CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125554Orig1s000

OTHER REVIEW(S)

Attachment B: Sample 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.

PMR/PMC Description: Re-evaluate and tighten the endotoxin limits for the following in-process samples: (b) (4)

Re-evaluate and tighten the endotoxin limits for the following additional samples: (b) (4)

PMR/PMC Schedule Milestones:

Final protocol Submission Date:	MM/DD/YYYY
Study/Clinical trial Completion Date:	MM/DD/YYYY
Final Report Submission Date:	4/30/2016
Other:	MM/DD/YYYY

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 sponsor needs more data to understand the manufacturing capability before tightening the endotoxin limits. This is appropriate for a PMC because the risk of microbial contamination of the product is low. There are bioburden limits for the relevant samples.

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 current endotoxin limits for the relevant samples are high for the manufacturing process. The sponsor needs to tighten the endotoxin limits based on manufacturing experience.

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.

Re-evaluate and tighten the endotoxin limits for in-process samples, (b) (4) microbial monitoring samples after data from more lots are available.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies

Continuation of Question 4

☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (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?

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/

MEREDITH LIBEG
12/19/2014
Meredith Libeg on behalf of Bo Chi and Patricia Hughes

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: December 16, 2014

To: Meredith Libeg
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 BLA 125554
OPDIVO (nivolumab) injection, for intravenous use

OPDP has reviewed the proposed product labeling (PI) for OPDIVO (nivolumab) injection, for intravenous use (Opdivo) as requested in the consult dated September 11, 2014. The following comments, using the proposed substantially complete, marked-up version of the PI emailed to OPDP by Meredith Libeg on December 10, 2014, are provided below.

Please note that comments on the proposed Opdivo patient labeling will be provided under a separate cover as a collaborative review between OPDP and the Division of Medical Policy Programs.

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
12/16/2014

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:	December 16, 2014
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:	Sharon R. Mills, BSN, RN, CCRP Senior 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):	OPDIVO (nivolumab)
Dosage Form and Route:	injection, for intravenous use
Application Type/Number:	BLA 125554
Applicant:	Bristol-Myers Squibb Company

1 INTRODUCTION

On July 30, 2014, Bristol-Myers Squibb Company submitted for the Agency's review an original Biologics License Application (BLA) 125554 for OPDIVO (nivolumab) injection for intravenous use. The proposed indication for OPDIVO (nivolumab) injection is for the treatment of unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor.

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 September 11, 2014, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for OPDIVO (nivolumab) injection for intravenous use.

2 MATERIAL REVIEWED

- Draft OPDIVO (nivolumab) injection MG received on July 30, 2014, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on December 10, 2014.
- Draft OPDIVO (nivolumab) injection Prescribing Information (PI) received on July 30, 2014, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on December 10, 2014.
- Approve d KEYTRUDA (pembrolizumab) for injection, for intravenous use comparator labeling dated September 4, 2014.

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 have reformatted the MG document using the Verdana font, size 11.

In our collaborative review of the MG we have:

- 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)
- ensured that the MG is consistent with the approved comparator labeling where applicable.

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/

SHARON R MILLS
12/16/2014

NICHOLAS J SENIOR
12/16/2014

BARBARA A FULLER
12/16/2014

LASHAWN M GRIFFITHS
12/16/2014

PMR/PMC Development Template: Product Quality (CMC)

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

NDA/BLA # Product Name:	125554/Opdivo
PMC #1 Description:	To re-evaluate nivolumab drug substance lot release and stability specifications after 30 lots have been manufactured using the commercial manufacturing process. The corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be provided in the final report.

PMC Schedule Milestones:	Final Protocol Submission:	
	Study/Trial Completion:	
	Final Report Submission:	October 31, 2016
	Other:	

- **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

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

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

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

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

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

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

   Describe the agreed-upon study:

   The corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be provided following manufacture of additional commercial lots.

5. To be completed by ONDQA/OBP Manager:

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

PMR/PMC Development Coordinator:

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

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(signature line for BLAs only)

PMR/PMC Development Template: Product Quality (CMC)

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

NDA/BLA # Product Name:	125554/Opdivo
PMC #2 Description:	To re-evaluate nivolumab drug product lot release and stability specifications after 30 lots have been manufactured using the commercial manufacturing process. The corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be provided in the final report.

PMC Schedule Milestones:

Final Protocol Submission:	
Study/Trial Completion:	
Final Report Submission:	October 31, 2016
Other:	

- **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

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

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

Nivolumab Drug Product release and shelf-life specifications are based on clinical and manufacturing experience *provided in the BLA and assessed* during the BLA review; however, the number of lots to date do not allow for a robust statistical analysis of the data. Some specifications have a statistical component that should be re-assessed when a sufficient number of marketed product lots have been released.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

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

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

   Describe the agreed-upon study:

   The corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be provided following manufacture of additional commercial lots.

5. To be completed by ONDQA/OBP Manager:

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

PMR/PMC Development Coordinator:

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

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PMR/PMC Development Template: Product Quality (CMC)

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

NDA/BLA # 125554/Opdivo
Product Name:

PMC #3 Description: To develop and validate a process-specific host cell protein (HCP) assay that has improved sensitivity and capability to detect a greater range of potential HCPs compared to the current assay and to implement this assay in the nivolumab drug substance release program. The analytical procedure, validation report, proposed specification acceptance criterion, and data used to set the proposed acceptance criterion will be provided in the final study report.

PMC Schedule Milestones:

Final Protocol Submission:	
Study/Trial Completion:	
Final Report Submission:	March 31, 2016
Other:	

- **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

The current assay and acceptance criterion for the assessment of host cell proteins in drug substance release program are sufficient to ensure adequate quality and safety of nivolumab for the initial marketed product. However, the improvement and implementation of a process-specific assay for HCP will provide better control of HCP levels in DS.

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

The current nivolumab Drug Substance (DS) release specifications include an ELISA method for evaluating HCP levels in DS. (b) (4) The implementation of an improved, process-specific HCP assay will provide more accurate control of the host cell related impurities in DS.

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:

Development and validation of a process specific HCP assay with improved sensitivity and capability to detect a greater range of potential HCP.

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.*

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(signature line for BLAs only)

PMR/PMC Development Template: Product Quality (CMC)

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

NDA/BLA # 125554/Opdivo
Product Name:

PMC #4 Description: To optimize and re-validate a non-reduced CE-SDS method that has improved reproducibility. The analytical procedure, validation report, any proposed changes to specification acceptance criteria, and the data used to set the proposed acceptance criteria will be provided in the final study report.

PMC Schedule Milestones:

Final Protocol Submission:	
Study/Trial Completion:	
Final Report Submission:	March 31, 2016
Other:	

- **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

   The current assay and acceptance criterion for the purity by non-reduced CE-SDS in drug substance release program are sufficient to ensure adequate quality and safety of nivolumab for the initial marketed product. However, the improvement of the assay will provide better control of purity in DS and DP.

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

The current nivolumab Drug Substance (DS) and Drug Product (DP) release specifications include non-reduced CE-SDS for the assessment of purity. This method though sufficient for approval demonstrates higher than typical variability from run to run. The implementation of an improved method will provide more accurate control of purity in both drug substance and drug product.

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:

   Development and validation of a non-reduced CE-SDS method with improved assay variability.

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.*

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(signature line for BLAs only)

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/s/

MEREDITH LIBEG
12/15/2014
Meredith Libeg on behalf of Joel Welch and Laurie Graham

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

Division of Pediatric and Maternal Health Memorandum

Date: December 12, 2014 **Date consulted:** September 19, 2014

From: Miriam Dinatale, D.O., Medical Officer, Maternal Health
Division of Pediatric and Maternal Health

Through: Carrie Ceresa, Pharm D., MPH, Acting Team Leader, Maternal Health
Lynne P. Yao, MD, OND, Acting Division Director
Division of Pediatric and Maternal Health

To: Office of Hematology and Oncology Products (OHOP)/
Division of Oncology Products 2 (DOP2)

Drug: Opdivo (nivolumab) Injection for Intravenous Infusion

BLA: 125554

Applicant: Bristol-Myers Squibb Company

Subject: Pregnancy and Nursing Mothers Labeling

Materials Reviewed:

- DPMH consult request dated September 19, 2014, DARRTS Reference ID 3631212
- Sponsor's submitted background package for BLA 125554, Nivolumab
- Keytruda labeling from drugs@fda accessed October 31, 2014, website: http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/125514lbl.pdf
- Non-clinical Team Primary Review, Keytruda (pembrolizumab), BLA 125514, 7/30/2014, DARRTS Reference ID 3601748
- Clinical Team Secondary Review, Keytruda (pembrolizumab), BLA 125514, 2/27/2014, DARRTS Reference ID 3621494

Consult Question:
DOP2 requests DPMH assistance with pregnancy and nursing mothers labeling for a new BLA.

REGULATORY HISTORY

Opdivo (nivolumab) is a human immunoglobulin G4 (IgG4) monoclonal antibody (mAb) that blocks the interaction between the programmed death-1 (PD-1) membrane receptor and its ligands and promotes immune responses and antigen-specific T cell responses that target the PD-1 receptor.[1]

FDA granted nivolumab Fast Track Designation for the treatment of patients with unresectable or metastatic melanoma on October 4, 2012 and orphan drug designation on January 23, 2013 for the proposed indication of Stage IIb to IV melanoma. A Request for Breakthrough Therapy Designation was submitted to IND 115195 on July 18, 2014, and a determination is still pending. On July 30, 2014 Bristol-Myers Squibb Company submitted a request for a Priority Review, which the FDA granted on September 11, 2014, for the Biologics License Application (BLA 125554) for Opdivo to obtain approval to market Opdivo for the proposed indication of the treatment of unresectable or metastatic melanoma in patients previously treated with ipilimumab, regardless of BRAF[2] status.

OHOP/DOP2 consulted the Division of Pediatric and Maternal Health-Maternal Health Team (DPMH-MHT) on September 19, 2014 to provide input for appropriate labeling of the pregnancy and lactation subsections of Opdivo labeling.

BACKGROUND

Melanoma

Malignant melanoma (MM), a type of skin cancer that develops in melanocytes, is the fifth most common cancer in men and the seventh most common cancer in women. Four percent of all newly diagnosed cases of MM are metastatic. Once MM is metastatic, the five-year survival is less than 10%.[3] In 2014, there were 76,100 new cases and 9,710 death associated with MM.[4]

FDA-approved treatment options for treatment of metastatic MM include immunotherapy (interleukin-2, ipilimumab), chemotherapy (dacarbazine), and for patients with $BRAF^{V600}$ mutation (seen in 50% of MM patients), BRAF inhibitors (vemurafenib and dabrafenib). On September 4, 2014, pembrolizumab (a monoclonal antibody that blocks PD-1) was approved in the US to treat patients with metastatic melanoma who are refractory to ipilimumab and a BRAF inhibitor.[5]

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[1] Sponsor Packet: BLA 125554 for Nivolumab: Request for Priority Review Designation
[2] BRAF is a human gene that makes a protein called B-Raf. The gene is also referred to as proto-oncogene B-Raf and v-Raf murine sarcoma viral oncogene homolog B, while the protein is more formally known as serine/threonine-protein kinase B-Raf. http://en.wikipedia.org/wiki/BRAF_%28gene%29
[3] Clinical Team Secondary Review, Keytruda (pembrolizumab), BLA 125514, 2/27/2014, DARRTS Reference ID 3621494
[4] http://www.cancer.gov/cancertopics/types/melanoma
[5] Clinical Team Secondary Review, Keytruda (pembrolizumab), BLA 125514, 2/27/2014, DARRTS Reference ID 3621494

Melanoma in Pregnancy

About one third of women diagnosed with MM are of childbearing age. MM is considered the most common malignant tumor found during pregnancy, corresponding to 31% of all diagnosed malignant neoplasms. There is a 3.3% incidence of MM during pregnancy in women between 16 and 49 year old.[6] One hypothesis, regarding the increase in MM in pregnancy, is that hormonal changes during pregnancy may be involved with the increased incidence, but according to Mestnik *et al.*, the most probable explanation is delay in diagnosis.[7] In an article by Jhaveri *et al.*, the authors propose a different hypothesis attributing the higher incidence of MM in pregnancy to immunosuppression that occurs during pregnancy. Pregnancy, however, does not significantly change the characteristic or prognosis of MM.[8]

Nivolumab and Mechanism of Action

Nivolumab is an IgG4 mAb that binds to the PD-1 cell surface membrane receptor and prevents the interaction of PD-1 with its ligands, PD-L1 and PD-L2. Blocking this pathway results in down-regulation of lymphocyte activation and promotes antigen-specific T cell responses thereby enhancing tumor immunosurveillance and the anti-tumor immune response.[9]

In the FDA nonclinical review of pembrolizumab, another IgG4 mAb that blocks the PD-1 receptor, the author noted that data showed adverse pregnancy outcomes in PD-1 deficient mice and in mice treated with PD-L1 neutralizing antibodies suggesting that PD-1 pathway inhibition is abortifacient. Dams carrying hemi-allogenic fetuses had fetal loss that is seen in immunological rejection. PD-1 has a role in promoting maternal tolerance to fetal antigens at the maternal/placental interface to prevent fetal rejection.

