PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

| NDA/BLA # | BLA 761036 |
|--------------------------------------------------|
| Product Name: | Darzalex (daratumumab) |
| PMR/PMC Description: | Conduct a study to validate an assay for binding antibodies to daratumumab to assess the product’s potential for immunogenic reactions in treated patients. Submit a validation report for the validated, sensitive, and accurate assay for the detection of binding antibodies to daratumumab, including procedures for the accurate detection of binding antibodies to daratumumab in the presence of daratumumab levels expected in the serum or plasma at the time of patient sampling. |
| PMR-4: | |
| PMR/PMC Schedule Milestones: | Final Report Submission: 11/2018 |

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

- [ ] Unmet need
- [ ] Life-threatening condition
- [ ] Long-term data needed
- [ ] Only feasible to conduct post-approval
- [x] Prior clinical experience indicates safety
- [ ] Small subpopulation affected
- [ ] Theoretical concern
- [ ] Other

Limited data were provided to demonstrate the anti-drug antibody assay was capable of detecting antibodies against daratumumab at levels of drug expected to be present in serum samples at the time of collection. Given that the overall safety profile observed in the clinical studies was considered as part of the initial determination regarding approvability, the presence of anti-drug antibodies can be considered post-approval in the context of evaluating safety for a subset of patients.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”
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
  - [x] 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?
  - [x] 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

  - [x] 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)
PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

<table>
<thead>
<tr>
<th>NDA/BLA #</th>
<th>BLA 761036</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product Name:</td>
<td>Darzalex (daratumumab)</td>
</tr>
<tr>
<td>PMR/PMC Description:</td>
<td>Conduct a study to validate an assay for neutralizing antibodies to daratumumab to assess the potential for increased adverse outcome from loss of product effect in treated patients. Submit a validation report for the validated, sensitive, and accurate assay for the detection of neutralizing antibodies to daratumumab, including procedures for the accurate detection of neutralizing antibodies to daratumumab in the presence of daratumumab levels that are expected in the serum or plasma at the time of patient sampling.</td>
</tr>
<tr>
<td>PMR/PMC Schedule Milestones:</td>
<td>Final Report Submission: 12/2015</td>
</tr>
</tbody>
</table>

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

- [ ] Unmet need
- [ ] Life-threatening condition
- [ ] Long-term data needed
- [ ] Only feasible to conduct post-approval
- [x] Prior clinical experience indicates safety
- [ ] Small subpopulation affected
- [ ] Theoretical concern
- [ ] Other

Validation of an assay capable of detecting neutralizing antibodies against daratumumab was not included in the submission. Given that the overall safety profile observed in the clinical studies was considered as part of the initial determination regarding approvability, the presence of neutralizing antibodies can be considered post-approval in the context of evaluating safety for a subset of patients.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”
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
     - [x] 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?
     - [x] 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
     - [x] 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)

☐ 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.

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(signature line for BLAs)
PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review 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

<table>
<thead>
<tr>
<th>NDA/BLA #</th>
<th>BLA 761036</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product Name:</td>
<td>Darzalex (daratumumab)</td>
</tr>
<tr>
<td>PMC-7:</td>
<td>Perform a shipping study to confirm validation of the commercial daratumumab drug product shipping conditions. The study will include monitoring of temperature during the shipment, testing of pre- and post-shipping samples for product quality (purity by SEC, cSDS reduced and non-reduced, cIEF, sub-visible particles, and potency of daratumumab), and confirmation that the commercial shipping configuration minimizes physical damage to drug product containers.</td>
</tr>
</tbody>
</table>

PMC Schedule Milestones: Final Report Submission: 08/2016

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

   Data provided in the BLA were from a simulated transport study. The additional studies provide assurance of the safety and quality of the product when the drug product is shipped in the commercial shipping configuration.

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

   Shipping validation studies did not evaluate the impact to drug product under the final commercial shipping conditions. This study will provide validation of the commercial packaging and shipping configuration, including a direct assessment of product quality parameters pre- and post-shipment.

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:

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.

____________________________

(signature line for BLAs only)
This template should be completed by the review 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 #: BLA 761036
Product Name: Darzalex (daratumumab)

PMC - 8:
Provide quantitative extractables study data and a toxicological risk assessment for all compounds extracted from the and drug substance long term storage containers.

PMC Schedule Milestones: Final Report Submission: 03/2016

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

   The containers used for long term storage of the and drug substance are manufactured using standard materials and are generally appropriate for this use. However, limited data were provided regarding the extractables study performed to evaluate the containers; the evaluation of the data did not take into account the complete set of materials that were extracted, and a toxicological risk assessment for extracted compounds was not performed. The additional study results and risk assessment will provide assurance of the safety of the product that had long term contact with these containers.

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

   The evaluation of the study data will allow for the identification of all compounds that were extracted from the and drug substance long term storage containers under the conditions that were tested and for a risk assessment to be provided to confirm the lack of impact of the identified compounds to safety.

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:

Quantitative extractables study data and a toxicological risk assessment for all compounds extracted from the 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:

☒ 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)
PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review 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.

<table>
<thead>
<tr>
<th>NDA/BLA #</th>
<th>BLA 761036</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product Name:</td>
<td>Darzalex (daratumumab)</td>
</tr>
<tr>
<td>PMC-9:</td>
<td>Re-evaluate lot release and stability data after at least 30 lots have been manufactured using the commercial manufacturing process. Submit the corresponding data, the analytical and statistical plan used to evaluate the specifications, and any proposed changes to the specifications.</td>
</tr>
</tbody>
</table>

PMC Schedule Milestones:
- Study/Trial Completion: 07/2016
- Final Report Submission: 09/2016

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)
   - [x] Long-term data needed (e.g., stability data)
   - [ ] Only feasible to conduct post-approval
   - [ ] Improvements to methods
   - [ ] Theoretical concern
   - [ ] Manufacturing process analysis
   - [ ] Other

   The lot release and shelf-life specifications approved under BLA are sufficient to ensure adequate quality and safety of daratumumab for the initial marketed product. Additional manufacturing and testing experience gained post licensure can facilitate improved specifications.

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

   The lot release and shelf-life specifications are based on clinical and manufacturing experience provided in the BLA and assessed during the BLA review; however, some new methods were implemented during development, and the number of lots to date do not allow for a robust analysis of the data. Some specifications have a statistical component that should be reassessed when a sufficient number of marketed product lots have been released.

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:

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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(signature line for BLAs only)
PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the 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.

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<th>BLA 761036</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product Name:</td>
<td>Darzalex (daratumumab)</td>
</tr>
</tbody>
</table>

PMR/PMC Development Template: Product Quality (CMC)

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

PMC Schedule Milestones:

<table>
<thead>
<tr>
<th>Study/Trial Completion:</th>
<th>07/2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>Final Report Submission:</td>
<td>09/2016</td>
</tr>
</tbody>
</table>

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)
- [x] Long-term data needed (e.g., stability data)
- [ ] Only feasible to conduct post-approval
- [ ] Improvements to methods
- [ ] Theoretical concern
- [ ] Manufacturing process analysis
- [ ] Other

The drug substance lot release and shelf-life specifications approved under BLA are sufficient to ensure adequate quality and safety of daratumumab for the initial marketed product. Additional manufacturing and testing experience gained post licensure can facilitate improved specifications.

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

The drug substance lot release and shelf-life specifications are based on clinical and manufacturing experience provided in the BLA and assessed during the BLA review; however, some new methods were implemented during development, and the number of lots to date do not allow for a robust analysis of the data. Some specifications have a statistical component that should be reassessed when a sufficient number of marketed product lots have been released.

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:

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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(signature line for BLAs only)
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

<table>
<thead>
<tr>
<th>NDA/BLA #</th>
<th>BLA 761036</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product Name:</td>
<td>Darzalex (daratumumab)</td>
</tr>
<tr>
<td>PMC-11:</td>
<td>Re-evaluate daratumumab drug product lot release and stability data after at least 30 lots have been manufactured using the commercial manufacturing process. Submit the corresponding data, the analytical and statistical plan used to evaluate the specifications, and any proposed changes to the specifications.</td>
</tr>
</tbody>
</table>

PMC Schedule Milestones: Study/Trial Completion: 07/2016  
Final Report Submission: 09/2016

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)
- [X] Long-term data needed (e.g., stability data)
- [ ] Only feasible to conduct post-approval
- [ ] Improvements to methods
- [ ] Theoretical concern
- [ ] Manufacturing process analysis
- [ ] Other

The drug product lot release and shelf-life specifications approved under BLA are sufficient to ensure adequate quality and safety of daratumumab for the initial marketed product. Additional manufacturing and testing experience gained post licensure can facilitate improved specifications.

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

The drug product lot release and shelf-life specifications are based on clinical and manufacturing experience provided in the BLA and assessed during the BLA review; however, some new methods were implemented during development, and the number of lots to date do not allow for a robust analysis of the data. Some specifications have a statistical component that should be reassessed when a sufficient number of marketed product lots have been released.

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:

| 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)
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
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 [stabilization or storage conditions] 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 [storage or transportation conditions] hours. In addition, the [stabilization or storage conditions] therefore, the risk of unacceptable bioburden levels 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 [surrogate or control agent] as a surrogate to demonstrate microbial control of daratumumab [product information]. However, the [control agent or surrogate] 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 [information]. The goal of the study is to demonstrate the suitability of the [control agent or surrogate] as a surrogate for daratumumab product [information].

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:

The agreed-upon study will consist of a comparison at small scale of the microbial growth promoting properties of the surrogate and the daratumumab .

In the event that the shows worse growth promoting properties than the , a second study should be conducted to demonstrate microbial control of the proposed by the applicant.

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

/s/

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JESSICA L BOEHMER
11/16/2015

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PATRICIA F HUGHES TROOST
11/16/2015

Reference ID: 3847309
PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

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

PMR/PMC Description:
Conduct the analysis and submit the complete final report and data showing clinical efficacy and safety from Trial MMY3003, a “Phase 3, 2-arm, Randomized, Parallel-group Trial of Lenalidomide and Dexamethasone with or without Daratumumab in Patients with Previously- treated Multiple Myeloma.”

