CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761049Orig1s000

OTHER REVIEW(S)

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

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 # BLA 761049
Product Name: Avelumab

PMC #1 Description: Implement the performance at least one media fill run per year which incorporates both the maximum sterile hold time after filtration and the maximum filing time starting from 2017. Submit the information and summary data from the first 2017 media fill as a post marketing commitment in accordance with 21 CFR 601.12.

PMC Schedule Milestones:

Final Report Submission: 3/23/2018

- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC/OBP NON-REPORTABLE PMCS *FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL*.USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**
- ***DO NOT USE THIS FORM* IF ANY STUDIES WILL BE REQUIRED UNDER FDAAA OR WILL BE PUBLICALY REPORTABLE**

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 from a single media fill run including both the maximum sterile hold time and maximum filing duration was submitted in the BLA application. With the current goal date, it may not be possible to complete additional media fill runs simulating the maximum allowed sterile hold time and fill duration in the same batch.

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

Maximum sterile hold time after filtration and maximum filling duration during media fill simulation are demonstrated using separate media fill runs. Data from a single media fill run including both the maximum sterile hold time and maximum filing duration was submitted. Performance of at least one of the media fill run per year including the maximum allowed sterile hold time and the maximum fill duration will simulate the commercial drug product filling process and ensure continued validation of the (b) (4) process during product life time.

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:

   Sponsor will perform at least one media fill run per year incorporating both the maximum sterile hold time after filtration and the maximum filing time starting from 2017. The information and summary data from the first 2017 media fill will be submitted as a post marketing commitment.

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)

PMR/PMC Development Template: CMC

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

NDA/BLA # BLA 761049
Product Name: Bavencio (avelumab)

PMC Description: Develop and validate an assay with improved sensitivity for the detection of neutralizing antibodies against avelumab in the presence of avelumab levels that are expected to be present in samples at the time of patient sampling. Patient samples should be banked for storage until the improved method is available.

PMR/PMC Schedule Milestones:

Final Report Submission: 3/31/2017

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

The safety profile observed in clinical studies indicates that the presence of anti-drug antibodies does not appear to be a significant safety issue. The development and implementation of a more sensitive assay for detecting neutralizing anti-drug-antibodies (ADAs) would provide better assessment and characterization of the patients' ADA response to avelumab.

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."

The goal of the study is to develop and validate an assay with sensitivity for the detection of neutralizing antibodies against avelumab in the presence of avelumab levels that are expected to be present in samples at the time of patient sampling.

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.

Development and validation of sensitive and drug tolerant methods to detect binding antibodies and neutralizing antibodies to avelumab in patients' serum 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
X Other (provide explanation)
More sensitive and appropriate treatment- emergent immunogenicity assessment

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)

X ☐ Other
Re- evaluating the immunogenicity assessment with a new method.

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: Clinical Pharmacology

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

NDA/BLA # 761049
Product Name: Bavencio (Avelumab)

PMR/PMC Description: Conduct an assessment of treatment-emergent binding and neutralizing anti-drug antibody (ADA) responses with validated assays (including an updated cutpoint for the screening and confirmatory ADA assays and for the neutralizing assay as requested in 3185-4) capable of sensitively detecting ADA responses in the presence of avelumab levels that are expected to be present in the serum at the time of patient sampling. The incidence of treatment-emergent ADA responses will be evaluated in at least 300 avelumab-treated patients. The final report will include information on the level of avelumab in each patient's test sample at each sampling point with an appropriate cutpoint.

PMR/PMC Schedule Milestones:

Final Report Submission: 8/31/2017

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

Bavencio (Avelumab) is a recombinant monoclonal antibody. With therapeutic proteins, there is a potential for treatment-emergent binding and neutralizing anti-drug antibody (ADA) responses. Based on review of the BLA submission the assays to detect Avelumab antibodies and neutralizing antibodies have not been fully developed, and the current PMC addresses this issue.

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."

The study will develop validated assays ((including an updated cutpoint for the screening and confirmatory ADA assay and the neutralizing assay as requested in PMC 1) capable of sensitively detecting ADA responses in the presence of avelumab levels that are expected to be present in the serum at the time of patient sampling.

The goal of the study is to reliably determine treatment-emergent binding and neutralizing anti-drug antibody (ADA) responses in patients receiving Avelumab.

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.

Conduct an assessment of treatment-emergent binding and neutralizing anti-drug antibody (ADA) responses with validated assays (including an updated cutpoint for the screening and confirmatory ADA assay and the neutralizing assay as requested in PMC 1) capable of sensitively detecting ADA responses in the presence of avelumab levels that are expected to be present in the serum at the time of patient sampling. The ADA response will be evaluated in at least 300 avelumab-treated patients.

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)

  Validation of assays for assessment of treatment-emergent binding and neutralizing anti-drug antibody (ADA) responses.
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
- ☐ Immunogenicity as a marker of safety
- ☐ Other (provide explanation)

Agreed upon:

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

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

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

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

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

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

PMR/PMC Development Coordinator:

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

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(signature line for BLAs)

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/s/

SAFAA BURNS
03/21/2017

JEANNE FOURIE ZIRKELBACH
03/21/2017

JEFFERY L SUMMERS
03/23/2017

PMR/PMC Development Template: Clinical Pharmacology

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

NDA/BLA # 761049
Product Name: Bavencio (Avelumab)

PMR/PMC Description: Conduct an assessment of treatment-emergent binding and neutralizing anti-drug antibody (ADA) responses with validated assays (including an updated cutpoint for the screening and confirmatory ADA assays and for the neutralizing assay as requested in 3185-5) capable of sensitively detecting ADA responses in the presence of avelumab levels that are expected to be present in the serum at the time of patient sampling. The incidence of treatment-emergent ADA responses will be evaluated in at least 300 avelumab-treated patients. The final report will include information on the level of avelumab in each patient's test sample at each sampling point with an appropriate cutpoint.

PMR/PMC Schedule Milestones:

Final Report Submission: 8/31/2017

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

Bavencio (Avelumab) is a recombinant monoclonal antibody. With therapeutic proteins, there is a potential for treatment-emergent binding and neutralizing anti-drug antibody (ADA) responses. Based on review of the BLA submission the assays to detect Avelumab antibodies and neutralizing antibodies have not been fully developed, and the current PMC addresses this issue.

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."

The study will develop validated assays ((including an updated cutpoint for the screening and confirmatory ADA assay and the neutralizing assay as requested in PMC 1) capable of sensitively detecting ADA responses in the presence of avelumab levels that are expected to be present in the serum at the time of patient sampling.

The goal of the study is to reliably determine treatment-emergent binding and neutralizing anti-drug antibody (ADA) responses in patients receiving Avelumab.

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.

Conduct an assessment of treatment-emergent binding and neutralizing anti-drug antibody (ADA) responses with validated assays (including an updated cutpoint for the screening and confirmatory ADA assay and the neutralizing assay as requested in PMC 1) capable of sensitively detecting ADA responses in the presence of avelumab levels that are expected to be present in the serum at the time of patient sampling. The ADA response will be evaluated in at least 300 avelumab-treated patients.

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)

Validation of assays for assessment of treatment-emergent binding and neutralizing anti-drug antibody (ADA) responses.

☐ 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)

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

/s/

IDARA UDOH
03/22/2017

JEANNE FOURIE ZIRKELBACH
03/22/2017

JEFFERY L SUMMERS
03/23/2017

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.

BLA # 761049
Product Name: Bavencio (avelumab)

PMR Description: Conduct a trial in a sufficient number of pediatric patients ages 12-18 to adequately characterize baseline risk factors, safety outcomes, and clinical responses following exposure to avelumab.

PMR Schedule Milestones:		
	Final Protocol Submission:	10/21/2017
	Interim Report Submission:	10/31/2018
	Interim Report Submission:	10/31/2019
	Interim Report Submission:	10/31/2020
	Interim Report Submission:	10/31/2021
	Trial Completion:	10/31/2022
	Final Report Submission:	06/30/2023

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

Merkel cell carcinoma (MCC) is a life-threatening disease that typically presents in adult patients. The average age at diagnosis is 75 years. While extremely rare, there have been case reports of MCC occurring in pediatric patients. Avelumab will be approved for adult and pediatric patients 12 years and older with metastatic MCC. The use of avelumab in pediatric patients 12 years and older is supported by evidence of safety and effectiveness in adults with MCC in the context of pharmacokinetic data demonstrating that age and body weight have no clinically meaningful effect on the steady state exposure of avelumab, drug exposure being generally similar between adults and pediatric patients age 12 years and older for monoclonal antibodies, and no evidence that the natural history of MCC in pediatric patients 12 years and older is different than that in adults. The required postmarketing trial in pediatric patients 12 and older will provide supportive safety data in this age group.

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."

MCC is extremely rare in pediatric patients; however, there are case reports of MCC occurring in children and adolescents. Efficacy of avelumab can be extrapolated from the adult data to pediatric patients 12 and older based on PK data demonstrating that age and body weight have no effect on avelumab exposure and because it is reasonable to assume that the MCC disease course, including response to treatment, is similar in adults and pediatric patients. While the safety of avelumab in patients 12 and older is supported by the adult clinical experience, the required postmarketing study will collect and analyze safety data, including the risk for immune-mediated adverse reactions and infusion reactions with avelumab use in this age group.

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.

The required study is a prospective trial conducted in pediatric patients 12 and older.

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)

_____

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)

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/s/

IDARA UDOH
03/23/2017

DENISE A CASEY
03/23/2017

JEFFERY L SUMMERS
03/23/2017

PMR/PMC Development Template: Nonclinical

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

NDA/BLA # 761049
Product Name: Bavencio (avelumab)

PMR/PMC Description: Conduct an animal study that will measure the effect of PD-L1 inhibition on the magnitude of the primary (1st vaccination) and recall (2nd vaccination) antibody responses to antigen challenge (e.g. KLH). This study will evaluate the effect of PD-L1 inhibition on the primary immune response once steady state plasma levels have been achieved and will reassess the magnitude of the recall response after a suitable period in the presence or absence of continued dosing. The study should include, if possible, an evaluation of cytokine production by T cells at appropriate timepoints.

PMR/PMC Schedule Milestones:

Final Protocol Submission:	5/31/2017
Study/Trial Completion:	10/31/2017
Final Report Submission:	1/15/2018

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

To further characterize the effect of avelumab on the immune response

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."

The PMC is to conduct an animal study that will measure the effect of PD-L1 inhibition on the magnitude of the primary (1st vaccination) and recall (2nd vaccination) antibody responses to antigen challenge (e.g. KLH). This study will evaluate the effect of PD-L1 inhibition on the primary immune response once steady state plasma levels have been achieved and will reassess the magnitude of the recall response after a suitable period in the presence or absence of continued dosing. The study should include, if possible, an evaluation of cytokine production by T cells at appropriate timepoints.

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.

The animal study will measure the effect of PD-L1 inhibition on the magnitude of the primary (1st vaccination) and recall (2nd vaccination) antibody responses to antigen challenge (e.g. KLH). This study will evaluate the effect of PD-L1 inhibition on the primary immune response once steady state plasma levels have been achieved and will reassess the magnitude of the recall response after a suitable period in the presence or absence of continued dosing. The study should include, if possible, an evaluation of cytokine production by T cells at appropriate timepoints.

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)

_____

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)
  Study to further characterize the effect of avelumab on the immune response
- ☐ Other

_____

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

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

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

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

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

PMR/PMC Development Coordinator:

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

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/s/

ALEXANDER H PUTMAN
03/21/2017

WHITNEY S HELMS
03/21/2017

JEFFERY L SUMMERS
03/21/2017

PMR/PMC Development Template: Clinical

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

NDA/BLA # 761049
Product Name: Avelumab

PMR/PMC Description: Conduct and submit the results of a multicenter clinical trial confirming the clinical benefit of avelumab in patients with metastatic Merkel cell carcinoma (MCC) who have not received prior systemic therapies for metastatic MCC. The trial will enroll at least 100 patients followed for a minimum of 12 months, in order to establish the objective response rate and characterize the durability of response for first-line treatment of metastatic MCC. All patients will be followed for overall survival until at least 70% of patients have died in order to characterize effects on survival. An analysis of overall survival compared to historical control data will be provided.

PMR/PMC Schedule Milestones:

Trial Completion:	6/30/2026
Final Report Submission:	12/30/2026

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

Currently available efficacy and safety data are sufficient to support approval of Bavencio (avelumab) as treatment for patients with metastatic Merkel cell carcinoma (MCC) who have progressive disease following at least one prior systemic chemotherapy regimen. Efficacy data for avelumab as a treatment for patients with metastatic MCC who have not received prior systemic chemotherapy (i.e., frontline) is limited. Metastatic MCC is a rare and life-threatening illness with no available therapy. There is biologic rationale to support extrapolation of efficacy results from the chemotherapy-refractory setting to the frontline setting to provide patients access to avelumab which is likely to offer clinical benefit. However, additional efficacy data in chemotherapy-naïve patients is required to more accurately characterize response rate and durability of responses in the frontline setting.

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."

Avelumab will receive approval under the accelerated approval regulations for the treatment of patients with metastatic MCC. The objective of the PMR is to provide evidence of clinical benefit in patients with metastatic MCC who have not received prior systemic chemotherapy by evaluating overall response rate and durability of response in this subgroup.

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.

Single-arm, multicenter trial of avelumab in patients with mMCC who have not received prior chemotherapy for metastatic disease.

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)

_____

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

The agreed upon trial to convert the accelerated approval to regular approval is a single-arm, multicenter trial of avelumab in patients with mMCC who have not received prior chemotherapy for metastatic disease. (b) (4)

[redacted]

_____

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

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PMR/PMC Development Coordinator:

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

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/s/

DENISE A CASEY
03/20/2017

JEFFERY L SUMMERS
03/20/2017

Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Biotechnology Products

LABEL AND LABELING REVIEW

Date:	March 9, 2017
Reviewer:	Jibril Abdus-Samad, PharmD Office of Biotechnology Products (OBP)
Through:	Arulvathani Arudchandran, PhD OBP/Division of Biotechnology Review and Research II
Application:	BLA 761049/0
Product:	Bavencio (avelumab)
Applicant:	EMD Serono, Inc.
Submission Dates:	September 23, 2016; February 10, 21, 24; March 7, 2017

I) RECOMMENDATION

The prescribing information, medication guide, container label, and carton labeling for Bavencio (avelumab) Injection 200 mg/10 mL single-dose vial (see Appendix D) submitted on the following dates are acceptable from a quality perspective:

- Prescribing Information: March 7, 2017
  \\cdsesub1\evsprod\bla761049\0045\m1\us\114-labeling\1141-draft-label\clean-us-pi-pdf-version.pdf
- Medication Guide: March 7, 2017
  \\cdsesub1\evsprod\bla761049\0045\m1\us\114-labeling\1141-draft-label\avelumab-medication-guide-mcc-2016-09-14-sub.pdf
- Container Label: February 10, 2017
  \\cdsesub1\evsprod\bla761049\0034\m1\us\114-labeling\1141-draft-label\us-ip-avelumab-200mg-10ml-2017-02-10-sub-en-vial.pdf
- Carton Labeling: February 24, 2017
  \\cdsesub1\evsprod\bla761049\0042\m1\us\114-labeling\1141-draft-label\us-op-avelumab-200mg-10ml-2017-02-24-sub-en-carton.pdf

BACKGROUND AND SUMMARY DESCRIPTION

The Applicant, EMD Serono, Inc. submitted the final piece of the rolling submission for BLA 761049/0 Bavencio (avelumab) Injection 200 mg/10 mL single-dose vial on September 23, 2016 (Application 761049 - Sequence 0003 - 0003 (4) 09/23/2016 ORIG-1 /Multiple Categories/Subcategories).

Table 1: Proposed Product Characteristics of Bavencio (avelumab).

Proprietary Name:	Bavencio
Nonproprietary Name Name:	Avelumab
Dosage Form:	Injection
Strength and Container-Closure:	200 mg/10 mL (20 mg/mL)
Route of Administration:	Intravenous infusion
Storage and Handling:	Store refrigerated at 36°F to 46°F (2°C to 8°C) in original package to protect from light. Do not freeze or shake the vial. Store diluted BAVENCIO solution: - At room temperature up to 77°F (25°C) for no more than 4 hours from the time of dilution. Or - Under refrigeration at 36°F to 46°F (2°C to 8°C) for no more than 24 hours from the time of dilution. If refrigerated, allow the diluted solution to come to room temperature prior to administration. Do not freeze or shake diluted solution.
Indication:	programmed death ligand 1 (PD-L1) blocking antibody indicated for the treatment of patients with metastatic Merkel cell carcinoma (MCC)
Dose and Frequency:	10 mg/kg as an intravenous infusion over 60 minutes every 2 weeks.

II) MATERIALS REVIEWED

We considered the materials listed in Table 2 for this review.

Table 2: Materials Considered for this Label and Labeling Review

Materials Reviewed	Appendix Section
Proposed Labels and Labeling	A
Other	B (n/a)
Relevant Code of Federal Regulations and CDER Labeling Best Practices	C
Acceptable Labels and Labeling	D

n/a = not applicable for this review

III) DISCUSSION

The proposed label and labeling were evaluated for compliance to the applicable code of federal regulations (CFR), United States Pharmacopeia (USP) standards, and CDER Labeling Best Practices (see Appendix C).

IV) CONCLUSION

The prescribing information, medication guide, container label, and carton labeling for Bavencio (avelumab) Injection 200 mg/10 mL single-dose vial 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 USP/NF 39/34. The labels and labeling (see Appendix D) submitted on the following dates are acceptable from a quality perspective:

- Prescribing Information: March 7, 2017
- Medication Guide: March 7, 2017
- Container Label: February 10, 2017
- Carton Labeling: February 24, 2017

APPENDICES

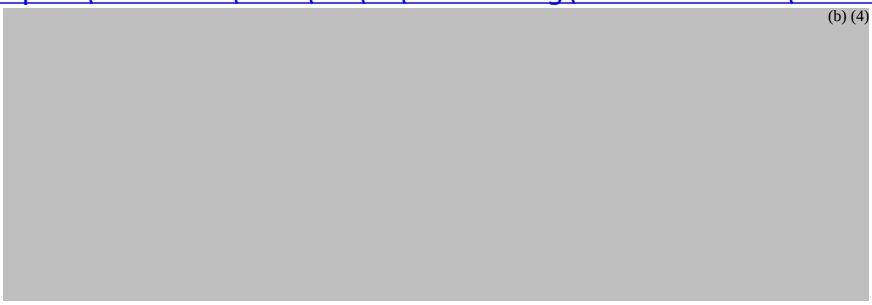
Appendix A: Proposed Labeling

- Prescribing Information
  \\cdsesub1\evsprod\bla761049\0003\m1\us\114-labeling\1141-draft-label\avelumab-pi-medication-guide.pdf

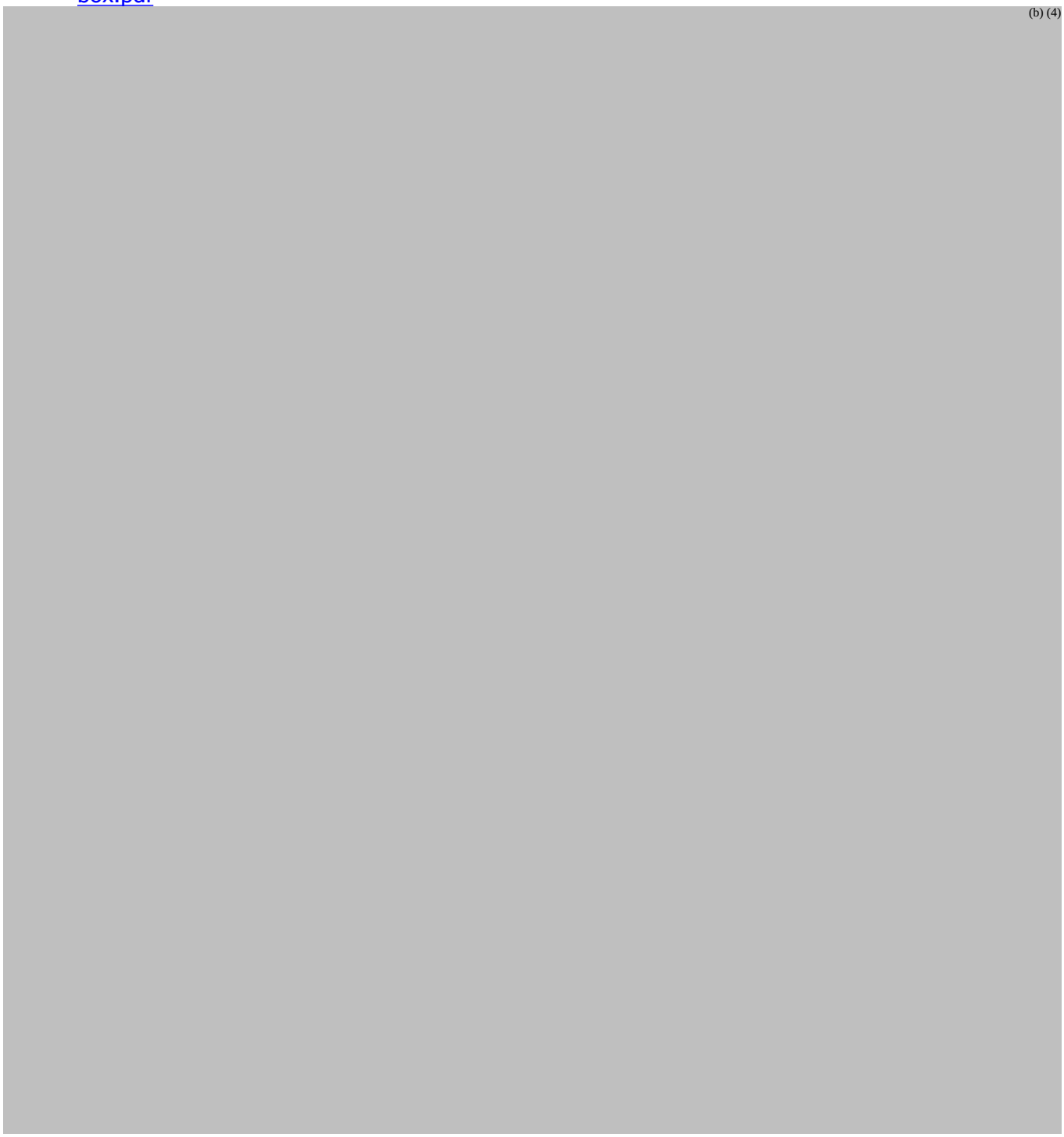
- Medication Guide
  \\cdsesub1\evsprod\bla761049\0003\m1\us\114-labeling\1141-draft-label\avelumab-medication-guide-mcc-2016-09-14-sub.pdf

- Container Label
  \\cdsesub1\evsprod\bla761049\0003\m1\us\114-labeling\1141-draft-label\avelumab-vial.pdf

(b) (4)



- Carton Labeling
  \\cdsesub1\evsprod\bla761049\0003\m1\us\114-labeling\1141-draft-label\avelumab-box.pdf



Appendix B: n/a

Appendix C: Applicant CFR and CDER Best Labeling Practices

Table 3: Label[1,2] and Labeling[3] Standards

Container[4] Label Evaluation

Regulations	**Comply**			**Comments and Recommendations**
	Yes	No	n/a	
21 CFR 610.60 Container Label				
(a) *Full label*. The following items shall appear on the label affixed to the container of a product capable of bearing a full label:			x	*We consider this a partial label. (see below). However, there was space on the label to allow for placement of some of the items recommended for the full label.*
(b) *Package label information*			x	
(c) *Partial label*; proper name, lot, and manufacturer; individual dose for multiple dose containers; partial labels placed in a package with all items required for a package label	x			See DMEPA'S Memorandum regarding approval of the proper name as designated without a suffix.[5]

[1] Per 21 CFR 1.3 (b) *Label* means any display of written, printed, or graphic matter on the immediate container of any article, or any such matter affixed to any consumer commodity or affixed to or appearing upon a package containing any consumer commodity.