Although there are no reports of fetal malformations associated with PD-1 deficiency in mice, there is limited evidence of the risk of malformations caused by PD-1 deficiency in animals in literature. Since many adverse autoimmune reactions (pneumonitis, colitis, elevated liver enzymes, nephritis and hypo- and hyperthyroidism, thyroiditis) are seen in adult patients taking IgG4 mAbs that block the PD-1 receptor, the concern is that autoimmune disease may be seen in the fetus and neonate. The effect of PD-1 inhibition during organogenesis and the risk of malformations is not discussed in literature.[10]

Literature has shown that IgG4 mAb can cross the placental barrier. In a study by Garty *et al.,* the blood from 34 fetuses was obtained by percutaneous umbilical blood sampling via amniocentesis and peripheral venous blood was drawn from the mothers at the time of the procedure. The authors showed that although all IgG subclasses cross the human placenta, their transport is not uniform. IgG1 and IgG4 are transported more efficiently than IgG2 and

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[6] Jhaveri *et al*. Melanoma in Pregnancy. Clinical Obstetrics and Gynecology. 2011; 54(4): 537-545.
[7] Mestnik *et al*. Melanoma developed during pregnancy-A case report. Anais Brasileiros De Dermatologica. 2013; 89(1): 157-159.
[8] Jhaveri *et a*l. Melanoma in Pregnancy. Clinical Obstetrics and Gynecology. 2011; 54(4): 537-545.
[9] Non-clinical Team Secondary Review, Keytruda (pembrolizumab), BLS 125514, 8/5/2014, DARRTS Referance ID 3604766
[10] Non-clinical Team Primary Review, Keytruda (pembrolizumab), BLA 125514, 7/30/2014, DARRTS Reference ID 3601748

IgG3. Fetal IgG subclass concentrations are similar to maternal concentrations at 38 weeks gestation and on occasion, IgG concentrations may be higher than maternal concentrations at delivery.[11]

DISCUSSION

Pregnancy and Nursing Mothers Labeling

On December 4, 2014, the Food and Drug Administration (FDA) announced the publication of the "*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*,"[12] also known as the Pregnancy and Lactation Labeling Rule (PLLR). The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation and create a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) will be removed from all prescription drug and biological product labeling and a new format will be required for all products that are subject to the 2006 Physicians Labeling Rule[13] format to include information about the risks and benefits of using these products during pregnancy and lactation.

Nivolumab and Pregnancy

The sponsor did not conduct studies with nivolumab in pregnant women. A search of published literature in Pubmed was performed and no publications were found evaluating the use of nivolumab in pregnant women.

Animal reproduction studies have shown adverse effects (fetal and infant death) in cynomolgus monkeys and a disruption to tolerance to the fetus resulting in an increase in fetal loss was observed in murine models of pregnancy. Nivolumab will likely cross the human placenta as it is an IgG4 antibody, and IgG4 antibodies cross the placenta. Although human pregnancy outcome data is not available for nivolumab, the likelihood of adverse fetal and infant effects is high based on the drug's mechanism of action, adverse fetal and infant outcomes observed in animal models and animal reproduction studies, as well as the ability of the antibody to cross the placenta.

Nivolumab and Lactation

The sponsor did not provide human or animal data on the use of nivolumab during lactation. The Drugs and Lactation Database (LactMed)[14] and Pubmed were searched for available lactation data on the use of nivolumab, and no information was found. However, IgG is

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

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

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

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

present in breast milk; therefore, it is likely that nivolumab, an IgG4 antibody, will be present in breast milk. Serious autoimmune reactions (pneumonitis, colitis, elevated liver enzymes, nephritis and hypo/hyperthyroidism, thyroiditis) were observed in adult patients in clinical trials with nivolumab. Therefore, breastfeeding with maternal use of Opdivo is not recommended due to the potential for adverse reactions in a breast feed infant because of the likelihood of exposure to the drug through breastfeeding and the known serious adverse reactions observed in adult clinical trials.

Nivolumab and Use in Females of Reproductive Potential
MM occurs in females of reproductive potential, and due to the potential for adverse fetal and infant effects, females of reproductive potential should use effective contraception during treatment with nivolumab and for five months following completion of therapy. Continuation of female contraception use after drug therapy is generally related to the half-life of a drug. Drugs usually clear the systemic circulation in 4 to 5 half-lives. The half-life of nivolumab was measured at 26.7 days. Therefore, using a five month time period for continued contraception after therapy is appropriate to ensure low to no systemic drug levels in a female of reproductive potential.

CONCLUSIONS AND RECOMMENDATIONS
DPMH-MHT has the following recommendations for Opdivo labeling:

- **Warnings and Precautions, Section 5.7**
  - A subsection describing embryo- and/or fetal risks ("Embryofetal Toxicity") as well as mitigation measures must be placed in the Warnings and Precautions section of labeling as required by regulation (21 CFR 201.57(c)(9)(i)(A)(4).
- **Pregnancy, Section 8.1**
  - The "Pregnancy" subsection of Opdivo labeling was formatted in the PLLR format to include "Risk Summary" and "Data" subsections[15].
- **Lactation, Section 8.2**
  - The "Lactation" subsection of Opdivo labeling was formatted in the PLLR format to include the "Risk Summary" subsection[16].
- **Females and Males of Reproductive Potential, Section 8.3**
  - The "Females and Males of Reproductive Potential" subsection of Opdivo labeling was added and formatted in the PLLR format to include "Contraception" to advise females of reproductive potential to use effective contraception during treatment with Opdivo and for five months (4 to 5 half-lives) following completion of therapy with Opdivo to minimize potential fetal exposure because of the potential for adverse fetal

[15] Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format. December 2014. Part IV Specific Subsection A-8.1 Pregnancy, 2-Risk Summary.
[16] Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format. December 2014. Part IV Specific Subsection, B- 8.2 Lactation, 1- Risk Summary.

and infant effects from maternal exposure. This additional subsection is consistent with the PLLR for drugs with a likelihood of embryofetal toxicity.[17]

DPMH-MHT OPDIVO (NIVOLUMAB) LABELING

DPMH-MHT discussed our labeling recommendations with OHOP/DOP2 at a labeling meeting on November 19, 2014. DPMH-MHT and the DOP2 Pharmacology/Toxicology team recommendations are below. Final labeling will be negotiated with the applicant and may not fully reflect changes suggested here.

HIGHLIGHTS OF PRESCRIBING INFORMATION

----------WARNINGS AND PRECAUTIONS----------

- Embryofetal Toxicity: Can cause fetal harm. Advise of potential risk to a fetus and use of effective contraception (5.11, 8.1, 8.3).

----------USE IN SPECIFIC POPULATIONS----------

- Lactation: Discontinue breastfeeding (8.2).

FULL PRESCRIBING INFORMATION

5 WARNINGS AND PRECAUTIONS

5.7 Embryofetal Toxicity

Based on its mechanism of action and data from animal studies, OPDIVO can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of nivolumab to cynomolgus monkeys from the onset of organogenesis through delivery resulted in increased abortion and premature infant death. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with OPDIVO and for at least 5 months after the last dose of OPDIVO *[see Use in Specific Populations (8.1, 8.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action *[see Clinical Pharmacology (12.1)]* and data from animal studies, OPDIVO can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1)]*. In animal reproduction studies, administration of nivolumab to cynomolgus monkeys from the onset of organogenesis through delivery resulted in increased abortion and premature infant death *[see Data]*. Human IgG4 is known to cross the placental barrier and nivolumab is an immunoglobulin G4 (IgG4); therefore, nivolumab has the potential to be transmitted from the mother to the developing fetus. The effects of OPVIDO are likely to be greater during the second and third trimesters of pregnancy. There are no available human data informing the drug-associated risk. Advise pregnant women of the potential risk to a fetus.

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

The background risk of major birth defects and miscarriage for the indicated population is unknown. However, the background risk in the U.S. general population of major birth defects is 2-4% and of miscarriage is 15-20% of clinically recognized pregnancies.

Data

Animal data

A central function of the PD-1/PD-L1 pathway is to preserve pregnancy by maintaining maternal immune tolerance to the fetus. Blockade of PD-L1 signaling has been shown in murine models of pregnancy to disrupt tolerance to the fetus and to result in an increase in fetal loss. The effects of nivolumab on prenatal and postnatal development were evaluated in monkeys that received nivolumab twice weekly from the onset of organogenesis through delivery, at exposure levels of between (b) (4) times higher than those observed at the clinical dose of 3 mg/kg of nivolumab (based on AUC). Nivolumab administration resulted in a non-dose-related increase in spontaneous abortion and increased neonatal death. Based on its mechanism of action, fetal exposure to nivolumab may increase the risk of developing immune-mediated disorders or altering the normal immune response and immune-mediated disorders have been reported in PD-1 knockout mice. In surviving infants (b) (4) of 32 compared to 11 of 16 vehicle-exposed infants) of cynomolgus monkeys treated with nivolumab, there were no apparent malformations and no effects on, neurobehavioral, immunological, or clinical pathology parameters throughout the 6-month postnatal period.

8.2 Lactation

Risk Summary

It is not known whether OPDIVO is present in human milk. Because many drugs, including antibodies are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from OPDIVO, advise women to discontinue breastfeeding during treatment with OPDIVO.

8.3 Females and Males of Reproductive Potential

Contraception

Based on its mechanism of action, OPDIVO can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*. Advise females of reproductive potential to use effective contraception during treatment with OPDIVO and for at least 5 months following the last dose of OPDIVO.

17 PATIENT COUNSELING INFORMATION

- Advise females of reproductive potential of the potential risk to a fetus and to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.7), Use in Specific Populations (8.1)]*.
- Advise females of reproductive potential to use effective contraception during treatment with OPDIVO and for at least 5 months following the last dose of OPVIDO *[see Use in Specific Populations (8.3)]*.
- Advise women not to breastfeed during treatment with OPDIVO *[see Use in Specific Populations (8.2)]*.

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/s/

MIRIAM C DINATALE
12/12/2014

CARRIE M CERESA
12/12/2014

LYNNE P YAO
12/12/2014

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 # 125554
Product Name: Opdivo (Nivolumab)

PMR/PMC Description: Confirmatory trial(s) for nivolumab

PMR/PMC Schedule Milestones:
- Final Protocol Submission: _____
- Study/Trial Completion: _____
- Final Report Submission: 12/31/2016
- Other: _____ _____

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.

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

Nivolumab is being approved under subpart E (accelerated approval); therefore, confirmatory trial(s) are required to verify and describe the clinical benefit of nivolumab in the proposed population, i.e., patients with unresectable or metastatic melanoma. These patients have a serious and life-threatening condition with an unmet medical need.

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."

N/A

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

X 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 and submit the results of a multicenter, randomized trial or trials establishing the superiority of nivolumab over standard therapy in adult patients with unresectable or metastatic melanoma who are refractory to ipilimumab or who have not been previously treated with ipilimumab.

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)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☒ Other (provide explanation)
Confirmatory trial(s) required under the accelerated approval regulations (Subpart E).

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?

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/

MAITREYEE HAZARIKA
12/12/2014

MARC R THEORET
12/12/2014

JEFFERY L SUMMERS
12/12/2014

M E M O R A N D U M

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

CLINICAL INSPECTION SUMMARY

DATE: December 11, 2014

TO: Meredith Libeg, Regulatory Health Project Manager
Maitreyee Hazarika, M.D., Medical Reviewer
Meredith Chuk, M.D., Medical Reviewer
Division of Oncology Products 2

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

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

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

SUBJECT: Evaluation of Clinical Inspections

BLA: 125554

APPLICANT: Bristol-Myers Squibb (BMS) Company

DRUG: Opdivo (Nivolumab; BMS-936558)

NME: Yes

THERAPEUTIC CLASSIFICATION: Priority

INDICATION(S): For the treatment of unresectable or metastatic melanoma in patients previously treated with ipilimumab, regardless of BRAF status.

CONSULTATION REQUEST DATE: September 8, 2014
INSPECTION SUMMARY GOAL DATE: December 5, 2014
DIVISION ACTION GOAL DATE: December 19, 2014
PDUFA DATE: March 30, 2015

I. BACKGROUND:

Bristol-Myers Squibb (BMS) Company seeks approval to market nivolumab for the treatment of patients with unresectable or metastatic melanoma in patients previously treated with ipilimumab, regardless of BRAF status. Nivolumab is a fully human immunoglobulin G4 (IgG4) monoclonal antibody (mAb) that selectively binds to the programmed death-1 (PD-1) membrane receptor.

A key study supporting this application is Study CA209037. This was a randomized, open-label, Phase 3, multicenter, global study designed to evaluate nivolumab monotherapy (3 mg/kg every two weeks [Q2W]) vs. investigator's choice (dacarbazine or carboplatin and paclitaxel) in advanced (unresectable or metastatic) melanoma patients who have progressed on or after anti-CTLA-4 therapy, and for those with BRAF V600 mutations, who have progressed on or after a BRAF inhibitor, in addition to anti-CTLA-4-therapy. The primary efficacy endpoint was Objective Response Rate (ORR), based upon radiographic assessments on imaging collected at 9 weeks (±1 week) following randomization and every 6 weeks (± 1 week) for the first 12 months, and then every 12 weeks (± 1 week) until disease progression or treatment discontinuation, whichever occurred later.

A total of 631 subjects were enrolled at 90 sites in 14 countries (United States, Austria, Belgium, Brazil, Canada, Denmark, France, Germany, Israel, Italy, Netherlands, Spain, Switzerland and United Kingdom). Of the 631 enrolled subjects, 370 were treated (268: nivolumab and 102: investigator's choice) across 78 sites (United States, 29 sites; Austria, 1 site; Belgium, 2 sites; Brazil, 2 sites; Canada, 4 sites; Denmark, 3 sites; France, 6 sites; Germany, 10 sites; Israel, 1 site; Italy, 8 sites; Netherlands, 2 sites; Spain, 3 sites; Switzerland, 2 sites; and United Kingdom, 5 sites).

This study was conducted under IND 115195 which was administratively split from the existing IND 100052 which is the parent IND that includes all the Chemistry, Manufacturing and Controls and nonclinical information for nivolumab.

Three clinical sites were chosen for inspection: Site 28 (Dr. Sandra Pierina D'angelo, New York, NY), Site 50 (Dr. David Minor, San Francisco, CA), and Site 16 (Jeffrey Weber, Tampa, FL), based on enrollment of large numbers of study subjects and significant primary efficacy results pertinent to decision making. The study sponsor, (b) (4) and CRO (b) (4) who performed the function of Independent Radiology Review Committee (IRRC), were also inspected.

II. RESULTS (by Site):

Name of CI or Sponsor/CRO, Location	Protocol #, Site #, and # of Subjects	Inspection Date	Final Classification
CI#1: D'angelo, Sandra Pierina 1275 York Ave., Inpatient Hospital & Main Campus New York, NY 10065	Protocol: CA209037 Site Number: 28 Number of Subjects: 16	November 10-14, 2014	Pending Interim classification: NAI
CI#2: Minor, David 2100 Webster St., Ste 326 San Francisco, CA 94115	Protocol: CA209037 Site Number: 50 Number of Subjects: 21	October 9-23, 2014	Pending Interim classification: VAI
CI#3: Weber, Jeffrey 12902 Magnolia Dr. Tampa, FL 33612	Protocol: CA209037 Site Number: 16 Number of Subjects: 15	October 6-9, 2014	Pending Interim classification: NAI
Sponsor: Bristol-Myers Squibb (BMS) Company Route 206 and Province Line Road Princeton, NJ 08540-4000	Protocol: CA209037 Site Numbers: 16, 28, and 50	October 7-16, 2014	Pending Interim classification: NAI
CRO: (b) (4) (b) (4)	Protocol: CA209037 Site Numbers: (b) (4)	(b) (4)	Pending Interim classification: VAI

Key to 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.