PMR/PMC Schedule Milestones:
- Trial Completion (primary endpoint): 04/2017
- Final Report Submission: 07/2017

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

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Relapsed multiple myeloma is a life-threatening and incurable malignancy. Survival for patients with multiple myeloma who have been treated with multiple agents is generally less than one year. New treatments are needed.

In the single arm, single agent trials reviewed in the BLA, response rates were approximately 30% with several patients demonstrating clearance of disease from their bone marrow. Response lasted a median of about 6 months. These results are comparable with single and combination responses observed in trials of other approved agents in multiple myeloma.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

FDA has previously accepted response rate supported by duration of response from single arm trials as a basis for accelerated approval. The goal of the PMR is to obtain long term efficacy outcomes including progression free survival and long term safety from a randomized controlled clinical trial. Time to event endpoints cannot be adequately interpreted in single arm clinical trials due to confounding effects of the natural history of the disease.
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

Reference ID: 3847184
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.

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(signature line for BLAs)
PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

<table>
<thead>
<tr>
<th>NDA/BLA #</th>
<th>BLA 761036</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product Name:</td>
<td>Darzalex (daratumumab)</td>
</tr>
</tbody>
</table>

**PMR/PMC Description:**
Conduct the analysis and submit the complete final report and data showing clinical efficacy and safety from Trial MMY3004, a “Phase 3, 2-arm, Randomized, Parallel-group Trial of Bortezomib and Dexamethasone with or without Daratumumab in Patients with Previously- treated Multiple Myeloma.”

**PMR/PMC Schedule Milestones:**
- Trial Completion (primary endpoint): 02/2017
- Final Report Submission: 05/2017

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.
   - ☒ Unmet need
   - ☒ Life-threatening condition
   - ☑ Long-term data needed
   - ☐ Only feasible to conduct post-approval
   - ☐ Prior clinical experience indicates safety
   - ☐ Small subpopulation affected
   - ☐ Theoretical concern
   - ☐ Other

   Relapsed multiple myeloma is a life-threatening and incurable malignancy. Survival for patients with multiple myeloma who have been treated with multiple agents is generally less than one year. New treatments are needed. In the single arm, single agent trials reviewed in the BLA, response rates were approximately 30% with several patients demonstrating clearance of disease from their bone marrow. Response lasted a median of about 6 months. These results are comparable with single and combination responses observed in trials of other approved agents in multiple myeloma.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

   FDA has previously accepted response rate supported by duration of response from single arm trials as a basis for accelerated approval. The goal of the PMR is to obtain long term efficacy outcomes including progression free survival and long term safety from a randomized controlled clinical trial. Time to event endpoints cannot be adequately interpreted in single arm clinical trials due to confounding effects of the natural history of the disease.
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 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)
   - [ ] 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.

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PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

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

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

PMR/PMC Schedule Milestones: Final Report Submission: 11/2018

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

☐ Unmet need
☐ Life-threatening condition
☐ Long-term data needed
☐ Only feasible to conduct post-approval
☐ Prior clinical experience indicates safety
☐ Small subpopulation affected
☒ Theoretical concern
☐ Other

Immunogenicity related adverse events, such as extended neutropenia or loss of efficacy were not observed in the daratumumab trials. In the absence of safety or loss-of-efficacy signals that could be attributed to anti-drug antibodies it is acceptable to address the lack of immunogenicity data post-marketing. It is critical that this data be obtained to more fully understand the safety profile of the agent. In addition these assays should be available in the post-marketing environment to allow for the rapid evaluation of serum samples from patients with adverse events that might be attributable to the presence of anti-drug antibodies.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Limited data were provided to demonstrate that the anti-drug antibody assay was capable of detecting antibodies against daratumumab at levels of drug expected to be present in serum samples at the time of collection. The study can only be conducted after an assay is validated to appropriately detect anti-drug antibodies.
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.

   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)
   - □ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
   - □ Pharmacokinetic studies or clinical trials
   - □ Drug interaction or bioavailability studies or clinical trials

Reference ID: 3847184
☐ 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)
☐ 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)
PMR/PMC Development Template Version 2

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

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

PMR/PMC Description: Collect, analyze, and submit additional safety data from ongoing clinical trials to characterize the safety of daratumumab in patients with baseline hepatic impairment.

PMR/PMC Schedule Milestones: Study/Trial Completion: 04/2017
Final Report Submission: 07/2017

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

☐ Unmet need
☐ Life-threatening condition
☐ Long-term data needed
☐ Only feasible to conduct post-approval
☒ Prior clinical experience indicates safety
☐ Small subpopulation affected
☐ Theoretical concern
☐ Other

Use sufficient additional clinical data from ongoing clinical trials to characterize the daratumumab safety profile in patients with baseline hepatic impairment. This is needed because preliminary data indicated a numerically higher incidence of treatment emergent adverse events in patients with hepatic impairment.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Although the preliminary clinical safety data suggested higher incidence of treatment emergent adverse events in patients with hepatic impairment, the available data is insufficient to characterize an adequate safety profile in this patient population. Additional data from patients with baseline hepatic impairment, being enrolled in current clinical trials, will be collected and used to characterize the safety profile of daratumumab in patients with hepatic impairment. The needed more extensive safety data will be used in order to determine:

1) Appropriate package insert labeling language
2) The need for additional safety evaluations in patients with more severe degrees of hepatic impairment (moderate and severe hepatic impairment)
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
     - [x] 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?
     - [x] 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
     - [x] 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
Additional data or analysis required for a previously submitted or expected study/clinical trial
(please 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 (please 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.

_______________________________________

(signature line for BLAs)
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
11/14/2015

DIANE V LEAMAN
11/16/2015
for Ann Farrell, MD
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 (IgG1κ) monoclonal antibody that binds to the cell surface molecule CD38. CD38 is a cell surface glycoprotein that has enzymatic activity as well as receptor functions. 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 bone. 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) days.

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 annually. 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 phase. Progress has been made over the last

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 1998 to 6 to 10 years today, with a 5 year survival rate of 46.6%.

Treatment options for the disease continuum are broadly summarized below.

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 40. 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 relapse. 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 proliferation. 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), fertility may be preserved, and

ovarian function may recover, in selected patients, even those receiving more than one autologous stem cell transplant (ASCT)\textsuperscript{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)\textsuperscript{13}.

Based on review of case series describing management of patients with multiple myeloma during pregnancy\textsuperscript{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 literature\textsuperscript{15} (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,”\textsuperscript{16} also known as the

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\textsuperscript{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.

\textsuperscript{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 Rule\textsuperscript{17} 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 details\textsuperscript{2}.

The nonclinical team has communicated the following information request to the applicant\textsuperscript{18}:

“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 \textit{29}th \textit{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:

\textsuperscript{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).
\textsuperscript{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).
\textsuperscript{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), CD38 expression varies significantly with age and during pregnancy. 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 infants. 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 alone. 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. 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

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Reference ID: 3843003
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) 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) L, 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 tract.

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 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 3 months after cessation of daratumumab treatment. DPMH agrees with this statement, given the potential for myeloid and lymphoid cell depletion.

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23 The 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

The applicant also includes a statement that DPMH recommends deleting this statement, since actual daratumumab are unknown and the sponsor did not provide any data to support this statement.

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,” subsections.

- **Lactation, Section 8.2**
  - The “Lactation” subsection of daratumumab labeling was formatted in the PLLR format to include the “Risk Summary” subsection.

- **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 toxicity.

- **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.

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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 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.

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 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

Reference ID: 3843003
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**

<table>
<thead>
<tr>
<th><strong>BLA Number</strong></th>
<th>761036</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Supporting Document Number</strong></td>
<td>New BLA (1)</td>
</tr>
<tr>
<td><strong>Proprietary Name</strong></td>
<td>Darzalex</td>
</tr>
<tr>
<td><em>(nonproprietary name)</em></td>
<td>Daratumumab</td>
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<tr>
<td><strong>Receipt Date</strong></td>
<td>06/05/2015</td>
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<tr>
<td><strong>PDUFA Goal Date</strong></td>
<td>02/05/2016 (8 mos.)</td>
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<tr>
<td><em>(Internal Goal Date)</em></td>
<td>11/17/2015 (5 mos)</td>
</tr>
<tr>
<td><strong>Review Classification</strong></td>
<td>Priority (expedited)</td>
</tr>
<tr>
<td><strong>Proposed Indication (or current indication if unchanged)</strong></td>
<td>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.</td>
</tr>
<tr>
<td><strong>Dosing Regimen</strong></td>
<td>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.</td>
</tr>
<tr>
<td><strong>From</strong></td>
<td>Virginia Kwitkowski, MS, ACNP-BC</td>
</tr>
<tr>
<td><em>(Associate Director for Labeling, DHP)</em></td>
<td></td>
</tr>
</tbody>
</table>

**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 IMiD.

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.
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/s/

VIRGINIA E KWITKOWSKI
11/04/2015
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)

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

BARBARA A FULLER
10/28/2015

LASHAWN M GRIFFITHS
10/28/2015
FINAL LABEL AND LABELING REVIEW

Date: October 27 2015

Reviewer: Jibril Abdus-Samad, PharmD, Labeling Reviewer
Office of Biotechnology Products
Jibril Abdus-Samad  
S

Through: Tura Camilli, PhD, Quality Reviewer
Division of Biotechnology Review and Research I
Tura C. Camilli -S

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).

<table>
<thead>
<tr>
<th>Proprietary Name:</th>
<th>Darzalex™</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proper Name:</td>
<td>daratumumab</td>
</tr>
<tr>
<td>Indication:</td>
<td>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</td>
</tr>
<tr>
<td>Dose:</td>
<td>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)</td>
</tr>
<tr>
<td>Route of Administration:</td>
<td>Intravenous infusion</td>
</tr>
<tr>
<td>Dosage Form:</td>
<td>Injection</td>
</tr>
<tr>
<td>Strength and Container-Closure:</td>
<td>100 mg/5 mL or 400 mg/20 mL in single-dose vials</td>
</tr>
<tr>
<td>Storage and Handling:</td>
<td>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.</td>
</tr>
</tbody>
</table>

Materials Reviewed:
Container Labels
Carton Labeling
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. 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. 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.