[2] Per CFR 600.3(dd) *Label* means any written, printed, or graphic matter on the container or package or any such matter clearly visible through the immediate carton, receptacle, or wrapper.

[3] Per 21 CFR 1.3(a) *Labeling* includes all written, printed, or graphic matter accompanying an article at any time while such article is in interstate commerce or held for sale after shipment or delivery in interstate commerce.

[4] Per 21 CFR 600.3(bb) *Container* (referred to also as "final container") is the immediate unit, bottle, vial, ampule, tube, or other receptacle containing the product as distributed for sale, barter, or exchange.

[5] Stewart J. Memorandum Review of Revised Label and Labeling for Bavencio (BLA 761049). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2017 MAR 1.

Regulations	Comply			Comments and Recommendations
	Yes	No	n/a	
(d) *No container label*			x	
(e) *Visual inspection*		x		*Indicate how the label is affixed to the vial and where the visual area of inspection is located, per 21 CFR 610.60(e).* - **EMD Serono Response**: The label is affixed (b) (4) [redacted] *The Applicant's response is acceptable.*
21 CFR 201.1 Drugs;				
Name and place of business of manufacturer, packer, or distributor			x	Does not apply to BLAs.
21 CFR 201.2 Drugs and devices				
NDC numbers		x		Not required for partial labels however, the Applicant proposed it on the label. Since NDC numbers are often used as additional verification prior to drug dispensing in the pharmacy, when presented, it should be prominently displayed in the top third of the principal display panel (PDP) of the labeling in accordance with 21 CFR 207.35(b)(3)(i). *The Applicant's revision is acceptable.*

Regulations	Comply			Comments and Recommendations
	Yes	No	n/a	
21 CFR 201.5 Drugs				
Adequate directions for use	x			
21 CFR 201.6 Drugs				
Misleading statements	x			
21 CFR 201.10 Drugs				
Statement of ingredients	x			
21 CFR 201.15 Drugs				
Prominence of required label statements	x			
21 CFR 201.17 Drugs				
Location of expiration date	x			
21 CFR 201.25				
Bar code label requirements	x			Although not required for partial labels, we concurred with DMEPA's recommendation to add a vertical barcode per 21CFR 201.25(c)(2). *The Applicant's revision is acceptable.*
21 CFR 201.50 Statement of Identity				
Statement of identity	x			
21 CFR 201.51 Declaration of net quantity of contents				
Declaration of net quantity	x			
21 CFR 201.55 Statement of dosage				
Statement of dosage			x	We recommended removing the usual dosage statement from the partial label to make room for DMEPA's recommendation to include the linear barcode and NDC. *The Applicant's revision is acceptable.*
21 CFR 201.100 Prescription drugs for human use				
Prescription drugs for human use	x			Due to the partial label, all the required information appears on the carton labeling.

Package Label[6] Evaluation

Regulations	Comply			Comments and Recommendations
	Yes	No	n/a	
21 CFR 610.61 Package Label				
(a) Proper name	x			See DMEPA'S Memorandum regarding approval of the proper name as designated without a suffix.[7]
(b) Name, address, and license number of manufacturer	x			We recommended revision of the proposed country of origin statement. - It appears that "(b) (4)" is your attempt to fulfill the country of origin requirement per 19 CFR 134.11. If so, we recommend revising the statement to "Product of Switzerland". We are aiming to provide consistency with labeling the country of origin. *The Applicant's revision is acceptable.*
(c) Lot number or other lot identification	x			
(d) Expiration date	x			
(e) Preservative used and its concentration, if no preservative is use and the absence of a preservative is a safety factor, the words "no preservative"	x			
(f) Number of containers, if more than one			x	1 vial per carton.

[6] Per 21 CFR 600.3(cc) *Package* means the immediate carton, receptacle, or wrapper, including all labeling matter therein and thereon, and the contents of the one or more enclosed containers. If no package, as defined in the preceding sentence, is used, the container shall be deemed to be the package. Thus this includes the carton, prescribing information, and patient labeling.

[7] Stewart J. Memorandum Review of Revised Label and Labeling for Bavencio (BLA 761049). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2017 MAR 1.

Regulations	Comply			Comments and Recommendations
	Yes	No	n/a	
(g) Amount of product in the container	x			
(h) Recommended storage temperature	x			
(i) "Shake Well", "Do not Freeze" or equivalent	x			Labeling states "Do not freeze or shake."
(j) Recommended individual dose if multiple-dose container	x			Single-dose product
(k) Route of administration	x			
(l) Known sensitizing substances		x		Revise the statement on the side panel "(b) (4) " to comply with Recommendations for Labeling Medical Products to Inform Users that the Product or Product Container is not Made with Natural Rubber Latex Guidance for Industry and Food and Drug Administration Staff, March 2013. Additionally, "(b) (4)" is a regulatory term that is not commonly used in labeling. Consider the language you agreed to in the PI. For example: "The vial stopper is not made with natural rubber latex." *The Applicant's revision is acceptable*.
(m) Type and calculated amount of antibiotics added during manufacturing			x	
(n) Inactive ingredients in case of safety factor			x	
(o) Adjuvant, if present			x	

Regulations	Comply			Comments and Recommendations
	Yes	No	n/a	
(p) Source of the product when a factor in safe administration			x	
(q) Identity of each microorganism used in manufacturing			X	
(r) Minimum potency of product expressed in terms of official standard of potency, or "No U.S. standard of potency"	x			
(s) "Rx only" statement for prescription biologicals	x			
21 CFR 610.62 Proper name; package label: *Bavencio (avelumab) is a monoclonal antibody, which is a specified biological product per 21 CFR 601.2(a)and therefore exempt.*				
(a) Position: proper name			x	
(b) Prominence			x	
(c) Legible type			x	
21 CFR 610.63 Divided Manufacturing				
Divided manufacturing			x	- There is only one Applicant for this BLA.
21 CFR 610.64 Name and address of distributor				
Name and address may appear on the label provided the name, address, and license number of manufacturer appears on the label			x	

Regulations	Comply			Comments and Recommendations
	Yes	No	n/a	
21 CFR 610.67 Bar code				
Bar code	x			
21 CFR 610.68				
Exceptions or alternatives to labeling requirements for biological products held by the Strategic National Stockpile.			x	
21 CFR 201.2 Drugs and devices				
NDC numbers	x			
21 CFR 201.5 Drugs				
Adequate directions for use	x			
21 CFR 201.6 Drugs				
Misleading statements	x			
21 CFR 201.10 Drugs				
Statement of ingredients	x			
21 CFR 201.15 Drugs				
Prominence of required label statements	x			
21 CFR 201.17 Drugs				
Location of expiration date	x			
21 CFR 201.25				
Bar code label requirements	x			
21 CFR 201.50 Statement of identity				
Statement of identity	x			
21 CFR 201.51 Declaration of net quantity of contents				
Declaration of net quantity	x			

Regulations	Comply			Comments and Recommendations
	Yes	No	n/a	
21 CFR 201.55 Statement of dosage				
Statement of dosage		x		We concurred with DMEPA's recommendation to revise the statement "(b) (4)", which appears on the side panel to read "Usual Dose: See prescribing information." *The Applicant's revision is acceptable.*
21 CFR 201.100 Prescription drugs for human use				
Prescription drugs for humans	x			

Prescribing Information and Patient Labeling Evaluation

Labeling Standards	Comply			Comments and Recommendations
	Yes	No	n/a	
PRESCRIBING INFORMATION				
Highlights of prescribing information				
PRODUCT TITLE 21 CFR 201.57(a)(2)	x			
DOSAGE AND ADMINISTRATION 21 CFR 201.57(a)(7)	x			
DOSAGE FORMS AND STRENGTHS 21 CFR 201.57(a)(8)	x			
Full Prescribing Information				
2 DOSAGE AND ADMINISTRATION 21 CFR 201.57(c)(3)				We revised the presentation of the diluents. • Withdraw the required volume of BAVENCIO from the vial(s) and inject it to a 250 mL infusion bag containing 0.9% Sodium Chloride Injection. Alternatively, a 0.45% Sodium Chloride Injection can be used. We revised the storage instruction by proving a maximum temperature for room temperature storage and decreased the storage time of storage of diluted solution based on microbiology data. • At room temperature up to 77°F (25°C) for no more than 4 hours from the time of dilution (b) (4)

Labeling Standards	Comply			Comments and Recommendations
	Yes	No	n/a	
				[redacted] (b) (4) or • Under refrigeration at 36°F to 46°F (2°C to 8°C) for no more than 24 hours from the time of dilution. If refrigerated, allow the diluted solution to come to room temperature prior to administration. *The Applicant accepted our revision.*
3 DOSAGE FORMS AND STRENGTHS 21 CFR 201.57(c)(4)				We added a description of the identifying characteristics. **DOSAGE FORMS AND STRENGTHS** Injection: 200 mg/10 mL (20 mg/mL), clear liquid, practically free from visible particles, in a single-dose vial. *The Applicant accepted our revision.*
6.2 IMMUNOGENICITY	x			
11 DESCRIPTION 21 CFR 201.57(c)(12)				We added the dosage form(s) and routes of administration. DOP2 requested relocating the route of administration closer to the dosage form within the paragraph describing the drug product. BAVENCIO (avelumab) Injection for intravenous use is a sterile, preservative-free, non-pyrogenic, clear, colorless to slightly yellow solution. Each single-dose vial contains 200 mg avelumab in 10 mL (20 mg/mL). Each mL contains 20 mg avelumab, D-mannitol (51 mg), glacial acetic acid (0.6 mg), polysorbate 20 (0.5 mg), sodium hydroxide (0.3 mg), and Water for Injection. The pH range of the solution is 5.0 – 5.6 *The Applicant accepted our revision.*
16 HOW SUPPLIED/ STORAGE AND HANDLING 21 CFR 201.57(c)(17)				We added the dosage form(s) and identifying characteristics. We revised this section to align with Recommendations for Labeling Medical Products to Inform Users that the Product or Product Container is not Made with Natural Rubber Latex Guidance for Industry and Food and Drug Administration Staff,

Labeling Standards	Comply			Comments and Recommendations
	Yes	No	n/a	
				March 2013. The vial stopper is not made with natural rubber latex. *The Applicant accepted our revision.*
Manufacturer information For BLAs: 21 CFR 610.61, 21 CFR 610.64 For NDAs: 21 CFR 201.1	x			We recommended revision of the proposed country of origin statement. It appears that "(b) (4)" is your attempt to fulfill the country of origin requirement per 19 CFR 134.11. If so, we recommend revising the statement to "Product of Switzerland". We are aiming to provide consistency with labeling the country of origin. *The Applicant accepted our revision.*
MEDICATION GUIDE, INSTRUCTIONS FOR USE, AND PATIENT INFORMATION				
Title (names and dosage form)	x			
Storage and Handling			x	
Ingredients			x	
Manufacturer Information For BLAs: 21 CFR 610.61, 21 CFR 610.64 For NDAs: 21 CFR 201.1	x			Add the country of origin, Product of Switzerland. *The Applicant's revision is acceptable.*

Additional CDER Labeling Best Practices
We provided the following requests to align with CDER Best Labeling Practices.

1. Confirm there is no text on the ferrule and cap overseal of the vials to comply with a revised United States Pharmacopeia (USP), General Chapters: <1> Injections, Packaging, Labeling on Ferrules and Cap Overseals.

   EMD Serono Response: EMD Serono, Inc. confirms that the proposed packaging system complies with the USP General Chapter <1> Injections, section Packaging, Labeling on Ferrules and Cap Overseals. (b) (4)

   (b) (4)

   The Applicant's response is acceptable.

2. Revise the dosage form "injection" to read "Injection" per USP General Chapters <1>Injections, Nomenclature and Definitions.
   The Applicant's revision is acceptable.

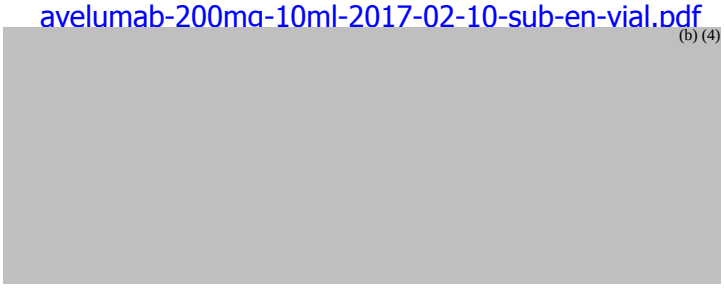
APPENDIX D. Acceptable Labels and Labeling

- Prescribing Information
  \\cdsesub1\evsprod\bla761049\0045\m1\us\114-labeling\1141-draft-label\clean-us-pi-pdf-version.pdf

- Medication Guide
  \\cdsesub1\evsprod\bla761049\0045\m1\us\114-labeling\1141-draft-label\avelumab-medication-guide-mcc-2016-09-14-sub.pdf

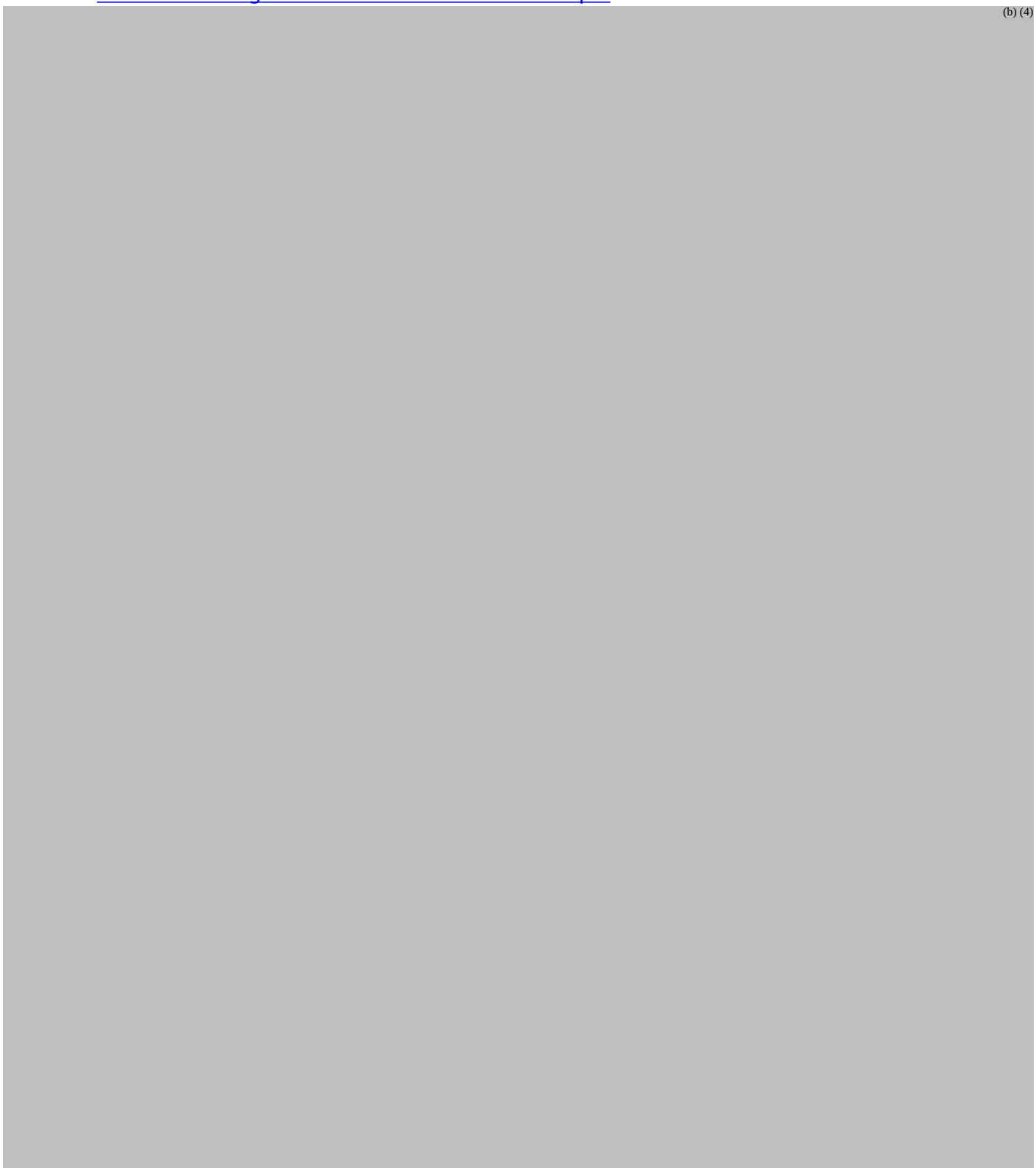
- Container Label
  \\cdsesub1\evsprod\bla761049\0034\m1\us\114-labeling\1141-draft-label\us-ip-avelumab-200mg-10ml-2017-02-10-sub-en-vial.pdf

(b) (4)



- Carton Labeling
  \\cdsesub1\evsprod\bla761049\0042\m1\us\114-labeling\1141-draft-label\us-op-avelumab-200mg-10ml-2017-02-24-sub-en-carton.pdf

(b) (4)



Jibril Abdus-Samad

Digitally signed by Jibril Abdus-Samad
Date: 3/09/2017 02:37:28PM
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Arulvathani Arudchandran

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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

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)

Date of This Memorandum:	March 1, 2017
Requesting Office or Division:	Division of Oncology Products 2 (DOP2)
Application Type and Number:	BLA 761049
Product Name and Strength:	Bavencio (avelumab) Injection, 200 mg/10 mL (20 mg/mL)
Submission Date:	February 10, 2017
Applicant Name:	EMD Serono, Inc.
OSE RCM #:	2016-2000-1
DMEPA Primary Reviewer:	Janine Stewart, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD, BCPS
OMEPRM Acting Deputy Director:	Lubna Merchant, MS, PharmD

1 PURPOSE OF MEMO

The Division of Oncology Products 2 (DOP2) requested that we review the revised container label and carton labeling for Bavencio (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

Additionally, FDA recently issued a final guidance entitled *Nonproprietary Naming of Biological Products* on January 13, 2017 stating the Agency's intention to designate proper names for certain biological products that include four-digit distinguishing suffixes. This 351(a) application is within the scope of this guidance. However, the issuing of the guidance occurred at a point in our review of the application that did not allow for sufficient time for FDA to designate a proper name with a suffix, as described in the guidance. Therefore, in order to avoid delaying the

[a] Stewart J. Label and Labeling Review for Bavencio (BLA 761049). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2017 JAN 06. 13 p. OSE RCM No.: 2016-2000.

approval of the application and in the interest of public health, we will approve the proper name as designated without a suffix [and intend to work with the applicant post-approval to implement a proper name consistent with the principles outlined in the guidance].

2 CONCLUSION

The revised container label and carton labeling for Bavencio is acceptable from a medication error perspective. We have no further recommendations at this time.

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/s/

JANINE A STEWART
03/01/2017

CHI-MING TU
03/02/2017

LUBNA A MERCHANT
03/02/2017

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

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)

Date of This Memorandum:	March 1, 2017
Requesting Office or Division:	Division of Oncology Products 2 (DOP2)
Application Type and Number:	BLA 761049
Product Name and Strength:	Bavencio (avelumab) Injection, 200 mg/10 mL (20 mg/mL)
Submission Date:	February 10, 2017
Applicant Name:	EMD Serono, Inc.
OSE RCM #:	2016-2000-1
DMEPA Primary Reviewer:	Janine Stewart, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD, BCPS
OMEPRM Acting Deputy Director:	Lubna Merchant, MS, PharmD

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[a] Stewart J. Label and Labeling Review for Bavencio (BLA 761049). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2017 JAN 06. 13 p. OSE RCM No.: 2016-2000.

approval of the application and in the interest of public health, we will approve the proper name as designated without a suffix [and intend to work with the applicant post-approval to implement a proper name consistent with the principles outlined in the guidance].

2 CONCLUSION

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/s/

JANINE A STEWART
03/01/2017

CHI-MING TU
03/01/2017

LUBNA A MERCHANT
03/01/2017

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

PATIENT LABELING REVIEW

Date:	February 21, 2017
To:	Patricia Keegan, MD Director **Division of Oncology Products 2 (DOP2)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Morgan Walker, PharmD, MBA, CPH Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Nicholas Senior, PharmD, JD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	BAVENCIO (avelumab)
Dosage Form and Route:	injection, for intravenous use
Application Type/Number:	BLA 761049
Applicant:	EMD Serono, Inc.

1 INTRODUCTION

On September 23, 2016, EMD Serono, Inc. submitted for the Agency's review a Biologics License Application (BLA) 761049 for BAVENCIO (avelumab) injection. The proposed indication for BAVENCIO is for the treatment of patients with metastatic Merkel cell carcinoma (MCC).

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 Oncology Products 2 (DOP2) on November 3, 2016, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for BAVENCIO (avelumab) injection.

2 MATERIAL REVIEWED

- Draft BAVENCIO (avelumab) injection MG received on September 23, 2016, and received by DMPP and OPDP on February 10, 2017.
- Draft BAVENCIO (avelumab) injection Prescribing Information (PI) received on September 23, 2016, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on February 10, 2017.

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 MG 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 reformatted the MG document using the Arial font, size 10.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG 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 MG 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 MG.

Please let us know if you have any questions.

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/s/

MORGAN A WALKER
02/21/2017

TRUNG-HIEU B TRAN on behalf of NICHOLAS J SENIOR
02/21/2017

BARBARA A FULLER
02/21/2017

LASHAWN M GRIFFITHS
02/21/2017

Clinical Inspection Summary

Date	February 17, 2017
From	Lauren Iacono-Connors, Ph.D., Reviewer Susan Thompson, M.D., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Idara Udoh, Regulatory Project Manager Denise Casey, Clinical Reviewer Division of Oncology Products 2
BLA #	761049
Applicant	EMD Serono, Inc.
Drug	Bavencio™ (Avelumab; MSB0010718C)
NME	Yes
Therapeutic Classification	Priority
Proposed Indication	Bavencio™ for the treatment of patients with Metastatic Merkel Cell Carcinoma (mMCC). This request is based on the results from primarily Study EMR100070-003.
Consultation Request Date	October 20, 2016
Summary Goal Date	February 23, 2017
Action Goal Date	May 23, 2017
PDUFA Date	May 23, 2017

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The data from Study EMR100070-003 were submitted to the Agency in support of BLA 761049. Four clinical sites, Dr. Shailender Bhatia (Site 206), Dr. Howard Kaufman (Site 204), Dr. Jeffery Russell (Site 133), Dr. Kent Shih (Site 102), the study sponsor, EMD Serono, Inc., and one CRO (b) (4) who performed the function of Independent Endpoint Review Committee (IERC) for confirmation of Objective Response (OR), were selected for audit.