1. CI#1: Sandra Pierina D'angelo, M.D. (Site 28)

a. What was inspected: The site screened 25 subjects, 16 subjects were enrolled, and 16 completed at least one cycle of treatment. At the time of the inspection five subjects are currently on treatment. The study records of 16 enrolled subjects were audited. The record audit was in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included comparison of source documentation to CRFs and data listings submitted to BLA 125554, with particular attention paid to inclusion/exclusion criteria compliance, adverse events, treatment regimens, and reporting of AEs in accordance with the protocol. The FDA investigator also assessed informed consent documents, test article accountability, and monitoring reports.

b. General observations/commentary: Generally, the investigator's execution of the protocol was found to be adequate. The inspection revealed no significant deficiencies. Records and procedures were clear, and generally well organized. The primary and secondary efficacy endpoints were verified. The source records audited at this site also supported the independent central review-reported efficacy outcome measure submitted to BLA 125554. There was no evidence of underreporting of adverse events. Review of source documentation for eligibility, randomization, treatment regimens, study drug administration cycles, and drug accountability found no discrepancies. A Form FDA 483 was not issued.

c. Assessment of data integrity: The data for Dr. D'angelo's site, associated with Study CA209037 submitted to the Agency in support of BLA 125554, appear reliable based on available information.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

2. CI#2: David Minor, M.D. (Site 50)

a. What was inspected: The site screened 35 subjects, 27 subjects were enrolled, and 21 were randomized. At the time of this inspsection, seven subjects were on treatment, nine had discontinued due to disease progression but were alive, and five had died. Study records of 16 subjects were audited. The record audit was in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included comparison of source documentation to CRFs and data listings submitted to BLA 125554, with particular attention paid to protocol compliance, adverse events, treatment regimens, and reporting of AEs in accordance with the protocol. The FDA investigator also assessed informed consent documents, test article accountability, and monitoring reports.

b. General observations/commentary: Generally, the investigator's execution of the protocol was found to be adequate. Records and procedures were clear, and generally well organized. The primary and secondary efficacy endpoints were verified. The source records audited at this site also supported the independent central review-reported efficacy outcome measure submitted to BLA 125554. Review of source documentation for eligibility, randomization, treatment regimens, study drug administration cycles and drug accountability found no discrepancies. There was evidence of underreporting or late reporting of adverse events (see Observation 1 below). Data listings matched except for the SAEs and protocol deviations listed on the Form FDA 483 Inspectional Observations issued to the site.

Observation 1. An investigation was not conducted in accordance with the signed statement of the investigator and investigational plan.

Specifically,

A. The protocol states Serious Adverse Events (SAEs) will be reported to the sponsor within 24 hours. Seven SAEs were not reported to the sponsor within the 24 hour time frame as follows:
   1) Death occurred for Subject 37150 on (b) (6) The study site was made aware of the SAE on (b) (6). There is no documentation on site for reporting the SAE to the sponsor
   2) Hospitalization occurred for Subject 37150 on (b) (6) The study site was made aware of the SAE on (b) (6) but did not report the event to the sponsor until (b) (6)
   3) Death occurred for Subject 37131 on (b) (6). The study site was made aware of the SAE on (b) (6). There is no documentation on site for reporting the SAE to the sponsor.
   4) Death occurred for Subject 37189 on (b) (6). The study site was made aware of the SAE on (b) (6) but did not report the event to the sponsor until (b) (6)
   5) Death occurred for Subject 37594 on (b) (6) The study site was made aware ofthe SAE on (b) (6). There is no documentation on site for the reporting the SAE.
   6) Hospitalization occurred for Subject 37006 on (b) (6). The study site was made aware of the SAE on (b) (6) There is no documentation on site for reporting the SAE to the sponsor.
   7) The SAE of dehydration occurred for Subject 37006 on (b) (6) There is no documentation on site for reporting the SAE to the sponsor.

B. The protocol specifies that the test drug (nivolumab) is to be given every 14 days. Subject 37267 received the test drug on 1/21/2014 and 1/30/2014. There is no documentation on site of reporting the deviation from the protocol to the sponsor.

OSI Reviewer Note: The dosing schedule protocol deviation for Subject 37267 is reported in the current application data listing, and listed in the data listing Appendix 1.16 Significant Protocol Deviations. Cycle 8 (January 21st, 2014) visit and dosing was late, apparently due to a planned vacation. Cycle 9 (January 30th, 2014) visit and dosing was on schedule for this subject. The subject did not experience an AE associated with the protocol deviation. The protocol deviation is valid, but does not represent a systemic pattern of dosing deviations at this site.

C. There is no documentation of sub-investigator training to ensure they were informed of their obligations for the conduct of the study.

Observation 2. Failure to report promptly to the IRB all unanticipated problems involving risk to human subjects or others.

Specifically, the SAEs for Subjects 37150, 37131, 37189, 37694, 37006 and the protocol violations for subject 37267 were not reported to the IRB.

OSI Reviewer Notes: Regarding observations of unreported SAEs including SAEs due to death, in each case (Subjects 37150, 37131, 37189 and 37594) an SAE was reported on the death dates for disease progression in the current application data listings. Review of the eCRFs submitted to the application show each SAE listed under item 1.A., was reported to the sponsor and the death dates were also reported as part of the SAE as well as documented for the OS endpoint. Therefore, the application properly reflects the SAEs and deaths for each of these four subjects.

The OSI reviewer, Lauren Iacono-Connors, shared these preliminary findings with the DOP2 CDTL Mark Theoret, and Clinical Reviewers Meredith Chuk and Maitreyee Hazarika on November 21, 2014 and requested a meeting to discuss the findings and determine the impact, if any, on study outcome. A meeting was held between OSI and the clinical review team including Dr. Chuk, Dr. Hazarika, and Dr. Theoret on December 1, 2014. It was confirmed that death events noted during this inspection are correctly reported in the application. Therefore, these observations should not importanty impact study outcome because the SAEs were reported to the sponsor, albeit late.

Dr. Minor also stated in his written response, dated November 7, 2014, to the Form FDA 483 inspectional observations, that the four deaths were due to disease progression and the remaining three SAEs were for hospitalizations. For Subject 37006, the 2 SAE events were found in the current application data listings properly reported. With respect to the lack of source documentation at the site for reporting these SAEs to the sponsor, Dr. Minor stated that in those cases, the source documentation was the eCRF or electronic SAE form, as the information was directly entered by study staff into the subjects' electronic study record.

According to the written response, dated November 7, 2014, to the Form FDA 483 inspectional observations, from Dr. Minor, the site has already developed a corrective action plan and is in the process of implementing the CAP to mitigate these findings moving forward.

c. Assessment of data integrity: Notwithstanding these inspectional observations, the data for Dr. Minor's site, associated with Study CA209037 submitted to the Agency in support of BLA 125554, appear reliable based on available information.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

3. CI#3: Jeffrey Weber, M.D. (Site 16)

a. What was inspected: The site screened 22 subjects, and 15 subjects were enrolled. The study records of all subjects, enrolled and screen failures, were audited. The record audit was in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included comparison of source documentation to CRFs and data listings submitted to BLA 125554, with particular attention paid to inclusion/exclusion criteria compliance, adverse events, treatment regimens, and reporting of AEs in accordance with the protocol. The FDA investigator also assessed informed consent documents, test article accountability, and monitoring reports.

b. General observations/commentary: Generally, the investigator's execution of the protocol was found to be adequate. The inspection revealed no significant deficiencies. Records and procedures were clear, and generally well organized. The primary and secondary efficacy endpoints were verified. The source records audited at this site also supported the independent central review-reported efficacy outcome measure submitted to BLA 125554. There was no evidence of underreporting of adverse events. Review of source documentation for eligibility, randomization, treatment regimens, study drug administration cycles and drug accountability found no discrepancies. A Form FDA 483 was not issued.

c. Assessment of data integrity: The data for Dr. Weber's site, associated with Study CA209037 submitted to the Agency in support of BLA 125554, appear reliable based on available information.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

4. Sponsor: Bristol-Myers Squibb (BMS) Company

a. What was inspected: The sponsor was inspected in accordance with the Sponsor/Monitor/CRO data validation compliance program, CP 7348.810. The inspection focused on study Sites 16, 28, and 50. The inspection assessed Adverse Events/Serious Adverse Events reporting; stability of test article, shipment, and labeling; validation for software used for the eCRF; validation of the software used for QoL surveys (presented to the subjects on a tablet); Principal Investigator site qualification (financial disclosure, IRB, curriculum vitae); study specific training (image readers and adjudicator, monitors, clinical sites); CV and job description for the following personnel: medical monitors, clinical site monitors, Principal Investigator, readers, and adjudicator; IRB compliance; Form FDA 1572 and investigator agreements for Principal Investigators located outside the U.S.; Site monitors for sites 16, 28 and 50 (training, curriculum vitae, and position description); Monitoring reports (for sites 16, 28, and 50); CRO (selection, evaluation, training); and CRO (Transfer of Regulatory Obligations [TORO], contractual agreements for at least three contract research organizations).

b. General observations/commentary: Records and procedures were clear, and generally well organized. The sponsor maintained adequate oversight over the study. Monitoring appeared to be adequate; AEs were verifiable. There was no evidence of under-reporting AEs/SAEs by the sponsor. The primary efficacy endpoint data were not verifiable during the sponsor inspection because the study is still ongoing. However, the data generated by the Independent Radiology Review Committee (IRRC), performed by CRO (b) (4) were verified during the inspection of the CRO. Compliance with the study protocol, the sponsor's own SOPs, and relevant regulatory requirements appeared to be adequate.

There were three observations discussed with the site management during the inspection. First, software validation for the software loaded and used on the tablet by study subjects to complete the QoL survey revealed the user acceptance test scripts conducted by BMS was performed by BMS employees; however, the test scripts were written by the vendor. It was recommended that the user acceptance test scripts should not be written by the vendor who is providing the software as the vendor may only write user acceptance test scripts that would ensure the testing passed. Second, IRB compliance documentation was reviewed for the three sites indicated above. It was noted that documents collected from two of the three IRBs were inadequate to ensure that the IRBs were properly constituted. Recommendations were discussed with the sponsor suggesting additional documentation that may be obtained from each IRB moving forward. Third, there was a potential bias of two PIs. Financial disclosure was reviewed for 14 clinical sites. Of the 14 clinical sites reviewed, clinical investigators at two sites (b) (6) reported receiving "significant payments" in excess of $25,000. Specifically, (b) (6) Sub-

Investigator for Site (b) (6) received two grants totaling $235,000 between (b) (6) (b) (6) Principal Investigator for Site (b) (6) received a grant for $100,000 beginning (b) (6) and a grant of $10,000 beginning (b) (6)

In both of these incidences, a Memo to File was written by Ms. Gwen Ouellette, Senior Protocol Manager, Global Operations & Strategy, BMS. This memo stated "impact of the potential bias on the study outcome is limited" based on four criteria; use of an IRRC to determine primary efficacy endpoint, small number of site-specific study subjects, and routine monitoring and oversight at these sites. No Form FDA 483 was issued.

c. **Assessment of data integrity:** The data generated at this site, as it pertains to Study CA209037 were audited in accordance with the sponsor-monitor oriented BIMO compliance program, CP 7348.810. The findings are that the data from this sponsor submitted to the Agency in support of BLA 125554 appear reliable based on available information.

5. (b) (4) (IRRC, Vendor)

a. **What was inspected:** The CRO was inspected in accordance with the Sponsor/Monitor/CRO data validation compliance program, CP 7348.810. The inspection focused primarily on assessing the integrity of the tumor response and disease progression source records for data generated by the Independent Radiology Review Committee (IRRC), for the clinical study, CA209037. Inspectional coverage included review of the following areas: (1) organization and personnel; (2) training and qualification records of Clinical Team Members; (3) transfer of responsibilities; (4) charters; (5) financial disclosures; (6) subject records/source documents; (7) practices for training the sites; (8) media receipt; (9) data handling and transferring to the sponsor; and (10) computer systems and validations.

b. **General observations/commentary:** Records and procedures were adequate, and generally well organized. The IRRC generated a total of 182 study subject endpoints for Study CA209037. The primary efficacy endpoints generated by this IRRC and submitted to BLA 125554 for Study CA209037 were verified for five clinical sites (b) (4) a total of 39 subjects' endpoints. There were no discrepancies. There were no major inspection observations. (b) (4) These have been discussed with the CRO during the inspection which is still ongoing.

A Form FDA 483 is expected to be issued on (b) (4) and may include the following two observations:

(b) (4)

c. Assessment of data integrity: The data generated at this site, as it pertains to Study CA209037 were audited in accordance with the sponsor-monitor oriented BIMO compliance program, CP 7348.810. The data from this CRO submitted to the Agency in support of BLA 125554 appear reliable.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Based on the review of preliminary inspectional findings for clinical investigators Dr. D'angelo (Site 28), Dr. Minor (Site 50), Dr. Weber (Site 16), the sponsor, Bristol-Myers Squibb Company (BMS), and the CRO (b) (4) (IRRC), the Study CA209037 data appear reliable.

The preliminary classification for clinical investigators Dr. D'Angelo, Dr. Weber, and for the sponsor, BMS, is No Action Indicated (NAI). The preliminary classification for clinical investigator Dr. Minor and the (b) (4) is Voluntary Action Indicated (VAI).

With respect to the inspectional findings at Dr. Minor's site (Site 50), there was evidence of underreporting or late reporting of adverse events. However, review of the eCRFs submitted to the application confirm that each SAE listed as late for Dr. Minor's site was reported to the sponsor, and the death dates were also reported as part of the SAE as well as documented for the OS endpoint. Therefore these observations should not importanty impact study outcome because the SAEs were reported to the sponsor, albeit late.

With respect to the inspection of (b) (4), there were procedural issues related to Charter compliance and documentation of training for one employee. These observations should not importantly impact the endpoint data generated by the CRO. The FDA field investigator did not find evidence that the protocol deviations importantly impact data integrity.

Based upon available information the overall data for Study CA209037 in support of this application may be considered reliable based on available information.