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 "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.

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
Carton labeling, 400 mg/20 mL

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 biologics; *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 ‘Market 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 "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

*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] of the vials to comply with USP General Chapters: <7> Labeling, Labels and Labeling for Injectable Products, [redacted] [redacted].

**B. Carton Labeling**
1. Add the dosage form to the diluent “[redacted]” to read “0.9% Sodium Chloride Injection, USP”.
2. Delete [redacted] that appears on the side panel. This product will be used only in clinical settings.

**Discussion of Applicant’s Proposals**
[Redacted]
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).
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.

<table>
<thead>
<tr>
<th>Section</th>
<th>Statement from draft</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highlights, Indications</td>
<td>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.</td>
<td>In draft promotional materials, the sponsor is currently positioning DARZALEX... If this is a concern, please consider revising the Indications and Usage section.</td>
</tr>
<tr>
<td>and Usage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indications and Usage</td>
<td>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 double-refractory to a PI and an immunomodulatory agent.</td>
<td></td>
</tr>
<tr>
<td>Section</td>
<td>Statement from draft</td>
<td>Comment</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>2 Dosage and Administration</td>
<td>Consider incremental escalation of the infusion rate only if the previous infusion of DARZALEX as defined in Table 2.</td>
<td>The bolded term is promotional in tone and could be used to minimize the risks of Darzalex. Please consider revising or deleting this term.</td>
</tr>
<tr>
<td></td>
<td>* Escalate only if no Grade 1 (mild) or greater infusion reactions during the first 3 hours.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>* Escalate only if no Grade 1 (mild) or greater infusion reactions during a final infusion rate of ≥100 mL/hr.</td>
<td></td>
</tr>
<tr>
<td>12 Clinical Pharmacology</td>
<td>Daratumumab is an IgG1k human monoclonal antibody (mAb) that binds to the CD38</td>
<td>Is the bolded language needed? It could be used promotionally to imply efficacy in various hematological malignancies beyond multiple myeloma.</td>
</tr>
<tr>
<td>12 Clinical Pharmacology</td>
<td>NK cells express CD38 and are susceptible to daratumumab mediated cell lysis. Decreases in absolute counts and percentages of total NK cells (CD16+CD56+) and activated (CD16+CD56dim) NK cells in peripheral whole blood and bone marrow were observed with DARZALEX treatment.</td>
<td>Are the bolded terms and statements needed? They could be used promotionally to overstate the efficacy of Darzalex.</td>
</tr>
<tr>
<td></td>
<td>T cells (CD3+, CD4+, and CD8+) are also known to express CD38 depending on the stage of development and the level of activation.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>T cell absolute counts, percentages of lymphocytes, with DARZALEX treatment peripheral blood and bone marrow.</td>
<td></td>
</tr>
<tr>
<td>Section</td>
<td>Statement from draft</td>
<td>Comment</td>
</tr>
<tr>
<td>--------------------------</td>
<td>--------------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>12 Clinical Pharmacology</td>
<td>DARZALEX as a large protein has a low likelihood of direct ion channel interactions</td>
<td>Is Darzalex a “large” 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 than it is.</td>
</tr>
<tr>
<td>14 Clinical Studies</td>
<td>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 VGPR. The median time to response was 1 month (range: 0.5 to 3.2 months). The median duration of response was not</td>
<td>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.</td>
</tr>
</tbody>
</table>
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

NISHA PATEL
10/21/2015
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 ΔQTcF 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 × 7 weeks; 16 mg/kg every 2 weeks × 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, [redacted], 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)

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

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)

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


Part 2

ECGs were performed according to the schedule described in the following table.
Table 3: ECG Collection Schedule (Part 2)

<table>
<thead>
<tr>
<th>Visit ID in CRF</th>
<th>Visit ID in EG SDTM Dataset</th>
<th>ECGs Collected Cohorts A, B, C</th>
<th>ECGs Collected Cohorts D, E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening</td>
<td>Visit 0</td>
<td>Triplet ECGs</td>
<td>Triplet ECGs</td>
</tr>
<tr>
<td>Visit 1</td>
<td>Visit 1 (Schedules A &amp; B)</td>
<td>Single ECG before and after infusion</td>
<td></td>
</tr>
<tr>
<td>Visit 2</td>
<td>Visit 2</td>
<td>Triplet ECGs before and after infusion</td>
<td>Triplet ECGs before and after infusion</td>
</tr>
<tr>
<td>Visit 3/Visit 4</td>
<td>Visit 3-4</td>
<td>Single ECG before and after infusion</td>
<td></td>
</tr>
<tr>
<td>Visit 5</td>
<td>Visit 5</td>
<td>Triplet ECGs before and after infusion</td>
<td></td>
</tr>
<tr>
<td>Visit 6</td>
<td>Visit 6</td>
<td>Single ECG before and after infusion</td>
<td></td>
</tr>
<tr>
<td>Visit 7</td>
<td>Visit 7</td>
<td>Single ECG before and after infusion</td>
<td>Triplet ECGs before and after infusion</td>
</tr>
<tr>
<td>Visit 8-21</td>
<td>Visit 8-21</td>
<td>Single ECG before and after infusion</td>
<td></td>
</tr>
<tr>
<td>End of Study</td>
<td>End of Trial</td>
<td>Single ECG</td>
<td>Single ECG</td>
</tr>
</tbody>
</table>

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)

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

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 $T_{\text{max}}$ 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)

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

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)

<table>
<thead>
<tr>
<th>Source</th>
<th>GEN501 clinical study report page 1055.</th>
</tr>
</thead>
</table>

**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.

<table>
<thead>
<tr>
<th>Subject ID</th>
<th>Age/Sex</th>
<th>Treatment Group</th>
<th>Cardiac-Related Medical History</th>
<th>Concomitant Medication</th>
<th>Study Day of TEAE</th>
<th>Serious/Toxicity Grade</th>
<th>Action Taken With Study Drug</th>
<th>Baseline QTc (ms)</th>
<th>Maximum QTc (ms)</th>
<th>Change from Baseline (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>501003</td>
<td>76/M</td>
<td>0.1 mg/kg</td>
<td>History of atrial fibrillation, baseline ECG showed left side anterior fascicular block</td>
<td>Gliclazide, zopiclone</td>
<td>23</td>
<td>N/1*</td>
<td>None</td>
<td>QTcF: 391-418</td>
<td>QTcF: 461</td>
<td>&lt;60</td>
</tr>
<tr>
<td>501006</td>
<td>65/M</td>
<td>0.1 mg/kg</td>
<td>Baseline ECG showed right bundle branch block</td>
<td>Acetylsalicylic acid</td>
<td>31</td>
<td>N/3*</td>
<td>None</td>
<td>QTcF: 430-453</td>
<td>QTcF: 502</td>
<td>&lt;60</td>
</tr>
<tr>
<td>501009</td>
<td>69/M</td>
<td>0.5 mg/kg</td>
<td>None reported</td>
<td>Methylprednisolone</td>
<td>21</td>
<td>N/2*</td>
<td>None</td>
<td>QTcF: 423-425</td>
<td>QTcF: 455</td>
<td>&lt;30</td>
</tr>
<tr>
<td>501012</td>
<td>61/F</td>
<td>1.0 mg/kg</td>
<td>Hypertension</td>
<td>Acetylsalicylic acid, amitriptyline, anolodipine, ciprofloxacin, fentanyl, gabapentin, pancreonate disodium, pantoprazole, potassium chloride, hypomelasure</td>
<td>22</td>
<td>N/1*</td>
<td>None</td>
<td>QTcF: 440</td>
<td>QTcF: 470</td>
<td>&lt;60</td>
</tr>
<tr>
<td>501014</td>
<td>44/F</td>
<td>1.0 mg/kg</td>
<td>Hypertension, myasthenia</td>
<td>Acyclovir, gabapentin, levotyrosine sodium, omeprazole, esycodone hydrochloride, pancreonate disodium, panaxanax, bendroflumethasulizde, zoledron, vitamin NOS, olizum, magnesium chloride</td>
<td>22</td>
<td>N/2*</td>
<td>Drug interrupted</td>
<td>QTcB: 440</td>
<td>QTcB: 483</td>
<td>&lt;60</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>31</td>
<td>N/2*</td>
<td>None</td>
<td>QTcB: 440</td>
<td>QTcB: 483</td>
<td>&lt;60</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>32</td>
<td>N/1*</td>
<td>None</td>
<td>QTcB: 440</td>
<td>QTcB: 483</td>
<td>&lt;60</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>38</td>
<td>N/2*</td>
<td>None</td>
<td>QTcB: 440</td>
<td>QTcB: 483</td>
<td>&lt;60</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>45</td>
<td>N/2*</td>
<td>None</td>
<td>QTcB: 440</td>
<td>QTcB: 483</td>
<td>&lt;60</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>52</td>
<td>N/2*</td>
<td>None</td>
<td>QTcB: 440</td>
<td>QTcB: 483</td>
<td>&lt;60</td>
</tr>
</tbody>
</table>

Relationship to study drug according to investigator:

*Possible/probable

*Not related

*Adverse event outcome

*Resolved

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)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>0.1 mg/kg</th>
<th>0.5 mg/kg</th>
<th>1 mg/kg</th>
<th>2 mg/kg</th>
<th>4 mg/kg</th>
<th>8 mg/kg</th>
<th>16 mg/kg</th>
<th>24 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 6</td>
<td>N = 3</td>
<td>N = 6</td>
<td>N = 3</td>
<td>N = 3</td>
<td>N = 3</td>
<td>N = 3</td>
<td>N = 3</td>
</tr>
<tr>
<td><strong>Cmax (µg/mL)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>0.297</td>
<td>0.621</td>
<td>0.862</td>
<td>1.373</td>
<td>1.585</td>
<td>2.139</td>
<td>2.412</td>
<td>3.000</td>
</tr>
<tr>
<td>SD</td>
<td>0.125</td>
<td>0.406</td>
<td>0.582</td>
<td>1.097</td>
<td>1.375</td>
<td>1.956</td>
<td>2.229</td>
<td>2.752</td>
</tr>
<tr>
<td><strong>CV (%)</strong></td>
<td>91.7</td>
<td>78.7</td>
<td>78.9</td>
<td>58.2</td>
<td>47.3</td>
<td>37.5</td>
<td>31.9</td>
<td>27.0</td>
</tr>
<tr>
<td><strong>Tmax (h)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>5.83</td>
<td>4.03</td>
<td>6.07</td>
<td>8.04</td>
<td>7.88</td>
<td>9.55</td>
<td>11.00</td>
<td>11.00</td>
</tr>
<tr>
<td>Range</td>
<td>5.83–6.00</td>
<td>4.03–21.92</td>
<td>5.67–8.00</td>
<td>8.42–11.00</td>
<td>7.58–9.92</td>
<td>9.50–11.00</td>
<td>8.00–12.17</td>
<td>8.35–10.72</td>
</tr>
<tr>
<td><strong>AUC(0–t) (µg h/mL)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>1.126</td>
<td>1.148</td>
<td>1.041</td>
<td>0.941</td>
<td>2.522</td>
<td>1.739</td>
<td>3.419</td>
<td>2.739</td>
</tr>
<tr>
<td>SD</td>
<td>0.125</td>
<td>0.386</td>
<td>0.367</td>
<td>0.278</td>
<td>0.757</td>
<td>0.668</td>
<td>1.480</td>
<td>1.194</td>
</tr>
<tr>
<td><strong>CV (%)</strong></td>
<td>138.9</td>
<td>138.9</td>
<td>139.8</td>
<td>140.0</td>
<td>27.0</td>
<td>24.4</td>
<td>20.6</td>
<td>27.0</td>
</tr>
<tr>
<td><strong>AUC(0–inf) (µg h/mL)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>1.126</td>
<td>1.148</td>
<td>1.041</td>
<td>0.941</td>
<td>2.522</td>
<td>1.739</td>
<td>3.419</td>
<td>2.739</td>
</tr>
<tr>
<td>SD</td>
<td>0.125</td>
<td>0.386</td>
<td>0.367</td>
<td>0.278</td>
<td>0.757</td>
<td>0.668</td>
<td>1.480</td>
<td>1.194</td>
</tr>
<tr>
<td><strong>CV (%)</strong></td>
<td>138.9</td>
<td>138.9</td>
<td>139.8</td>
<td>140.0</td>
<td>27.0</td>
<td>24.4</td>
<td>20.6</td>
<td>27.0</td>
</tr>
<tr>
<td><strong>AUC(0–72h) (µg h/mL)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
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<td>0.386</td>
<td>0.367</td>
<td>0.278</td>
<td>0.757</td>
<td>0.668</td>
<td>1.480</td>
<td>1.194</td>
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<td>138.9</td>
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<td>0.668</td>
<td>1.480</td>
<td>1.194</td>
</tr>
<tr>
<td><strong>CV (%)</strong></td>
<td>138.9</td>
<td>138.9</td>
<td>139.8</td>
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<td>27.0</td>
<td>24.4</td>
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<th>4 mg/kg</th>
<th>6 mg/kg</th>
<th>8 mg/kg</th>
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<td><strong>Tmax (h)</strong></td>
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<td>8.475</td>
<td>11.100</td>
<td>9.475</td>
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<td><strong>AUC(0-Inf) (μg h/mL)</strong></td>
<td></td>
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<td>1104.011</td>
<td>3623.94</td>
<td>7845.37</td>
<td>51844.82</td>
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<td><strong>AUC(0-24 h) (μg h/mL)</strong></td>
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<td>N = 3</td>
<td>N = 3</td>
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<tr>
<td>Mean</td>
<td>159.690</td>
<td>1542.216</td>
<td>4231.701</td>
<td>12815.094</td>
<td>16651.920</td>
<td>371595.322</td>
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<td>SD</td>
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<td>122.9</td>
<td>118.3</td>
<td>48.6</td>
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<tr>
<td><strong>T(1/2) (h)</strong></td>
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<td></td>
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<td></td>
</tr>
<tr>
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<td>N = 3</td>
<td>N = 3</td>
<td>N = 3</td>
</tr>
<tr>
<td>Mean</td>
<td>12.682</td>
<td>35.694</td>
<td>72.140</td>
<td>396.487</td>
<td>289.499</td>
<td>215.329</td>
<td>566.364</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>12.654</td>
<td>87.540</td>
<td>72.140</td>
<td>396.487</td>
<td>289.499</td>
<td>215.329</td>
<td>566.364</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**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.
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).

Source: GEN501 clinical study report page 180.
Figure 1: Δ QTcF vs. Daratumumab Concentration (Part 1, Sponsor’s Analysis)

\[ \text{CHG}_{\text{QTcF}} = 4.71234367 + (-0.00000384) \times \text{Daratumumab concentration} \]

Source: GEN501 clinical study report page 261.
Figure 2: Δ QTcF vs. Daratumumab Concentration (Part 2, Sponsor’s Analysis)

CHG_QTcF = 1.49630161 + (0.01548926)(Daratumumab concentration)

Source: GEN501 clinical study report page 1068.

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

<table>
<thead>
<tr>
<th>QT Parameter</th>
<th>Overall Dose Level</th>
<th>Overall Model Fit [1]</th>
<th>Predicted Δ QTc at Average Cmax [700 μg/mL]</th>
<th>One-sided Upper 95% Confidence Bound of Predicted Δ QTc [2]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Δ QTcF</td>
<td>0.01548926</td>
<td>0.00381245</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>QTcB</td>
<td>0.02730648</td>
<td>0.00455003</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

[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 ΔQTcF for Daratumumab Doses 4 mg/kg up to 24 mg/kg (Part 1, By Time)

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

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

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

Visit=7
### 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 \( \leq 450 \) ms, between 450 ms and 480 ms, between 480 ms and 500 ms; and changes from baseline QTc \( \leq 30 \) 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)

<table>
<thead>
<tr>
<th>TREAT</th>
<th>Value( \leq 450 ) ms</th>
<th>450 ms &lt; Value( \leq 480 ) ms</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>H: 8 mg/kg</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>I: 16 mg/kg</td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>J: 24 mg/kg</td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>G: 4 mg/kg</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>10</td>
<td>1</td>
<td>11</td>
</tr>
</tbody>
</table>

#### Table 11: Categorical Analysis for QTcF (Part 2)

<table>
<thead>
<tr>
<th>TREAT</th>
<th>Value( \leq 450 ) ms</th>
<th>450 ms &lt; Value( \leq 480 ) ms</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schedule E - 16mg/kg - No Pre-dose 1000 mL 1st 2 Infusions</td>
<td>19</td>
<td>3</td>
<td>22</td>
</tr>
<tr>
<td>Schedule D - 16mg/kg - Opt. Pre-dose 1000 mL 1st 2 Infusions</td>
<td>20</td>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td>Schedule A - 8mg/kg - Dose Chosen By IDMC</td>
<td>16</td>
<td>0</td>
<td>16</td>
</tr>
<tr>
<td>Schedule B - 8mg/kg - 500 mL 1st Full Infusion</td>
<td>8</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>Schedule C - 8mg/kg - No Pre-dose 1000 mL 1st Full Infusion</td>
<td>6</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>69</td>
<td>3</td>
<td>72</td>
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### Table 12: Categorical Analysis for ΔQTcF (Part 1)

<table>
<thead>
<tr>
<th>TREAT</th>
<th>QTCF_CFB</th>
<th>Value&lt;=30 ms</th>
<th>30 ms&lt;Value&lt;=60 ms</th>
<th>Total</th>
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</thead>
<tbody>
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<td>H: 8 mg/kg</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>I: 16 mg/kg</td>
<td>3</td>
<td>0</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>J: 24 mg/kg</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>G: 4 mg/kg</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td></td>
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<tr>
<td><strong>Total</strong></td>
<td>8</td>
<td>3</td>
<td>11</td>
<td></td>
</tr>
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### Table 13: Categorical Analysis for ΔQTcF (Part 2)

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<th>QTCF_CFB</th>
<th>Value&lt;=30 ms</th>
<th>30 ms&lt;Value&lt;=60 ms</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schedule E - 16mg/kg - No Pre-dose 1000 mL 1st 2 Infusions</td>
<td>19</td>
<td>3</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Schedule D - 16mg/kg - Opt. Pre-dose 1000 mL 1st 2 Infusions</td>
<td>19</td>
<td>1</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Schedule A - 8mg/kg - Dose Chosen By IDMC</td>
<td>13</td>
<td>3</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Schedule B - 8mg/kg - 500 mL 1st Full Infusion</td>
<td>7</td>
<td>1</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Schedule C - 8mg/kg - No Pre-dose 1000 mL 1st Full Infusion</td>
<td>6</td>
<td>0</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>64</td>
<td>8</td>
<td>72</td>
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</tr>
</tbody>
</table>

### 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 ΔHR of Daratumumab Doses 4 mg/kg up to 24 mg/kg (Part 1, By Time)