The primary efficacy endpoint, objective response rate (ORR) as determined by the clinical investigators and the IERC, was verified with the source records generated at the inspected clinical sites. There were no significant inspectional findings for clinical investigators Dr. Shailender Bhatia, Dr. Howard Kaufman, Dr. Jeffery Russell, Dr. Kent Shih, the study sponsor, EMD Serono, Inc., and CRO, (b) (4). The data from Study EMR100070-003 submitted to the Agency in support of BLA 761049, appear reliable based on available information.

II. BACKGROUND

EMD Serono, Inc. (EMD) seeks approval of Bavencio™ (Avelumab; MSB0010718C) for the treatment of patients with Metastatic Merkel Cell Carcinoma (mMCC). This request is based on the results from primarily Study EMR100070-003.

Study EMR100070-003 is entitled, "A Phase II Open-label, Multicenter Trial to Investigate the Clinical Activity and Safety of Avelumab (MSB0010718C) in Subjects with Merkel Cell Carcinoma." The study is designed in 2 Parts; Part A and Part B. Only data from Part A is included in the submission. The study planned to enroll 84 subjects. The study screened 125 subjects and 88 subjects were enrolled at 38 clinical centers in North America, Europe, Australia, and Asia.

Study Period: First patient enrolled: July 3, 2014
Data cut-off date for primary analysis: March 3, 2016 (Part A)
Primary efficacy endpoint: objective response rate (ORR); the proportion of subjects with a best response of Complete Response (CR) or Partial Response (PR) using RECIST v1.1 as assessed by the IERC.
Objectives of Inspections:

a. Verify best confirmed response of CR or PR as assessed by the IERC using RECIST Version 1.1.
b. Identification, documentation, and reporting of adverse events (AEs) for a sample of enrolled subjects.
c. General compliance with the investigational plan.

III. RESULTS (by site):

Name of CI, Site #, Address	Protocol # and # of Subjects	Inspection Date	Final Classification
CI#1: Shailender Bhatia (Site 206) Associate Professor/University of Washington 825 Eastlake Ave East, G3-303, Seattle, Washington 98109	Protocol: EMR100070-003 Subjects: 7	November 16-30, 2016	Preliminary Classification VAI
CI#2: Howard Kaufman (Site 204) 195 Little Albany St New Brunswick, NJ 08901	Protocol: EMR100070-003 Subjects: 7	December 12-19, 2016	Preliminary Classification NAI
CI#3: Jeffery Russell (Site 133) Moffitt Cancer Center 10920 McKinley Dr. SRB 22031 Tampa, FL 33612	Protocol: EMR100070-003 Subjects: 8	December 12-16, 2016	Preliminary Classification NAI

Name of CI, Site #, Address	Protocol # and # of Subjects	Inspection Date	Final Classification
CI#4: Kent Shih (Site 102) 250 25th Ave North, Suite 100 Nashville, TN 37203	Protocol: EMR100070-003 Subjects: 4	November 7-15, 2016	Preliminary Classification VAI
Sponsor: EMD Serono, Inc. 1 Technology Place Rockland, MA 02370-1071	Protocol: EMR100070-003 Site Numbers: 102, 133, 204, 206 and 801	January 5-13, 2017	Preliminary Classification VAI
CRO: (b) (4)	Protocol: EMR100070-003 Site Numbers: 102, 133, 204, 206, 407 and 608	January 9-12, 2017	Preliminary Classification NAI

Key to Compliance Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

1. Dr. Shailender Bhatia, M.D. (Site 206)

The site screened and enrolled seven subjects. At the time of this inspection, three subjects were deceased due to disease progression and four subjects are still enrolled, active, and receiving the study drug. Records of all subjects screened and enrolled were reviewed during the inspection. The inspection included assessment of IRB submissions and approvals, all informed consent forms and subject source data. The source data was randomly compared to the e-CRF. No discrepancies were observed. Serious Adverse Event (SAE) and all adverse events were also reviewed.

The primary endpoint is the confirmed Best Overall Response for each subject, per RECIST 1.1, as determined by the Independent Endpoint Review Committee (IERC). Source documents at the site corroborated primary efficacy endpoint data reported by the IERC.

There was no evidence of under-reporting of AEs; however, there was one instance where the site did not report a SAE within the protocol-specified timeframe. In addition, post infusion ECGs were not always performed for three subjects. A Form FDA 483 was issued citing these inspectional observations. Briefly, Subject 2060007

had an SAE of Multifactorial Encephalopathy and Physical Deconditioning on 3/24/15. The SAE was included in the datasets submitted to the application. The Principal Investigator signed the SAE report form on 3/31/15. However, the SAE was not reported to the sponsor until 4/9/15. Also, Subjects 2060002, 2060006, and 2060004 each missed approximately 20% of their protocol-specified post-infusion (2 hours ± 20 minutes after the end of infusion) ECGs. The missed ECGs were reflected in the datasets submitted to the application, but not specifically reported as protocol violations. While these are regulatory violations, these should not importantly impact study outcomes or have placed the subjects at undue risk. The missed ECGs represent a very small fraction of all ECGs captured by this site during the conduct of the study.

OSI Reviewer Notes: Prior to the completion of the inspection, the clinical study site staff discovered the root cause of the missed ECGs and developed a corrective action plan that should minimize these observations moving forward.

The data from Site 206, associated with Study EMR100070-003 appear reliable.

2. Dr. Howard Kaufman, M.D. (Site 204)

The site screened 15 subjects and enrolled seven subjects into Part A. At the time of this inspection four subjects had completed the study. A complete record review was done for 13 enrolled subjects.

The inspection covered a review of the source data and compared it to the data listings submitted to the application. Special attention was given to primary efficacy endpoints, adverse events reporting, concomitant medications, and adherence to protocol. The inspection also covered 100% review of Informed Consent Forms. Review of regulatory documentation, monitoring practices, study medication accountability, and delegation of authority was also completed. There were some minor recordkeeping issues that were discussed with the site.

The inspection revealed no significant deficiencies. There was no evidence of under-reporting of AEs. Source documents at the site corroborated primary efficacy endpoint data reported by the IERC.

The data from Site 204, associated with Study EMR100070-003, appear reliable.

3. Dr. Jeffery Russell, M.D. (Site 133)

The site screened 14 subjects and enrolled eight subjects into Part A. At the time of this inspection two subjects were still alive and one is in follow up. A complete record review was done for all enrolled subjects.

The inspection covered a review of the source data and compared it to the data listings submitted to the application. Special attention was given to primary efficacy endpoints, adverse events reporting, concomitant medications, and adherence to protocol. The inspection also

covered 100% review of Informed Consent Forms for all screened subjects, regulatory documentation, monitoring practices, study medication accountability and delegation of authority.

The inspection revealed no significant deficiencies. There was no evidence of under-reporting of AEs. Source documents at the site corroborated primary efficacy endpoint data reported by the IERC.

The data from Site 133, associated with Study EMR100070-003, appear reliable.

4. Dr. Kent Shih, M.D. (Site 102)

Six subjects were screened, two were screen failures, and four were enrolled into the study. One subject died during the study, and three were discontinued due to disease progression. A complete record review was done for all subjects. The inspection included but was not limited to review of informed consent documentation, subject records, adverse events, computer source records, laboratory results, CRFs, drug accountability records, clinical investigator agreements, financial disclosure documents, and training records.

With the exception of AE reporting, the inspection revealed no significant deficiencies. Source documents at the site corroborated primary efficacy endpoint data reported by the IERC. Efficacy endpoints as determined by the clinical investigator were also verified. There was no evidence of under-reporting of SAEs. However, there were numerous instances where AEs were documented in subject source records, but were not included in the data listings submitted to the application. All four subjects had numerous AEs that occurred prior to the data cut-off date for primary analysis, March 2016, recorded in visit notes and, in some cases on the subject-specific AE Log, but were not reported to the sponsor prior to the current inspection. The FDA inspection found approximately 15 unreported AEs. Then the site staff conducted a comprehensive record review and found an additional 37 unreported AEs.

As such, these unreported AEs, in many cases, were not assessed for grade, study drug relationship, and whether these were serious events. Based upon a preliminary review of the Establishment Inspection Report, Subject 1020001 had 13 unreported AEs, Subject 1020002 had 10 unreported AEs, Subject 1020004 had 11 unreported AEs, and Subject 1020006 had 18 unreported AEs prior to the current inspection.

During the course of the inspection, the clinical site study staff updated records as appropriate to capture the unreported AEs as well as the minor protocol deviations identified during the inspection. Dr. Shih indicated in a written response to the Form FDA 483, inspectional observations, dated December 6, 2016, that protocol deviations associated with pre-medication administration requirements and unreported AEs discovered during the inspection were transcribed into each subject's eCRF. The AE entries to the eCRF were completed on November 10, 2016, prior to the inspection close out date of November 15, 2016.
The majority of the approximately 50 unreported AEs appear to be relatively minor and low grade, including chills, fatigue, gastro-intestinal issues such as constipation, pain, numbness, tingling and weight changes. Notable missing AEs include Subject 1020001 for a grade 3

cataract surgery on January 21, 2015 and Subject 1020006 for grade 3 abdominal pain, grade 3 fatigue, and grade 3 generalized muscle weakness on September 16, 2015, and grade 3 gait disturbance on October 6, 2015. None of these AEs were reportedly related to the study drug. The under-reporting of AEs by Site 102, Dr. Shih, is a serious regulatory violation. The data listings submitted to the application for Site 102 documented a combined total of approximately 31 AEs (including 5 SAEs), representing approximately 37% (31/83) of all AEs documented in subject source documents. The majority of AEs that occurred at this site, albeit non-serious and non-infusion-related, were not submitted to the application.

Two out of four subjects failed to receive protocol-specified pre-medication, acetaminophen and an H1 blocker, within the required timeframe of 30-60 minutes prior to each avelumab infusion. For example, four out of eleven pre-medication events for Subject 1020001 and eight out of 17 pre-medication events were administered ≤15 minutes prior to IP infusion, or 106 to 98 minutes prior to IP infusion. Infusion-related reactions include fever, chills, rigors, diaphoresis and headache, as specified in the protocol. There was no evidence of acute infusion-related reactions for these subjects. This observation should not affect study outcomes or have placed subjects at undue risk.

A Form FDA 483, inspectional observations, was issued for failure to follow the protocol regarding adverse event reporting and dosing of pre-medications. Dr. Shih indicated in a written response, dated December 6, 2016, to the Form FDA 483, inspectional observations that he concurred with the inspectional observations of protocol deviations associated with pre-medication administration requirements and unreported AEs, discovered during the inspection.

OSI Reviewer Notes: All other aspects of the conduct of the study at Site 102 appeared to be adequate. The AEs discovered to be missing from the application during the inspection have since been reviewed, characterized, and entered into each subject's eCRF. Documentation of the audit trail for each subject's entries for additional AEs was collected during the inspection. Updated subject adverse event logs, study visit notes documenting AEs and finally audit trails for each AE entered into the eCRFs per protocol were reviewed. Each of these AEs was determined by the investigator to be unrelated to the study drug.

In the written response, dated December 6, 2016, to the Form FDA 483, inspectional observations Dr. Shih described what he believed to be the root cause of under-reported AEs throughout the study. Briefly, the Research Study Nurse (RSN) was responsible for reviewing interim medical history (i.e., progress notes) and confirming AE status with the subject during their clinical site visits. The RSN, in conjunction with the principal investigator, assesses AEs and documents them on the subject AE log maintained in subject source records. Finally, the Clinical Trial Manager (CTM) is responsible for CRF completion and may query the RSN for data resolution or discrepancies between medical records and the AE log prior to entry into the CRF. According to Dr. Shih, the RSN(s) did not consistently follow the process described above, because the training for the RSN(s) on the process for collecting AEs and the importance of capturing AEs involving subject safety and data integrity in the clinical study setting versus the standard of care AE assessments in non-research setting were inadequate. In addition, Dr. Shih stated that data queries by the CTM to the RSN(s) were not consistently

addressed per local SOP. The site also experienced unexpected RSN turnover during the conduct of the study.

Dr. Shih concluded that the delayed reporting of AEs to the sponsor should not have impacted subjects' safety because subjects were under the care of the treating investigator throughout the study. This is a true statement; however, reporting all AEs throughout the conduct of the study by every clinical site that enrolled subjects is critical to the management and oversight of subject safety. The combined safety information may reveal a safety signal that could require amendments to the protocol and/or the corresponding informed consent document. The corrective actions described by Dr. Shih in the written response to the Form FDA 483 included identification of all unreported AEs, related concomitant medications and procedures noted during the inspection, investigator assessment for each entry for causality, severity and drug relationship, follow by the site staff entering the information into the eCRFs. This was completed on November 10, 2016, prior to the completion of the inspection. Dr. Shih also provided preventive actions, some of which have already been implemented, to mitigate the inspectional observations moving forward.

The data submitted by the sponsor for Site 102 to the application were verifiable with source records at the site. However, the AE reporting from the site to the sponsor was inadequate resulting in a substantial under-representation of actual AEs documented at the site. As a result, the datasets submitted by the sponsor to the application were not an accurate representation of AE data from Site 102. While the number of missing AEs from Site 102, approximately 52, is substantial for the site, it represents a small proportion of all AEs reported for the 88 subjects enrolled in this study. According to the BLA 761049 Clinical Site Selection Tool v2.4.14, specifically for Study 100070-003, the NSAE reporting average rate was approximately 10.6 NSAE events per subject. Therefore, the 88 enrolled subjects in the study might have collectively experienced approximately 933 NSAEs. The missing NSAEs from Site 102, approximately 47, represent approximately 5% of the estimated NSAEs for the study. The missing NSAEs from Site 102 should not importantly impacted overall study outcomes or have placed subjects at undue risk.

Notwithstanding the inspectional observations noted above, the data from Site 102, associated with Study EMR100070-003 appear reliable and may be used in support of the respective indication.

5. CRO: (b) (4) (Independent Endpoint Review Committee [IERC])

This inspection was issued to review the conduct of one clinical study (EMR100070-003), performed in support of BLA 761049. The inspection focused primarily on assessing the accuracy of the tumor response and disease progression source records as it pertains to the contractual obligations of the CRO. Subject source documents/records generated by the CRO for 33 subjects from six clinical sites were compared to the eCRF and data listings. Assessment of (b) (4) conduct of the Charter-Specified CRO responsibilities included training, education, and qualifications of radiologists, data collection and management, computer system validation, and Independent Review Charter review and adherence.

All reviewed subjects' image readings performed by the CRO radiologists were verified against the data listings submitted to the application. There were no discrepancies noted. There was no evidence of CRO non-compliance with the Charter.

The data from this CRO, associated with Study EMR100070-003 appear reliable.

6. Sponsor: EMD Serono, Inc.

The inspection focused on the sponsor's control, oversight, and management of Study EMR100070-003. Records reviewed included but were not limited to organizational charts, standard operating procedures, monitoring plans, monitoring reports, transfer of responsibilities, correspondence, training records, FDA 1572s, financial disclosure forms, eCRFs, protocol deviations, Integrated Project Management Plans, Clinical Operations Plans, Clinical Monitoring Plans, Standard Operations Procedures, Imaging Review Charters, Meeting Minutes, Work Instructions, safety plans, serious adverse events, and investigational product accountability records. There were no clinical investigator sites where studies were terminated or activities were suspended.

Per the quality agreement between the sponsor and CRO (b) (4) is responsible for providing qualified monitors and for selecting and training monitors. (b) (4) required the CRA's to have one year of oncology experience in order to act as monitors. A list of the CRA's responsible for monitoring the four clinical sites that were linked inspections to this sponsor inspection and the CV and training documentation records were reviewed. All four monitors had qualifications to meet their job descriptions as CRAs and had received required training on the protocol. All four had training and experience in monitoring clinical studies.

Monitoring records were reviewed for five clinical sites (102, 133, 204, 206, and 801). The record review for all five sites focused specifically on whether there was evidence of systemic under-reporting of AEs and pre-medication administration errors (out of the protocol-specified window of 30-60 minutes prior to the start time of avelumab infusion), as these were key inspectional observations noted during the inspection of Site 102. The monitoring records review confirmed that the inspectional observations were unique to Site 102 and that the CRA responsible for monitoring did not discover these protocol deviations during routine monitoring visits. There were as many as 47 unreported adverse events that were not picked up by the monitor. The remaining four clinical sites whose monitoring reports were reviewed found no major issues.

In general, the sponsor maintained adequate control and oversight of the conduct of Study EMR100070-003. However, there were procedural issues related to study management documents and clinical monitoring of Site 102 was deficient; as a result, numerous NSAEs documented in subject source records were not reported to the sponsor per the protocol. As such, approximately 47 NSAEs, from Site 102, were not included in the datasets submitted to BLA 761049 for Study EMR100070-003.

A Form FDA 483 was issued citing 2 inspectional observations. These observations are summarized below.

The sponsor failed to ensure proper monitoring of the study and ensure the study is conducted in accordance with the protocol and/or investigational plan. Briefly, the CRA responsible for monitoring Site 102 did not observe and report all protocol deviations. The CRA was removed from monitoring the site due to concerns regarding workload but continued monitoring three other sites for this study, Sites 101, 106, and 135. In addition, the protocol required pre-medication with acetaminophen and an H1 blocker within 30 to 60 minutes prior to infusion. Out of 12 instances discovered during FDA inspection of clinical Site 102 where subjects did not receive premedication within the time frame, the CRA responsible for monitoring did not report them as protocol deviations in five instances.

OSI Reviewer Notes: The CRA assigned to monitor Site 102 was identified by the (b) (4) *Project Leader, through routine oversight of performance indicators, as having a low production of SDV due to workload burden. This CRA conducted monitoring visits to Site 102 from December 11, 2014 to November 6, 2015. On December 2, 2015 two CRAs were sent to Site 102 and conducted monitoring visits from December 2015 to March 2016, until a permanent site CRA was assigned. The sponsor became aware of the missed protocol deviations after FDA inspection in November 2016. There has been no review of the CRA's past monitoring activities at the other three clinical sites.*

According to the Integrated Project Management Plan (IPMP) dated March 7, 2014, the first version of plans and charters to be developed by March 19th, 2014 include the Clinical Operations Plan (COP); however, Version 1.0 of the COP has an effective date of October 13, 2015. Activities covered by the COP include but are not limited to Study Start-Up Procedures, Site Selection Procedures, Site Initiation Procedures, Site Monitoring Procedures and Source Data Verification. Version 1.0 of the IPMP and the only version created of the COP were never approved. The COP effective date was over one year after the first subject had been enrolled. Four clinical sites were initiated, thirteen subjects were screened, six subjects were enrolled and received study drug, and four interim monitoring visits were conducted prior to the effective date of Version 1.0 of the Clinical Monitoring Plan, October 13, 2015.

OSI Reviewer Notes: The documents described are developed and used by the sponsor and associated CROs to guide the oversight, control, and quality management of the conduct Study EMR100070-003. The development, approval, version management, and the implementation dates for use as compared to clinical site activity are concerning, but, the inspectional findings do not suggest that these observations had a significant impact on overall study conduct and outcome.

Finally, the sponsor did not always provide information for Suspected Unexpected Serious Adverse Event Reaction (SUSAR). An SAE report for Subject 1050006, for development of paraneoplastic syndrome and gait disturbance, was first received by the CRO (b) (4) on May 31, 2016 but the IND safety report was not sent to FDA until July 1, 2016 and to the participating investigators until June 30, 2016.

OSI Review Notes: The AE dataset submitted to the application included a total of 1047 AEs: 952 NSAEs and 95 SAEs. The approximately 47 NSAEs from Site 102 that were not included in the dataset represent a very small proportion of the total NSAEs, 4.7%. While this is a regulatory violation, the inspectional observation should not importantly impact study outcomes. The failure of Site 102 study staff to follow the protocol for AE reporting and the failure of the CRA assigned to monitor this site to identify protocol violations during the monitoring visits, led to under-reporting of AEs to the sponsor.

Notwithstanding the inspectional observations noted above, the data from this sponsor, associated with Study EMR100070-003 appear reliable and may be used in support of the respective indication.

{See appended electronic signature page}

Lauren Iacono-Connors, Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

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

CONCURRENCE:

{See appended electronic signature page}

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

CC:
Central Doc. Rm. BLA #761049
DOP2/Division Director/Patricia Keegan
DOP2/Clinical Team Leader/Suzanne Demko
DOP2/Project Manager/Idara Udoh
DOP2/Medical Officer/Denise Casey
OSI/Office Director (Acting)/David Burrow
OSI/DCCE/ Division Director/Ni Khin
OSI/DCCE/Branch Chief/Kassa Ayalew
OSI/DCCE/Team Leader/Susan D. Thompson
OSI/DCCE/GCP Reviewer/Lauren Iacono-Connors
OSI/ GCP Program Analysts/Joseph Peacock/Yolanda Patague
OSI/Database PM/Dana Walters

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/s/

LAUREN C IACONO-CONNORS
02/17/2017

SUSAN D THOMPSON
02/17/2017

KASSA AYALEW
02/17/2017

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****PRE-DECISIONAL AGENCY MEMO****

Date: February 16, 2017

To: Idara Udoh
Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products

From: Nick Senior, PharmD, JD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: OPDP Comments on the proposed product labeling for BLA 761049 BAVENCIO (avelumab) injection, for intravenous use

---

OPDP has reviewed the proposed product labeling (PI) for BAVENCIO (avelumab) injection, for intravenous use (Bavencio) as requested in the consult dated November 3, 2016. The following comments, using the proposed substantially complete, marked-up version of the PI emailed to OPDP by Idara on February 10, 2017, are provided below.

Comments regarding the Med Guide will be provided at a later time.

If you have any questions, please feel free to contact me (contact information: 240-402-4256; Nicholas.Senior@fda.hhs.gov)

Thank you! OPDP appreciates the opportunity to provide comments on these materials.

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/s/

NICHOLAS J SENIOR
02/16/2017

LABEL AND LABELING REVIEW

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

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

Date of This Review:	January 6, 2017
Requesting Office or Division:	Division of Oncology Products 2 (DOP2)
Application Type and Number:	BLA 761049
Product Name and Strength:	Bavencio (avelumab) Injection, 200 mg/10 mL (20 mg/mL)
Product Type:	Single Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	EMD Serono, Inc.
Submission Date:	September 23, 2016 and December 13, 2016
OSE RCM #:	2016-2000
DMEPA Primary Reviewer:	Janine Stewart, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

1 REASON FOR REVIEW

As part of the approval process for this new molecular entity under BLA 761049, Bavencio (avelumab) Injection, this review evaluates the proposed container label, carton labeling, and Prescribing Information (PI) for areas of vulnerability that can lead to medication errors. This review is in response to a consult request from the Division of Oncology Products 2 (DOP2).

2 MATERIALS REVIEWED

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

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
Human Factors Study	C- N/A
ISMP Newsletters	D- N/A
FDA Adverse Event Reporting System (FAERS)*	E- N/A
Other	F- N/A
Labels and Labeling	G
Prescribing Information (PI)	H

N/A=not applicable for this review
*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

DMEPA performed a risk assessment of the proposed Bavencio Prescribing Information, the container label, and carton labeling to identify deficiencies that may lead to medication errors and areas for improvement.

We provide minor recommendations for improvement to the *Dosage and Administration*, *Dosage Forms and Strength*, and the *How Supplied* Sections of the proposed PI and have provided them in tracked changes in Appendix H.

We note the lack of prominence of the proper name as it appears on the proposed container label and carton labeling. In addition, the order and prominence of product information on the proposed container label and carton labeling can be revised for improved readability and clarity. Moreover, the proposed carton labeling can be improved by minimizing clutter.