Note: The certain observations noted above are based on the preliminary communications provided by the FDA field investigators. An inspection summary addendum will be generated if conclusions change significantly upon receipt and complete review of the EIRs.

{See appended electronic signature page}

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

/s/

LAUREN C IACONO-CONNORS
12/11/2014

SUSAN D THOMPSON
12/11/2014

KASSA AYALEW
12/11/2014

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

Division of Monoclonal Antibodies
Office of Biotechnology Products

FINAL LABEL AND LABELING REVIEW

Date: November 20, 2014

Reviewer: Jibril Abdus-Samad, PharmD, Labeling Reviewer
Division of Monoclonal Antibodies

Through: Joel Welch, PhD, Product Quality Reviewer
Division of Monoclonal Antibodies

Laurie Graham, MS, Team Leader
Division of Monoclonal Antibodies

Application: BLA 125554

Product: Opdivo (nivolumab)

Applicant: Bristol-Myers Squibb Company

Submission Dates: July 30, 2014 and November 3, 2014

Executive Summary

The container labels and carton labeling for Opdivo (nivolumab) were reviewed and found to comply with the following regulations: 21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57, 21 CFR 201.100 and United States Pharmacopeia [8/1/2014 to 11/30/2014] USP 37/NF 32. Labeling deficiencies were identified, mitigated, and resolved. The container labels and carton labeling submitted on November 3, 2014 are acceptable.

Background and Summary Description

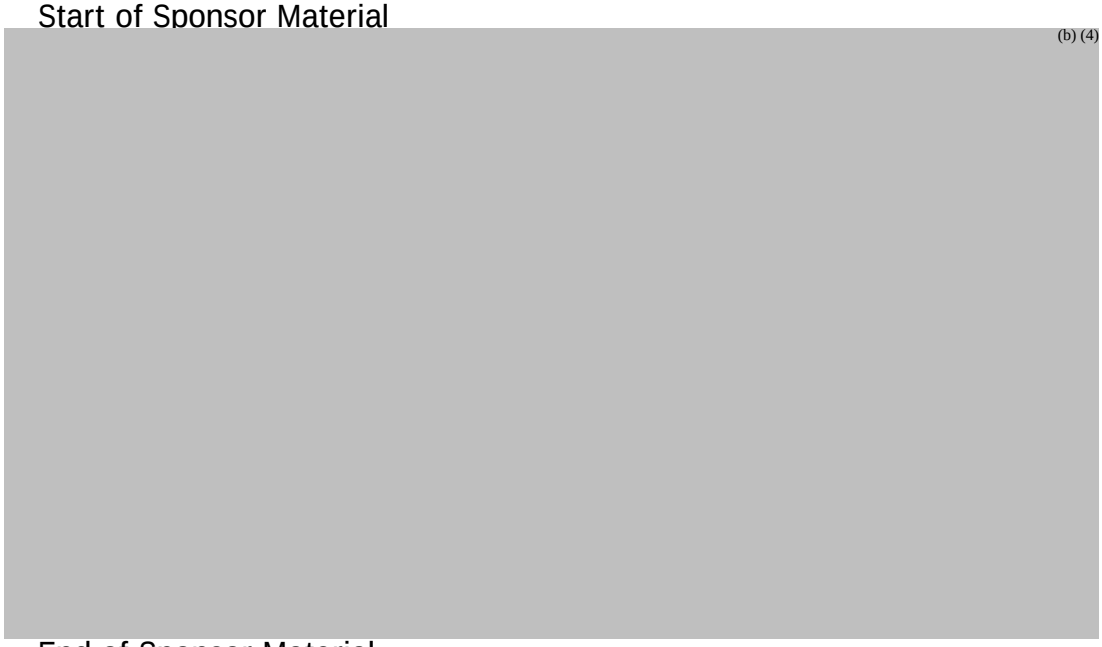
BLA 125554 Opdivo (nivolumab) has a proposed indication for the treatment of unresectable or metastatic melanoma in patients previously treated with ipilimumab regardless of BRAF status. Opdivo is supplied in single-dose vials containing 40 mg/4 mL or 100 mg/10 mL of solution. The recommended dosage is 3 mg/kg administered as an intravenous infusion over 60 minutes every 2 weeks.

Materials Reviewed:

- Vial Container Label 40 mg/4 mL
- Vial Container Label 100 mg/10 mL
- Carton Labeling 40 mg/4 mL
- Carton Labeling 100 mg/10 mL

Start of Sponsor Material

(b) (4)



End of Sponsor Material

Subpart G-Labeling Standards
Subpart A-General Labeling Provisions

I. Container

A. 21 CFR 610.60 Container Label

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

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

(2) The name, address, and license number of manufacturer; *does not conform.*

FDA Request: Revise the manufacturer information to comply with the definition of manufacturer per 21 CFR 600.3(t). Thus, the manufacturer name and address should match the *Applicant* on your 356h form. Additionally, the 356h form must include the U.S. License number. *Applicant revised as requested.*

(3) The lot number or other lot identification; *Conforms*.

(4) The expiration date; *conforms*.

(5) The recommended individual dose, for multiple dose containers. *Not applicable*.

(6) The statement: "'Rx only'" for prescription biologicals. *Conforms*.

(7) If a Medication Guide (MG) is required under part 208 of the chapter, the statement required under §208.24(d) of this chapter instructing the authorized dispenser to provide a MG to each patient to whom the drug is dispensed and stating how the MG is provided, except where the container label is too small, the required statement may be placed on the package label. *Conforms, MG appears on package label (carton labeling)*.

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

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

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

(e) Visual inspection. When the label has been affixed to the container, a sufficient area of the container shall remain uncovered for its full length or circumference to permit inspection of the contents.

FDA Request: Indicate how the label is affixed to the vial and where the visual area of inspection is located per 21 CFR 610.60(e). *Applicant's response is acceptable*.

B. 21 CFR 201.2 Drugs and devices; National Drug Code numbers – The National Drug Code (NDC) number is located at the top of the label. [See 21 CFR 207.35]; *Conforms*.

C. 21 CFR 201.5 Drugs; adequate directions for use; *Conforms. We concur with DMEPA's recommendation to add "Usual Dosage"*.

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

E. 21 CFR 201.10 Drugs; statement of ingredients; [Placement and prominence]. *Conforms*. *Appears on package label (carton labeling)*.

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

FDA Request: Revise the strength statement to emphasize the strength per total volume in the vial is more prominent than the strength per mL. Unbold the strength per mL statement. Thus, the strength should appear as:

40 mg/4 mL
(10 mg/mL)

or

100 mg/10 mL
(10 mg/mL)

Applicant revised as requested.

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

H. 21 CFR 201.25 Bar code; *Conforms*.

I. 21 CFR 201.50 Statement of identity; *Conforms*.

J. 21 CFR 201.51 Declaration of net quantity of contents; *does not conform.*

FDA Request: Provide justification for additional overfill in 40 mg/4 mL vial. The 40 mg/4 mL vial contains (b) (4) overfill, however USPC 8/1/2014 – 11/30/2014 General Chapters: <1151> Pharmaceutical Dosage Forms recommends (b) (4) overfill.

Applicant's Response: For the 100 mg/10 mL presentation, an overfill of (b) (4) was selected to account for USP <1151> recommended excess volume (b) (4) plus variability of fill volume (b) (4) at BMS-Manati. Because both presentations are packaged in the same 10-cc vial, it was found that the vial, needle and syringe hold up volumes were similar. Therefore, a (b) (4) overfill was also applied to the 40 mg/4 mL presentation. The drug product release test requires the extractable volume to be ≥ 4.0 mL for 40 mg/4 mL presentation and ≥ 10.0 mL for 100 mg/10 mL presentation. All drug product batches manufactured at BMS-Manati have met this testing requirement.

FDA's response: Acceptable.

K. 21 CFR 201.55 Statement of dosage; *conforms. We concur with DMEPA's recommendation to add "Usual Dosage"*.

L. 21 CFR 201.100 Prescription drugs for human use; *conforms. Concur with DMEPA's recommendation to add "Usual Dosage"*.

Start of Sponsor Material

Carton Labeling 40 mg/4 mL

(b) (4)

Carton Labeling 100 mg/10 mL

(b) (4)

End of Sponsor Material

II. Carton

A. 21 CFR 610.61 Package Label

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

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

FDA Request: Revise the manufacturer information to comply with the definition of manufacturer per 21 CFR 600.3(t). Thus the manufacturer name and address should match the *Applicant* on your 356h

form. Additionally, the 356h form must include the U.S. License number. *Applicant revised as requested*.

c) The lot number or other lot identification; *conforms.*

d) The expiration date; *conforms.*

e) The preservative used and its concentration, if no preservative is used and the absence of a preservative is a safety factor, the words “no preservative”. *Conforms.*

f) The number of containers, if more than one; *not applicable*.

g) The amount of product in the container expressed as (1) the number of doses, (2) the volume, (3) units of potency, (4) weight, (5) equivalent volume (for dried product to be reconstituted), or (6) such combination of the foregoing as needed for an accurate description of the contents, whichever is applicable; *conforms.*

h) The recommended storage temperature; *conforms*.

i) The words “Do not Freeze” or the equivalent, as well as other instructions, when indicated by the character of the product; *conforms*.

j) The recommended individual dose if the enclosed container(s) is a multiple-dose container; *not applicable*.

k) The route of administration recommended, or reference to such directions in and enclosed circular; *conforms*.

l) Known sensitizing substances, or reference to enclosed circular containing appropriate information; *not applicable*.

m) The type and calculated amount of antibiotics added during manufacture; *not applicable*.

n) The inactive ingredients when a safety factor, or reference to enclosed circular containing appropriate information; *not applicable*.

o) The adjuvant, if present; *not applicable*.

p) The source of the product when a factor in safe administration; *not applicable*.

q) The identity of each microorganism used in manufacture, and, where applicable, the production medium and the method of inactivation, or reference to an enclosed circular containing appropriate information; *not applicable*.

r) Minimum potency of product expressed in terms of official standard of potency or, if potency is a factor and no U.S. standard of potency has been prescribed, the words "No U.S. standard of potency"; *conforms*.

s) The statement "Rx only" for prescription biologicals; *conforms*.

- Note: If product has a medication guide, a statement is required on the package label if it is not on the container label (see above). It is recommended on both labels. *Conforms*.

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

a) Position. The proper name of the product on the package label shall be placed above any trademark or trade name identifying the product and symmetrically arranged with respect to other printing on the label. *Exempt.*

b) Prominence. The point size and typeface of the proper name shall be at least as prominent as the point size and typeface used in designating the trademark and trade name. The contrast in color value between the proper name and the background shall be at least as great as the color value between the trademark and trade name and the background. Typography, layout, contrast, and other printing features shall not be used in a manner that will affect adversely the prominence of the proper name. *Exempt.*

c) Legible type. All items required to be on the container label and package label shall be in legible type. "Legible type" is type of a size and character which can be read with ease when held in a good light and with normal vision. *Exempt.*

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

D. 21 CFR 610.64 Name and address of distributor

The name and address of the distributor of a product may appear on the label provided that the name, address, and license number of the manufacturer also appears on the label and the name of the distributor is qualified by one of the following phrases: "Manufactured for _____". "Distributed by _____", "Manufactured by _____ for _____", "Manufactured for _____ by _____", "Distributor: _____", or 'Marketed by _____". The qualifying phrases may be abbreviated. *Not applicable*.

E. 21 CFR 610.67 Bar code label requirements

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

F. 21 CFR 201.2 Drugs and devices; National Drug Code numbers – The National Drug Code (NDC) number is located on top of the label. [See 21 CFR 207.35]. *Conforms.*

G. 21 CFR 201.5 Drugs; adequate directions for use; *conforms. We concur with DMEPA's recommendation to add "Usual Dosage".*

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

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

FDA Request: Revise the statement of ingredients to comply with USPC Official 8/1/2014 – 11/30/2014, USP 37/NF 32, <1091> Labeling of Inactive Ingredients such that the names of the inactive ingredients are in alphabetical order in the following format: inactive ingredient (amount). *Applicant revised as requested*.

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

FDA Request: Revise the strength statement to emphasize the strength per total volume in the vial is more prominent than the strength per mL. Unbold the strength per mL statement. Thus the strength should appear as

40 mg/4 mL
(10 mg/mL)

or

100 mg/10 mL
(10 mg/mL)

Applicant revised as requested.

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

L. 21 CFR 201.25 Bar code label requirements; *conforms*.

M. 21 CFR 201.50 Statement of identity; *conforms*.

N. 21 CFR 201.51 Declaration of net quantity of contents; does not conform. See comments above on Container Label.

O. 21 CFR 201.55 Statement of dosage; *Conforms. We concur with DMEPA's recommendation to add "Usual Dosage"*.

P. 21 CFR 201.100 Prescription drugs for human use; conforms. *Conforms. Concur with DMEPA's recommendation to add "Usual Dosage"*.

CDER Labeling Preferences

This section describes additional concerns provided to the Applicant that address CDER Labeling preferences. For all these concerns, the Applicant's response was acceptable.

A. General Comment for the Vial

1. Confirm there is no text on the ferrule and cap overseal of the vials to comply with a revised United States Pharmacopeia (USP) standard [USPC Official 8/1/2014 – 11/30/2014, USP 37/NF 32, <1> Injections/General Requirements] that went into effect on December 1, 2010. We refer you to the following address: http://www.usp.org/sites/default/files/usp_pdf/EN/USPNF/genChapter1Labeling.pdf

B. General Comments for Container Label and Carton Labeling

1. Revise the presentation of the proprietary name so only the first letter in the proprietary name is capitalized. Words written in all-capital letters are less legible than words written in mixed case letters.

Conclusions

The Applicant addressed the identified deficiencies. The container labels and carton labeling submitted on November 3, 2014 are acceptable.