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

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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Time(H)</th>
<th>N</th>
<th>Mean</th>
<th>Std Dev</th>
<th>90% CI for Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Visit=2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schedule A - 8mg/kg - Dose Chosen By IDMC</td>
<td>Predose</td>
<td>16</td>
<td>2.8</td>
<td>11.1</td>
<td>(-2.0, 7.7)</td>
</tr>
<tr>
<td></td>
<td>0 to 1 hr</td>
<td>14</td>
<td>5.8</td>
<td>9.5</td>
<td>(1.3, 10.3)</td>
</tr>
<tr>
<td>Schedule B - 8mg/kg - 500 mL 1st Full Infusion</td>
<td>Predose</td>
<td>8</td>
<td>1.3</td>
<td>9.9</td>
<td>(-5.4, 8.0)</td>
</tr>
<tr>
<td></td>
<td>0 to 1 hr</td>
<td>8</td>
<td>0.5</td>
<td>10.5</td>
<td>(-6.5, 7.5)</td>
</tr>
<tr>
<td>Schedule C - 8mg/kg - No Pre-dose 1000 mL 1st Full Infusion</td>
<td>Predose</td>
<td>4</td>
<td>-4.4</td>
<td>1.1</td>
<td>(-5.7, -3.1)</td>
</tr>
<tr>
<td></td>
<td>0 to 1 hr</td>
<td>6</td>
<td>10.3</td>
<td>15.6</td>
<td>(-2.5, 23.1)</td>
</tr>
<tr>
<td>Schedule D - 16mg/kg - Opt. Pre-dose 1000 mL 1st 2 Infusions</td>
<td>Predose</td>
<td>19</td>
<td>-1.5</td>
<td>7.8</td>
<td>(-4.6, 1.6)</td>
</tr>
<tr>
<td></td>
<td>0 to 1 hr</td>
<td>20</td>
<td>8.8</td>
<td>7.7</td>
<td>(5.8, 11.8)</td>
</tr>
<tr>
<td>Schedule E - 16mg/kg - No Pre-dose 1000 mL 1st 2 Infusions</td>
<td>Predose</td>
<td>21</td>
<td>-2.8</td>
<td>7.1</td>
<td>(-5.5, -0.2)</td>
</tr>
<tr>
<td></td>
<td>0 to 1 hr</td>
<td>22</td>
<td>7.4</td>
<td>12.0</td>
<td>(3.0, 11.7)</td>
</tr>
</tbody>
</table>
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>
<thead>
<tr>
<th>Treatment</th>
<th>Time(H)</th>
<th>N</th>
<th>Mean</th>
<th>Std Dev</th>
<th>90% CI for Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predose</td>
<td>14</td>
<td>-3.0</td>
<td>9.4</td>
<td></td>
<td>(-7.4, 1.5)</td>
</tr>
<tr>
<td>0 to 1 hr</td>
<td>19</td>
<td>3.1</td>
<td>10.4</td>
<td></td>
<td>(-1.0, 7.3)</td>
</tr>
</tbody>
</table>

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 ΔPR of Daratumumab Doses 4 mg/kg up to 24 mg/kg (Part 1, By Time)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Time(H)</th>
<th>N</th>
<th>Mean</th>
<th>Std Dev</th>
<th>90% CI for Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>G: 4 mg/kg</td>
<td>0</td>
<td>6</td>
<td>-8.1</td>
<td>10.5</td>
<td>(-16.7, 0.5)</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>3</td>
<td>-9.4</td>
<td>1.7</td>
<td>(-12.2, -6.5)</td>
</tr>
<tr>
<td>H: 8 mg/kg</td>
<td>0</td>
<td>9</td>
<td>-9.8</td>
<td>16.7</td>
<td>(-20.1, 0.5)</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>4</td>
<td>-12.9</td>
<td>2.2</td>
<td>(-15.5, -10.3)</td>
</tr>
<tr>
<td>I: 16 mg/kg</td>
<td>0</td>
<td>7</td>
<td>-0.2</td>
<td>15.1</td>
<td>(-11.3, 10.9)</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>5</td>
<td>-7.5</td>
<td>6.5</td>
<td>(-13.6, -1.3)</td>
</tr>
<tr>
<td>J: 24 mg/kg</td>
<td>0</td>
<td>8</td>
<td>3.2</td>
<td>9.2</td>
<td>(-3.0, 9.4)</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>6</td>
<td>-2.2</td>
<td>6.2</td>
<td>(-7.3, 2.9)</td>
</tr>
</tbody>
</table>
Table 19: Analysis Results of ΔPR of Daratumumab Doses of 8 mg/kg and 16 mg/kg (Part 2, By Time)

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

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)

<table>
<thead>
<tr>
<th>TREAT</th>
<th>PR &lt;= 200 ms</th>
<th>PR &gt;200 ms</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>H: 8 mg/kg</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>I: 16 mg/kg</td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>J: 24 mg/kg</td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>G: 4 mg/kg</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>10</td>
<td>1</td>
<td>11</td>
</tr>
</tbody>
</table>

Reference ID: 3834717
### Table 21: Categorical Analysis for PR (Part 2)

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

### 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 ΔQRS of Daratumumab Doses 4 mg/kg up to 24 mg/kg (Part 1, By Time)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Time(H)</th>
<th>N</th>
<th>Mean</th>
<th>Std Dev</th>
<th>90% CI for Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>G: 4 mg/kg</td>
<td>0</td>
<td>6</td>
<td>-3.1</td>
<td>3.7</td>
<td>(-6.1, -0.0)</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>3</td>
<td>-2.2</td>
<td>2.7</td>
<td>(-6.8, 2.4)</td>
</tr>
<tr>
<td>H: 8 mg/kg</td>
<td>0</td>
<td>9</td>
<td>-4.3</td>
<td>6.2</td>
<td>(-8.2, -0.5)</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>4</td>
<td>1.8</td>
<td>10.0</td>
<td>(-10.0, 13.5)</td>
</tr>
<tr>
<td>I: 16 mg/kg</td>
<td>0</td>
<td>7</td>
<td>-0.3</td>
<td>4.3</td>
<td>(-3.5, 2.9)</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>5</td>
<td>2.0</td>
<td>2.0</td>
<td>(0.1, 3.9)</td>
</tr>
<tr>
<td>J: 24 mg/kg</td>
<td>0</td>
<td>8</td>
<td>5.8</td>
<td>7.6</td>
<td>(0.7, 10.9)</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>6</td>
<td>0.6</td>
<td>9.4</td>
<td>(-7.2, 8.3)</td>
</tr>
</tbody>
</table>
Table 23: Analysis Results of ΔQRS of Daratumumab Doses 8 mg/kg and 16 mg/kg (Part 2, By Time)

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

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).
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.
The relationships between $\DeltaQTcF$ 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 $\DeltaQTcF$ 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 $\DeltaQTcF$ is less than 10 ms with upper bound less than 20 ms at the therapeutic Cmax of 1000 ug/mL.
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

<table>
<thead>
<tr>
<th>Therapeutic dose</th>
<th>16 mg/kg weekly for 8 weeks, every 2 weeks for 16 weeks, and then every 4 weeks thereafter.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum tolerated dose</td>
<td>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).</td>
</tr>
<tr>
<td>Principal adverse events</td>
<td>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, hypercalcaemia, pneumonia, and cough (Mod2.7.4/Sec2.6). For more information, see Mod2.7.4.</td>
</tr>
<tr>
<td>Maximum dose tested</td>
<td>Single 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). No single dose studies were performed.</td>
</tr>
<tr>
<td>Exposures Achieved at Maximum Tested Dose</td>
<td>Single (1st) Dose: Mean Cmax (%CV) - 500.10 μg/mL (16.1%). Mean AUCinf (%CV) - 97,175.65 μg·h/mL (41.1%). (Mod5.3.5.2/GEN501/Table18)</td>
</tr>
<tr>
<td></td>
<td>Multiple (7th) Dose: Mean Cmax (%CV) - 1163.34 μg/mL (28.7%). Mean AUCinf (%CV) - 1018233.50 μg·h/mL (101.1%) (Mod5.3.5.2/GEN501/Table19)</td>
</tr>
<tr>
<td>Range of linear PK</td>
<td>Daratumumab elimination showed nonlinear characteristics; clearance is concentration and time dependent.</td>
</tr>
<tr>
<td>Accumulation at steady state</td>
<td>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%).</td>
</tr>
<tr>
<td>Metabolites</td>
<td>No metabolites of daratumumab have been identified and none are expected as an IgG-based monoclonal antibody.</td>
</tr>
<tr>
<td>Absorption</td>
<td>Absolute Bioavailability: 100% (administered as intravenous infusion)</td>
</tr>
<tr>
<td></td>
<td>Tmax: Median (range) 8 (8.00 to 12.17) h after start of first infusion (infusion duration is variable)</td>
</tr>
<tr>
<td>Distribution</td>
<td>Vd: Mean (%CV) population pharmacokinetic estimate of the central volume of distribution is 56.98 mL/kg (31.7% CV)</td>
</tr>
<tr>
<td></td>
<td>% bound: 0%; daratumumab is not bound in the systemic circulation</td>
</tr>
<tr>
<td>Elimination</td>
<td>Route: Elimination presumably follows the same catabolic pathway as endogenous IgG.</td>
</tr>
<tr>
<td></td>
<td>Terminal t½: The terminal half-life is concentration and time dependent.</td>
</tr>
<tr>
<td></td>
<td>• Mean Terminal t½ (%CV) following the first dose of 16 mg/kg of daratumumab: 216.06 h [9.0 days] (48.2%)</td>
</tr>
<tr>
<td></td>
<td>• Mean (%CV) model-derived linear elimination t½ (which can be expected upon complete saturation of target-mediated clearance and repeat dosing of daratumumab): 18 days (50%).</td>
</tr>
</tbody>
</table>
| Intrinsic Factors | CL/F or CL | The clearance is concentration and time dependent.  
- 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%) |
|---|---|---|
| Age | 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:  
  - Age <65 years: 415.52 (354.59, 484.58) μg/mL  
  - Age ≥65 years: 441.54 (368.95, 528.41) μg/mL |
| Sex | 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:  
  - Male: 400.83 (344.05, 466.98) μg/mL  
  - Female: 465.20 (387.03, 559.16) μg/mL |
| Race | 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:  
  - White: 419.61 (370.18, 475.63) μg/mL  
  - Non-white: 477.17 (337.95, 673.75) μg/mL |
| Hepatic & Renal Impairment | 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:  
  - Normal: 448.95 (395.47, 509.66) μg/mL  
  - Mild: 317.95 (235.77, 428.78) μg/mL  
  Mean (95%CI) predicted maximal pre-infusion concentration (trough at the end of weekly dosing period) by renal function subgroups:  
  - 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 | 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.  
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 |
| 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 | In 3 daratumumab monotherapy studies (GEN501. MMY2002 and MMY1002), of 237 subjects treated with daratumumab, a total of 6 subjects (2.5%) reported and 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 group (0.005 mg/kg to 1 mg/kg group) (details are described in the CSR). Only 1 subject (100005) 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 1.8-2.6 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.