Therefore, we provide recommendations in Section 4 in order to promote the safe use of this product.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed Bavencio PI can be improved to increase clarity of information, and the Bavencio carton labeling can be improved to increase readability and the prominence of important information to promote the safe use of this product.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information

1. Based on this review, we recommend minor revisions to the proposed PI in tracked changes for review and consideration by OPQ. See Appendix H for tracked change edits in the proposed PI.

4.2 RECOMMENDATIONS FOR EMD SERONO, INC.

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

A. Container Label and Carton Labeling

1. The dosage form portion of the established name lacks prominence commensurate with the proprietary name. Increase the prominence of the dosage form statement on the container and carton labels in accordance with 21 CFR 201.10(g)(2) such that the established name, including the dosage form, is at least half the font size of the proprietary name.

2. Consider revising the NDC numbers of the container label and carton labeling. The container label and carton labeling can be assigned the same NDC since the product is supplied as a single vial within a single carton.

B. Container Label

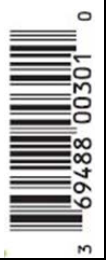
1. As currently presented, the NDC number is located on the side panel of the container label. Since NDC numbers are often used as additional verification prior to drug dispensing in the pharmacy, when presented, it should be prominently displayed in the top third of the principal display panel (PDP) of the labeling in accordance with 21 CFR 207.35(b)(3)(i).

2. The drug barcode is often used as an additional verification before drug administration in the inpatient setting; therefore it is an important safety feature

that should be part of the container label whenever possible. Therefore, we request you add the product barcode to the container label as required per 21CFR 201.25(c)(2). Consider orienting the barcode in a vertical position to make the barcode easier to scan using a barcode scanner.

3. The container label appears crowded. Delete the statement, "(b) (4) ." This statement is not required on a partial label per 21 CFR 610.60(c).

4. The container label appears crowded. Important product information should be displayed with prominence on the Principal Display Panel (PDP). This may be achieved by creating a side panel and relocating other information to the side panel. Example layout below demonstrates our recommendation only (not to size, spacing, color, etc.). Of note, we recommend mix case letters "For Intravenous Use Only" instead of all upper case to improve readability. Also, ensure barcode placement (horizontal vs. vertical) can be easily scanned.

PDP	Side Panel
NDC 44087-3535-2 Bavencio (avelumab) Injection 200 mg/ 10 mL (20 mg/ mL) For intravenous infusion after dilution Single-dose vial. Discard unused portion.	Rx only Storage and handling information. Warning statement Manufacturer information Lot Exp 

C. Carton Labeling

1. Revise the statement "(b) (4)" which appears on the side panel to read "Usual Dose: See prescribing information."

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Bavencio that EMD Serono, Inc. submitted on December 13, 2016.

Table 2. Relevant Product Information for Bavencio	
Initial Approval Date	N/A
Active Ingredient	avelumab
Indication	For the treatment of patients with metastatic Merkel Cell Carcinoma (MCC)
Route of Administration	Intravenous
Dosage Form	Injection
Strength	200 mg/10 mL (20 mg/mL)
Dose and Frequency	The recommended dose of BAVENCIO is 10 mg/kg administered as an intravenous infusion over 60 minutes every 2 weeks until disease progression or unacceptable toxicity.
How Supplied	Single-Dose vials packed in individual cartons
Storage	Store at 36°F to 46°F (2°C to 8°C) in original package to protect from light.
Container Closure	The primary container consists of a 16 mL nominal capacity colorless type I (b) (4) glass vial. The closure consists of two components: • A grey (b) (4) rubber stopper, (b) (4) . • An aluminum seal fitted with a removable plastic cap (not in contact with the product).

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/s/

JANINE A STEWART
01/06/2017

CHI-MING TU
01/06/2017

Interdisciplinary Review Team for QT Studies Consultation: QT Study Review

BLA	761049
Brand Name	Bavencio
Generic Name	Avelumab
Sponsor	EMD Serono, Inc
Indication	For the treatment of patients with metastatic Merkel Cell Carcinoma (mMCC) whose disease has progressed after at least one previous chemotherapy regimen.
Dosage Form	Injection: 200 mg/10 mL (20 mg/mL) solution in a single-dose vial
Drug Class	human antibody of the IgG1
Therapeutic Dosing Regimen	Administer 10 mg/kg as an intravenous infusion over 60 minutes once every 2 weeks.
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	MTD not reached in human; 20mg/kg Q2W was studied and was found to be well tolerated in human. NOAEL: 140 mg/kg in cynomolgus monkeys
Submission Number and Date	SDN004; 26 Oct 2016
Review Division	DOP2

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

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

Avelumab 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 avelumab has the potential to delay ventricular repolarization.

In these three open-label, phase 1 and phase 2 studies, an approximately 1200 patients were administrated avelumab. No large changes in the mean change from baseline QTc interval were detected when avelumab was administered at the therapeutic dosing 10.0 mg/kg (Table 1). QTcF >500 ms was detected in a total of 33 subjects (2.1%) in the 10 mg/kg dose cohorts from all three studies. ΔQTcF > 60 ms was noted for 63 subjects (4.1%) in the 10 mg/kg dose cohorts.

Table 1: The Point Estimates and the 90% CIs for Avelumab Treatments at Last Visit (FDA Analysis)

Study	Treatment	ΔQTcF (ms)			
		N	Mean	Lower 90% CI Limit	Upper 90% CI Limit
001	10.0 mg/kg	15	1.4	-6.7	9.5
	10.0 mg/kg Expansion	1418	1.7	0.6	2.8
002	10.0 mg/kg	6	23.1	14.7	31.4
	10.0 mg/kg Expansion	34	0.4	-4.9	5.8
003	10.0 mg/kg Expansion	73	1.9	-1.7	5.5

There was no evident relationship between avelumab concentrations and ΔQTcF. The 10 mg/kg dose selected for expansion phases in the studies is the therapeutic dose. Since the avelumab is a human antibody of the IgG1 isotype with elimination primarily by proteolytic catabolism, there is no expectation of drug-drug interaction (DDI) and organ impairment affecting PK. The applicant's population pharmacokinetic analysis showed no effect of age, sex, race or renal/hepatic impairment.

2 PROPOSED LABEL

Our proposed language is a recommendation only. We defer final labeling language to the Division.

12.2 Pharmacodynamics

Cardiac Electrophysiology

Avelumab as a large targeted protein has a low likelihood of direct ion channel interactions. The effect of BAVENCIO on the QTc interval was evaluated in three open label clinical studies in patients with advanced solid tumors. No large changes in the mean QTc interval (i.e., > 20 ms) were detected in the studies.

3 BACKGROUND

3.1 PRODUCT INFORMATION

Avelumab is a fully human antibody of the IgG1 isotype that specifically targets and blocks the ligand (PD-L1) for PD-1. By blocking the interaction between PD-L1 and PD-1, it releases anti-tumor CD8+ T cells from the suppressive effects of PD-L1, resulting in the restoration of cytotoxic T cell response.

3.2 MARKET APPROVAL STATUS

Avelumab 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 avelumab's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The sponsor submitted the study reports EMR100070-001, EMR100070-002 and EMR100070-003 for avelumab, including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

EMR100070-001: A Phase I, open-label, multiple-ascending dose trial to investigate the safety, tolerability, pharmacokinetics, biological and clinical activity of avelumab (MSB0010718C) in subjects with metastatic or locally advanced solid tumors and expansion to selected indications.

EMR100070-002: A Phase I trial to investigate the tolerability, safety, pharmacokinetics, biological and clinical activity of MSB00107618C in Japanese subjects with metastatic or locally advanced solid tumors, with expansion part in Asian subjects with gastric cancer

EMR100070-003: Phase II, open-label, multicenter trial to investigate the clinical activity and safety of avelumab (MSB0010718C) in subjects with Merkel cell carcinoma

4.2.2 Protocol Number

EMR100070-001, EMR100070-002 and EMR100070-003

4.2.3 Study Dates

EMR100070-001:

- First subject in: Q1, 2013
- Data cutoff date: 05 November 2015

EMR100070-002:

- First subject in: September 2013
- Data cutoff date: 17 December 2015

EMR100070-003:

- First subject in: Q2, 2014
- Data cutoff date: 17 December 2015

4.2.4 Objectives

EMR100070-001:

The primary objective is to assess the clinical activity of avelumab as determined by the ORR according to RECIST 1.1 by an Independent Endpoint Review Committee in subjects with metastatic MCC after failing first-line chemotherapy.

EMR100070-002:
The primary objective is to assess the safety and tolerability of avelumab in Japanese subjects with solid tumors including gastric cancer and to determine the maximum tolerated dose (MTD) administered as monotherapy by investigating the occurrence of dose-limiting toxicities (DLTs) for the first 3 weeks of avelumab in the dose-escalation part.

EMR100070-003:
The primary objective is to demonstrate superiority with regard to progression free survival with avelumab over investigator's choice of platinum containing chemotherapy regimen as first-line treatment.

4.2.5 Study Description

4.2.5.1 Design

EMR100070-001:

The study has two phases: the dose-ranging phase and the expansion phase. The dose-ranging portion of this study is complete.

Dose ranging

Doses were escalated from 1 mg/kg (n=4) to 3 (n=13), 10 (n=15), and 20 mg/kg (n=21) using a standard 3+3 trial design in subjects with metastatic or advanced solid tumors. Avelumab was given as a 1 hour infusion every 2 weeks (q2w) for all dose administrations.

Expansion phase

A dose of 10 mg/kg every two weeks (q2w) was recommended based upon PK and PD observations made during the dose ranging phase of the study. The efficacy and safety of avelumab was explored in several solid tumor types that exhibit PD-L1 expression:

Four primary cohorts (N=150 subjects each):

- Non-small cell lung cancer (NSCLC), post platinum doublet
- NSCLC, first-line, does not carry an epidermal growth factor receptor (EGFR) activating
- mutation or anaplastic lymphoma kinase (ALK) re-arrangements
- Gastric or gastric-esophageal-jejunum (GEJ) cancer
- Metastatic breast cancer (MBC)

Eight secondary cohorts:

- Colorectal cancer (CRC) (N=20)
- Castration-resistant prostate cancer (CRPC) (N=20)
- Adenoid cystic carcinoma (ACC) (N=50)
- Melanoma (N=50)

- Mesothelioma (N=50)
- Urothelial carcinoma (N=50; enrollment stopped at N=44)
- Ovarian cancer (N=75)
- Renal cell carcinoma (RCC), second-line (N=20)

Four efficacy expansion cohorts

- Ovarian cancer, second-line only, platinum refractory (N=100)
- Urothelial carcinoma, platinum ineligible or progressed after at least 1 line of platinum- based therapy (N=100)
- Gastric and GEJ cancer, third-line (N=150)
- Head and neck squamous-cell carcinoma (HNSCC), platinum ineligible or progressed after at least 1 line of platinum-based therapy (N=150)

EMR100070-002:

The study has two phases: the dose ranging phase and the expansion phase. The numbers of subjects below reflect the total number of treated subjects.

Dose ranging

Doses were escalated from 3 mg/kg (n=5) to 10 (n=6) and 20 mg/kg (n=6) using a standard 3+3 trial design in subjects with metastatic or advanced solid tumors. Avelumab was given as a 1 hour infusion q2w for all dose administrations.

Expansion phase

A dose of 10 mg/kg q2w was recommended based upon PK and PD observations made during the dose ranging phase of the study. The efficacy and safety of avelumab was explored in Japanese subjects with gastric cancer (n=34).

EMR100070-003:

This Phase II study is designed to evaluate the efficacy of 10 mg/kg avelumab q2w for the treatment of subjects with Merkel cell carcinoma (mMCC). The study subjects need to have received at least one line of chemotherapy for the treatment of mMCC. There were 88 subjects enrolled in the 2L cohort (Part A).

For all 3 studies, the study subjects continued to receive treatment q2w until a confirmed progression, unacceptable toxicity, or reason for withdrawal occurred. Those subjects who experienced a confirmed CR were treated for a maximum of 12 months and a minimum of 6 months after confirmation.

4.2.5.2 Blinding

The study was conducted in an open-label manner.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

EMR100070-001: Avelumab administered via IV infusion once every 2 weeks.

Dose escalation phase:

- 1.0 mg/kg (n = 4)

- 3.0 mg/kg (n =13)
- 10.0 mg/kg (n =15)
- 20.0 mg/kg (n =21)

Treatment expansion phase: 10.0 mg/kg

EMR100070-002: Avelumab administered via IV infusion once every 2 weeks.

Dose escalation phase:

- 3.0 mg/kg (n = 5)
- 10.0 mg/kg (n = 6)
- 20.0 mg/kg (n = 6)

Treatment expansion phase: 10.0 mg/kg (n = 34)

EMR100070-003: 10 mg/kg of avelumab administered via IV infusion once every 2 weeks (n=88).

4.2.6.2 Sponsor's Justification for Doses

Reviewer's Comment: 10 mg/kg intravenous (IV) once every 2 weeks is the proposed therapeutic dose.

4.2.6.3 Instructions with Regard to Meals

As avelumab is administered via iv infusion, time of day and relationship to meals for study drug administration were not specified in the protocol.

Reviewer's Comment: Acceptable.

4.2.6.4 ECG and PK Assessments

12-lead singlet ECG measurements were collected prior to infusion and 2 hours post the end of infusion every 2 weeks until Week 13, and every 6 weeks thereafter for study 001 and 003 (every 4 weeks thereafter for study 002).

Collection for avelumab sampling and ECG measurements is summarized in Table 2.

Table 2: Overview of Clinical Studies for ECG Assessment

Protocol No/Location	Study population	PK/ECG assessment	Treatments
EMR100070-001 (Phase 1/1b) US (IND 115747), Belgium, Czech Republic, France, Germany, Hungary, Korea, Poland, Taiwan, and UK EudraCT number: 2013-002834-19 (VHP No. 341)	Adult subjects with metastatic or locally advanced solid tumors and expansion to selected indications	Serial PK sampling in the dose escalation cohorts (53 subjects) and expansion cohorts (25 subjects) including colorectal cancer (CRC) expansion cohort and castrate-resistant prostate cancer (CRPC) expansion cohort: prior to and at the end of the 1-hour infusion, and at 0.5, 1, 2, 4, 6, and 12 hours, and optional 24, 36, 48 hours post the first infusion Sparse PK sampling at trough and/or the end of infusion throughout the study on multiple visits in all cohorts including the aforementioned dose escalation and expansion phases on visits beyond the first dose interval ECG assessment: 12-lead singlet, local machine read, prior to infusion and within 2 hours post the end of infusion every 2 weeks until Week 13, and every 6 weeks thereafter	Avelumab administered via IV infusion once every 2 weeks Dose escalation phase: 1.0 mg/kg (n = 4) 3.0 mg/kg (n =13) 10.0 mg/kg (n =15) 20.0 mg/kg (n =21) Treatment expansion phase: 10.0 mg/kg
EMR100070-002 (Phase 1/1b) Japan	Adult Japanese subjects with metastatic or locally advanced solid tumors, with expansion in subjects with gastric cancer	Serial PK sampling during the first dose interval of the dose escalation cohorts: prior to and at the end of the 1-hour infusion, and at 0.5, 1, 2, 4, 6, and 12 hours, and optional 24, 36, 48 hours post the first infusion Sparse PK sampling at trough and/or the end of infusion throughout the study in the expansion cohorts and on multiple visits beyond first dose interval in the dose escalation cohort ECG assessment: 12-lead singlet, local machine read, prior to infusion and 2 hours post the end of infusion every 2 weeks until Week 13, and every 4 weeks thereafter	Avelumab administered via IV infusion once every 2 weeks. Dose escalation phase: 3.0 mg/kg (n = 5) 10.0 mg/kg (n = 6) 20.0 mg/kg (n = 6) Treatment expansion phase: 10.0 mg/kg (n = 34)
EMR100070-003 (Phase 2 Pivotal) US (IND 119394), Australia, Austria, France, Germany, Italy, Japan, Spain, and Switzerland EudraCT number: 2014-000445-79 (VHP No. 531)	Adult subjects who have received at least 1 line of previous chemotherapy for the treatment of metastatic MCC (88 enrolled and on treatment as of March, 03 2016)	Sparse PK sampling including pre-dose, at the end of infusion and 2 to 8 hours after the end of infusion on multiple visits throughout the study ECG assessment: 12-lead singlet, local machine read, prior to infusion and 2 hours post the end of infusion every 2 weeks until Week 13, and every 6 weeks thereafter	10 mg/kg of avelumab administered via IV infusion once every 2 weeks (n=88)

Reviewer's Comment: Acceptable. The timing of ECGs is able to capture the potential effects around the steady state Tmax.

4.2.6.5 Baseline

Baseline is defined as the last non-missing observation prior to the administration of first dose of trial treatment. Additionally, ECG baseline was to be derived from the visit where no RR, PR, QRS, or QT was missing.

4.2.7 ECG Collection

The ECGs were machine-read locally.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

Adult subjects with metastatic or locally advanced solid tumors and expansion to selected indications, adult Japanese subjects with metastatic or locally advanced solid tumors with expansion in subjects with gastric cancer, adult subjects who have received at least 1 line of previous chemotherapy for the treatment of metastatic MCC were included in studies EMR100070-001, EMR100070-002, and EMR100070-003, respectively.

There were 1474, 51, and 86 subjects included in the dataset from studies EMR100070-001, EMR100070-002, and EMR100070-003, respectively. Compared with the two other studies the proportion of elderly subjects (≥75 years) enrolled in study EMR100070-003 was higher with 34.9% (14.2% and 3.9% in EMR100070-001 and EMR100070-002, respectively) with a predominance of male subjects with 73.3% in EMR100070-003 and 68.6% in EMR100070-002 and with 47.6% rather a balanced sex ratio in EMR100070-001.

4.2.8.2 Statistical Analyses

4.2.8.2.1 Central Tendency Analysis

The sponsor presented descriptive summary of QTcF by pooling 10mg/kg data from both dose escalation phase and expansion phase in study 001. The FDA reviewer performed an independent analysis by treatment phase and dose regimen for all 3 studies. Please refer to results in section 5.

Table 3: ECG Summary Statistics by Visit 25 – Study EMR100070-001 and Dose level – 10 mg/kg – QTCF

			Absolute Value (N=1436)			Change from Baseline (N=1436)	
Parameter	Visit	Planned Time Point	N (Missing	Mean	95% CI	Mean	90% CI
QTcF (msec)	BASELINE	PRIOR TO INFUSION	1414 (22)	413.1	(411.8 ; 414.3)		
	WEEK 1 DAY 1	2 HOURS AFTER INFUSION	1387 (49)	415.9	(414.6 ; 417.2)	2.8	(1.8 ; 3.7)
	WEEK 3 DAY 15	PRIOR TO INFUSION	1280 (156)	412.9	(411.6 ; 414.2)	-0.5	(-1.5 ; 0.4)
		2 HOURS AFTER INFUSION	1246 (190)	418.4	(417.0 ; 419.8)	4.5	(3.4 ; 5.6)
	WEEK 5 DAY 29	PRIOR TO INFUSION	1149 (287)	413.0	(411.6 ; 414.4)	-0.7	(-1.6 ; 0.3)
		2 HOURS AFTER INFUSION	1122 (314)	419.3	(417.9 ; 420.6)	5.6	(4.6 ; 6.5)
	WEEK 7 DAY 43	PRIOR TO INFUSION	919 (517)	414.0	(412.5 ; 415.5)	0.1	(-0.9 ; 1.1)
		2 HOURS AFTER INFUSION	878 (558)	420.4	(418.8 ; 422.0)	6.2	(5.1 ; 7.3)
	WEEK 9 DAY 57	PRIOR TO INFUSION	799 (637)	414.3	(412.6 ; 415.9)	-0.3	(-1.3 ; 0.8)
		2 HOURS AFTER INFUSION	765 (671)	419.4	(417.7 ; 421.1)	4.6	(3.4 ; 5.8)
	WEEK 11 DAY 71	PRIOR TO INFUSION	712 (724)	414.2	(412.5 ; 416.0)	-0.9	(-2.1 ; 0.3)
		2 HOURS AFTER INFUSION	679 (757)	418.6	(416.2 ; 420.9)	3.1	(1.2 ; 5.0)
	WEEK 13 DAY 85	PRIOR TO INFUSION	505 (931)	416.7	(414.8 ; 418.7)	1.6	(0.2 ; 3.0)
		2 HOURS AFTER INFUSION	487 (949)	421.3	(419.3 ; 423.4)	6.3	(4.8 ; 7.7)
	WEEK 19 DAY 127	PRIOR TO INFUSION	274 (1162)	417.3	(414.5 ; 420.1)	1.6	(-0.3 ; 3.5)
		2 HOURS AFTER INFUSION	268 (1168)	422.0	(419.1 ; 424.8)	6.2	(4.1 ; 8.2)
	WEEK 25 DAY 169	PRIOR TO INFUSION	169 (1267)	415.6	(412.2 ; 418.9)	2.8	(0.2 ; 5.4)
		2 HOURS AFTER INFUSION	166 (1270)	421.0	(417.3 ; 424.8)	8.0	(5.0 ; 10.9)

Source: Sponsor's ECG report page 47.

4.2.8.2.2 Assay Sensitivity

The sponsor did not present assay sensitivity analysis.

4.2.8.2.3 Categorical Analysis

An integrated analysis of potentially clinically significant ECG abnormalities (PCSA) pooled from all studies (EMR100070-001, EMR100070-002, and EMR100070-003) is presented in sponsor's report. No clinically meaningful changes in heart rate were observed throughout the various dose groups in all 3 studies.

Increased values for QRS (≥ 120 msec) and PR interval (≥ 220 msec and increase ≥ 20 msec) were observed in the 10 mg/kg dose group (8.7% for QRS and 5.6% for PR) and 20 mg/kg dose group (14.8% for both intervals).

According to local machine read of ECG measurements from the large pooled population receiving avelumab treatment, an on-treatment QTcF > 500 msec was detected in a total of 33 subjects (2.1%) only in the 10 mg/kg dose cohorts from all three studies. Delta QTcF > 60 msec was noted for 59 subjects (3.9%) in the 10 mg/kg dose cohorts and in one patient (3.7%) from the 20 mg/kg dose cohorts.

4.2.8.3 Safety Analysis

Safety information (e.g. AEs) was not provided in the sponsor's ECG report.

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

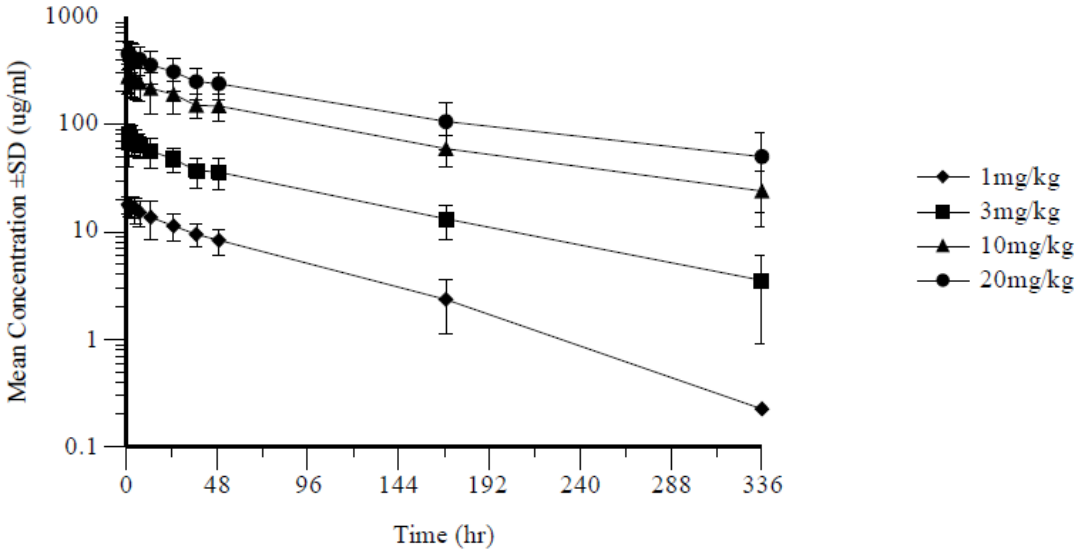
The PK results are presented in Table 4 and Figure1. Following single iv administration the mean avelumab serum concentrations appeared to increase with ascending doses.