Vial Container Label 40 mg/4 mL
\\cdsesub1\evsprod\bla125554\0015\m1\us\31oct-init-bla-40mg-nivol-con.pdf

Vial Container Label 100 mg/10 mL
\\cdsesub1\evsprod\bla125554\0015\m1\us\31oct-init-bla-100mg-nivol-con.pdf

Carton Labeling 40 mg/4 mL
\\cdsesub1\evsprod\bla125554\0015\m1\us\31oct-init-bla-40mg-nivol-car.pdf

Carton Labeling 100 mg/10 mL
\\cdsesub1\evsprod\bla125554\0015\m1\us\31oct-init-bla-100mg-nivol-con.pdf

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:	October 22, 2014
Requesting Office or Division:	Division of Oncology Products 2 (DOP2)
Application Type and Number:	BLA 125554
Product Name and Strength:	Opdivo (nivolumab) Injection, 100 mg/10 mL and 40 mg/4 mL (10 mg/mL)
Product Type:	Single Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Bristol Myers Squibb
Submission Date:	October 17, 2014
OSE RCM #:	2014-1845
DMEPA Primary Reviewer:	Otto L. Townsend, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

1 REASON FOR REVIEW

This review evaluates the proposed Opdivo (Nivolumab) prescribing information, container labels, and carton labeling for areas of vulnerability that could lead to medication errors.

2 MATERIALS REVIEWED

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

Table 1. Materials Considered for this Label and Labeling Review

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

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We identified that the proposed container labels, carton labeling, and prescribing information (PI) can be improved to provide clarity and important safety and prescribing information.

4 CONCLUSION & RECOMMENDATIONS

The proposed container label, carton labeling, and prescribing information (PI) can be improved to promote the safe use of the product.

4.1 COMMENTS TO DIVISION OF ONCOCOLOGY PRODUCTS 2

Prescribing Information

1. The PI can be improved by using active voice throughout, but we defer to the Division and SEALD on this issue.

2. Throughout the PI, the unit of measure should be added after each numeral used to express a range.

For example,
Change the statement, '…ranging from 1 to 10 mg/mL' to '…ranging from 1 mg/mL to 10 mg/mL.
Change the statement, 'pore size of 0.2-1.2m micrometer' to 'pore size of 0.2 micrometer to 1.2 micrometer'.

4.2 RECOMMENDATIONS FOR THE BRISTOL MYERS SQUIBB

A. Container Labels

1. Revise the presentation of the proprietary name so only the first letter in the proprietary name is capitalized. Words written in all-capital letters are less legible than words written in mixed case letters.[1]

2. To emphasize the total amount of drug in the container, the strength per total volume statement should appear more prominent than the strength per milliliter statement. We recommend unbolding the strength per mL statement.[1]

   For example:

   Change from: **100 mg/10 mL (10 mg/mL)**

   To: **100 mg/10 mL** (10 mg/mL)

B. Carton Labeling

1. See Comments A1 and A2.

2. To emphasize "Usual Dosage", we recommend separating the "Usual Dosage" statement from the "Administration" section (**Administration:** Administer the infusion over 60 minutes… See prescribing information for dosage and administration). This can be accomplished by creating a new section, such as "**Usual Dosage:** See prescribing information".

[1] Guidance for Industry: Safety considerations for container labels and carton labeling design to minimize medication errors (Draft Guidance). April 2013.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Opdivo that Bristol Myers Squibb submitted on October 17, 2014.

Table 2. Relevant Product Information for Opdivo	
Initial Approval Date	N/A
Active Ingredient	nivolumab
Indication	Treatment of previously treated non-small cell lung cancer
Route of Administration	Intravenous Infusion
Dosage Form	Injection Solution
Strength	100 mg/10 mL and 40 mg/4 mL (10 mg/mL)
Dose and Frequency	3 mg/kg intravenously every two weeks
How Supplied	100 mg and 40 mg vials
Storage	This product should be stored at 2°C to 8°C. Protect from light and freezing. (b) (4)

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

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/s/

OTTO L TOWNSEND
10/22/2014

CHI-MING TU
10/22/2014

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

IND or NDA	125,554
Brand Name	Opdivo
Generic Name	Nivolumab
Sponsor	Bristol-Myers Squibb Company
Indication	Melanoma
Dosage Form	Intravenous Infusion
Drug Class	Programmed death-1 (PD-1) immune checkpoint inhibitor
Therapeutic Dosing Regimen	0.3 kg/mg, 2.0 kg/mg and 10 kg/mg
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	Not established
Submission Number and Date	SDN# 000/ Sept 24 2013
Review Division	DOP1

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

No large change (i.e., > 20 ms) in the QTc interval was detected when nivolumab infusion (doses of 0.3, 2, or 10 mg/kg) was administrated. Using Fridericia corrected QT (QTcF) interval, the largest upper bounds of the 2-sided 90% CI mean changes from baselines in QTcF are less than 20 ms. The sponsor did not use placebo and positive control (moxifloxacin) arms. Therefore, no assay sensitivity was established. An overall summary of results is provided in Table 1.

In this Phase 2, randomized, double-blind, 3-arm dose-ranging, 167 subjects received 0.3 kg/mg, 2 kg/mg, and 10 mg/kg. An overall summary of findings is presented in Table 1.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Nivolumab (0.3, 2 and 10 kg/mg) (FDA Analysis)

Treatment	Day/Time	ΔQTcF (ms)	Std Dev	90% CI for Mean (ms)
NIVOLUMAB 0.3 mg/kg	Cycle 1 Day 1 - end of infusion	3.5	8.0	(1.5, 5.5)
	Cycle 7 Day 1 - End of infusion	4.9	13.4	(-0.6, 10.4)
NIVOLUMAB 2.0 mg/kg	Cycle 1 Day 1 - 3 hour	1.2	10.1	(-1.3, 3.6)
	Cycle 7 Day 1 - End of infusion	-3.2	12.7	(-7.5, 1.2)
NIVOLUMAB 10.0 mg/kg	Cycle 1 Day 1 - end of infusion	2.0	8.8	(-0.3, 4.2)
	Cycle 7 Day 1 - End of infusion	-0.4	19.0	(-7.6, 6.7)

The proposed dose of nivolumab is 3 mg/kg administered intravenously (IV) every two weeks (Q2W). The top dose (10 mg/kg, Q3W) in this trial is considered to be a supratherapeutic dose because it results in higher exposure (C_{max} and AUC) compared to the therapeutic dose. The highest 10 mg/kg-dose group reached mean (sd) concentrations of 366 µg (112) at end of infusion. Concentrations up to ~600 µg were observed in a small number of individuals. The therapeutic dose (3 mg/kg Q3W) is expected to result in peak concentration below 200 µg at steady state. The distribution of concentrations observed in this study, is expected to cover and exceed future observations in the target population. Nivolumab, a therapeutic protein, is not expected to be a victim of drug-drug interactions that may result in increased exposure. Covariates identified in the population pharmacokinetic analysis are unlikely to result in exposures at or above the one observed with the supratherapeutic dose.

2 PROPOSED LABEL

2.1 THE CURRENT LABEL

(b) (4)

Reviewer's comments: QT-IRT considers the current label is still valid. We defer the final labeling decisions to the review division.

3 BACKGROUND

3.1 PRODUCT INFORMATION

Nivolumab (also referred to as BMS-936558 or MDX-1106) is a fully human monoclonal immunoglobulin G4 (IgG4-S228P) antibody (HuMAb) that targets the programmed death–1 (PD-1, cluster of differentiation 279 [CD279]) cell surface membrane receptor.

Nivolumab is [redacted] (b) (4) The clinical study product is a sterile solution for parenteral administration.

3.2 MARKET APPROVAL STATUS

Opdivo has received manufacturing and marketing approval in Japan for the treatment of patients with unresectable melanoma

3.3 PRECLINICAL INFORMATION

No *iv vitro* hERG study was conducted. No cardiac findings were observed from monkey studies.

3.4 PREVIOUS CLINICAL EXPERIENCE

Table 2 summarizes the estimated number of subjects treated with the proposed product and the proposed regiment in sponsor's studies.

Table 2. Estimated Number of Subjects Treated with Nivolumab 3 mg/kg Monotherapy Every 2 Weeks in BMS-Sponsored Studies

Study Number	Phase	Study Design	No. of Nivolumab-treated subjects at 3 mg/kg Q2W (No. of Total Treated Subjects)	Status at Time of SCS	SCS Database Lock Date
Melanoma					
CA209037	3	Randomized, open-label vs. investigator's choice	268 (370)	Ongoing[a]	30-Apr-2014
CA209038	1	Exploratory study of nivolumab	85 (85)	Ongoing	01-Apr-2014
CA209066	3	Randomized, double-blind vs. dacarbazine	197 (394)	Ongoing	26-Feb-2014
CA209067	3	Randomized, double-blind, nivolumab monotherapy or combined with ipilimumab vs. ipilimumab monotherapy	302 (906)	Ongoing	27-Mar-2014
Refractory and advanced malignancies, including melanoma					
MDX1106-03 (melanoma and NSCLC combined)	1	Open-label, multicenter, multidose, dose escalation (0.1, 0.3, 1, 3, 10 mg/kg nivolumab)	54 (306)	Completed	04-Feb-2013
NSCLC					
CA209063	2	Single arm with nivolumab	117 (117)	Completed	06-Mar-2014
CA209017	3	Open-label randomized vs. docetaxel	130 (259)	Ongoing	03-Feb-2014
CA209057	3	Open-label randomized vs. docetaxel	278 (555)	Ongoing	30-Jan-2014
RCC[b]					
CA209025	3	Randomized, open-label vs. everolimus	395 (790)	Ongoing	11-Mar-2014
TOTAL			**1826 (3782)**		

[a] An interim CSR is available for this study. CA209037 is not considered completed because analyses of both primary endpoints are not yet available. OS data will be reported in a subsequent final CSR, estimated to be available in the first half of 2015.

[b] Completed Study CA209010 in RCC is not included in this table because the 3 mg/kg dose of nivolumab was not assessed in CA209010.

Abbreviations: NSCLC = non-small cell lung cancer; RCC = renal cell carcinoma; SCS = Summary of Clinical Safety

Source: Summary of Clinical Safety, Table 1.1-1, page 16

3.5 CLINICAL PHARMACOLOGY

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

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting this study under (b) (4) IND (b) (4) The sponsor submitted the study report CA209010 for the study drug, including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

A Randomized, Blinded, Phase 2 Dose-Ranging Study of Nivolumab (MDX-1106, BMS-936558) in Subjects with Progressive Advanced/Metastatic Clear-Cell Renal Cell Carcinoma (RCC) Who Have Received Prior Anti-Angiogenic Therapy

4.2.2 Protocol Number

CA209010

4.2.3 Study Dates

Study initiation date: 31-May-2011

Study cutoff date: 15-May-2013

4.2.4 Objectives

Primary Objective: To evaluate the dose-response relationship in the 0.3, 2, and 10 mg/kg nivolumab arms as measured by progression-free survival (PFS)

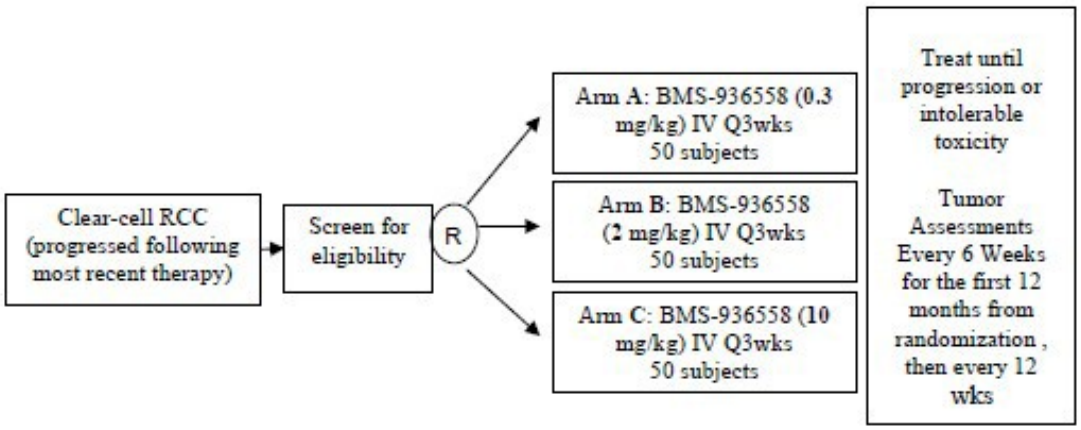
Secondary Objectives:

- To estimate PFS in the nivolumab arms
- To estimate the Objective Response Rate (ORR) in the nivolumab arms
- To estimate the Overall Survival (OS) in the nivolumab arms
- To estimate the rate of adverse events (AEs) in the nivolumab arms

4.2.5 Study Description

4.2.5.1 Design

This was a randomized, double-blind, 3-arm dose-ranging, Phase 2 study of nivolumab (0.3, 2, or 10 mg/kg) in adult (aged ≥18 years) male and female subjects with advanced/metastatic RCC with a clear-cell component who had received prior treatment with at least 1 anti-angiogenic therapy (e.g., sunitinib, sorafenib, pazopanib, axitinib, tivozanib, bevacizumab) in the advanced/metastatic setting. Subjects who additionally received prior immunotherapies (e.g., interleukin-2 [IL-2], interferon [IFN]-2α, vaccines), cytotoxic drugs, or other targeted agents (mTOR inhibitors) were also eligible so long as no more than 3 prior treatment regimens for metastatic disease were received. Progression from most recent therapy was to be documented within 6 months prior to enrollment in the study. The study consisted of 3 phases: screening, treatment, and follow-up. The study design is illustrated in Figure below:



Abbreviations: RCC = renal cell carcinoma; R = randomization; IV = intravenously; Q3wks = every 3 weeks.

4.2.5.2 Controls

No placebo and positive (moxifloxacin) control arms.

4.2.5.3 Blinding

This was a double-blind study, with subjects, investigators, study site personnel (except the pharmacist), and sponsor blinded to the subjects' nivolumab dose assignment. The site pharmacists were unblinded to facilitate accurate preparation of study drug. Designated staff of the Sponsor's Research and Development was unblinded prior to database lock to enable an interim analysis of safety and efficacy data for business purposes, to allow the Sponsor to make initial considerations regarding future development before completion of the final analysis. This interim analysis was performed after randomization was completed and after at least 63 subjects were followed for at least 12 weeks.

4.2.6 Treatment Regimen

Subjects were randomized in a 1:1:1 ratio to 1 of 3 treatment arms (0.3, 2, or 10 mg/kg for Arm A, B, or C, respectively) and received nivolumab as an intravenous (IV) infusion over 60 minutes every 3 weeks (Q3 wks), with allowances for delay up to a maximum of 3 additional weeks. Each treatment period was considered 1 cycle.