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 death), 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 syncope episode was most likely suggestive of vasovagal syncope or hypervolemic 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.

In summary, daratumumab does not induce the pro-arrhythmic risk associated with QT prolongation.
<table>
<thead>
<tr>
<th>Analysis set: all treated</th>
<th>Total number of subjects with treatment-emergent cardiac events*</th>
<th>MedDRA system organ class / Preferred term investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.005 mg/kg</td>
<td>0.05 mg/kg</td>
<td>0.1 mg/kg</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Electrocardiogram QT prolonged</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Syncope</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Cardiac events include QT prolongation, syncope, seizures, ventricular tachycardia, ventricular tachyarrhythmias, ventricular fibrillation, fibrillation, tachycardia, torsade de pointes, or sudden death.

Adverse events are reported using MedDRA version 17.0.

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

Reference ID: 3834717
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/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

Reference ID: 3834717
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-idiotype HuMax-CD38 (anti-dara) were provided to the clinical laboratory by the drug sponsor. It is unknown how and if the sponsor...
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 µg/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 µg/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 µg/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 µg/mL and in all 10 samples at 200 µg/mL. For the normal samples dara could be detected in 8/10 samples at 100 µg/mL and in all 10 samples at 200 µg/mL.

   iii. The sponsor concludes LoD is 200 µg/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.

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 ≥ 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.

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

/s/

JENNIFER S DICKEY
10/16/2015
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 Orencia, 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 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 IgG1κ 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:**

<table>
<thead>
<tr>
<th>Name of CI Location</th>
<th>Study Site/Protocol/Number of Subjects Enrolled (n)</th>
<th>Inspection Date</th>
<th>Classification*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jacob Laubach, M.D. Dana Farber Cancer Institute 450 Brookline Ave. Boston, MA 02215</td>
<td>Site #50125 Protocol JNJ54767414GEN501 (Part 2) Subjects=20</td>
<td>July 13-21, 2015</td>
<td>Preliminary: VAI</td>
</tr>
<tr>
<td>Saad Usmani, M.D. Carolinas Medical Center 6940 Columbia Gateway Dr. Suite 110 Charlotte, NC 21046</td>
<td>Site #US10782 Protocol 54767414MMY2002 Subjects=9</td>
<td>July 13-15, 2015</td>
<td>Preliminary: NAI</td>
</tr>
</tbody>
</table>

*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.

Reference ID: 3826145
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.

CONCURRENCE:

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CONCURRENCE:

Susan D. Thompson, M.D.
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Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations
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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***

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

Reference ID: 3823858
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>
<thead>
<tr>
<th>Material Reviewed</th>
<th>Appendix Section (for Methods and Results)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product Information/Prescribing Information</td>
<td>A</td>
</tr>
<tr>
<td>FDA Adverse Event Reporting System (FAERS)</td>
<td>B – N/A</td>
</tr>
<tr>
<td>Previous DMEPA Reviews</td>
<td>C – N/A</td>
</tr>
<tr>
<td>Human Factors Study</td>
<td>D – N/A</td>
</tr>
<tr>
<td>ISMP Newsletters</td>
<td>E – N/A</td>
</tr>
<tr>
<td>Other</td>
<td>F – N/A</td>
</tr>
<tr>
<td>Labels and Labeling</td>
<td>G</td>
</tr>
</tbody>
</table>

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.

Reference ID: 3823858
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 ‘intravenously’.
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’.

4.2 RECOMMENDATIONS FOR JANSSEN 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 sizes.

B. Carton Labeling
1. Relocate where it appears before the proprietary name, ‘Darzalex’ as users may interpret the letter as a “A”, “Z”, or “X”.
2. Relocate the “Single Use Only”, “Discard unused portion” and “(b)(4) dilute before” 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.

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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.”

Reference ID: 3823858
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**          | Pre-medication with corticosteroids, antipyretics and antihistamines to prevent delayed infusion-related reactions (IRRs) |
|                                 | Recommended dose is 16 mg/kg body weight: |
|                                 | • Weekly: Weeks 1 to 8 |
|                                 | • Every two weeks: Weeks 9 to 24 |
|                                 | • Every four weeks: Week 25 onwards until disease progression. |
|                                 | Post-infusion medication with oral corticosteroid to prevent delayed IRRs to patients the first and second day after all infusions. |
| **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
1. Regulatory History and Applicant’s Main Proposals

Daratumumab is a human IgG1κ 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:

<table>
<thead>
<tr>
<th>Section</th>
<th>Required/Optional</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highlights Heading</td>
<td>Required</td>
</tr>
<tr>
<td>Highlights Limitation Statement</td>
<td>Required</td>
</tr>
</tbody>
</table>
## Selected Requirements of Prescribing Information

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

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

### Comment:

**HIGHLIGHTS DETAILS**

#### Highlights Heading

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

#### Highlights Limitation Statement

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.

#### Product Title in Highlights

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

#### Initial U.S. Approval in Highlights

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.

#### Boxed Warning (BW) in Highlights

12. All text in the BW must be **bolded**.

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 UPPERCASE 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 UPPERCASE letters and bolded.

Comment:

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

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

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.

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

**Comment:** 8.2 and 8.3 are updated per PLLR.

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:**
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

[Image] 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:
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]

RECENT MAJOR CHANGES
[section (X.X.X)]
[section (X.X.X)]

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]

WARNINGS AND PRECAUTIONS
• [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]

USE IN SPECIFIC POPULATIONS
• [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
  2.1 [text]
  2.2 [text]
2 DOSAGE AND ADMINISTRATION
  2.1 [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)]

<table>
<thead>
<tr>
<th>Application Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>BLA# 761036</td>
</tr>
<tr>
<td>NDA Supplement #: N/A</td>
</tr>
<tr>
<td>BLA Supplement #: N/A</td>
</tr>
<tr>
<td>Efficacy Supplement Category: N/A</td>
</tr>
<tr>
<td>☐ New Indication (SE1)</td>
</tr>
<tr>
<td>☐ New Dosing Regimen (SE2)</td>
</tr>
<tr>
<td>☐ New Route Of Administration (SE3)</td>
</tr>
<tr>
<td>☐ Comparative Efficacy Claim (SE4)</td>
</tr>
<tr>
<td>☐ New Patient Population (SE5)</td>
</tr>
<tr>
<td>☐ Rx To OTC Switch (SE6)</td>
</tr>
<tr>
<td>☐ Accelerated Approval Confirmatory Study (SE7)</td>
</tr>
<tr>
<td>☐ Labeling Change With Clinical Data (SE8)</td>
</tr>
<tr>
<td>☐ Manufacturing Change With Clinical Data (SE9)</td>
</tr>
<tr>
<td>☐ Animal Rule Confirmatory Study (SE10)</td>
</tr>
</tbody>
</table>

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):  
☐ Type 1- New Molecular Entity (NME); NME and New Combination  
☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination  
☐ Type 3- New Dosage Form; New Dosage Form and New Combination  
☐ Type 4- New Combination  
☐ Type 5- New Formulation or New Manufacturer  
☐ Type 7- Drug Already Marketed without Approved NDA  
☐ 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  

If 505(b)(2): Draft the “505(b)(2) Assessment” review found at: http://www.fda.gov/Drugs/InformationOnDrugs/ApprovalApplications/NewDrugs/ucm027499.
Type of BLA

If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team

Review Classification:

- The application will be a priority review if:
  - 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)
  - The product is a Qualified Infectious Disease Product (QIDP)
  - A Tropical Disease Priority Review Voucher was submitted
  - A Pediatric Rare Disease Priority Review Voucher was submitted

Resubmission after withdrawal? □  Resubmission after refuse to file? □

Part 3 Combination Product? □

If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults

- Convenience kit/Co-package
- Pre-filled drug delivery device/system (syringe, patch, etc.)
- Pre-filled biologic delivery device/system (syringe, patch, etc.)
- Device coated/impregnated/combined with drug
- Device coated/impregnated/combined with biologic
- Separate products requiring cross-labeling
- Drug/Biologic
- Possible combination based on cross-labeling of separate products
- Other (drug/device/biological product)

Fast Track Designation
- Breakthrough Therapy Designation
  - set the submission property in DARTTS and notify the CDER Breakthrough Therapy Program Manager
- Rolling Review
- Orphan Designation

PMC response
- PMR response:
  - FDAAA [505(o)]
  - PREA deferred pediatric studies (FDCA Section 505B)
  - Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41)
  - Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)

Other:

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? | × | □ | | |
- If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.

Are the established/proper and applicant names correct in tracking system?

- If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name

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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)? Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: [http://inside.fda.gov/9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm](http://inside.fda.gov/9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm)

If no, ask the document room staff to make the appropriate entries.

### Application Integrity Policy

<table>
<thead>
<tr>
<th></th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the application affected by the Application Integrity Policy (AIP)?</td>
<td>☒</td>
<td>☐</td>
<td>☐</td>
<td><a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></td>
</tr>
<tr>
<td>If yes, explain in comment column.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>If affected by AIP, has OC been notified of the submission?</td>
<td>☐</td>
<td>☐</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If yes, date notified:</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

### User Fees

<table>
<thead>
<tr>
<th></th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?</td>
<td>☒</td>
<td>☐</td>
<td>☐</td>
<td>Included in June 5, 2015 rolling submission</td>
</tr>
<tr>
<td>User Fee Status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>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.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Payment for this application (check daily email from <a href="mailto:UserFeeAR@fda.hhs.gov">UserFeeAR@fda.hhs.gov</a>):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>☐ Paid</td>
<td>☐ Exempt (orphan, government)</td>
<td>☐ Waived (e.g., small business, public health)</td>
<td>☐ Not required</td>
<td></td>
</tr>
<tr>
<td>User Fee Bundling Policy</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Has the user fee bundling policy been appropriately applied? If no, or you are not sure, consult the User Fee Staff.</td>
<td>☒ N/A</td>
<td>☐ Yes</td>
<td>☐ No</td>
<td></td>
</tr>
</tbody>
</table>

### 505(b)(2)

<table>
<thead>
<tr>
<th></th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the application a 505(b)(2) NDA? (Check the 358h form,</td>
<td>☐</td>
<td>☒</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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?
  - No
  - No
  - 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)].
  - No
  - No
  - 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)]?
  - No
  - No
  - N/A

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.

- Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?
  - No
  - No
  - N/A

Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm

If yes, please list below:

<table>
<thead>
<tr>
<th>Application No.</th>
<th>Drug Name</th>
<th>Exclusivity Code</th>
<th>Exclusivity Expiration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tbody>
</table>

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.

**Exclusivity**

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/odplisting/odp/index.cfm

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)]?

If yes, consult the Director, Division of Regulatory Policy, Office of Regulatory Policy

**NDAs/NDA efficacy supplements only:** Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity?

If yes, # years requested:

**Note:** An applicant can receive exclusivity without requesting it;
therefore, requesting exclusivity is not required.

| NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use? | ☐ | ☐ | ☒ |
| 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)? | ☐ | ☐ | ☒ |
| If yes, contact the Orange Book Staff (CDER-Orange Book Staff). | | | |
| BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? | ☒ | ☐ | ☐ | Marlene has been notified.
| If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager |

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.

Format and Content

Do not check mixed submission if the only electronic component is the content of labeling (COL).

| All paper (except for COL) | ☐ |
| All electronic | ☒ |
| Mixed (paper/electronic) | |
| CTD | ☒ |
| Non-CTD | ☐ |
| Mixed (CTD/non-CTD) | |

If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format? N/A

<table>
<thead>
<tr>
<th>Overall Format/Content</th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>If electronic submission, does it follow the eCTD guidance? (^1)</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>If not, explain (e.g., waiver granted).</td>
<td></td>
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</tr>
<tr>
<td>Index: Does the submission contain an accurate comprehensive index?</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>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:</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


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<table>
<thead>
<tr>
<th>Form</th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Application Form</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>If foreign applicant, a U.S. must sign the form [see 21 CFR 314.50(a)(5)].</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Are all establishments and their registration numbers listed on the form/attached to the form?</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Patent Information</strong></td>
<td>YES</td>
<td>NO</td>
<td>NA</td>
<td>Comment</td>
</tr>
<tr>
<td>(NDAs/NDA efficacy supplements only)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?</td>
<td></td>
<td>☒</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Financial Disclosure</strong></td>
<td>YES</td>
<td>NO</td>
<td>NA</td>
<td>Comment</td>
</tr>
<tr>
<td>Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</td>
<td></td>
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</tr>
<tr>
<td><strong>Clinical Trials Database</strong></td>
<td>YES</td>
<td>NO</td>
<td>NA</td>
<td>Comment</td>
</tr>
<tr>
<td>Is form FDA 3674 included with authorized signature?</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>If yes, ensure that the application is also coded with the supporting document category, “Form 3674.”</td>
<td></td>
<td></td>
<td></td>
<td>Is coded in DARRTS with “Form 3674”</td>
</tr>
</tbody>
</table>
If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant

<table>
<thead>
<tr>
<th>Debarment Certification</th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>☒</td>
<td>☐</td>
<td>☐</td>
<td>Signed by Janssen Research &amp; Development, LLC</td>
</tr>
</tbody>
</table>

Certification is not required for supplements if submitted in the original application. If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].

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..."

<table>
<thead>
<tr>
<th>Field Copy Certification (NDAs/NDA efficacy supplements only)</th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</td>
<td>☒</td>
<td>☐</td>
<td>☐</td>
<td></td>
</tr>
</tbody>
</table>

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).

If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.

<table>
<thead>
<tr>
<th>Controlled Substance/Product with Abuse Potential</th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</td>
<td>☐</td>
<td>☐</td>
<td>☒</td>
<td></td>
</tr>
</tbody>
</table>

If yes, date consult sent to the Controlled Substance Staff:

For non-NMEs:
Date of consult sent to Controlled Substance Staff:

<table>
<thead>
<tr>
<th>Pediatrics</th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>PREA</td>
<td>☐</td>
<td>☒</td>
<td></td>
<td>Orphan Designation</td>
</tr>
</tbody>
</table>

Does the application trigger PREA?

If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting.

Note: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage


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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.

<table>
<thead>
<tr>
<th>If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)?</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
</table>

If no, may be an RTF issue - contact DPMH for advice.

<table>
<thead>
<tr>
<th>If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application?</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
</table>

If no, may be an RTF issue - contact DPMH for advice.

<table>
<thead>
<tr>
<th>BPCA: Is this submission a complete response to a pediatric Written Request?</th>
<th></th>
<th></th>
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</tr>
</thead>
</table>

If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³

<table>
<thead>
<tr>
<th>Proprietary Name</th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is a proposed proprietary name submitted?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

If yes, ensure that the application is also coded with the supporting document category, “Proprietary Name/Request for Review.”

<table>
<thead>
<tr>
<th>REMS</th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is a REMS submitted?</td>
<td></td>
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</tbody>
</table>

If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox

<table>
<thead>
<tr>
<th>Prescription Labeling</th>
<th></th>
<th></th>
<th></th>
<th>Not applicable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Check all types of labeling submitted.</td>
<td></td>
<td></td>
<td></td>
<td>Package Insert (PI)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Patient Package Insert (PPI)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Instructions for Use (IFU)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Medication Guide (MedGuide)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Carton labels</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Immediate container labels</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Diluent</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Other: Patient Education Materials</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Is Electronic Content of Labeling (COL) submitted in SPL format?</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
</table>

If no, request applicant to submit SPL before the filing date.

<table>
<thead>
<tr>
<th>Is the PI submitted in PLR format?⁴</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
</table>

³ [http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/uncm027837.htm](http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/uncm027837.htm)

⁴
<table>
<thead>
<tr>
<th>If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? <strong>If requested before application was submitted</strong>, what is the status of the request?</th>
</tr>
</thead>
<tbody>
<tr>
<td>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</td>
</tr>
<tr>
<td>For applications submitted on or after June 30, 2015: Is the PI submitted in PLLR format?</td>
</tr>
<tr>
<td>Has a review of the available pregnancy and lactation data been included?</td>
</tr>
<tr>
<td>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? <strong>If requested before application was submitted</strong>, what is the status of the request?</td>
</tr>
<tr>
<td>All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?</td>
</tr>
<tr>
<td>MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)</td>
</tr>
<tr>
<td>Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?</td>
</tr>
</tbody>
</table>

**OTC Labeling**

Not Applicable

---

[5](http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm)

[5](http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm)

Version: 7/10/2015

Reference ID: 3814312
Check all types of labeling submitted.

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐ Outer carton label</td>
<td>☐ Immediate container label</td>
<td>☐ Blister card</td>
<td>☐ Blister backing label</td>
</tr>
<tr>
<td>☐ Consumer Information Leaflet (CIL)</td>
<td>☐ Physician sample</td>
<td>☐ Consumer sample</td>
<td>☐ Other (specify)</td>
</tr>
</tbody>
</table>

Is electronic content of labeling (COL) submitted?

*If no, request in 74-day letter.*

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐</td>
<td>☐</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Are annotated specifications submitted for all stock keeping units (SKUs)?

*If no, request in 74-day letter.*

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐</td>
<td>☐</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

If representative labeling is submitted, are all represented SKUs defined?

*If no, request in 74-day letter.*

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐</td>
<td>☐</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

All labeling/packaging sent to OSE/DMEPA?

*If yes, specify consult(s) and date(s) sent:*

<table>
<thead>
<tr>
<th>Meeting Minutes/SPAs</th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>End-of Phase 2 meeting(s)?</td>
<td>☒</td>
<td>☐</td>
<td></td>
<td>Minutes were included in the Filing Meeting invitation</td>
</tr>
<tr>
<td>Date(s): July 31, 2013</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*If yes, distribute minutes before filing meeting*

<table>
<thead>
<tr>
<th>Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)?</th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date(s): March 31, 2015</td>
<td>☒</td>
<td>☐</td>
<td></td>
<td>Minutes were included in the Filing Meeting invitation</td>
</tr>
</tbody>
</table>

*If yes, distribute minutes before filing meeting*

<table>
<thead>
<tr>
<th>Any Special Protocol Assessments (SPAs)?</th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date(s):</td>
<td>☐</td>
<td>☒</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*If yes, distribute letter and/or relevant minutes before filing meeting*
**DATE**: August 14, 2015

**BACKGROUND**: Daratumumab is a human IgG1κ 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:**

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

Reference ID: 3814312
<table>
<thead>
<tr>
<th>Reviewer Area</th>
<th>Reviewer Name</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Pharmacology</td>
<td>Jeanne Fourie Zirkelbach</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>TL: Bahru Habtemariam</td>
<td>Y</td>
</tr>
<tr>
<td>Genomics</td>
<td>TBD (not yet determined if needed)</td>
<td>N/A</td>
</tr>
<tr>
<td>Pharmacometrics</td>
<td>Lian Ma</td>
<td>Y</td>
</tr>
<tr>
<td>Biostatistics</td>
<td>Yaping Wang</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>TL: Yuan-Li Shen</td>
<td>Y</td>
</tr>
<tr>
<td>Nonclinical (Pharmacology/Toxicology)</td>
<td>Emily Place</td>
<td>N</td>
</tr>
<tr>
<td></td>
<td>TL: Chris Sheth</td>
<td>Y</td>
</tr>
<tr>
<td>Product Quality (CMC) Review Team:</td>
<td>ATL: Jee Chung</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>RBPM: Anita Brown</td>
<td>Y</td>
</tr>
<tr>
<td>Drug Substance</td>
<td>Maria Jose Lopez-Barragan</td>
<td>Y</td>
</tr>
<tr>
<td>Drug Product</td>
<td>Natalia Pripuzova</td>
<td>Y</td>
</tr>
<tr>
<td>Process</td>
<td>Tura Camilli</td>
<td>Y</td>
</tr>
<tr>
<td>Microbiology</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Facility</td>
<td>Laura Fontan</td>
<td>N</td>
</tr>
<tr>
<td>Biopharmaceutics</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Immunogenicity</td>
<td>N/A (incl. in CMC review)</td>
<td>N/A</td>
</tr>
<tr>
<td>Labeling (BLAs only)</td>
<td>Jibril Abdus-Samad</td>
<td>Y</td>
</tr>
<tr>
<td>Other (e.g., Branch Chiefs, EA Reviewer)</td>
<td>Sarah Kennett, Review Chief, OBP Patricia Hughes, Micro TL</td>
<td>Y</td>
</tr>
<tr>
<td>OMP/OMPI/DMPP (Patient labeling: MG, PPI, IFU)</td>
<td>TBD</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>TL: TBD</td>
<td>N/A</td>
</tr>
<tr>
<td>OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labels)</td>
<td>Nisha Patel</td>
<td>Y</td>
</tr>
<tr>
<td>OSE/DMEPA (proprietary name, carton/container labels)</td>
<td>Michelle Rutledge Cathy Miller (labeling)</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>TL: Yelena Maslov</td>
<td>N</td>
</tr>
<tr>
<td>OSE/DRISK (REMS)</td>
<td>Joyce Weaver</td>
<td>N</td>
</tr>
<tr>
<td></td>
<td>TL: Naomi Redd</td>
<td>Y</td>
</tr>
<tr>
<td>Bioresearch Monitoring (OSI)</td>
<td>Anthony Orenicia</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>TL: Janice Pohlman</td>
<td>N</td>
</tr>
</tbody>
</table>
Other reviewers/disciplines