Table 4: Pharmacokinetic Parameters after the First Dose of Avelumab for subjects with Solid Tumors (EMR100070-001)

Variable	Dose Group	N[a]	GM[b]	CV% GM[b]	Mean	Median	StDev
C_{max} (µg/mL)	1 mg/kg	4	18.4	21.8	18.7	18.9	3.96
	3 mg/kg	13	78.9	29.5	81.9	82.6	22.1
	10 mg/kg	48	294	32.5	310	291	109
	20 mg/kg	21	470	29.9	489	494	140
C_{trough} (µg/mL)	1 mg/kg	3	NC	NC	0.227	0.00	0.393
	3 mg/kg	13	NC	NC	3.55	2.98	2.61
	10 mg/kg	39	20.9	57.4	24.0	19.8	13.3
	20 mg/kg	19	36.9	112.0	50.1	44.3	34.6
AUC_{0-t} (hr*µg/mL)	1 mg/kg	4	976	40.7	1040	889	443
	3 mg/kg	13	5740	37.6	6080	7000	1970
	10 mg/kg	48	22800	48.2	24800	24100	9150
	20 mg/kg	21	42200	40.8	45100	45600	15600
$AUC_{0-336hr}$ (hr*µg/mL)	1 mg/kg	2	1180	52.2	1250	1250	591
	3 mg/kg	12	6080	32.1	6340	7020	1800
	10 mg/kg	39	25200	25.3	25900	24300	6680
	20 mg/kg	15	38300	42.0	41100	45400	14800
$AUC_{0-\infty}$ (hr*µg/mL)	1 mg/kg	2	1200	56.7	1290	1290	650
	3 mg/kg	12	6520	34.8	6850	7570	2100
	10 mg/kg	39	27700	27.0	28600	27400	7700
	20 mg/kg	15	42700	47.6	46600	48400	18500
$t_{1/2}$ (hr)	1 mg/kg	2	59.5	37.4	61.4	61.4	21.7
	3 mg/kg	12	81.2	30.3	84.3	89.1	21.8
	10 mg/kg	39	94.6	22.0	96.6	97.7	18.6
	20 mg/kg	15	99.1	29.9	103	109	27.4

(Source: Applicant's study report for study EMR100070-001, Table 22)

Figure1: Mean ± Standard Deviation Serum Avelumab Concentrations versus Time Following First 1-Hour Intravenous Infusion to Subjects with Solid Tumors (EMR100070-001)



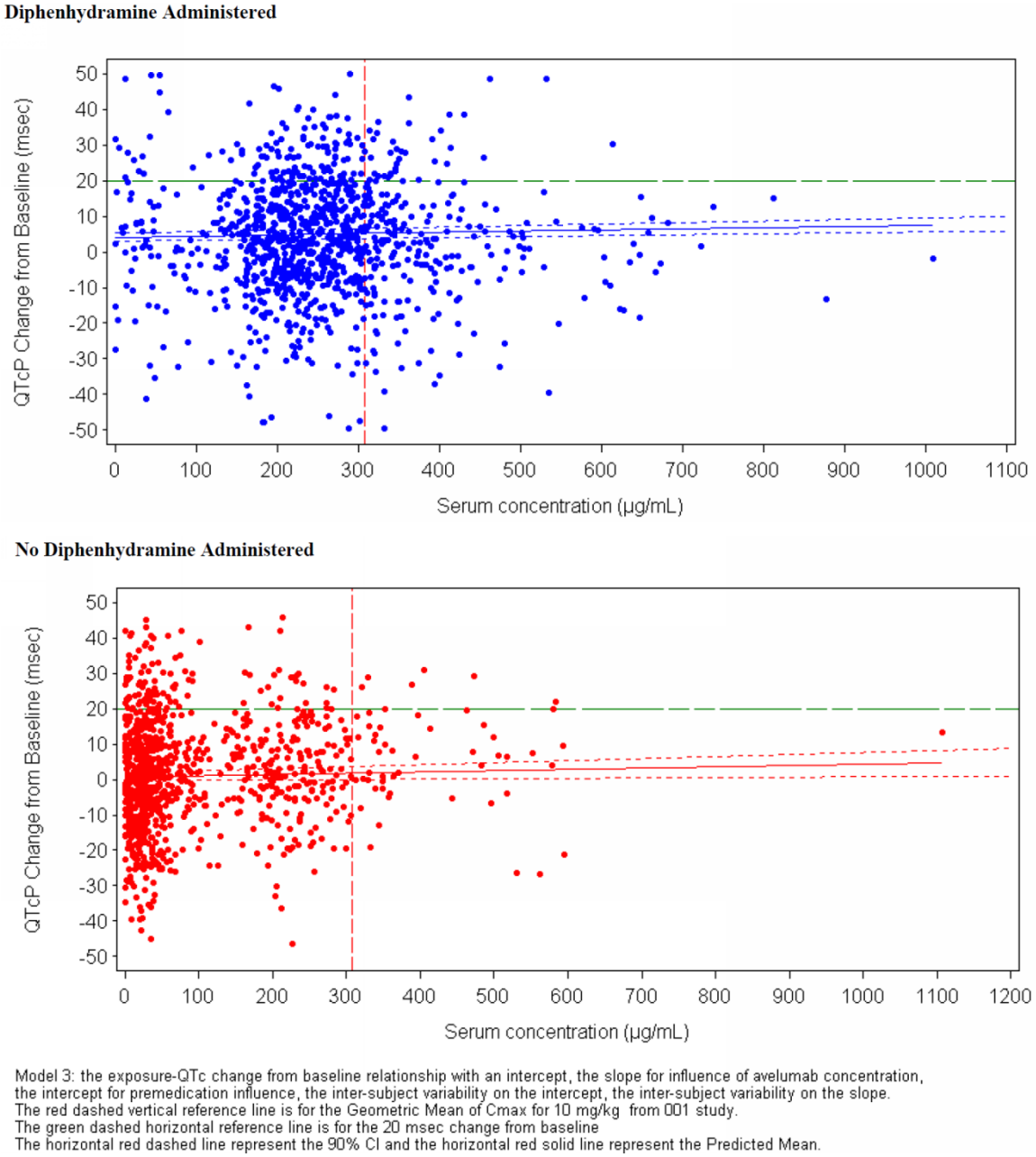
(Source: Applicant's study report for study EMR100070-001, Figure 3)

4.2.8.4.2 Exposure-Response Analysis

The exposure-QTc analysis set included all subjects from studies EMR100070-001, EMR100070-002, and EMR100070-003 for which at least one matched pair of PK and ECG measurement pre-dose and at least one matched pair of PK and ECG measurements within 0-2 hours post the end of infusion was available. Linear mixed effects models were used to describe the relationship between avelumab serum concentrations and the selected primary and secondary analysis variable of both observed QTc and delta QTc.

Specifically, QTcP or QTcF was used in the multivariable regression analyses of serum avelumab concentration-QTc relationship, with and without diphenhydramine (as a categorical variable) (Figure 2 and Figure 3). No evident concentration-QTc relationship was observed.

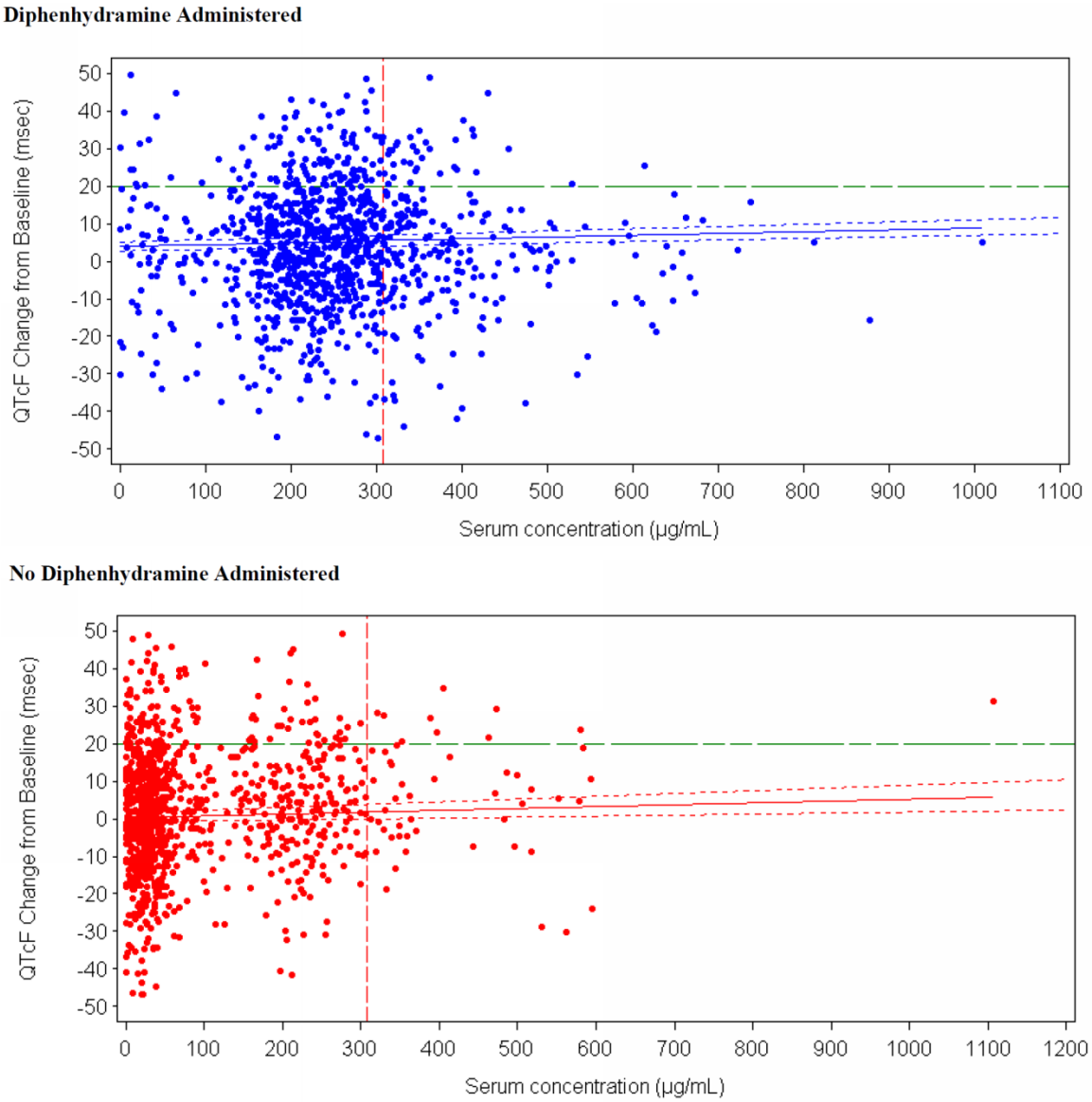
Figure 2: Multivariate Regression between Delta QTcP and Avelumab Concentrations using Model 3 (Full Model)



Model 3: the exposure-QTc change from baseline relationship with an intercept, the slope for influence of avelumab concentration, the intercept for premedication influence, the inter-subject variability on the intercept, the inter-subject variability on the slope.
The red dashed vertical reference line is for the Geometric Mean of Cmax for 10 mg/kg from 001 study.
The green dashed horizontal reference line is for the 20 msec change from baseline
The horizontal red dashed line represent the 90% CI and the horizontal red solid line represent the Predicted Mean.

(Source: Applicant's Corrected QT Interval Analysis Report, Figure 6)

Figure 3: Multivariate Regression between Delta QTcF and Avelumab Concentrations using Model 3 (Full Model)



Model 3: the exposure-QTc change from baseline relationship with an intercept, the slope for influence of avelumab concentration, the intercept for premedication influence, the inter-subject variability on the intercept, the inter-subject variability on the slope.
The red dashed vertical reference line is for the Geometric Mean of Cmax for 10 mg/kg from 001 study.
The green dashed horizontal reference line is for the 20 msec change from baseline
The horizontal red dashed line represent the 90% CI and the horizontal red solid line represent the Predicted Mean.

(Source: Applicant's Corrected QT Interval Analysis Report, Figure 7)

Reviewer's Analysis: The applicant's plots may have excluded the outliers, whose ΔQTc values were outside -50ms to 50ms. Reviewer's independent plots of ΔQTcF and ΔQTcP vs. drug concentrations are presented in Figure 5 and Figure 6 with no evident exposure-response relationship.

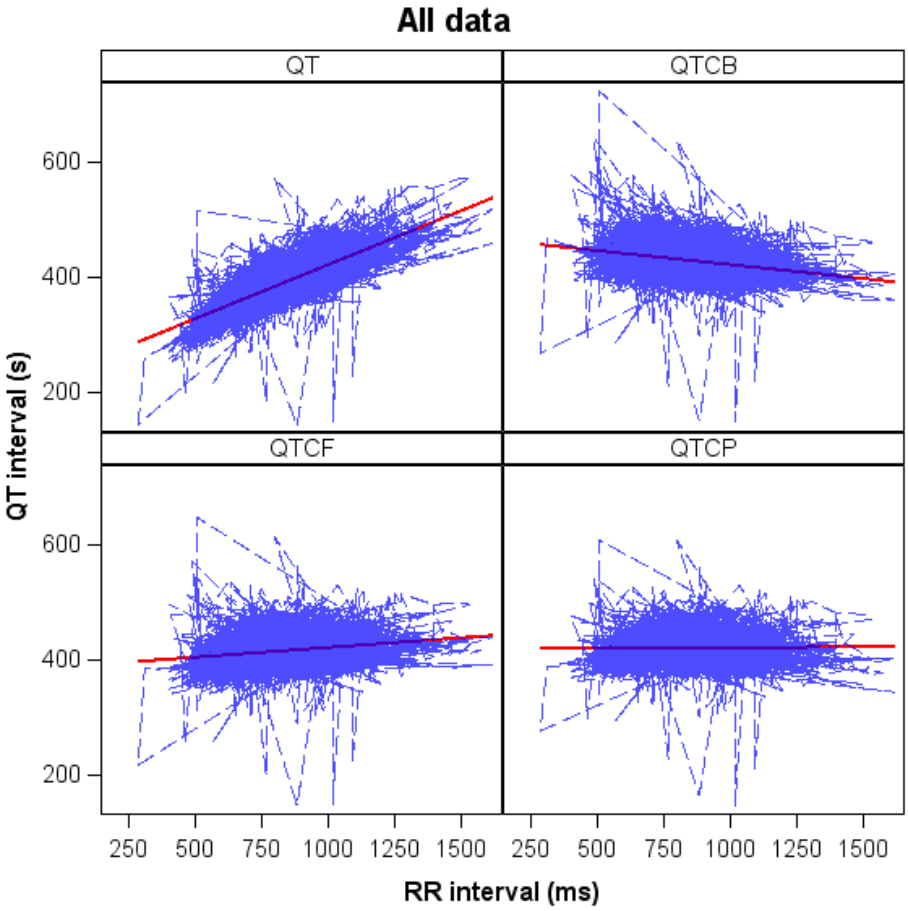
5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The relationship between different correction methods and RR is presented in Figure 4. A weak correlation was observed between QTcF and RR. The correlation between QTcP and RR was not evident.

The QTcF values were used for the primary statistical analysis. Reviewer's exposure-response analyses were performed for both QTcP and QTcF.

Figure 4: QT, QTcB, QTcF, and QTcP vs. RR (Each Subject's Data Points are Connected with a Line)



5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 Central Tendency Analysis

The statistical reviewer performed by-time point descriptive summary of the ΔQTcF effect for each study. Those descriptive results are listed in the following tables.

Table 5: Descriptive Summary of ΔQTcF (Study EMR100070-001)

Treatment	VISIT	Planned Time Point	N	Mean	Standard Deviation	Lower 90% CI Limit	Upper 90% CI Limit
1.0 mg/kg	Week 1 Day 1	2 HOURS AFTER INFUSION	4	-0.2	11.55	-13.8	13.4
	Week 3 Day 5-18	PRIOR TO INFUSION	3	3.1	6.77	-8.3	14.5
	Week 3 Day 5-18	2 HOURS AFTER INFUSION	3	11.4	12.12	-9.0	31.9
	Week 5 Day 26-36	PRIOR TO INFUSION	1	20.4			
	Week 5 Day 26-36	2 HOURS AFTER INFUSION	2	4.5	18.18	-76.7	85.6
	Week 7 Day 37-50	PRIOR TO INFUSION	2	8.0	7.79	-26.8	42.8
	Week 7 Day 37-50	2 HOURS AFTER INFUSION	2	-7.8	3.62	-23.9	8.4
	Week 9 Day 51-64	PRIOR TO INFUSION	2	12.9	3.17	-1.3	27.1
	Week 9 Day 51-64	2 HOURS AFTER INFUSION	2	8.5	5.19	-14.6	31.7
	Week 11 Day 65-78	PRIOR TO INFUSION	1	26.6			
	Week 11 Day 65-78	2 HOURS AFTER INFUSION	1	3.5			
	Last Visit		4	8.4	13.31	-7.3	24.1
3.0 mg/kg	Week 1 Day 1	2 HOURS AFTER INFUSION	11	1.0	16.73	-8.2	10.1
	Week 3 Day 5-18	PRIOR TO INFUSION	12	5.3	14.79	-2.4	13.0
	Week 3 Day 5-18	2 HOURS AFTER INFUSION	12	1.2	18.21	-8.2	10.6
	Week 5 Day 26-36	PRIOR TO INFUSION	11	-4.1	15.04	-12.3	4.1
	Week 5 Day 26-36	2 HOURS AFTER INFUSION	11	6.1	15.47	-2.4	14.5
	Week 7 Day 37-50	PRIOR TO INFUSION	8	1.8	13.84	-7.5	11.0
	Week 7 Day 37-50	2 HOURS AFTER INFUSION	6	9.4	11.31	0.1	18.7
	Week 9 Day 51-64	PRIOR TO INFUSION	8	-2.1	8.66	-7.9	3.7
	Week 9 Day 51-64	2 HOURS AFTER INFUSION	8	1.0	11.51	-6.7	8.7
	Week 11 Day 65-78	PRIOR TO INFUSION	6	-6.7	6.88	-12.3	-1.0
	Week 11 Day 65-78	2 HOURS AFTER INFUSION	6	7.0	5.33	2.6	11.4
	Week 13 Day 79-106	PRIOR TO INFUSION	3	7.0	8.08	-6.6	20.6
	Week 13 Day 79-106	2 HOURS AFTER INFUSION	3	-3.0	17.31	-32.2	26.2
	Week 19 Day 107-148	PRIOR TO INFUSION	3	2.4	4.06	-4.5	9.2
	Week 19 Day 107-148	2 HOURS AFTER INFUSION	3	7.0	7.75	-6.0	20.1
	Week 25 Day 149-190	PRIOR TO INFUSION	2	-16.6	41.89	-203.6	170.5
	Week 25 Day 149-	2 HOURS AFTER INFUSION	2	3.2	6.84	-27.3	33.8

	190						
	Week 31 Day 191-232	PRIOR TO INFUSION	2	-9.4	3.00	-22.8	4.0
	Week 31 Day 191-232	2 HOURS AFTER INFUSION	2	8.2	13.00	-49.9	66.2
	Last Visit		12	-1.5	22.75	-13.3	10.3
Treatment	VISIT	Planned Time Point	N	Mean	Standard Deviation	Lower 90% CI Limit	Upper 90% CI Limit
10.0 mg/kg	Week 1 Day 1	2 HOURS AFTER INFUSION	14	-1.4	10.88	-6.5	3.8
	Week 3 Day 5-18	PRIOR TO INFUSION	12	2.0	15.84	-6.2	10.2
	Week 3 Day 5-18	2 HOURS AFTER INFUSION	12	1.2	11.90	-4.9	7.4
	Week 5 Day 26-36	PRIOR TO INFUSION	11	0.7	18.13	-9.2	10.6
	Week 5 Day 26-36	2 HOURS AFTER INFUSION	11	6.3	21.61	-5.5	18.1
	Week 7 Day 37-50	PRIOR TO INFUSION	11	2.8	10.59	-3.0	8.6
	Week 7 Day 37-50	2 HOURS AFTER INFUSION	10	2.3	6.40	-1.4	6.0
	Week 9 Day 51-64	PRIOR TO INFUSION	9	0.0	15.75	-9.8	9.7
	Week 9 Day 51-64	2 HOURS AFTER INFUSION	10	-1.4	15.21	-10.3	7.4
	Week 11 Day 65-78	PRIOR TO INFUSION	10	-1.1	14.22	-9.4	7.1
	Week 11 Day 65-78	2 HOURS AFTER INFUSION	10	3.8	13.75	-4.2	11.7
	Week 13 Day 79-106	PRIOR TO INFUSION	6	12.8	16.18	-0.5	26.1
	Week 13 Day 79-106	2 HOURS AFTER INFUSION	5	4.1	7.43	-3.0	11.2
	Week 19 Day 107-148	PRIOR TO INFUSION	6	6.4	12.61	-4.0	16.8
	Week 19 Day 107-148	2 HOURS AFTER INFUSION	7	13.9	13.13	4.2	23.5
	Week 25 Day 149-190	PRIOR TO INFUSION	2	18.5	1.12	13.5	23.5
	Week 25 Day 149-190	2 HOURS AFTER INFUSION	3	23.7	6.80	12.2	35.1
	Week 31 Day 191-232	PRIOR TO INFUSION	1	2.8			
	Week 31 Day 191-232	2 HOURS AFTER INFUSION	1	18.3			
	Last Visit		15	1.4	17.80	-6.7	9.5
20.0 mg/kg	Week 1 Day 1	2 HOURS AFTER INFUSION	21	-0.5	18.71	-7.5	6.6
	Week 3 Day 5-18	PRIOR TO INFUSION	19	8.7	15.59	2.5	14.9
	Week 3 Day 5-18	2 HOURS AFTER INFUSION	18	7.6	13.72	2.0	13.3
	Week 5 Day 26-36	PRIOR TO INFUSION	16	0.2	13.01	-5.5	5.9
	Week 5 Day 26-36	2 HOURS AFTER INFUSION	15	3.7	11.30	-1.4	8.9
	Week 7 Day 37-50	PRIOR TO INFUSION	13	0.1	9.55	-4.6	4.9
	Week 7 Day 37-50	2 HOURS AFTER INFUSION	13	3.0	11.04	-2.4	8.5
	Week 9 Day 51-64	PRIOR TO INFUSION	12	-0.6	11.16	-6.4	5.1
	Week 9 Day 51-64	2 HOURS AFTER INFUSION	13	3.4	14.90	-4.0	10.8
	Week 11 Day 65-78	PRIOR TO INFUSION	12	-0.2	9.26	-5.0	4.6