4.2.6.1 Sponsor's Justification for Doses

The sponsor has not formally justified the doses in this trial.

Reviewer's Comment: The three doses tested in this trial are considered to be supra- and subtherapeutic. Together they are expected to cover the exposure range of the therapeutic dose in the target population.

4.2.6.2 Instructions with Regard to Meals

The proposed route of administration is IV.

4.2.6.3 ECG and PK Assessments

The PK and the ECG sampling schedule is shown in Table 3.

Table 3. PK and ECG sampling scedule

Study Day [a]	Time (Relative To Dosing) Hour	Time (Relative To Dosing) Hour: Min	Pharmacokinetic Blood Sample Schedule	Immunogenicity Blood Sample Schedule	ECG Measurements
Day -3 to +1 (post randomization)	0 (Predose)	00:00		X	X
Cycle 1 Day 1	1.0 (EOI)[b]	01:00	X		X[c]
Cycle 1 Day 1	3.0	3:00	X		X
Cycle1 Day 3 - 5[d]	0.0	48:00 - 96:00	X		
Cycle 1 Day 7 - 15[d]	0.0	144:00 - 336:00	X		
Cycle 2 Day 1	0.0 (predose)	00:00	X		
Cycle 4 Day 1	0.0 (predose)	00:00	X	X	
Cycle 7 Day 1	0 (Predose)	00:00	X		X
Cycle 7 Day 1	1.0 (EOI)[b]	01:00	X		X[c]
Cycle 7 Day 1	3.0	3:00	X		X
Cycle 7 Day 3 - 5[d]	0.0	48:00 - 96:00	X		
Cycle 7 Day 7 - 15[d]	0.0	144:00 - 336:00	X		
Cycle 8 dose Day 1	0 (Predose)	00:00	X		
Follow-up visit X 1 & 2			X	X	

Reviewer's Comment: The sampling schedule is able to capture the peak concentration after the 1 h. infusion. A matching ECG sample is collected at the same time point. The sampling schedule is deemed adequate.

4.2.6.4 Baseline

The sponsor used pre-dose QTc values as baselines.

4.2.7 ECG Collection

In the ECG substudy, 12-lead ECGs were to be collected in triplicate from all subjects at baseline and during Cycles 1 and 7 at predose, end-of-infusion, and 3 hours postdose.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

A total of 198 subjects were enrolled. Of these, 168 were randomized, and 167 were treated with nivolumab (59, 54, and 54 subjects in the 0.3-, 2-, and 10-mg/kg groups, respectively) at 39 sites (33 in the US and 6 in other countries). One subject randomized to the 0.3-mg/kg group was not treated because the subject no longer met study criteria.

Table 4: Subject Disposition

	Nivolumab			
	0.3 mg/kg	2 mg/kg	10 mg/kg	Total
No. of Subjects Enrolled				198
No. of Subjects Randomized	60	54	54	168
No. of Subjects Treated	59	54	54	167
No. of Subjects excluded from Analysis	0	0	0	0
No. (%) of Subjects Discontinued	50 (84.7)	49 (90.7)	44 (81.5)	143 (85.6)
Reason for Not Continuing Study Treatment				
Disease Progression	48 (81.4)	40 (74.1)	37 (68.5)	125 (74.9)
Study Drug Toxicity	1 (1.7)	5 (9.3)	4 (7.4)	10 (6.0)
AE Unrelated to Study Drug	1 (1.7)	2 (3.7)	3 (5.6)	6 (3.6)
Subject Request to Discontinue Treatment	0	2 (3.7)	0	2 (1.2)

One subject randomized to the 0.3 mg/kg group was not treated because the subject no longer met study criteria.

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

The primary endpoint was mean differences between baseline to nivolumab dosed groups of 0.3 mg/kg, 2.0 mg/kg and 10 mg/kg in QTcF. The sponsor's summary results are presented in Table 5 and Table 6.

Table 5: Sponsor's QTcF Interval Summary Statistics by Dose, Day and Time

Day	Time	Nivolumab Dose								
		0.3 mg/kg, IV			2.0 mg/kg, IV			10.0 mg/kg, IV		
		Mean QTcF (msec) (SD)	Mean ΔQTcF (msec) (SD)	N	Mean QTcF (msec) (SD)	Mean ΔQTcF (msec) (SD)	N	Mean QTcF (msec) (SD)	Mean ΔQTcF (msec) (SD)	N
C1 D1	predose	411.7 (19.15)	NA	49	415.3 (18.56)	NA	51	415.2 (23.34)	NA	46
	EOI	414.5 (17.69)	3.5 (8.05)	46	416.2 (19.36)	0.9 (9.11)	51	417.2 (20.35)	2.0 (8.85)	44
	3 hour	413.3 (17.83)	1.9 (7.29)	47	416.2 (18.60)	1.2 (10.13)	49	415.2 (21.00)	0.0 (13.91)	46
C7 D1	predose	418.4 (18.32)	2.8 (12.26)	16	416.3 (19.27)	-4.7 (14.85)	23	417.7 (19.07)	-0.1 (17.60)	21
	EOI	419.5 (17.87)	4.9 (13.36)	18	417.0 (17.29)	-3.2 (12.75)	25	420.8 18.48)	-0.4 (19.01)	21
	3 hour	418.3 (15.27)	3.7 (10.17)	18	412.5 (9.96)	-7.2 (16.84)	24	415.6 (16.38)	-4.1 (16.80)	23

Abbreviations: IV = intravenous; QTcF = corrected QT interval, Fridericia formula; C1/7 = Cycle 1/7; D1 = Day 1; EOI = end of infusion; NA = not applicable.

Source: Clinical Study Report CA209010, Section 8.8.1.1, Table 8.8.1.1-1, page 141/10155

Table 6: Sponsor's QTcF Interval Summary Statistics by Dose and Day

Nivolumab Dose	Study Day	Mean Predicted ΔQTcF	90% CI	Nivolumab Concentration (µg/mL)
	Model 1: Pooled Across Days			
0.3 mg/kg, IV	Pooled	0.0	(-0.1, 0.1)	9.02
2.0 mg/kg, IV	Pooled	0.0	(-0.9, 0.9)	57.96
10.0 mg/kg, IV	Pooled	0.0	(-4.3, 4.3)	272.78
Estimated Population Slope	Pooled	0.00	(-0.02, 0.02)	Time-Matched
	Model 2: Including Study Day as Factor			
0.3 mg/kg, IV	C1D1	0.1	(0.0, 0.2)	7.82
	C7D1	-0.3	(-0.7, 0.1)	10.48
2.0 mg/kg, IV	C1D1	0.4	(-0.2, 0.9)	44.64
	C7D1	-2.0	(-4.7, 0.7)	70.34
10.0 mg/kg, IV	C1D1	-1.7	(-0.7, 4.1)	200.69
	C7D1	-10.3	(-23.8, 3.3)	353.36
Estimated Population Slope	C1D1	0.01	(-0.01. 0.02)	Time-Matched
	C7D1	-0.03	(-0.08, 0.02)	

Note: The mean steady-state Cmax for nivolumab for the Phase 3 dose (3 mg/kg, IV q2weeks) is 112 µg/mL.

Abbreviations: max = maximum; QTcF = corrected QT interval, Fridericia formula; ECG = electrocardiogram; CI = confidence interval; IV = intravenous; C1/7 = Cycle 1/7; D1 = Day 1.

Source: Clinical Study Report CA209010, Section 8.8.1.1, Table 8.8.1.1-1, page 141/10155

Reviewer's Comments: We will provide our independent analysis results in Section 5.2. Our results are similar to those sponsor's findings.

4.2.8.2.1 Assay Sensitivity

There is no assay sensitivity established because no positive control arm included in the study.

4.2.8.2.2 Categorical Analysis

Categorical analysis was used to summarize in the categories of QTc ≤450 ms, between 450 ms and 480 ms, between 480 ms and 500 ms, and >500 ms, and changes from baseline QTc ≤30 ms, between 30 and 60 ms, and >60 ms. No subject's absolute QTc > 480 ms and ΔQTc >60 ms.

Nivolumab Dose	Max QTcF Interval (msec) N (%)			Max ΔQTcF Interval (msec) N (%)		
	≤ 450	451 - 480	> 480	≤ 30	31 - 60	> 60
0.3 mg/kg, IV (N = 49)	46 (93.9)	3 (6.1)	0	48 (98.0)	1 (2.0)	0
2.0 mg/kg, IV (N = 51)	49 (96.1)	2 (3.9)	0	51 (100)	0	0
10.0 mg/kg, IV (N = 46)	43 (93.5)	3 (6.5)	0	44 (95.7)	2 (4.3)	0

Abbreviations: QTcF = corrected QT interval, Fridericia formula; max = maximum; IV = intravenous.

Source: Clinical Study Report CA209010, Section 8.8.1.2, Table 8.8.2.1-1, page 142/10155

4.2.8.2.3 Additional Analyses

Categorical analysis was used to summarize in the categories of PR ≤200 ms and >200 ms, and QRS≤120 ms, and >120 ms. Twenty-three subjects' PR > 200 ms and Twelve subjects' QRS>120 ms.

Nivolumab Dose	Max PR Interval (msec) N (%)		Max QRS Interval (msec) N (%)	
	≤ 200	> 200	≤ 120	> 120
0.3 mg/kg, IV (N = 48)	44 (91.7)	8 (8.3)	46 (93.9)	3 (6.1)
2.0 mg/kg, IV (N = 51)	44 (86.3)	7 (13.7)	49 (96.1)	2 (3.9)
10.0 mg/kg, IV (N = 44)	36 (81.8)	8 (18.2)	39 (84.8)	7 (15.2)

Abbreviations: max = maximum; IV = intravenous.

4.2.8.3 Clinical Pharmacology

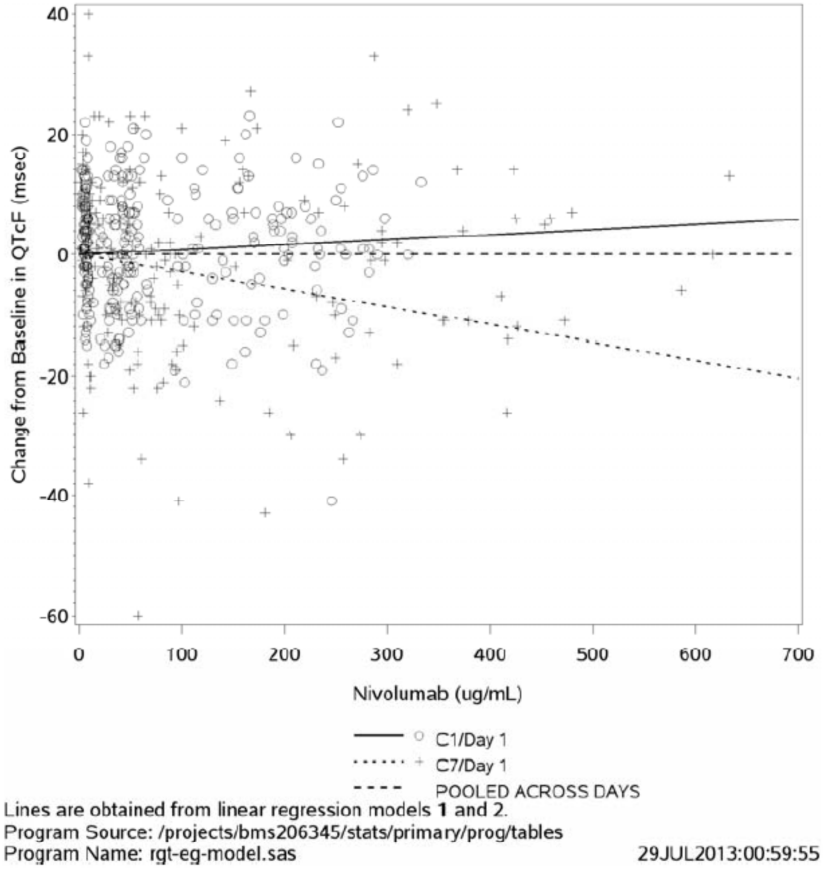
4.2.8.3.1 Pharmacokinetic Analysis

The mean end-of-infusion concentrations after the first dose (Cycle 1-1 h) were 7.24, 40.80 and 190.28 µg/mL for the 0.3, 2, and 10 mg/kg dose groups, respectively. The corresponding mean end-of-infusion concentrations at approximately steady state of cycle 7-1 h were 9.89, 69.16, and 356.74 µg/mL, respectively. The mean trough concentrations after the first dose (cycle 2-0 h) were 1.36, 10.96, and 55.41 µg/mL, and the corresponding mean steady state trough concentrations after Q3wk of treatment (cycle 8-0 h) were 3.85, 27.68, and 164.46 µg/mL for the 0.3, 2, and 10 mg/kg dose groups, respectively. End-of-infusion and trough concentrations after the first dose and at steady state indicate a dose-related increase in serum nivolumab concentration.

4.2.8.3.2 Exposure-Response Analysis

A linear mixed-effects regression model was fitted for ΔQTcF on nivolumab serum concentration. When the model included study day as a factor, a shallow, nonsignificant,positive slope (0.01) was associated with nivolumab treatment on Day 1 of Cycle 1. On Day 1 of Cycle 7, there was a non-significant, negative slope (-0.03). When the model pooled data across days, the population slope was 0.00 (see the following figure).

Figure 8.8.3-1: QTcF Change from Baseline vs. Time-Matched Nivolumab Concentrations



Note: The mean steady-state C_{max} for nivolumab for the Phase 3 dose (3 mg/kg, IV Q2weeks) is 112 µg/mL.

Source: Sponsor's Final Clinical Study Report CA209010, Page 144.

Reviewer's Analysis: A plot of ΔQTcF vs. drug concentrations is presented in Figure 3. The linear mixed pharmacokinetic/pharmacodynamics model shows that there was no statistically significant relationship between nivolumab plasma concentration and QTcF.