<table>
<thead>
<tr>
<th>OSE/DPV</th>
<th>Reviewer: Shaily Arora</th>
<th>Y</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TL: Tracy Salaam</td>
<td>Y</td>
</tr>
</tbody>
</table>

Other attendees

- Peter Waldron, Medical Officer, DPV: Y
- Robert Schuck, Pharmacologist, OCP: Y

**FILING MEETING DISCUSSION:**

**GENERAL**

- 505(b)(2) filing issues:
  - 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?

  
  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):

- Per reviewers, are all parts in English or English translation?
  - **If no**, explain:

- Electronic Submission comments
  - **List comments**:

**CLINICAL**

**Comments:** Clinical and Stats will do a combined review for this application.

- Clinical study site(s) inspections(s) needed?
  - **If no**, explain:

<table>
<thead>
<tr>
<th>Version: 7/10/2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference ID: 3814312</td>
</tr>
</tbody>
</table>
| **Advisory Committee Meeting needed?** | □ YES  
Date if known: □  
☑ NO  
☐ To be determined |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Comments:</td>
<td>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.</td>
</tr>
<tr>
<td>If no, for an NME NDA or original BLA, include the reason. For example:</td>
<td></td>
</tr>
<tr>
<td>o this drug/biologic is not the first in its class</td>
<td></td>
</tr>
<tr>
<td>o the clinical study design was acceptable</td>
<td></td>
</tr>
<tr>
<td>o the application did not raise significant safety or efficacy issues</td>
<td></td>
</tr>
<tr>
<td>o 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</td>
<td></td>
</tr>
<tr>
<td>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?</td>
<td></td>
</tr>
<tr>
<td>Comments:</td>
<td>☒ Not Applicable</td>
</tr>
<tr>
<td><strong>CONTROLLED SUBSTANCE STAFF</strong></td>
<td>☒ Not Applicable</td>
</tr>
<tr>
<td>• Abuse Liability/Potential</td>
<td>Comments:</td>
</tr>
<tr>
<td><strong>CLINICAL MICROBIOLOGY</strong></td>
<td>☒ Not Applicable</td>
</tr>
<tr>
<td>Comments:</td>
<td></td>
</tr>
<tr>
<td><strong>CLINICAL PHARMACOLOGY</strong></td>
<td>☒ Not Applicable</td>
</tr>
<tr>
<td>Comments: Genomics reviewer may be needed, decision is pending</td>
<td></td>
</tr>
<tr>
<td>• Clinical pharmacology study site(s) inspections(s) needed?</td>
<td></td>
</tr>
</tbody>
</table>
| ☐ Not Applicable  
☐ FILE  
☐ REFUSE TO FILE |
| ☒ No  
☐ Review issues for 74-day letter |
| **BIOSTATISTICS**                  | ☐ Not Applicable  
☐ FILE  
☐ REFUSE TO FILE |
| Comments: Clinical and Stats will do a combined review for this application. |
| ☐ Review issues for 74-day letter |
| NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) | □ Not Applicable  
| | ☒ FILE  
| | ☐ REFUSE TO FILE  
| | ☐ Review issues for 74-day letter  
| Comments: |  

| PRODUCT QUALITY (CMC) | □ Not Applicable  
| | ☒ FILE  
| | ☐ REFUSE TO FILE  
| | ☐ Review issues for 74-day letter  
| Comments: | The DP Reviewer has review issues for inclusion in the filing letter  

| New Molecular Entity (NDAs only) | ☒ Not Applicable  
| |  
| • Is the product an NME? |  

| Environmental Assessment | ☒ YES  
| | ☐ NO  
| • Categorical exclusion for environmental assessment (EA) requested? |  
| If no, was a complete EA submitted? | N/A  
| Comments: |  

| Facility Inspection | □ Not Applicable  
| | ☒ YES  
| | ☐ NO  
| • Establishment(s) ready for inspection? |  
| Comments: |  

| Facility/Microbiology Review (BLAs only) | □ Not Applicable  
| | ☒ FILE  
| | ☐ REFUSE TO FILE  
| Comments: |  

| CMC Labeling Review (BLAs only) | ☐ Review issues for 74-day letter  
| Comments: | No issues  

| | ☐ Review issues for 74-day letter  

Reference ID: 3814312
### APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)

- 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?
  - [ ] N/A
  - [X] YES
  - [ ] NO

- If so, were the late submission components all submitted within 30 days?
  - [ ] YES
  - [X] NO

- What late submission components, if any, arrived after 30 days?
  - CMC Stability Data

- Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?
  - [X] YES
  - [ ] NO

- Is a comprehensive and readily located list of all clinical sites included or referenced in the application?
  - [X] YES
  - [ ] NO

- Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?
  - [X] YES
  - [ ] NO

### 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

- [ ] The application is unsuitable for filing. Explain why:

- [X] The application, on its face, appears to be suitable for filing.
**Review Issues:**

- [x] No review issues have been identified for the 74-day letter.
- [ ] Review issues have been identified for the 74-day letter.

**Review Classification:**

- [ ] Standard Review
- [x] Priority Review

### ACTION ITEMS

<table>
<thead>
<tr>
<th>Task</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>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).</td>
<td>[ ]</td>
</tr>
<tr>
<td>If RTF, notify everyone who already received a consult request, OSE PM, and RBPM</td>
<td>[ ]</td>
</tr>
<tr>
<td>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.</td>
<td>[ ]</td>
</tr>
<tr>
<td>If priority review, notify applicant in writing by day 60 (see CST for choices)</td>
<td>[x]</td>
</tr>
<tr>
<td>Send review issues/no review issues by day 74</td>
<td>[ ]</td>
</tr>
<tr>
<td>Conduct a PLR format labeling review and include labeling issues in the 74-day letter</td>
<td>[x]</td>
</tr>
<tr>
<td>Update the PDUFA V DARRTS page (for applications in the Program)</td>
<td>[ ]</td>
</tr>
<tr>
<td>Other</td>
<td>[ ]</td>
</tr>
</tbody>
</table>

Annual review of template by OND ADRAs completed: September 2014
<table>
<thead>
<tr>
<th>TASK</th>
<th>21ST CENTURY REVIEW TIMELINE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Applicant Orientation</td>
<td><strong>July 31, 2015</strong></td>
</tr>
<tr>
<td>Filing Meeting</td>
<td><strong>August 14, 2015</strong></td>
</tr>
<tr>
<td>Filing Date (Day 60)- Communicate</td>
<td><strong>September 7, 2015</strong></td>
</tr>
<tr>
<td>review issues</td>
<td><strong>September 21, 2015</strong></td>
</tr>
<tr>
<td>Day 74</td>
<td></td>
</tr>
<tr>
<td>Mid-cycle Meeting</td>
<td><strong>September 16, 2015</strong></td>
</tr>
<tr>
<td>Mid-cycle Communication</td>
<td><strong>September 24, 2015</strong></td>
</tr>
<tr>
<td>Pre-Meeting for LCM</td>
<td><strong>October 6, 2015</strong></td>
</tr>
<tr>
<td>LCM Briefing Doc Due</td>
<td><strong>October 7, 2015 (due 12 days before LCM)</strong></td>
</tr>
<tr>
<td>Late-cycle Meeting</td>
<td><strong>October 19, 2015</strong></td>
</tr>
<tr>
<td>Labeling Meetings</td>
<td><strong>September 21, 2015</strong></td>
</tr>
<tr>
<td></td>
<td><strong>October 9, 2015</strong></td>
</tr>
<tr>
<td></td>
<td><strong>October 16, 2015</strong></td>
</tr>
<tr>
<td></td>
<td><strong>October 30, 2015</strong></td>
</tr>
<tr>
<td>Primary Reviews Completed</td>
<td><strong>October 18, 2015</strong></td>
</tr>
<tr>
<td>Secondary Reviews</td>
<td><strong>October 22, 2015</strong></td>
</tr>
<tr>
<td>Send proposed Labeling/PMC/PMR/REMS</td>
<td><strong>October 25, 2015</strong></td>
</tr>
<tr>
<td>Complete Cross Discipline TL Review</td>
<td><strong>October 25, 2015</strong></td>
</tr>
<tr>
<td>Wrap-up Meeting</td>
<td><strong>November 4, 2015</strong></td>
</tr>
<tr>
<td>Compile and Circulate action letter and</td>
<td><strong>October 25, 2015</strong></td>
</tr>
<tr>
<td>action package</td>
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<tr>
<td>Complete Office Director Review and</td>
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<tr>
<td>Sign-off <strong>PDUFA Goal Date</strong></td>
<td><strong>March 9, 2015</strong>; <strong>Planned Action Date=November 17, 2015</strong></td>
</tr>
</tbody>
</table>
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