7

<i>forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>				
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)? <i>If no, may be an RTF issue - contact DPMH for advice.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? <i>If no, may be an RTF issue - contact DPMH for advice.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<u>BPCA:</u> Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input checked="" type="checkbox"/> Other : Patient Education Materials			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the PI submitted in PLR format? ⁴	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

3

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837.htm>

4

<p>If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted, what is the status of the request?</p> <p><i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<p>For applications submitted on or after June 30, 2015: Is the PI submitted in PLLR format?⁵</p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<p>Has a review of the available pregnancy and lactation data been included?</p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	From the PI: There are no human or animal data informing the risk of daratumumab use in pregnancy. It is not known whether daratumumab is excreted into human or animal milk or affects milk production. There are no studies to assess the effect of daratumumab on the breast-fed infant.
<p>For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format, was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted, what is the status of the request?</p> <p><i>If no waiver or deferral, request applicant to submit labeling in PLR/PLLR format before the filing date.</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<p>All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?</p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Consult will be completed by day 60
<p>MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)</p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	DRISK reviewer assigned to the application review team
<p>Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?</p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

Check all types of labeling submitted.	<input type="checkbox"/>									
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ATTACHMENT

MEMO OF FILING MEETING

DATE: August 14, 2015

BACKGROUND: Daratumumab is a human IgG1k mAb that binds with high affinity to a unique epitope on CD38. It is a targeted immunotherapy that binds to tumor cells that overexpress CD38, a transmembrane glycoprotein. Plasma cells from patients with multiple myeloma express high levels of CD38. This target is distinct from those of other approved agents for multiple myeloma therapy.

On April 1, 2013, daratumumab was granted Fast Track 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.

On May 1, 2013, daratumumab was granted Breakthrough Therapy Designation for the proposed 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.

On May 8, 2013, daratumumab was granted Orphan Drug Designation.

The Applicant is seeking accelerated approval for this indication under Subpart E.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Jessica Boehmer	Y
	CPMS/TL:	Theresa Carioti	N
		Amy Baird	Y
		Mara Miller	Y
	Patty Garvey	N	
Cross-Discipline Team Leader (CDTL)	Albert Deisseroth		Y
Division Director/Deputy	Ann Farrell, Director, DHP		Y
	Edvardas Kaminskas, Deputy Director, DHP		N
Office Director/Deputy	Richard Pazdur, Director, OHOP		Y
	Paul Kleutz, Acting Deputy Director, OHOP		Y
Clinical	Reviewer:	Barry Miller	Y
	TL:	Albert Deisseroth	Y

Clinical Pharmacology	Reviewer:	Jeanne Fourie Zirkelbach	Y
	TL:	Bahru Habtemariam	Y
• Genomics	Reviewer:	TBD (not yet determined if needed)	N/A
• Pharmacometrics	Reviewer:	Lian Ma	Y
Biostatistics	Reviewer:	Yaping Wang	Y
	TL:	Yuan-Li Shen	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Emily Place	N
	TL:	Chris Sheth	Y
Product Quality (CMC) Review Team:	ATL:	Jee Chung	Y
	RBPM:	Anita Brown	Y
• Drug Substance	Reviewer:	Maria Jose Lopez-Barragan	Y
• Drug Product	Reviewer:	Natalia Pripuzova	Y
• Process	Reviewer:	Tura Camilli	Y
• Microbiology	Reviewer:	N/A	N/A
• Facility	Reviewer:	Laura Fontan	N
• Biopharmaceutics	Reviewer:	N/A	N/A
• Immunogenicity	Reviewer:	N/A (incl. in CMC review)	N/A
• Labeling (BLAs only)	Reviewer:	Jibril Abdus-Samad	Y
• Other (e.g., Branch Chiefs, EA Reviewer)		Sarah Kennett, Review Chief, OBP	Y
		Patricia Hughes, Micro TL	Y
OMP/OMPI/DMPP (Patient labeling: MG, PPI, IFU)	Reviewer:	TBD	N/A
	TL:	TBD	N/A
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labels)	Reviewer:	Nisha Patel	Y
OSE/DMEPA (proprietary name, carton/container labels)	Reviewer:	Michelle Rutledge Cathy Miller (labeling)	Y Y
	TL:	Yelena Maslov	N
OSE/DRISK (REMS)	Reviewer:	Joyce Weaver	N
	TL:	Naomi Redd	Y
Bioresearch Monitoring (OSI)	Reviewer:	Anthony Orenca	Y
	TL:	Janice Pohlman	N