	Week 11 Day 65-78	2 HOURS AFTER INFUSION	10	5.4	6.26	1.8	9.0
	Week 13 Day 79-106	PRIOR TO INFUSION	9	-0.3	16.77	-10.7	10.1
	Week 13 Day 79-106	2 HOURS AFTER INFUSION	9	11.1	22.26	-2.7	24.9
	Week 19 Day 107-148	PRIOR TO INFUSION	3	19.8	18.58	-11.5	51.1
Treatment	VISIT	Planned Time Point	N	Mean	Standard Deviation	Lower 90% CI Limit	Upper 90% CI Limit
	Week 19 Day 107-148	2 HOURS AFTER INFUSION	4	4.4	9.39	-6.6	15.5
	Week 25 Day 149-190	PRIOR TO INFUSION	2	13.1	11.22	-37.0	63.2
	Week 25 Day 149-190	2 HOURS AFTER INFUSION	2	21.6	5.31	-2.1	45.3
	Week 31 Day 191-232	PRIOR TO INFUSION	1	15.0			
	Last Visit		21	7.2	19.25	-0.1	14.4
10.0 mg/kg Expansion	Week 1 Day 1	2 HOURS AFTER INFUSION	1367	2.8	22.07	1.8	3.8
	Week 3 Day 5-18	PRIOR TO INFUSION	1249	-0.4	20.17	-1.4	0.5
	Week 3 Day 5-18	2 HOURS AFTER INFUSION	1210	4.6	23.77	3.5	5.7
	Week 4 Day 19-25	PRIOR TO INFUSION	21	-0.7	27.45	-11.0	9.7
	Week 4 Day 19-25	2 HOURS AFTER INFUSION	20	10.2	25.64	0.3	20.1
	Week 5 Day 26-36	PRIOR TO INFUSION	1145	-0.7	19.11	-1.7	0.2
	Week 5 Day 26-36	2 HOURS AFTER INFUSION	1109	5.5	19.02	4.6	6.5
	Week 7 Day 37-50	PRIOR TO INFUSION	940	0.2	18.93	-0.8	1.3
	Week 7 Day 37-50	2 HOURS AFTER INFUSION	874	6.5	20.06	5.4	7.6
	Week 9 Day 51-64	PRIOR TO INFUSION	790	-0.4	18.16	-1.4	0.7
	Week 9 Day 51-64	2 HOURS AFTER INFUSION	750	4.7	20.17	3.5	5.9
	Week 11 Day 65-78	PRIOR TO INFUSION	712	-0.9	19.54	-2.1	0.3
	Week 11 Day 65-78	2 HOURS AFTER INFUSION	671	4.1	22.97	2.7	5.6
	Week 13 Day 79-106	PRIOR TO INFUSION	520	1.3	18.70	-0.1	2.6
	Week 13 Day 79-106	2 HOURS AFTER INFUSION	486	6.0	19.83	4.5	7.5
	Week 19 Day 107-148	PRIOR TO INFUSION	278	1.7	18.95	-0.2	3.5
	Week 19 Day 107-148	2 HOURS AFTER INFUSION	265	6.4	19.95	4.3	8.4
	Week 25 Day 149-190	PRIOR TO INFUSION	173	2.7	20.73	0.1	5.3
	Week 25 Day 149-190	2 HOURS AFTER INFUSION	166	8.0	22.65	5.1	10.9
	Week 31 Day 191-232	PRIOR TO INFUSION	99	3.4	19.29	0.2	6.6
	Week 31 Day 191-232	2 HOURS AFTER INFUSION	87	7.8	21.41	4.0	11.7
	Last Visit		1418	1.7	25.93	0.6	2.8

Table 6: Descriptive Summary of ΔQTcF (Study EMR100070-002)

Treatment	VISIT	Planned Time Point	N	Mean	Standard Deviation	Lower 90% CI Limit	Upper 90% CI Limit
3.0 mg/kg	WEEK 1 DAY 1	2 HOURS AFTER INFUSION	5	3.0	18.18	-14.4	20.3
	WEEK 3 DAY 15	PRIOR INFUSION	5	12.0	16.76	-4.0	27.9
	WEEK 3 DAY 15	2 HOURS AFTER INFUSION	5	14.4	15.47	-0.4	29.1
	WEEK 5 DAY 29	PRIOR INFUSION	4	12.3	19.81	-11.0	35.7
	WEEK 5 DAY 29	2 HOURS AFTER INFUSION	4	11.9	16.80	-7.9	31.6
	WEEK 7 DAY 43	PRIOR INFUSION	4	2.0	21.98	-23.9	27.8
	WEEK 7 DAY 43	2 HOURS AFTER INFUSION	4	17.0	21.28	-8.1	42.0
	WEEK 13 DAY 85	PRIOR INFUSION	3	-0.8	20.73	-35.7	34.2
	WEEK 13 DAY 85	2 HOURS AFTER INFUSION	3	9.4	9.01	-5.8	24.5
	WEEK 25 DAY 169	PRIOR INFUSION	1	47.9			
	WEEK 25 DAY 169	2 HOURS AFTER INFUSION	1	37.8			
	LAST VISIT		5	12.6	14.76	-1.4	26.7
10.0 mg/kg	WEEK 1 DAY 1	2 HOURS AFTER INFUSION	6	8.3	4.63	4.5	12.1
	WEEK 3 DAY 15	PRIOR INFUSION	5	0.4	10.34	-9.4	10.3
	WEEK 3 DAY 15	2 HOURS AFTER INFUSION	6	12.0	8.62	4.9	19.1
	WEEK 5 DAY 29	PRIOR INFUSION	6	1.2	10.61	-7.5	10.0
	WEEK 5 DAY 29	2 HOURS AFTER INFUSION	6	7.4	11.83	-2.3	17.1
	WEEK 7 DAY 43	PRIOR INFUSION	6	4.0	20.24	-12.6	20.7
	WEEK 7 DAY 43	2 HOURS AFTER INFUSION	6	14.8	10.02	6.6	23.1
	WEEK 13 DAY 85	PRIOR INFUSION	3	12.8	8.56	-1.7	27.2
	WEEK 13 DAY 85	2 HOURS AFTER INFUSION	3	17.5	6.97	5.7	29.2
	WEEK 25 DAY 169	PRIOR INFUSION	3	17.1	9.74	0.7	33.5
	WEEK 25 DAY 169	2 HOURS AFTER INFUSION	3	26.9	5.28	18.0	35.8
	LAST VISIT		6	23.1	10.19	14.7	31.4
20.0 mg/kg	WEEK 1 DAY 1	2 HOURS AFTER INFUSION	6	1.8	14.92	-10.5	14.1
	WEEK 3 DAY 15	PRIOR INFUSION	6	-1.1	29.77	-25.6	23.4
	WEEK 3 DAY 15	2 HOURS AFTER INFUSION	6	8.2	26.15	-13.3	29.8
	WEEK 5 DAY 29	PRIOR INFUSION	5	1.9	28.14	-24.9	28.8
	WEEK 5 DAY 29	2 HOURS AFTER INFUSION	5	10.1	34.00	-22.3	42.5
	WEEK 7 DAY 43	PRIOR INFUSION	4	9.0	35.79	-33.2	51.1
	WEEK 7 DAY 43	2 HOURS AFTER INFUSION	4	15.0	32.50	-23.3	53.2
	WEEK 13 DAY 85	PRIOR INFUSION	2	24.1	46.06	-181.6	229.7
	WEEK 13 DAY 85	2 HOURS AFTER INFUSION	2	19.4	51.40	-210.1	248.9
	WEEK 25 DAY 169	PRIOR INFUSION	1	65.1			
	WEEK 25 DAY 169	2 HOURS AFTER INFUSION	1	60.4			
	LAST VISIT		6	8.6	28.62	-14.9	32.1
10.0 mg/kg Expansion	WEEK 1 DAY 1	2 HOURS AFTER INFUSION	34	1.0	11.80	-2.4	4.5
	WEEK 3 DAY 15	PRIOR INFUSION	31	-1.2	18.98	-7.0	4.6

Treatment	VISIT	Planned Time Point	N	Mean	Standard Deviation	Lower 90% CI Limit	Upper 90% CI Limit
	WEEK 5 DAY 29	PRIOR INFUSION	27	1.5	16.12	-3.8	6.8
	WEEK 7 DAY 43	PRIOR INFUSION	25	1.1	23.64	-6.9	9.2
	WEEK 13 DAY 85	PRIOR INFUSION	10	0.0	30.91	-17.9	17.9
	WEEK 25 DAY 169	PRIOR INFUSION	2	4.7	1.49	-2.0	11.3
	LAST VISIT		34	0.4	18.49	-4.9	5.8

Table 7: Descriptive Summary of ΔQTcF (Study EMR100070-003)

Treatment	VISIT	Planned Time Point	N	Mean	Standard Deviation	Lower 90% CI Limit	Upper 90% CI Limit
10.0 mg/kg Expansion	WEEK 1 DAY 1	2 HOURS AFTER INFUSION	46	3.6	19.51	-1.3	8.4
	WEEK 3 DAY 15	PRIOR INFUSION	58	-2.8	14.55	-6.0	0.4
	WEEK 5 DAY 29	PRIOR INFUSION	58	-2.3	17.68	-6.2	1.5
	WEEK 7 DAY 43	PRIOR INFUSION	49	4.3	18.01	0.0	8.6
	WEEK 7 DAY 43	2 HOURS AFTER INFUSION	39	5.7	13.85	2.0	9.5
	WEEK 9 DAY 57	PRIOR INFUSION	45	3.0	14.25	-0.6	6.6
	WEEK 11 DAY 71	PRIOR INFUSION	37	0.8	11.12	-2.3	3.9
	WEEK 13 DAY 85	PRIOR INFUSION	34	2.7	16.63	-2.1	7.5
	WEEK 13 DAY 85	2 HOURS AFTER INFUSION	23	3.5	14.44	-1.7	8.7
	WEEK 25 DAY 169	PRIOR INFUSION	22	-0.5	17.25	-6.8	5.9
	WEEK 25 DAY 169	2 HOURS AFTER INFUSION	16	5.0	17.50	-2.7	12.6
	WEEK 31 DAY 211	PRIOR INFUSION	1	24.5			
	WEEK 37 DAY 253	PRIOR INFUSION	9	-8.5	19.39	-20.5	3.5
	WEEK 37 DAY 253	2 HOURS AFTER INFUSION	12	4.3	21.24	-6.7	15.3
	WEEK 49 DAY 337	PRIOR INFUSION	2	1.8	13.18	-57.1	60.6
	WEEK 49 DAY 337	2 HOURS AFTER INFUSION	2	6.6	13.39	-53.2	66.3
	WEEK 61 DAY 421	PRIOR INFUSION	2	0.8	14.91	-65.8	67.3
	WEEK 61 DAY 421	2 HOURS AFTER INFUSION	3	5.1	33.99	-52.2	62.4
	LAST VISIT		73	1.9	18.50	-1.7	5.5

5.2.1.2 Categorical Analysis

Table 8, Table 9, Table 10, and Table 11 list the number of subjects as well as the number of observations whose QTcF values are ≤ 450 ms, between 450 ms and 480 ms, between 480 ms and 500 ms, and above 500 ms. In study 001, two subjects treated with 20.0 mg/kg during dose escalation phase had QTcF value at least 480 ms; There are 76 subjects in the expansion phase with QTcF value at least 480 ms. In study 002, no subjects during dose escalation phase had QTcF value at least 480 ms; one subject in the expansion phase had QTcF value at least 480 ms. In study 003, 9 subjects in the

expansion phase had QTcF value at least 480 ms. In the 10 mg/kg dose cohorts pooled from all three studies, there are 33 subjects with QTCF value at least 500 ms.

Table 8: Categorical Analysis for QTcF (Study EMR100070-001)

	Total N		Value<=450 ms		450 ms<Value<=480 ms		480 ms<Value<=500 ms		Value>500	
Treatment Group	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**
1.0 mg/kg	4	28	4 (100%)	28 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
3.0 mg/kg	13	154	10 (76.9%)	150 (97.4%)	3 (23.1%)	4 (2.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
10.0 mg/kg	15	188	13 (86.7%)	186 (98.9%)	2 (13.3%)	2 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
20.0 mg/kg	21	221	12 (57.1%)	171 (77.4%)	7 (33.3%)	48 (21.7%)	2 (9.5%)	2 (0.9%)	0 (0.0%)	0 (0.0%)
10.0 mg/kg Expansion	1421	14630	1099 (77.3%)	13423 (91.7%)	246 (17.3%)	1012 (6.9%)	46 (3.2%)	147 (1.0%)	30 (2.1%)	48 (0.3%)

Table 9: Categorical Analysis for QTcF (Study EMR100070-002)

	Total N		Value<=450 ms		450 ms<Value<=480 ms		480 ms<Value<=500 ms	
Treatment Group	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**
3.0 mg/kg	5	39	4 (80.0%)	32 (82.1%)	1 (20.0%)	7 (17.9%)	0 (0.0%)	0 (0.0%)
10.0 mg/kg	6	53	5 (83.3%)	50 (94.3%)	1 (16.7%)	3 (5.7%)	0 (0.0%)	0 (0.0%)
20.0 mg/kg	6	42	6 (100%)	42 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
10.0 mg/kg Expansion	34	129	30 (88.2%)	123 (95.3%)	3 (8.8%)	5 (3.9%)	1 (2.9%)	1 (0.8%)

Table 10: Categorical Analysis for QTcF (Study EMR100070-003)

	Total N		Value<=450 ms		450 ms<Value<=480 ms		480 ms<Value<=500 ms		Value>500	
Treatment Group	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**
10.0 mg/kg Expansion	84	532	64 (76.2%)	477 (89.7%)	11 (13.1%)	29 (5.5%)	6 (7.1%)	18 (3.4%)	3 (3.6%)	8 (1.5%)

Table 11: Categorical Analysis for QTcF (Pooled)

	Total N		Value<=450 ms		450 ms<Value<=480 ms		480 ms<Value<=500 ms		Value>500	
Treatment Group	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**
10.0 mg/kg Pooled	1560	15532	1211 (77.6%)	14259 (91.8%)	263 (16.9%)	1051 (6.8%)	53 (3.4%)	166 (1.1%)	33 (2.1%)	56 (0.4%)

Table 12, Table 13, Table 14, and Table 15 list the categorical analysis results for ΔQTcF. In study 001, no subject's change from baseline was above 60 ms during the dose escalation phase; 62 subjects treated with 10.0 mg/kg in expansion phase had change from baseline value above 60 ms. In study 002, there was one subject with change from baseline above 60 ms during the dose escalation phase; one subject's change from baseline was above 60 ms during the expansion phase. In study 003, no subject's change from baseline was above 60 ms during the expansion phase. In the 10 mg/kg dose cohorts pooled from all three studies, there are 63 subjects with change from baseline QTcF value at least 60 ms.

Table 12: Categorical Analysis of ΔQTcF (Study EMR100070-001)

	Total N		Value<=30 ms		30 ms<Value<=60 ms		Value>60 ms	
Treatment Group	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
1.0 mg/kg	4	28	4 (100%)	28 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
3.0 mg/kg	12	140	8 (66.7%)	133 (95.0%)	4 (33.3%)	7 (5.0%)	0 (0.0%)	0 (0.0%)
10.0 mg/kg	15	188	12 (80.0%)	184 (97.9%)	3 (20.0%)	4 (2.1%)	0 (0.0%)	0 (0.0%)
20.0 mg/kg	21	221	14 (66.7%)	211 (95.5%)	7 (33.3%)	10 (4.5%)	0 (0.0%)	0 (0.0%)
10.0 mg/kg Expansion	1418	14610	1052 (74.2%)	13726 (93.9%)	304 (21.4%)	784 (5.4%)	62 (4.4%)	100 (0.7%)

Table 13: Categorical Analysis of ΔQTcF (Study EMR100070-002)

	Total N		Value<=30 ms		30 ms<Value<=60 ms		Value>60 ms	
Treatment Group	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
3.0 mg/kg	5	39	3 (60.0%)	33 (84.6%)	2 (40.0%)	6 (15.4%)	0 (0.0%)	0 (0.0%)
10.0 mg/kg	6	53	4 (66.7%)	51 (96.2%)	2 (33.3%)	2 (3.8%)	0 (0.0%)	0 (0.0%)
20.0 mg/kg	6	42	5 (83.3%)	32 (76.2%)	0 (0.0%)	5 (11.9%)	1 (16.7%)	5 (11.9%)
10.0 mg/kg Expansion	34	129	32 (94.1%)	124 (96.1%)	1 (2.9%)	2 (1.6%)	1 (2.9%)	3 (2.3%)

Table 14: Categorical Analysis of ΔQTcF (Study EMR100070-003)

	Total N		Value<=30 ms		30 ms<Value<=60 ms	
Treatment Group	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
10.0 mg/kg Expansion	73	458	61 (83.6%)	438 (95.6%)	12 (16.4%)	20 (4.4%)

Table 15: Categorical Analysis of ΔQTcF (Pooled)

	Total N		Value<=30 ms		30 ms<Value<=60 ms		Value>60 ms	
Treatment Group	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
10.0 mg/kg Pooled	1546	15438	1161 (75.1%)	14523 (94.1%)	322 (20.8%)	812 (5.3%)	63 (4.1%)	103 (0.7%)

5.2.2 HR Analysis

The outlier analysis results for HR are presented in Table 16. This outlier analysis was performed only for study 001 as relevant data for studies 002 and 003 were not available. In study 001, there were 1, 3, 2, and 6 subjects treated with 1.0 mg/kg, 3.0 mg/kg, 10.0 mg/kg, and 20.0 mg/kg had HR value above 100 bpm during the dose escalation phase, respectively. There were 344 subjects with value above 100 bpm during expansion phase.

Table 16: Categorical Analysis of HR (Study EMR100070-001)

	Total N		Value<=100 bpm		Value>100 bpm	
Treatment Group	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
1.0 mg/kg	4	28	3 (75.0%)	27 (96.4%)	1 (25.0%)	1 (3.6%)
3.0 mg/kg	13	154	10 (76.9%)	141 (91.6%)	3 (23.1%)	13 (8.4%)
10.0 mg/kg	15	188	13 (86.7%)	186 (98.9%)	2 (13.3%)	2 (1.1%)
20.0 mg/kg	21	221	15 (71.4%)	204 (92.3%)	6 (28.6%)	17 (7.7%)
10.0 mg/kg Expansion	1421	14633	1077 (75.8%)	13800 (94.3%)	344 (24.2%)	833 (5.7%)

5.2.3 PR Analysis

The outlier analysis results for PR are presented in Table 17. This outlier analysis was performed only for study 001 as relevant data for studies 002 and 003 were not available. In study 001, there were 1, 1, 2, and 7 subjects treated with 1.0 mg/kg, 3.0 mg/kg, 10.0 mg/kg and 20.0 mg/kg had PR value above 200 ms during the dose escalation phase, respectively. There were 205 subjects with value above 200 ms during expansion phase.

Table 17: Categorical Analysis of PR (Study EMR100070-001)

	Total N		Value<=200 ms		Value>200 ms	
Treatment Group	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
1.0 mg/kg	4	28	3 (75.0%)	27 (96.4%)	1 (25.0%)	1 (3.6%)
3.0 mg/kg	13	154	12 (92.3%)	153 (99.4%)	1 (7.7%)	1 (0.6%)
10.0 mg/kg	15	187	13 (86.7%)	177 (94.7%)	2 (13.3%)	10 (5.3%)
20.0 mg/kg	21	221	14 (66.7%)	196 (88.7%)	7 (33.3%)	25 (11.3%)
10.0 mg/kg Expansion	1403	14265	1198 (85.4%)	13076 (91.7%)	205 (14.6%)	1189 (8.3%)

5.2.4 QRS Analysis

The outlier analysis results for QRS are presented in Table 18. This outlier analysis was performed only for study 001 as relevant data for studies 002 and 003 were not available. In study 001, there were 1, 2, and 5 subjects treated with 3.0 mg/kg, 10.0 mg/kg, and 20.0 mg/kg with QRS value above 110 ms during the dose escalation phase, respectively. There were 197 subjects with value above 110 ms during expansion phase.

Table 18: Categorical Analysis for QRS (Study EMR100070-001)

	Total N		Value<=100 ms		100 ms<Value<=110 ms		Value>110 ms	
Treatment Group	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
1.0 mg/kg	4	28	3 (75.0%)	25 (89.3%)	1 (25.0%)	3 (10.7%)	0 (0.0%)	0 (0.0%)
3.0 mg/kg	13	154	7 (53.8%)	136 (88.3%)	5 (38.5%)	17 (11.0%)	1 (7.7%)	1 (0.6%)
10.0 mg/kg	15	188	12 (80.0%)	174 (92.6%)	1 (6.7%)	11 (5.9%)	2 (13.3%)	3 (1.6%)
20.0 mg/kg	21	221	15 (71.4%)	185 (83.7%)	1 (4.8%)	10 (4.5%)	5 (23.8%)	26 (11.8%)
10.0 mg/kg Expansion	1421	14629	1008 (70.9%)	12244 (83.7%)	216 (15.2%)	1283 (8.8%)	197 (13.9%)	1102 (7.5%)

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The relationships between ΔQTcF, ΔQTcP and avelumab concentrations were investigated by linear mixed-effects modeling and no evident relationship was observed (Figure 5 and Figure 6).

Figure 5: Δ QTcF vs. Avelumab Concentration

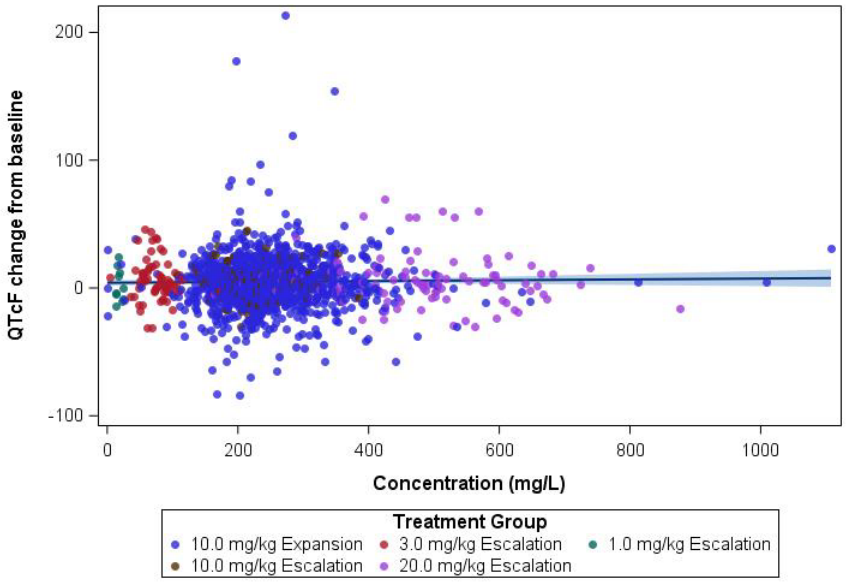
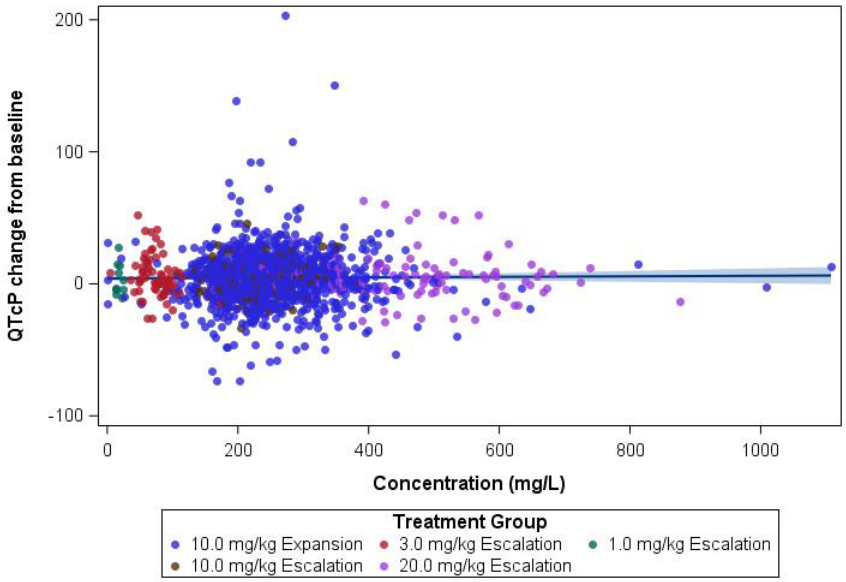


Figure 6: Δ QTcP vs. Avelumab Concentration



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

According to local machine read of ECG measurements from the large pooled population receiving avelumab treatment, an on-treatment QTcF > 500 ms was detected in a total of 33 subjects (2.1%) only in the 10 mg/kg dose cohorts from all 3 studies. Delta QTcF > 60

ms was noted for 59 subjects (3.9%) in the 10 mg/kg dose cohorts and in 1 patient from the 20 mg/kg dose cohort.