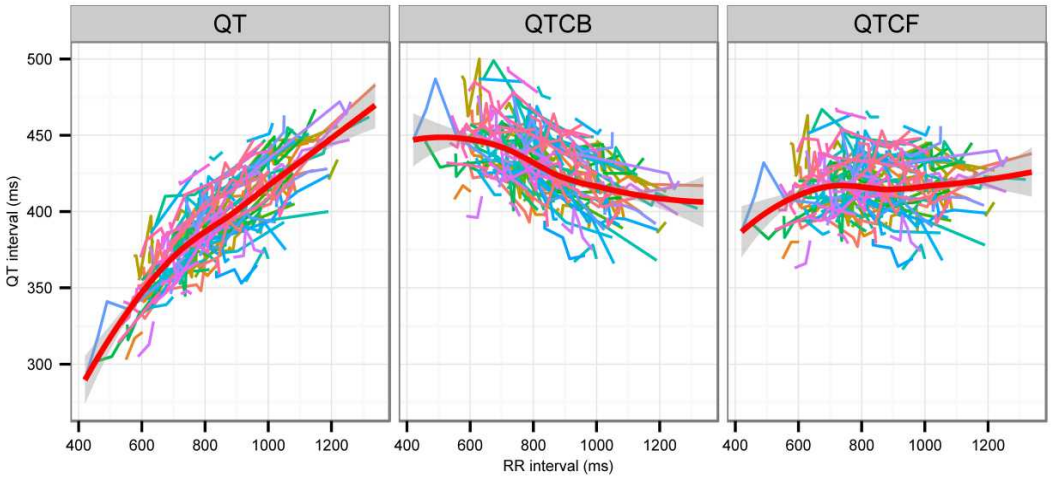
5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

This review did not evaluate QT/RR correction method because the sponsor provided QTcB and QTcF correction intervals. This reviewer chooses to present QTcF as the primary statistical analysis.

The relationship between different correction methods and RR is presented in Figure 1.

Figure 1: QT, QTcB and QTcF vs. RR (Each Subject's Data Points are Connected with a Line)



The shaded area and the red line are solely used for illustration purposes and are derived from a non-parametric smoother function.

5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for the Study Drug

This primary endpoint is the change from baseline of QTcF. The descriptive statistics are listed in Table 7 and Table 8. The largest upper bounds of the 2-sided 90% CI for the mean differences between baselines and nivolumab infusion dose-groups by day and time or by day were below 20 ms.

Table 7: Analysis Results of ΔQTcF for Nivolumab dose of 0.3 kg/mg, 2 kg/mg and 10 kg/mg (by Day and Time)

Treatment	Day/Time	N	Mean	Std Dev	90% CI for Mean
NIVOLUMAB 0.3 mg/kg	Cycle 1 Day 1 - end of infusion	46	3.5	8.0	(1.5, 5.5)
	Cycle 1 Day 1 - 3 hour	47	1.9	7.3	(0.1, 3.7)
	Cycle 7 Day 1 - predose	16	2.8	12.3	(-2.6, 8.2)
	Cycle 7 Day 1 - End of infusion	18	4.9	13.4	(-0.6, 10.4)
	Cycle 7 Day 1 - 3 hour	18	3.7	10.2	(-0.5, 7.8)
NIVOLUMAB 2 mg/kg	Cycle 1 Day 1 - end of infusion	51	0.9	9.1	(-1.2, 3.0)
	Cycle 1 Day 1 - 3 hour	49	1.2	10.1	(-1.3, 3.6)
	Cycle 7 Day 1 - predose	23	-4.7	14.8	(-10.0, 0.7)
	Cycle 7 Day 1 - End of infusion	25	-3.2	12.7	(-7.5, 1.2)
	Cycle 7 Day 1 - 3 hour	24	-7.2	16.8	(-13.1, -1.3)
NIVOLUMAB 10 mg/kg	Cycle 1 Day 1 - end of infusion	44	2.0	8.8	(-0.3, 4.2)
	Cycle 1 Day 1 - 3 hour	46	0.0	13.9	(-3.5, 3.4)
	Cycle 7 Day 1 - predose	21	-0.1	17.6	(-6.7, 6.5)
	Cycle 7 Day 1 - End of infusion	21	-0.4	19.0	(-7.6, 6.7)
	Cycle 7 Day 1 - 3 hour	23	-4.1	16.8	(-10.1, 1.9)

Table 8: Analysis Results of ΔQTcF for Nivolumab dose of 0.3 kg/mg, 2 kg/mg and 10 kg/mg (By Day)

Treatment	Day	N	Mean	Std Dev	90% CI for Mean
NIVOLUMAB 0.3 mg/kg	Cycle 1 Day 1	93	2.7	7.7	(1.4, 4.0)
	Cycle 7 Day 1	52	3.8	11.8	(1.1, 6.6)
NIVOLUMAB 2 mg/kg	Cycle 1 Day 1	100	1.0	9.6	(-0.6, 2.6)
	Cycle 7 Day 1	72	-5.0	14.8	(-7.9, -2.1)
NIVOLUMAB 10 mg/kg	Cycle 1 Day 1	90	1.0	11.7	(-1.1, 3.0)
	Cycle 7 Day 1	65	-1.6	17.6	(-5.3, 2.0)

5.2.1.2 Assay Sensitivity Analysis

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

5.2.1.3 Categorical Analysis

Table 9 and Table 10 list the number of subjects as well as the number of observations whose QTcF values are ≤ 450 ms, between 450 ms and 480 ms, between 480 ms and 500 ms, and changes from baseline QTc ≤30 ms, between 30 and 60 ms, and >60 ms. No subject's QTcF is above 480 ms (see Table 9). No subject's change from baseline is above 60 ms (see Table 10).

Table 9: Categorical Analysis for QTcF

TREAT	QTCF		
	Value<=450 ms	450 ms<Value<=480 ms	Total
NIVOLUMAB 0.3 mg/kg	52	3	55
NIVOLUMAB 2 mg/kg	51	2	53
NIVOLUMAB 10 mg/kg	48	4	52
Total	151	9	160

Table 10: Categorical Analysis for ΔQTcF

TREAT	QTCF_CFB		
	Value<=30 ms	30 ms<Value<=60 ms	Total
NIVOLUMAB 0.3 mg/kg	48	1	49
NIVOLUMAB 2 mg/kg	51	0	51
NIVOLUMAB 10 mg/kg	44	2	46
Total	143	3	146
Frequency Missing = 14			

5.2.2 HR Analysis

This primary endpoint is the change from baseline of HR. The descriptive statistics are listed in Table 11 and Table 12. The largest upper bounds of the 2-sided 90% CI for the mean differences between baselines to nivolumab infusion dose-groups by day and time or by day are below 10 bpm. Table 13 presents the categorical analysis of HR. Six subjects who experienced HR interval greater than 100 bpm are in nivolumab dose-groups.

Table 11: Analysis Results of ΔHR for Nivolumab dose of 0.3 kg/mg, 2 kg/mg and 10 kg/mg (by Day and Time)

Treatment	Day/Time	N	Mean	Std Dev	90% CI for Mean
NIVOLUMAB 0.3 mg/kg	Cycle 1 Day 1 - end of infusion	46	-0.9	6.6	(-2.5, 0.7)
	Cycle 1 Day 1 - 3 hour	47	2.0	5.6	(0.6, 3.4)
	Cycle 7 Day 1 - predose	16	-3.8	10.3	(-8.3, 0.8)
	Cycle 7 Day 1 - End of infusion	18	-2.6	9.8	(-6.6, 1.5)
	Cycle 7 Day 1 - 3 hour	18	-2.1	8.6	(-5.6, 1.4)
NIVOLUMAB 2 mg/kg	Cycle 1 Day 1 - end of infusion	51	-0.8	6.5	(-2.3, 0.8)
	Cycle 1 Day 1 - 3 hour	49	2.8	6.7	(1.2, 4.4)
	Cycle 7 Day 1 - predose	23	-3.7	15.2	(-9.1, 1.7)
	Cycle 7 Day 1- End of infusion	25	-2.3	14.5	(-7.3, 2.7)
	Cycle 7 Day 1 - 3 hour	24	-1.3	16.1	(-6.9, 4.3)
NIVOLUMAB 10 mg/kg	Cycle 1 Day 1 - end of infusion	44	0.6	5.4	(-0.8, 1.9)
	Cycle 1 Day 1 - 3 hour	46	2.9	8.7	(0.8, 5.1)
	Cycle 7 Day 1 - predose	21	-2.5	10.9	(-6.6, 1.6)
	Cycle 7 Day 1 - End of infusion	21	-8.4	14.5	(-13.8, -2.9)
	Cycle 7 Day 1 - 3 hour	23	-3.0	11.8	(-7.3, 1.2)

Table 12: Analysis Results of ΔHR for Nivolumab dose of 0.3 kg/mg, 2 kg/mg and 10 kg/mg (by Day)

Treatment	Day	N	Mean	Std Dev	90% CI for Mean
NIVOLUMAB 0.3 mg/kg	Cycle 1 Day 1	93	0.6	6.3	(-0.5, 1.6)
	Cycle 7 Day 1	52	-2.8	9.4	(-5.0, -0.6)
NIVOLUMAB 2 mg/kg	Cycle 1 Day 1	100	1.0	6.8	(-0.2, 2.1)
	Cycle 7 Day 1	72	-2.4	15.1	(-5.4, 0.5)
NIVOLUMAB 10 mg/kg	Cycle 1 Day 1	90	1.8	7.3	(0.5, 3.1)
	Cycle 7 Day 1	65	-4.6	12.5	(-7.2, -2.0)

Table 13: Categorical Analysis for HR

	HR		
TREAT	HR <= 100 bpm	HR >100 bpm	Total
NIVOLUMAB 0.3 mg/kg	52	3	55
NIVOLUMAB 2 mg/kg	52	1	53
NIVOLUMAB 10 mg/kg	50	2	52
Total	154	6	160

5.2.3 PR Analysis

This primary endpoint is the change from baseline of PR. The descriptive statistics are listed in Table 14 and Table 15. The largest upper bounds of the 2-sided 90% CI for the mean differences between baselines to nivolumab infusion dose-groups by day and time or by day are below 20 ms. Table 16 presents the categorical analysis of PR. Eighteen subjects who experienced PR interval greater than 200 ms are in nivolumab dose-groups.

Table 14: Analysis Results of ΔPR for Nivolumab dose of 0.3 kg/mg, 2 kg/mg and 10 kg/mg (by Day and Time)

Treatment	Day/Time	N	Mean	Std Dev	90% CI for Mean
NIVOLUMAB 0.3 mg/kg	Cycle 1 Day 1 - end of infusion	45	3.1	6.7	(1.4, 4.8)
	Cycle 1 Day 1 - 3 hour	46	2.5	6.9	(0.8, 4.2)
	Cycle 7 Day 1 - predose	16	5.4	14.0	(-0.7, 11.6)
	Cycle 7 Day 1 - End of infusion	18	6.9	16.7	(0.1, 13.8)
	Cycle 7 Day 1 - 3 hour	18	5.7	11.9	(0.8, 10.6)
NIVOLUMAB 2 mg/kg	Cycle 1 Day 1 - end of infusion	51	1.6	8.1	(-0.3, 3.5)
	Cycle 1 Day 1 - 3 hour	49	2.0	8.6	(-0.0, 4.1)
	Cycle 7 Day 1 - predose	21	2.7	12.4	(-2.0, 7.3)
	Cycle 7 Day 1 - End of infusion	23	2.8	15.7	(-2.8, 8.4)
	Cycle 7 Day 1 - 3 hour	22	2.4	15.8	(-3.4, 8.2)
NIVOLUMAB 10 mg/kg	Cycle 1 Day 1 - end of infusion	42	3.9	7.8	(1.9, 5.9)
	Cycle 1 Day 1 - 3 hour	44	4.0	9.4	(1.6, 6.4)
	Cycle 7 Day 1 - predose	20	3.6	9.4	(-0.0, 7.2)
	Cycle 7 Day 1 - End of infusion	20	6.8	11.3	(2.4, 11.1)
	Cycle 7 Day 1 - 3 hour	22	3.4	11.0	(-0.6, 7.5)

Table 15: Analysis Results of ΔPR for Nivolumab dose of 0.3 kg/mg, 2 kg/mg and 10 kg/mg (by Day)

Treatment	Day	N	Mean	Std Dev	90% CI for Mean
NIVOLUMAB 0.3 mg/kg	Cycle 1 Day 1	91	2.8	6.7	(1.6, 4.0)
	Cycle 7 Day 1	52	6.1	14.1	(2.8, 9.3)
NIVOLUMAB 2 mg/kg	Cycle 1 Day 1	100	1.8	8.3	(0.4, 3.2)
	Cycle 7 Day 1	66	2.6	14.6	(-0.4, 5.6)
NIVOLUMAB 10 mg/kg	Cycle 1 Day 1	86	3.9	8.6	(2.4, 5.5)
	Cycle 7 Day 1	62	4.5	10.5	(2.3, 6.8)

Table 16: Categorical Analysis for PR

TREAT	PR		
	PR <= 200 ms	PR >200 ms	Total
NIVOLUMAB 0.3 mg/kg	51	4	55
NIVOLUMAB 2 mg/kg	46	6	52
NIVOLUMAB 10 mg/kg	41	8	49
Total	138	18	156
Frequency Missing = 4			

5.2.4 QRS Analysis

This primary endpoint is the change from baseline of QRS. The descriptive statistics are listed in Table 17 and Table 18. The largest upper bounds of the 2-sided 90% CI for the mean differences between baseline to nivolumab infusion dose-groups are below 10 ms. Table 19 presents the categorical analysis of QRS. Eighteen subjects who experienced QRS interval greater than 110 ms are in nivolumab dose-groups.