Other reviewers/disciplines			
OSE/DPV	Reviewer:	Shaily Arora	Y
	TL:	Tracy Salaam	Y
Other attendees	Peter Waldron, Medical Officer, DPV		Y
	Robert Schuck, Pharmacologist, OCP		Y

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> • 505(b)(2) filing issues: <ul style="list-style-type: none"> ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):</p> 	<input checked="" type="checkbox"/> Not Applicable
<ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Electronic Submission comments <p>List comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> No comments
<p>CLINICAL</p> <p>Comments: Clinical and Stats will do a combined review for this application.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA, include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input type="text"/> <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason: During review of the application for filing, no significant safety or efficacy issues were identified that warrant a meeting of the Oncologic Drug Advisory Committee.
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable
<p>CONTROLLED SUBSTANCE STAFF</p> <ul style="list-style-type: none"> Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable
<p>CLINICAL PHARMACOLOGY</p> <p>Comments: Genomics reviewer may be needed, decision is pending</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments: Clinical and Stats will do a combined review for this application.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>PRODUCT QUALITY (CMC)</p> <p>Comments: The DP Reviewer has review issues for inclusion in the filing letter</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input checked="" type="checkbox"/> Review issues for 74-day letter</p>
<p><u>New Molecular Entity (NDAs only)</u></p> <ul style="list-style-type: none"> Is the product an NME? 	<p><input checked="" type="checkbox"/> Not Applicable</p>
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p>N/A</p>
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> Establishment(s) ready for inspection? <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>CMC Labeling Review (BLAs only)</u></p> <p>Comments: No issues</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>

<p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> • Were there agreements made at the application’s pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days? 	<p><input type="checkbox"/> N/A</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> • What late submission components, if any, arrived after 30 days? 	<p>CMC Stability Data</p>
<ul style="list-style-type: none"> • Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Richard Pazdur, MD, Director, OHOP

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V):
September 16, 2015

21st Century Review Milestones (see attached):

REGULATORY CONCLUSIONS/DEFICIENCIES

<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing.

	<p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter.</p> <p><u>Review Classification:</u></p> <p><input type="checkbox"/> Standard Review <input checked="" type="checkbox"/> Priority Review</p>
ACTION ITEMS	
<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
<input type="checkbox"/>	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input checked="" type="checkbox"/>	If priority review, notify applicant in writing by day 60 (see CST for choices)
<input type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for applications in the Program)
<input type="checkbox"/>	Other

Annual review of template by OND ADRA's completed: September 2014

TASK	21ST CENTURY REVIEW TIMELINE
Applicant Orientation	July 31, 2015
Filing Meeting	August 14, 2015
Filing Date (Day 60)- Communicate review issues Day 74	September 7, 2015 September 21, 2015
Mid-cycle Meeting Mid-cycle Communication Pre-Meeting for LCM LCM Briefing Doc Due Late-cycle Meeting	September 16, 2015 September 24, 2015 October 6, 2015 October 7, 2015 (due 12 days before LCM) October 19, 2015
Labeling Meetings	September 21, 2015 October 9, 2015 October 16, 2015 October 30, 2015
Primary Reviews Completed	October 18, 2015
Secondary Reviews	October 22, 2015
Send proposed Labeling/PMC/PMR/REMS	October 25, 2015
Complete Cross Discipline TL Review	October 25, 2015
Wrap-up Meeting	November 4, 2015
Compile and Circulate action letter and action package	October 25, 2015
Complete Office Director Review and Sign-off PDUFA Goal Date	March 9, 2015; Planned Action Date=November 17, 2015

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

/s/

JESSICA L BOEHMER
09/02/2015

PATRICIA N GARVEY
09/02/2015