These ECGs were re-evaluated by cardiologists in a central ECG laboratory. Excluding overall 47 subjects with ECGs that could not be re-evaluated (due to the deteriorated quality of the paper ECGs provided by local sites), only 1 of 12 subjects with a QTcF > 500 ms and 2 of 20 subjects with delta QTcF > 60 ms were confirmed after central read of all evaluable outlier ECGs. A further review of all these 3 confirmed QTc outlier subjects revealed that they all had relevant pre-existing cardiovascular history or were concomitantly treated with medication known to prolong the QT interval; 2 of 3 subjects had a cardiac pacemaker.

None of the 79 subjects identified as categorical QTcF or QTcP outliers by local machine-read ECGs experienced any on-treatment cardiac AEs (torsade de pointes, ventricular tachycardia, ventricular fibrillation, ventricular flutter, ventricular arrhythmia, syncope, seizure, sudden death) that could be suggestive of a QT interval prolongation as an underlying cause.

There were patients with increases in heart rate. In study EMR100070-001, 344 patients (24%) had heart rates >100 bpm.

5.4.2 ECG assessments

Overall ECG acquisition and interpretation in study 001 appears acceptable.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose	10 mg/kg every two weeks. At the single 10 mg/kg (maximum) proposed clinical dose: the observed geometric mean (CV%) of PK exposure after first dosing: C_{max} 294 µg /mL (32.5%); $AUC_{0\text{-}day14}$: 25200 µg*hr/mL (25.3%) and $AUC_{0\text{-}inf}$: 27700 µg*hr/mL (27.0%). At the steady state with the maximum proposed clinical dosing regimen observed geometric mean (CV%) is Cmax: 307 µg /mL (14.0%). Estimated steady state mean (CV%) of $AUC_{0\text{-}tau}$: 26090 µg*hr/mL (28.7%) based on PopPK	
Maximum tolerated dose	MTD not reached in human; 20mg/kg Q2W was studied and was found to be well tolerated in human. NOAEL: 140 mg/kg in cynomolgus monkeys	
Principal adverse events	No dose limiting adverse events were observed. As of 05 November 2015, The most frequently observed treatment-emergent adverse events (incidence > 5%) were fatigue (16.3%), infusion-related reaction (16.1%), nausea (8.3%), chills (7.8%), diarrhea (6.1%), and pyrexia (5.5%).	
Maximum dose tested	Single Dose	20 mg/kg
	Multiple Dose	20 mg/kg every two weeks and the median avelumab treatment duration was 10 weeks (ranging 1-64 weeks)
Exposures Achieved at Maximum Tested Dose	Single Dose	The observed geometric mean (CV%) of PK exposure after first dosing C_{max}: 470 µg /mL (29.9%); $AUC_{0\text{-}day14}$: 38300 µg*hr/mL (42.0%) and $AUC_{0\text{-}inf}$: 42700 µg*hr/mL (47.6%)
	Multiple Dose	Observed geometric mean (CV%) of C_{max}: 482 µg /mL (36.4%). The estimated mean (CV%) $AUC_{0\text{-}tau}$:56910 µg*hr/mL (34.4%) from PopPK
Range of linear PK	3 to 20 mg/kg every two weeks	
Accumulation at steady state	Estimated mean (%CV) of accumulation ratio: 1.22 (30.0%) from PopPK	
Metabolites	Amino acids	
Absorption	Absolute/Relative Bioavailability	Not applicable (N/A) for IV infusion
	Tmax	• Observed median (range) for parent: 1.5 hours (1- 7.1 hours) • Median (range) for metabolites: N/A
Distribution	Vd/F or Vd	Estimated mean (%CV): V1 (central): 2.97 L (19.2%); V2 (peripheral): 1.09 L (110%) from

		PopPK
	% bound	Mean (%CV): N/A
Elimination	Route	• Primary route; percent dose eliminated: expected to be 100%proteolytic catabolism • Other routes: N/A
	Terminal t½	• Observed geometric mean (%CV) of terminal t½ for parent: 94.6 hours or 3.9 days (22.0%) • Mean (%CV) for metabolites: N/A
	CL/F or CL	Estimated mean (%CV) of CL: 0.0261 L/hr (27.0%) from PopPK
Intrinsic Factors	Age	There is no influence of age on avelumab pharmacokinetic according to a Population PK analysis.
	Sex	Male subjects have a 13.2% higher clearance and a 22.1% higher V1 than female subjects according to a Population PK analysis.
	Race	There is no influence of race on avelumab pharmacokinetic according to a Population PK analysis.
	Hepatic & Renal Impairment	There is no influence of renal or hepatic impairment on avelumab pharmacokinetic according to a Population PK analysis.
	Other factors	CL is related to albumin concentration. As albumin levels increase, avelumab CL decreases which leads to increases in AUC values. For a 10mg/kg dose the median steady state AUC is predicted to range between 84.9% to 114% of the typical AUC across the albumin range 17 to 52 g/L. Baseline weight was found to influence CL, V1 and V2 in a Population PK analysis. As weight increases simulation show that the typical AUC decreases. For a 10 mg/kg dose the median steady state AUC, relative to the median AUC, is predicted to range between 69.5% (20-30 kg), 82.2% (82.2% (40-50 kg), 92.5% (60-70 kg) 103% (80-90 kg) and 116% (100-110 kg). (A selected set of weight ranges only has been included).
Extrinsic Factors	Drug interactions	DDI is not expected

	Food Effects	N/A
Expected High Clinical Exposure Scenario	A drastic increase in exposure in 10 mg/kg every 2 week is not expected. Steady state accumulation at 20 mg/kg dose level was found to range between 1.63-2.6 fold relative to the 10 mg/kg dose level, based on non-compartmental and population PK analyses.	
Preclinical Cardiac Safety	In line with guidelines ICH S6(R1) and S9, the investigation of safety pharmacologically relevant parameters of the cardiovascular (CV), respiratory and central nervous system (CNS) was included in the 4-week i.v. repeat-dose toxicity study and in the pivotal 13-week i.v. repeat dose toxicity study in cynomolgus monkeys. In both toxicity studies, heart rate, electrocardiogram, arterial blood pressure, respiratory rate, CNS parameters and body temperature were unaffected by the treatment with avelumab at the high dose level of 140 mg/kg. In vitro hERG study: N/A	
Clinical Cardiac Safety	Based on database cutoff date 17 December 2015, the number of subjects studied in phase I-III clinical studies at different drug dose levels are: 4 (1 mg/kg), 18 (3 mg/kg), 1726 (10 mg/kg), and 27 (20 mg/kg). Based on database cutoff date 5 November 2015, out of 1353 subjects treated with 1-20 mg/kg of avelumab every two weeks, 7 (0.5%) subjects had QT prolongation, 8 (0.5%) subjects had syncope and 7 (0.6%) had seizure. The Sponsor's continuous medical review and signal detection activities did not yield a proarrhythmic safety signal so far.	

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
12/12/2016

LIAN MA
12/12/2016

DALONG HUANG
12/12/2016

QIANYU DANG
12/12/2016

MICHAEL Y LI
12/12/2016

CHRISTINE E GARNETT
12/12/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

DATE: November 29, 2016

FROM: Patricia Keegan, M.D.
Director
Division of Oncology Products 2
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research

SUBJECT: Designation of BLA application review status

Sponsor:	EMD Serono, Inc.
Product:	Bavencio (avelumab)
Proposed Indication:	For the treatment of patients with metastatic Merkel cell carcinoma. This indication is approved under accelerated approval. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials

TO: BLA 761049 – NME original Application

The review status of this file submitted as an original BLA is designated to be:

☐ Standard (10 Months) ☒ Priority (6 Months)

BACKGROUND

The applicant, EMD Serono, did not request a review designation for this Biologics License Application (BLA). In the clinical summary of efficacy, EMD Serono stated that the clinical efficacy of avelumab was evaluated in Study EMR100070-003 Part A and is referenced to outcomes of subjects with [metastatic Merkel Cell Carcinoma (mMCC)] treated with chemotherapy in observational Study 100070-Obs001.

Study EMR100070-003 Part A is a single arm trial conducted in patients with histologically confirmed, mMCC who had received one prior line of chemotherapy

containing one of the following agents for treatment of mMCC: cyclophosphamide, topotecan, doxorubicin, epirubicin, vincristine, carboplatin, cisplatin, or etoposide in combination with carboplatin or cisplatin. All patients received avelumab 10 mg/kg intravenously every 2 weeks until disease progression or unacceptable toxicity. The primary endpoint of this study was overall response rate as determined by an independent review committee according to RECIST v1.1; secondary endpoints included estimation of duration of response, progression-free survival, and overall survival. The planned sample size of 84 patients assumed an ORR of 35% and was designed to rule out an ORR of is ≤ 20%.

Study 100070-Obs001 was a retrospective, chart review of electronic medical records obtained in community and academic centers, collecting information on the outcomes of patients with mMCC who were previously treated (second-line) or previously untreated (first-line). The primary objective of this retrospective chart review was ORR as determined by the treating physician according to "clinical judgment" (Part B) or by an independent auditor according to RECIST v1.1 (Part A).

A total of 88 patients were enrolled and received at least one dose of avelumab in Study EMR100070-003 Part A. Among these 88 patients, there were 8 patients identified as having a complete response and 20 patients identified as having a partial response by the independent review committee for an overall response rate of 32% (95% CI: 21.9, 43.1). The median duration of response is not estimable, with durations of response ranging from 2.8+ months to 17.5+ months.

EMD Serono contrasts these results with the database from Study 100070-Obs001 Part A. In this retrospective chart review of 686 patients with a diagnosis of MCC, a total of 39 potential patients were identified as having mMCC with evidence of receiving second-line chemotherapy for metastatic disease. Based on detailed chart review, 19 of these 39 patients were excluded from the dataset for the following reasons: 11 patients did not have evidence of metastatic disease, 4 patients were participants in a clinical trial, 3 patients did not receive second-line therapy, and 1 patient did not receive one of the selected chemotherapeutic agents as first-line therapy. Of the remaining 20 patients, 6 patients were excluded from the assessment of ORR based on immunosuppression. In the remaining 14 patients, the ORR was 28.6% (95% CI: 8.4, 58.1), with a median duration of response of 1.7 months (95% CI: 0.5, 3.0).

ASSESSMENT OF REQUEST

In evaluating the review designation for EMD Serono's Biologics License Application (BLA), I considered their rationale including the summary results of Study EMR100070-003 Part A and the results determined by independent review of ORR based on in a retrospective chart review of immunocompetent patients receiving chemotherapy for the second-line treatment of mMCC identified in Study 100070-Obs001 Part A, and the following FDA Guidance and MAPP:

- CDER MAPP 6020.3, Priority Review Policy (version 2)

- Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics (May 2014)

As stated in these FDA documents (above), an application for a drug will receive priority review designation if it is for a drug that treats a serious condition and, if approved, would provide a significant improvement in safety or effectiveness. In addition, specific statutory provisions provide for priority review for various types of applications

On a case-by-case basis, FDA determines at the time of NDA, BLA, or efficacy supplement filing whether the proposed drug would be a *significant improvement* in the safety or effectiveness of the treatment, prevention, or diagnosis of a serious condition compared to available therapies.

Significant improvement may be illustrated by the following examples:
- Evidence of increased effectiveness in treatment, prevention, or diagnosis of a condition
- Elimination or substantial reduction of a treatment-limiting adverse reaction
- Documented enhancement of patient compliance that is expected to lead to an improvement in serious outcomes
- Evidence of safety and effectiveness in a new subpopulation

For purposes of determining whether a significant improvement exists over available therapy, FDA generally considers *available therapy* (and the terms *existing treatment* and *existing therapy*) as a therapy that:
- Is approved or licensed in the United States for the same indication being considered for the new drug and
- Is relevant to current U.S. standard of care (SOC) for the indication

FDA's available therapy determination generally focuses on treatment options that reflect the current SOC for the specific indication (including the disease stage) for which a product is being developed. In evaluating the current SOC, FDA considers recommendations by authoritative scientific bodies (e.g., National Comprehensive Cancer Network, American Academy of Neurology) based on clinical evidence and other reliable information that reflects current clinical practice. When a drug development program targets a subset of a broader disease population (e.g., a subset identified by a genetic mutation), the SOC for the broader population, if there is one, generally is considered available therapy for the subset, unless there is evidence that the SOC is less effective in the subset.

A drug would not be considered available therapy if the drug is granted accelerated approval based on a surrogate endpoint or an intermediate clinical endpoint and clinical benefit has not been verified by post-approval studies.

Assessment*:*
This Biologics License Application (BLA) was not submitted under the statutory provisions for which priority review designation is required by statute.

Criterion 1: the drug treats a serious condition

The American Cancer Society states that there are an estimated 1500 new cases of MCC diagnosed in the US annually; however the incidence appears to be rising possibly due to greater recognition of the disease, better diagnostic criteria, but potentially an increase in individuals with risk factors for MCC.[1] The American Cancer Society further states that the 5-year survival rate for patients with Stage IV MCC is approximately 20%. [2] The 6-month survival rate for patients enrolled in Study EMR100070-003 Part A was 69%.

I concur that the indicated population has a serious, life-threatening condition.

Criterion 2: the drug would be a *significant improvement* in the safety or effectiveness of the treatment, prevention, or diagnosis compared to available therapies

There are no FDA-approved drugs for the treatment of patients with mMCC.

NCCN Practice Guidelines: The National Comprehensive Cancer Network (NCCN) clinical practice guidelines recommends enrollment in clinical trials as the preferred option and "as clinical judgment dictates, treatment with cisplatin alone or with etoposide, carboplatin alone or with etoposide, topotecan, CAV (cyclophosphamide, doxorubicin or epirubicin, and vincristine), or pembrolizumab. [3] The recommendations are category 2A (i.e., based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate), noting that "MCC is a chemosensitive disease although responses are not durable" and the "preliminary data from non-randomized trials in patients with MCC demonstrate that the response rates for pembrolizumab are similar to those previously reported for chemotherapy."

The data provided in the application indicate that treatment with avelumab results in an overall response rate of 32% (95% CI: 21.9, 43.1). The median duration of response cannot be estimated at this time; however the lower limit of the 95% confidence interval for the median response duration is reported to be 8.5 months and the observed durations of response range from 2.8+ months to 17.5+ months. This is similar to the ORR based on independent review of patients identified in a retrospective chart review who were similar in terms of prior treatment history those studied in where the ORR was 28.6% (95% CI: 8.4, 58.1). However it is notable that the median duration of response was 1.7 months (95% CI: 0.5, 3.0) among the 4 of 14 responding patients in Study 100070-Obs001 Part A, is considerable shorter than the range for duration of responses (2.8+ months to 17.5+ months) observed in the 28 responding patients in Study EMR100070-003 Part A.

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[1] http://www.cancer.org/cancer/skincancer-merkelcell/detailedguide/skin-cancer-merkel-cell-carcinoma-key-statistics. Accessed November 23, 2016.
[2] http://www.cancer.org/cancer/skincancer-merkelcell/detailedguide/skin-cancer-merkel-cell-carcinoma-survival-rates. Accessed on November 23, 2016.
[3] https://www.nccn.org/professionals/physician_gls/pdf/mcc.pdf. Accessed on November 23, 2016.

Recommendation: Priority Review

Based on the information described above, I have concluded that avelumab provides a significant improvement in effectiveness over available therapy for the treatment of patients with metastatic Merkel cell carcinoma based on the durability of the observed responses relative to an observational group.

{See appended electronic signature page}

Patricia Keegan, M.D.
Director
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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

/s/

PATRICIA KEEGAN
11/29/2016

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>
<tr><th colspan="3">Application Information</th></tr>
<tr><td>BLA# 761049</td><td>NDA Supplement #: S-
BLA Supplement #: S-</td><td>Efficacy Supplement Category:
☐ New Indication (SE1)
☐ New Dosing Regimen (SE2)
☐ New Route Of Administration (SE3)
☐ Comparative Efficacy Claim (SE4)
☐ New Patient Population (SE5)
☐ Rx To OTC Switch (SE6)
☐ Accelerated Approval Confirmatory Study (SE7)
☐ Labeling Change With Clinical Data (SE8)
☐ Manufacturing Change With Clinical Data (SE9)
☐ Animal Rule Confirmatory Study (SE10)</td></tr>
<tr><td colspan="3">Proprietary Name: Bavencio
Established/Proper Name: avelumab
Dosage Form: injection
Strengths: 200 mg/10 mL (20 mg/mL)</td></tr>
<tr><td colspan="3">Applicant: EMD Serono, Inc.
Agent for Applicant (if applicable): N/A</td></tr>
<tr><td colspan="3">Date of Application: September 23, 2016
Date of Receipt: September 23, 2016
Date clock started after Unacceptable for Filing (UN): N/A</td></tr>
<tr><td colspan="2">PDUFA/BsUFA Goal Date: May 23, 2017</td><td>Action Goal Date (if different): N/A</td></tr>
<tr><td colspan="2">Filing Date: November 22, 2016</td><td>Date of Filing Meeting: November 8, 2016</td></tr>
<tr><td colspan="3">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
☐ Type 9-New Indication or Claim (will <u>not</u> be marketed as a separate NDA after approval)
☐ Type 10-New Indication or Claim (will be marketed as a separate NDA after approval)</td></tr>
<tr><td colspan="3">Proposed indication(s)/Proposed change(s): for the treatment of patients with metastatic Merkel cell carcinoma (MCC)</td></tr>
<tr><td colspan="2">Type of Original NDA: N/A
AND (if applicable)
Type of NDA Supplement: N/A

If 505(b)(2)NDA/NDA Supplement: Draft the “505(b)(2) Assessment” review found at:
http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.</td><td>☐ 505(b)(1)
☐ 505(b)(2)
☐ 505(b)(1)
☐ 505(b)(2)</td></tr>
</table>

Type of BLA ***If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team***	☒ 351(a) ☐ 351(k)
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***	☐ Standard ☒ Priority ☐ Pediatric WR ☐ QIDP ☐ Tropical Disease Priority Review Voucher ☐ Pediatric Rare Disease Priority Review Voucher
Resubmission after withdrawal? ☒ N/A	Resubmission after refuse to file? ☒ N/A
Part 3 Combination Product? ☐ N/A ***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 DARRTS and notify the CDER Breakthrough Therapy Program Manager)*** ☒ Rolling Review ☒ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ 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)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): IND 119394	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA/BsUFA and Action Goal dates correct in the electronic archive? ***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 electronic archive? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into electronic***	☒	☐		

archive.				
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*** ***If no, ask the document room staff to make the appropriate entries.***	☒	☐	☐	Priority
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***	☐	☒		
If yes, explain in comment column.				
If affected by AIP, has OC been notified of the submission? **If yes,** date notified:	☐	☐		
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	☒	☐		Submitted on 7/6/2016 with the nonclinical portion of rolling review.

User Fee Status ***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 from receipt. Review stops. Contact the User Fee Staff. If appropriate, send UN letter.***	Payment for this application *(check daily email from UserFeeAR@fda.hhs.gov):* ☐ Paid ☒ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Contact the User Fee Staff. If appropriate, send UN letter.	Payment of other user fees: ☒ Not in arrears ☐ In arrears
User Fee Bundling Policy ***Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:*** ***http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf***	Has the user fee bundling policy been appropriately applied? ***If no, or you are not sure, consult the User Fee Staff.*** ☒ Yes ☐ No

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application a 505(b)(2) NDA? *(Check the 356h form, cover letter, and annotated labeling).* **If yes**, answer the bulleted	☐	☐	X	

questions below:				
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☐		
• 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)].**	☐	☐		
• 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)]?** ***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)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:	☐	☐		

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

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 orphan or 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/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)(14)]**? ***If yes, consult the Director, Division of Regulatory Policy II, 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? ***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?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
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: ☒ legible ☒ English (or translated into English)	☒	☐		

[1] http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm333969.pdf

☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐	☐	☒	

Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	CMC IR included in the Filing Issued Identified letter, item #10.
Patent Information **(NDAs/NDA efficacy supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☐	☐	☒	
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	☒			
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form***	☒	☐		

is included in the acknowledgement letter sent to the applicant				
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***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…"*	☒	☐	☐	
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***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.***	☐	☐	☒	
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* <u>For non-NMEs</u>: *Date of consult sent to Controlled Substance Staff* :	☐	☐	☒	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
<u>PREA</u> Does the application trigger PREA? ***If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting***[2]	☐	☒		Orphan designation granted for treatment of Merkel cell carcinoma on September 21, 2015.

[2] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027829.htm

***Note**: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage 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.*				
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☐	☒	Orphan designation granted for treatment of Merkel cell carcinoma on September 21, 2015.
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☐	☒	Orphan designation granted for treatment of Merkel cell carcinoma on September 21, 2015.
BPCA: Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required[3]***	☐	☒		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	☐	☒	☐	The proprietary name was submitted on August 22, 2016 for review.
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☐	☒	☐	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (Prescribing Information)(PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☒ Medication Guide (MedGuide) ☒ Carton labeling ☒ Immediate container labels ☐ Diluent labeling ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format?	☒	☐		

[3] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027837.htm

If no, request applicant to submit SPL before the filing date.				
Is the PI submitted in Physician Labeling Rule (PLR) format?[4]	☒	☐		
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	☒	
For applications submitted on or after June 30, 2015: Is the PI submitted in Pregnancy and Lactation Labeling Rule (PLLR) format? Has a review of the available pregnancy, lactation, and females and males of reproductive potential data (if applicable) been included?	☒ ☒	☐ ☐	☐ ☐	 Refer to nonclinical rolling pre-submission, received on July 6, 2016.
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLLR format before the filing date.***	☐	☐	☒	PI is submitted in PLLR format
Has all labeling [(PI, patient labeling (PPI, MedGuide, IFU), carton and immediate container labeling)] been consulted to OPDP?	☒	☐	☐	
Has PI and patient labeling (PPI, MedGuide, IFU) been consulted to OSE/DRISK? (*send WORD version if available*)	☒	☐	☐	
Has all labeling [PI, patient labeling (PPI, MedGuide, IFU) carton and immediate container labeling, PI, PPI been consulted/sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	☒	☐	☐	
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/LabelingDevelopmentTeam/ucm025576.htm

	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	☐	☐		
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	☐	☐	☐	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	☐	☐	☐	
All labeling/packaging sent to OSE/DMEPA?	☐	☐	☐	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:*** 1. OSI- uploaded in DARRTS on 10/20/2016 2. QT/IRT- uploaded in DARRTS on 10/6/2016 3. DMPP/Patient Labeling- uploaded in DARRTS on 11/3/2016 4. OSE-uploaded in DARRTS on 11/3/2016 5. DDMAC-uploaded in DARRTS on 11/3/2016	☒	☐	☐	
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** 2/2/2016 (Initial Comprehensive Multidisciplinary Breakthrough); 4/15/2016 (Clinical Pharmacology pre-BLA); 4/26/2016 (CMC pre-BLA); 6/8/2016 (nonclinical WRO pre-BLA); 6/16/2016 (Multidisciplinary pre-BLA)	☒	☐		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** 6/16/2016	☒	☐		
Any Special Protocol Assessments (SPAs)? N/A **Date(s):**	☐			Not applicable

ATTACHMENT

MEMO OF FILING MEETING

DATE: November 8, 2016

BACKGROUND:
This BLA proposes the use of avelumab for the treatment of patients with metastatic Merkel cell carcinoma (mMCC). Breakthrough Therapy designation, under IND 119394, was granted on November 17, 2015. A pre-BLA meeting was held on June 16, 2016 to discuss and reach agreement on the content and format BLA for avelumab for the proposed indication. During this meeting, the request for rolling review was granted. On July 6, September 2, and September 23, 2016 the nonclinical, CMC, and clinical components, respectively, were submitted to BLA.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Idara Udoh	Y
	CPMS/TL:	Monica Hughes	Y
Cross-Discipline Team Leader (CDTL)	Suzanne Demko		Y
Division Director/Deputy	Patricia Keegan		Y
Office Director/Deputy	Richard Pazdur		N
Clinical	Reviewer:	Denise Casey	Y
	TL:	Suzanne Demko	Y
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:		
	TL:		
Clinical Pharmacology	Reviewer:	Safaa Burns	Y

	TL:	Jeanne Fourie-Zirkelbach	Y
• Genomics	Reviewer:	Rosane Charlab Orbach	Y
• Pharmacometrics	Reviewer:	Nan Zheng	Y
Biostatistics	Reviewer:	Pallavi Mishra-Kalyani	Y
	TL:	Kun He	N

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Alexander Putman	Y
	TL:	Whitney Helms	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Product Quality (CMC) Review Team:	ATL:	Joel Welch	Y
	RBPM:	Truong Quach	Y
• Drug Substance	Reviewer:	Arulvathani Arudchandran	N
• Drug Product	Reviewer:	Arulvathani Arudchandran	Y
• Process	Reviewer:		
• Microbiology	Reviewer:	Maria Reyes Candau-Chacon (DS); Lakshmi Narashmhan (DP)	
• Facility	Reviewer:	Steven Fong	N
• Biopharmaceutics	Reviewer:		
• Immunogenicity	Reviewer:		
• Labeling (BLAs only)	Reviewer:	Jibril Abdus-Samad	
• Other (e.g., Branch Chiefs, EA Reviewer)			
OMP/OMPI/DMPP (MedGuide, PPI, IFU)	Reviewer:	Morgan Walker	N
	TL:	Barbara Fuller	N
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labeling)	Reviewer:	Nicholas Senior	N
	TL:	Trung-Hieu Tran	N
OSE/DMEPA (proprietary name, carton/container labeling)	Reviewer:	Janine Stewart	Y
	TL:	Alice Chi-Ming Tu	N
OSE/DRISK (REMS)	Reviewer:	Naomi Redd	N
	TL:	Cynthia LaCivita	
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:	Lauren Iacono-Connor	Y
	TL:	Susan Thompson	N
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers/disciplines			
• Discipline *For additional lines, highlight this group of cells, copy, then paste: select "insert as new rows"	Reviewer:		
	TL:		
Other attendees	Jennie Chang, Associate Director, Labeling		
	Latonia Ford, OSE SRPM		
	Shaily Arora, Pharmacovigilance Reviewer		
	Kimberly Maxfield, OCP		
	Afrouz Nayernama, OSE		
	Peter Waldron, DPV		

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues:	☒ Not Applicable
o Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐ YES ☐ NO
o Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature?	☐ YES ☐ NO
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:	☒ YES ☐ NO
• Electronic Submission comments	☐ Not Applicable

List comments: Rolling Submission **Nonclinical received 7/6/2016** **Product Quality received 9/2/2016** **Clinical received 9/23/2016**	☐ No comments

CLINICAL **Comments**: Clinical acknowledged receipt of financial disclosure information and lists of investigators who participated in studies supporting the BLA. However, there were 7 investigators for which financial disclosures were missing and the sponsor failed to certify that they acted with due diligence to obtain the missing information. RPM to issue information request.	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA, include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** 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***	☐ YES Date if known: ☒ NO ☐ To be determined Reason: This biologic is not the first in its class.
• 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? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CONTROLLED SUBSTANCE STAFF • Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL MICROBIOLOGY	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE

Comments:	☐ Review issues for 74-day letter

CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**: Review issues included in "Filing Review Issues Identified" letter.	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
New Molecular Entity (NDAs only) • Is the product an NME?	NA; this is an original BLA ☐ YES ☐ NO
Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **Comments**:	 ☒ YES ☐ NO ☐ YES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? **Comments**:	☐ Not Applicable ☒ YES ☐ NO

Facility/Microbiology Review (BLAs only) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review (BLAs only) **Comments**:	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)	☐ N/A
• 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?	☐ YES ☒ NO
• If so, were the late submission components all submitted within 30 days?	☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	N/A
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☒ YES ☐ NO
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☒ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☒ YES ☐ NO

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Richard Pazdur **Date of Mid-Cycle Meeting** (for NME NDAs/BLAs in "the Program" PDUFA V): 12/8/2016 **21st Century Review Milestones (see attached)** (listing review milestones in this document is optional): **Comments**: See attached agenda	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☐ 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 ☒ Priority Review
ACTION ITEMS	
☒	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).
☐	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
☐	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.
☒	If priority review, notify applicant in writing by day 60 (see CST for choices)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☒	Update the PDUFA V DARRTS page (for applications in the Program)
☐	Other

Annual review of template by OND ADRAs completed: April 2016

Filing Meeting Agenda
November 8, 2016

BLA: 761049, Type 1 New Molecular Entity
Rolling Submission:

- **Nonclinical eCTD submission—SDN 1 (received July 6, 2016)**
- **CMC eCTD submission—SDN 3 (received September 2, 2016)**
- **Clinical eCTD submission—SDN 4 (received September 23, 2016)**

Product: avelumab (MSB0010718C), injection for intravenous use, 20 mg/mL
Proposed Proprietary Name: Bavencio
Submission Date: September 23, 2016
Received Date: September 23, 2016
Sponsor: EMD Serono, Inc.

Proposed Indication: Treatment of patients with metastatic Merkel Cell Carcinoma

Review Team: Office Signatory—Richard Pazdur; Division Signatory—Patricia Keegan

Project Management
Monica Hughes, CPMS
Idara Udoh, Sr. Regulatory Project Manager (RPM)

Clinical
Suzanne Demko, Clinical Team Leader
Denise Casey, Clinical Reviewer

Nonclinical
Whitney Helms, Non-Clinical TL
Alexander Putman, Non-Clinical Reviewer

Clinical Pharmacology
Jeanne Fourie-Zirkelback, Clin Pharm TL
Safaa Burns, Clin Pharm Reviewer

Pharmacometric
Jiang Liu, TL
Nan Zheng, Reviewer

QT IRT
Janell Chen
Michael Li

Genomics
Rosane Charlab Orbach

Biometrics
Kun He, Biometrics TL
Pallavi Mishra-Kalyani, Biometrics Reviewer

Product Quality (OBP)
Truong Quach, Regulatory Business Project Manager
Joel Welch, OBP-ATL
Arulvathani Arudchandran, OBP Reviewer
Maria Reyes Candau-Chacon, DMA-DS
Lakshmi Narashmhan, DMA-DP
Colleen Thomas, DMA-QAL
Steven Fong, Facilities Reviewer, DIA

OSE
Latonia Ford, Safety RPM
DMEPA: Janine Stewart, Medication Error Reviewer
DMEPA: Alice Chi-Ming Tu, DMEPA TL
DRISK: Naomi Redd, Risk Management Reviewer

OPDP
Nicholas Senior

Labeling
Jennie Chang, Associate Director

OSI Inspections
Susan Thompson, OSI TL
Lauren Iacono-Connor, OSI Reviewer

Agenda Items:

1. **Dates Milestone Letters Must Issue**

Milestone	Priority review 8-month PDUFA review	Comments
Application Received	September 23, 2016	
Acknowledgment Letter	**Planned Target Date:** October 7, 2016	Issued October 14, 2016
Planning/Kickoff Meeting (Day 30)	**Planned Target Date:** Sunday, October 23, 2016	Scheduled Monday, October 17, 2016
Filing Meeting (Day 30)	**Planned Target Date:** Tuesday, November 8, 2016	Scheduled Tuesday, November 8, 2016
Filing Action Letter (Day 60) (Inform applicant of review designation, filing determination)	**Planned Target Date:** Tuesday, November 22, 2016	**Actual Due Date:** Tuesday, November 22, 2016
Deficiencies Identified Letter (74 Day Letter)	**Planned Target Date:** Tuesday, December 6, 2016	**Actual Due Date:** Tuesday, December 6, 2016
Hold Mid-Cycle Meeting	**Planned Target Date:** **Thursday, December 8, 2016**	**Actual Goal Date:** Thursday, December 8, 2016
Hold Post Mid-Cycle Communication With Sponsor	**Planned Target Date:** **TBD**	**Actual Goal Date:** Saturday, January 7, 2017
Send proposed labeling/PMR/PMC/REMS to applicant (with 1 week response)	**Planned Target Date:** **TBD**	**Actual Goal Date:** Thursday, February 23, 2017
Week after the proposed labeling has been sent, discuss the Labeling/PRM/PMC with Applicant	**Planned Target Date:** **TBD**	**Actual Goal Date:** Thursday, March 2, 2017

Milestone	Priority review 8-month PDUFA review	Comments
Late Cycle Meeting	**Planned Target Date:** **TBD**	**Actual Goal Date:** Thursday, March 23, 2017
Hold Wrap-Up meeting	**Planned Target Date:** **TBD**	**Actual Goal Date:** Tuesday, April 18, 2017
Review Target Due Dates: ***Primary Review Due*** ***Secondary Review Due*** ***CDTL Review Due*** ***Division Director Review Due*** ***Office Director Review Due/Sign-Off***	**Planned Target Dates:** Thursday, February 23, 2017 Saturday, February 25, 2017 Tuesday, April 25, 2017 Friday, May 12, 2017 Tuesday, May 23, 2017	**Actual Goal Dates:** Thursday, February 23, 2017 Saturday, February 25, 2017 **Issue Disciplinary Review letters (as needed) by February 26, 2017** **Tuesday, April 25, 2017** **Saturday, May 13, 2017** **Tuesday, May 23, 2017**
Compile and circulate Action Letter and Action Package	**Planned Target Date:** TBD	**Actual Goal Date:** **Tuesday, May 2, 2017**
REMS Finalized; DRISK Review of REMS Finalized	**Planned Target Date:** TBD	**Actual Goal Date:** **Tuesday, May 9, 2017**
FINAL Action Letter Due	**Planned Target Date:** Tuesday, May 23, 2017	**Actual Goal Date:** **Tuesday, May 23, 2017**
Post Action Timeline		
Send action letter (fax or e-mail) to applicant and confirm receipt; notify Press Office if necessary	**Planned Target Date:** Tuesday, May 23, 2017	**Actual Due Date:** Tuesday, May 23, 2017
Send approval letter and summary review to FOI	**Planned Target Date:** Wednesday, May 24, 2017	**Actual Due Date:** Wednesday, May 24, 2017

Milestone	Priority review 8-month PDUFA review	Comments
Complete Action Pkg, send to DDR/FOI	**Planned Target Date:** Thursday, May 25, 2017	**Actual Due Date:** Thursday, May 25, 2017
Post-Action Feedback Meeting/End of Review Conference (if requested by Applicant)	**TBD**	**TBD**

2. CONSULTS

OPDP	Nicholas Senior
OSE	DMEPA Janine Stewart DRISK Naomi Redd
OSI	Lauren Iacono-Connor
QT-IRT	Janell Chen Mike Li

3. INTERNAL MEETINGS

a. Mid-cycle Meeting: Scheduled Thursday, December 8, 2016

b. Team Meetings and Biweekly FDA/Sponsor calls to be scheduled.

c. Labeling Meetings

Meetings	Discipline Required	Label Sections	Date/Time/Location
#1	CMC, DMEPA, Clinical	3, 11, 16 and carton and container labeling	Mon 1/9/2017 12-1 PM WO22/Rm 2327
#2	Clinical, Statistics	1, 14	Thur 1/12/2017 12-1 PM WO22/Rm 3266
#3	DMEPA, Clinical	2, 7, 8.5, 8.6, 8.7, and 6.2 (Immunogenicity)	Tues 1/17/2017 2-3 PM WO22/Rm 2376
#4	Non-clinical, Clinical	12, 13, 8.1-8.4, 5 (if warning for embryo-fetal toxicity)	Thur 1/19/2017 12-1 PM WO22/Rm 2376
#5	Clinical	6	Mon 1/23/2017 12-1 PM WO22/Rm 2327
#6	Clinical	4, 5, 2, 17	Tues 1/24/2017 10-11:30 AM WO22/Rm 2327
#7	Clinical Pharmacology	12.2, 12.3	Fri 1/27/2017 10-11:30 AM WO22/Rm 2327
#8	All review disciplines	Any items not covered during	Tues 1/31/2017 2-3 PM

		originally scheduled time	WO22/Rm 3270

Labeling meeting #9 will be scheduled 2-3 weeks after labeling is sent to EMD Serono. It will include all disciplines, OPDP, and PLT.

4. Updates

a. Proprietary Name Granted October 28, 2016
b. Request for Risk Management Plan (RMP) issued October 20, 2016.
    i. Sponsor submitted RMP (which included Pharmacovigilance Plan) on October 27, 2016.

5. Filing Reviews by Discipline: Identify Potential RTF Issues: studies/information submitted; identification of information requests; **day 60/74 letter items**

a. **Pharm/Tox Review**
b. **Clinical Pharmacology**
Update: QT IRT consult submitted
Scoping meeting held 10/31/2016
c. **Clinical**
d. **Regulatory:** *RPM Filing Review*
e. **Labeling**—J. Chang, *SRPI Labeling Review*
f. **Biometrics**—P. Mishra-Kalyani (TL: K. He)
g. **Product Quality**—Microbiology, Drug Substance, Drug Product, Facilities
- Environmental Assessments; Categorical Exclusion requested in this application

6. MISCELLANEOUS ITEMS/ISSUES

- Press Release and Burst Planned-
Draft PR and Burst due to Press office 2 months prior to AGD

- No ODAC- For purpose of documenting in Filing Summary, reason needed.

- Current SGE list forwarded to Clinical. Will SGE be needed? Should we begin identifying?

- PMR/PMC Discussion

- Any Information Request to send to Sponsor?

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

/s/

IDARA UDOH
11/22/2016

MONICA L HUGHES
11/22/2016

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

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

Application: BLA 761049

Application Type: New BLA

Drug Name(s)/Dosage Form(s): Bavencio (avelumab) Injection, for intravenous use, 20 mg/mL

Applicant: EMD Serono, Inc.

Receipt Date: Rolling review pre-submissions received on July 6, 2016 and September 2, 2016. Final submission September 23, 2016

Goal Date: May 23, 2017

1. Regulatory History and Applicant's Main Proposals

Avelumab is a programmed death ligand-1 (PD-L1) blocking antibody indicated for the treatment of patients with metastatic Merkel cell carcinoma under IND IND 119394. This BLA proposes the use of avelumab for the treatment of patients with metastatic Merkel cell carcinoma (mMCC). Breakthrough Therapy designation, under IND 119394, was granted on November 17, 2015. A pre-BLA meeting was held on June 16, 2016, between FDA and EMD Serono under IND 119394. The purpose of this meeting was to discuss and reach agreement on the content and format of the BLA for avelumab for the proposed indication; to reach agreement that the data provided from clinical study EMR100070-003, entitled "A Phase II, Open-Label, Multicenter Trial to Investigate the Clinical Activity and Safety of Avelumab (MSB0010718C) in Subjects with Merkel Cell Carcinoma," is sufficient to support a biologic licensing application (BLA) for avelumab; and to discuss and reach agreement on the design of the trial EMR 100070-006 entitled "A Phase III multicenter study of avelumab (MSB0010718C) versus chemotherapy in systemic chemotherapy treatment naïve patients with metastatic Merkel cell carcinoma" intended to confirm clinical benefit. During this meeting, the request for rolling review was granted. Meeting minutes from this meeting issued on July 6, 2016. A separate CMC pre-NDA meeting was held April 26, 2016 and the meeting minutes issued May 24, 2016.

On July 6, September 2, and September 23, 2016 the nonclinical, CMC, and clinical components, respectively, were submitted to BLA.

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 of Prescribing Information (SRPI)" checklist (see Section 4 of this review).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies, see Section 4 of this review.

Additional labeling issues were identified. All SRPI format deficiencies of the PI, and additional labeling issues will be conveyed to EMD Serono, Inc. through FDA comments and questions included in the draft PI to be attached to the *Filing Review Issues Identified* letter. EMD Serono, Inc. will be asked to correct these deficiencies and resubmit the PI in Word format by December 13, 2016. The resubmitted PI will be used for further labeling review.

4. Selected Requirements of Prescribing Information

The Selected Requirement of Prescribing Information (SRPI) is a 41-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 for a sample tool illustrating Highlights format.

HIGHLIGHTS GENERAL FORMAT

NO 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: Applicant will be instructed to ensure that the format of the prescribing information is consistent with the labeling regulations/guidance as discussed in the Selected Requirements in Prescribing Information SRPI (e.g, half-inch margins on all sides and between columns in Highlights, and center the headings within the horizontal line), refer to http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/UCM373025.pdf Remove bullet if only one item statement is listed. Please use this convention throughout Highlights.

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), **and**
- TOC from the Full Prescribing Information (FPI).

Comment:

YES 4. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be **bolded** and presented in the center of a horizontal line. (Each horizontal line should extend over the

entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format.

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 for HL format.

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: *The numerical identifier for the "Dosage Forms and Strengths" reference needs to be corrected. It is italicized and in the wrong font size.*

YES 7. Headings in HL must be presented in the following order:

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

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

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

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

Highlights Limitation Statement

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

Comment:

Product Title in Highlights

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

Comment:

Initial U.S. Approval in Highlights

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

Comment: *Since the product is not yet approved, the 4-digit year appears as "YYYY".*

Boxed Warning (BW) in Highlights

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

Comment:

N/A 13. The BW must have a title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. Even if there is more than one warning, the term "**WARNING**" and not "**WARNINGS**" should be used. For example: "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings. The BW title 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 must be placed immediately beneath the BW title, and should be centered 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 title 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 five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. Labeling sections for RMC must be listed in the same order in HL as they appear in the FPI.

Comment: *This is a new molecular entity (NME) NDA Application*

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) --- 8/2015."

Comment:

N/A

18. A changed section must be listed under the RMC heading for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period. (No listing should be one year older than the revision date.)

Comment:

Dosage Forms and Strengths in Highlights

N/A 19. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

Comment: *This product has only a single dosage form (injection)for this biologic.*

Contraindications in Highlights

YES 20. All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word "None."

Comment:

Adverse Reactions in Highlights

YES 21. 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 which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**"

Comment:

Patient Counseling Information Statement in Highlights

NO 22. 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 (or will have)** 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: *The Patient Counseling Information Statement language in the Highlights is not one of the three bolded verbatim statement options. Sponsor states "See 17 for PATIENT COUNSELING INFORMATION and* (b) (4) *Medication Guide."*

Revision Date in Highlights

YES 23. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 8/2015** ").

Comment:

Contents: Table of Contents (TOC)

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

YES 24. The TOC should be in a two-column format.

Comment:

YES 25. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS."** This heading should be in all UPPER CASE letters and **bolded**.

Comment:

N/A 26. The same title for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

NO 27. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment: *They are in uppercase, but not bolded.* Applicant will be instructed to bold.

YES 28. 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 (for, of, to) and articles (a, an, the), or conjunctions (or, and)].

Comment:

YES 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

YES 30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading "**FULL PRESCRIBING INFORMATION: CONTENTS***" must be followed by an asterisk and the following statement must appear at the end of the TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment:

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

YES 31. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. (Section and subsection headings should be in UPPER CASE and title case, respectively.) If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation (if not required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, use "**Labor and Delivery**")
8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format, use "**Nursing Mothers**")
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES 32. 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)]*."

Comment: *In subsection 2.2, "precautions" needs to be capitalized in two areas.*

N/A 33. For each RMC listed in HL, the corresponding new or modified text in the FPI must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 34. The following heading "**FULL PRESCRIBING INFORMATION"** must be **bolded,** must appear at the beginning of the FPI, and should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

N/A 35. All text in the BW should be **bolded**.

Comment:

N/A 36. The BW must have a title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. (Even if there is more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used.) For example: "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings.

Comment:

CONTRAINDICATIONS Section in the FPI

YES 37. If no Contraindications are known, this section must state "None."

Comment:

ADVERSE REACTIONS Section in the FPI

YES 38. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions from clinical trials:

> "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 39. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection), 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:

Selected Requirements of Prescribing Information

PATIENT COUNSELING INFORMATION Section in the FPI

YES 40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:

- Advise the patient to read the FDA-approved patient labeling (Patient Information).
- Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Comment:

YES 41. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) 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: Highlights and Table of Contents Format

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use PROPRIETARY NAME safely and effectively. See full prescribing information for PROPRIETARY NAME.

PROPRIETARY NAME (non-proprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: YYYY

WARNING: TITLE OF WARNING
See full prescribing information for complete boxed warning.

- **Text (4)**
- **Text (5.x)**

----------RECENT MAJOR CHANGES----------
Section Title, Subsection Title (x.x) M/201Y
Section Title, Subsection Title (x.x) M/201Y

----------INDICATIONS AND USAGE----------
PROPRIETARY NAME is a (insert FDA established pharmacologic class text phrase) indicated for … (1)

Limitations of Use: Text (1)

----------DOSAGE AND ADMINISTRATION----------
- Text (2.x)
- Text (2.x)

----------DOSAGE FORMS AND STRENGTHS----------
Dosage form(s): strength(s) (3)

----------CONTRAINDICATIONS----------
- Text (4)
- Text (4)

----------WARNINGS AND PRECAUTIONS----------
- Text (5.x)
- Text (5.x)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are text (6.x)

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

----------DRUG INTERACTIONS----------
- Text (7.x)
- Text (7.x)

----------USE IN SPECIFIC POPULATIONS----------
- Text (8.x)
- Text (8.x)

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

Revised: M/201Y

FULL PRESCRIBING INFORMATION: CONTENTS*

* 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/

IDARA UDOH
11/22/2016

MONICA L HUGHES
11/22/2016