Table 17: Analysis Results of ΔQRS for Nivolumab dose of 0.3 kg/mg, 2 kg/mg and 10 kg/mg (by Day and Time)

Treatment	Cycle/Day/Hour	N	Mean	Std Dev	90% CI for Mean
NIVOLUMAB 0.3 mg/kg	Cycle 1 Day 1 - end of infusion	46	1.0	4.1	(-0.0, 2.0)
	Cycle 1 Day 1 - 3 hour	47	0.6	4.2	(-0.4, 1.7)
	Cycle 7 Day 1 - predose	16	2.6	4.6	(0.6, 4.7)
	Cycle 7 Day 1 - End of infusion	18	1.9	4.7	(0.0, 3.9)
	Cycle 7 Day 1 - 3 hour	18	1.9	4.5	(0.1, 3.8)
NIVOLUMAB 2 mg/kg	Cycle 1 Day 1 - end of infusion	51	-0.1	3.8	(-1.0, 0.8)
	Cycle 1 Day 1 - 3 hour	49	0.6	4.5	(-0.5, 1.7)
	Cycle 7 Day 1 - predose	23	-0.0	4.2	(-1.6, 1.5)
	Cycle 7 Day 1 - End of infusion	25	-0.5	5.5	(-2.4, 1.4)
	Cycle 7 Day 1 - 3 hour	24	-0.8	5.4	(-2.6, 1.1)
NIVOLUMAB 10 mg/kg	Cycle 1 Day 1 - end of infusion	44	0.6	3.4	(-0.2, 1.5)
	Cycle 1 Day 1 - 3 hour	46	0.1	3.6	(-0.8, 1.0)
	Cycle 7 Day 1 - predose	21	-1.1	5.9	(-3.3, 1.1)
	Cycle 7 Day 1 - End of infusion	21	-1.1	6.3	(-3.5, 1.2)
	Cycle 7 Day 1 - 3 hour	23	0.4	6.5	(-1.9, 2.8)

Table 18: Analysis Results of ΔQRS for Nivolumab dose of 0.3 kg/mg, 2 kg/mg and 10 kg/mg (by Day)

Treatment	Cycle	N	Mean	Std Dev	90% CI for Mean
NIVOLUMAB 0.3 mg/kg	Cycle 1 Day 1	93	0.8	4.1	(0.1, 1.5)
	Cycle 7 Day 1	52	2.2	4.5	(1.1, 3.2)
NIVOLUMAB 2 mg/kg	Cycle 1 Day 1	100	0.2	4.1	(-0.4, 0.9)
	Cycle 7 Day 1	72	-0.4	5.0	(-1.4, 0.6)
NIVOLUMAB 10 mg/kg	Cycle 1 Day 1	90	0.4	3.5	(-0.3, 1.0)
	Cycle 7 Day 1	65	-0.6	6.2	(-1.8, 0.7)

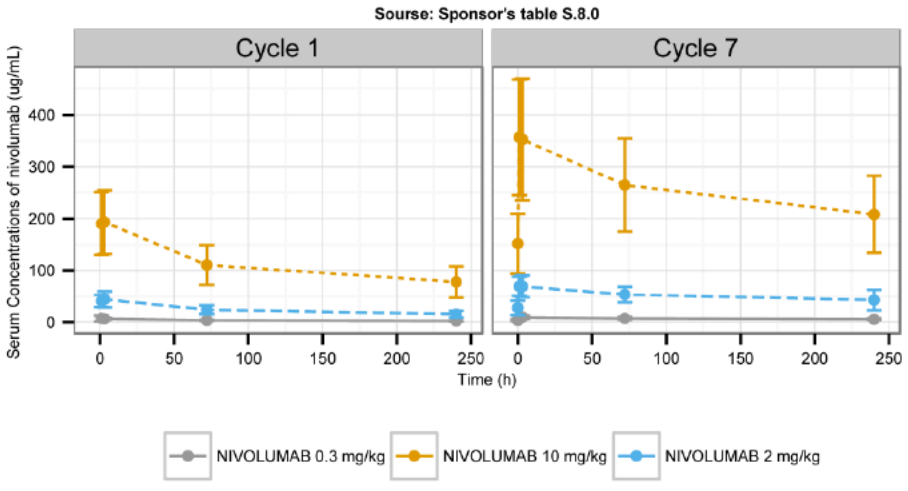
Table 19: Categorical Analysis for QRS

TREAT	QRS		
	QRS <= 110 ms	QRS > 110 ms	Total
NIVOLUMAB 0.3 mg/kg	51	4	55
NIVOLUMAB 2 mg/kg	48	5	53
NIVOLUMAB 10 mg/kg	43	9	52
Total	142	18	160

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

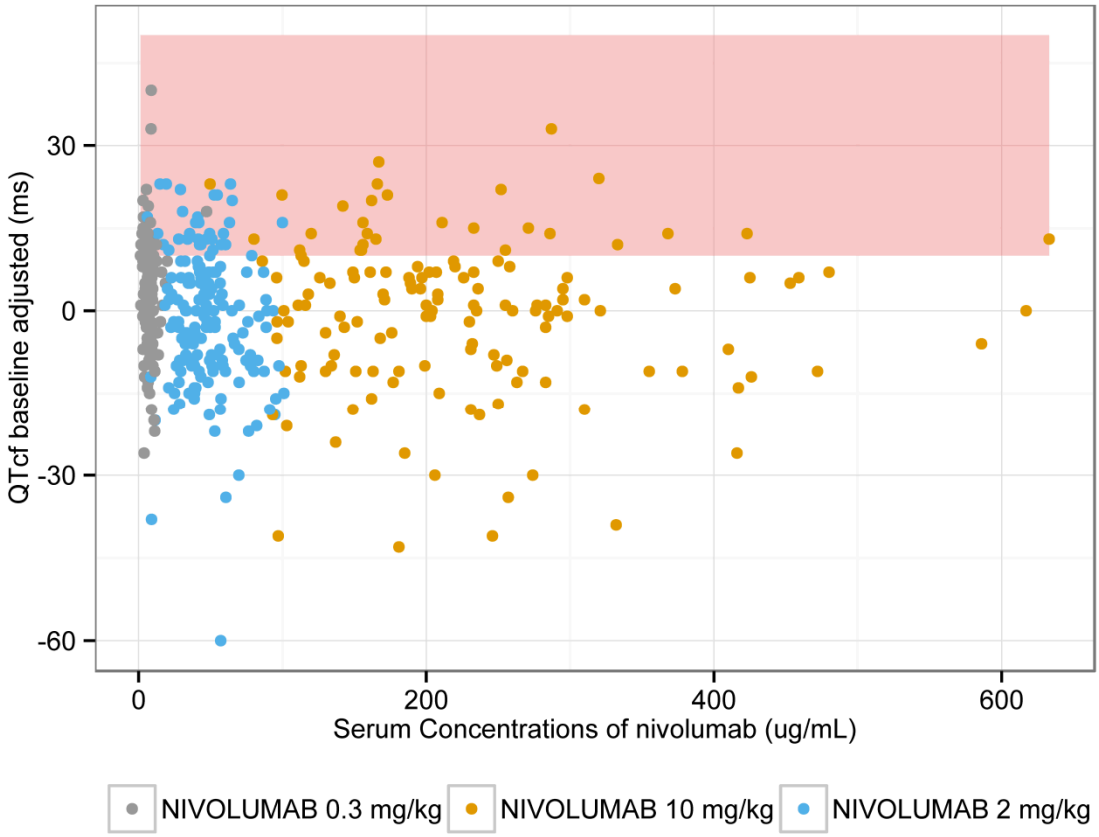
The mean drug concentration-time profile is illustrated in Figure 2.

Figure 2: Mean±SD Nivolumab Concentration-Time Profiles



The relationship between ΔQTcF and nivolumab concentrations is visualized in Figure 3 with no evident exposure-response relationship.

Figure 3: ΔQTcF vs. Nivolumab Concentration



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

Mortality was about 40% and discontinuation around 75%, both largely attributed to disease progression. Everyone reported adverse events, but few of these appeared to be cardiovascular.

5.4.2 ECG assessments

Overall ECG acquisition and interpretation in this study appears acceptable.

5.4.3 PR and QRS Interval

These is some evidence of a dose-related increase in both PR and QRS, but neither effect appears to be clinically relevant..

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose	3 mg/kg once every 2 weeks (Q2W)	
Maximum tolerated dose	Dose escalation up to 10 mg/kg was achieved without reaching a maximum tolerated dose (MTD).	
Principal adverse events	In the nivolumab group of the Phase 3 trial CA209037, the most frequently reported AEs (≥ 15% of subjects), regardless of causality, were fatigue (38.8%), nausea (23.9%), diarrhea (20.1%), pruritus (19.0%), anemia (15.7%), cough (15.3%), and dyspnea (15.3%). The most frequently reported (≥ 15% of subjects) drug-related AEs in the nivolumab group included fatigue (25.0%) and pruritus (16.0%). Drug-related AEs leading to discontinuation were reported in 6 (2.2%) subjects in the nivolumab arm, and no events were reported in more than 1 subject. All AEs leading to discontinuation were Grade 3-4 events (single events of colitis, pancreatitis, ALT increased, lipase increased, autoimmune neuropathy, and demyelination).	
Maximum dose tested	**Single Dose**	10 mg/kg (in BMS sponsored trials included in the submission dossier)
	Multiple Dose	10 mg/kg Q2W Additionally, 20 mg/kg was well tolerated in a clinical study ONO-4538-01, sponsored by Ono Pharmaceutical Co. Ltd., 3 patients received up to 20 mg/kg nivolumab for 3 doses without experiencing DLTs. The study consisted of a single-dose phase, multiple-dose phase, and extended treatment phase.
Exposures Achieved at Maximum Tested Dose	**Single Dose**	At 10 mg/kg, Geo. Mean (%CV) Cmax: 196.3 µg/mL (19.5%) Geo. Mean (%CV) AUC (INF): 76541.0 µg*h/mL (27.0%)
	Multiple Dose	At 10 mg/kg Q2W after the ninth dose, Geo. Mean (%CV) Cmax: 475.0 µg/mL (24.6%) Geo. Mean (%CV) AUC (TAU): 99621.7 µg*h/mL (26.0%)
Range of linear PK	0.1 to 20 mg/kg	
Accumulation at steady state	Nivolumab accumulation following administration every 2 weeks was in the range of 2.9 to 3.3 based on AUC(TAU), 2.0 to 2.4 based on Cmax, and 3.1 to 4.8 based on Cmin.	
Metabolites	The metabolic pathway of nivolumab has not been characterized. As a fully human IgG4 monoclonal antibody, nivolumab is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as	

	endogenous IgG.	
Absorption	**Absolute/Relative Bioavailability**	Not applicable, as nivolumab is administered intravenously.
	Tmax	Median (range): 3.1 hours (1-5 hours) Median (range) for metabolites: Not applicable
Distribution	**Vd/F or Vd**	Mean (%CV) for Vss = 8.36 L (30.4%)
	% bound	Not applicable
Elimination	**Route**	As a fully human IgG4 monoclonal antibody, nivolumab is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG.
	Terminal t½	Mean (%CV): 30.0 days (100.7%) Mean (%CV) for metabolites: Not applicable
	CL/F or CL	Mean (%CV): 10.4 mL/h (49.9%) Mean (%CV) for metabolites: Not applicable
Intrinsic Factors	**Age**	No clinically significant impact of age on the PK of nivolumab as determined via population PK (PPK) analysis. Patients with age > 65 years had 5% higher mean Cmax at steady state (Cmaxss) and 7% higher mean AUC at steady state (AUCss) compared to patients with age < 65 years.
	Sex	No clinically significant impact of sex on the PK of nivolumab as determined via PPK. Females had 5% higher mean Cmaxss and 3% higher mean AUCss compared to Males.
	Race	No clinically significant impact of race on the PK of nivolumab as determined via PPK. Blacks and Asians had 9% and 4% lower mean Cmaxss, respectively, compared to Whites; Blacks and Asians had 13% and 7% lower mean AUCss, respectively, compared to Whites.
	Hepatic & Renal Impairment	No formal renal or hepatic impairment studies were performed. However, renal function (measured by eGFR), and hepatic function (based on NCI-ODWG criteria) did not have a clinically significant impact on the PK of nivolumab based on the PPK analysis. Mild and moderate renal function groups had a mean higher Cmaxss of 6 and 21%, respectively, compared to normal renal function group; mild and moderate renal function groups had a mean higher AUCss of 8% and 30%, respectively, compared to the normal renal function group. Mild hepatic function group had 10% lower mean Cmaxss and 12% lower mean AUCss compared to the normal hepatic function group.
Extrinsic Factors	**Drug interactions**	No formal drug-drug interaction studies have been

		conducted with nivolumab. Nivolumab is considered to have low potential to affect the PK of other drugs based on the lack of effect on cytokines in peripheral circulation. The effect of other drugs on the PK of nivolumab has not been formally investigated. However, it is unlikely that other drugs will have an impact on the PK of nivolumab given nivolumab is a IgG4 mAb, which is likely eliminated by mechanisms similar to that of other antibodies, namely by non-specific catabolism.
	Food Effects	Not applicable as nivolumab is dosed intravenously.
Expected High Clinical Exposure Scenario	High clinical exposures are not expected to exceed PK exposures produced by the nivolumab 3 mg/kg Q2W dose given that: • Nivolumab is administered intravenously in the clinic (low likelihood of administration of incorrect dose) • Increase in nivolumab exposures due to drug interaction is not anticipated, given the expected route of elimination of IgGs (like nivolumab) is through non-specific catabolic degradation • Effect of intrinsic and extrinsic factors on clearance and volume of distribution of nivolumab (other than body weight) is < 20%	
Preclinical Cardiac Safety	In vitro hERG study: Not applicable Monkey study: No cardiac findings	
Clinical Cardiac Safety	The potential of nivolumab to prolong the QTc interval was evaluated in 146 patients in a Phase 2 study (CA209010) of nivolumab (0.3 mg/kg (N=49), 2 mg/kg (N=51), and 10 mg/kg (N=46)) with a Q3W regimen. No changes in mean QTc interval were detected in nivolumab-treated patients based on Fridericia correction method (QTcF). After careful examination of events of seizure/convulsion, syncope/presyncope, QTc prolongation and tachycardia, no event was determined to be associated with an abnormal ECG finding potentially related to proarrhythmia. Overall, nivolumab does not prolong the QTc interval in the dose range studied.	

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/s/

DINKO REKIC
10/20/2014

JIANG LIU
10/20/2014

MOH JEE NG
10/20/2014

QIANYU DANG
10/20/2014

MICHAEL Y LI
10/20/2014

NORMAN L STOCKBRIDGE
10/20/2014

Division of Oncology Products 2 (DOP2) Labeling Review

BLA:	125554
SDN:	
eCTD:	162
Submission date:	July 30, 2014
PDUFA goal date:	March 30, 2015
Potential early action date:	December 19, 2014
Review classification:	Priority
Proprietary (nonproprietary name:	Opdivo
Applicant:	Bristol-Myers Squibb
Indication:	For the treatment of unresectable or metastatic melanoma in patients previously treated with ipilimumab, regardless of BRAF status
Dosing regimen:	3 mg/kg intravenously every two weeks
Reviewer:	Jennie Chang, PharmD, Acting Associate Director for Labeling

Background:

The BLA for nivolumab, an anti-PD1 antibody, was submitted on July 30, 2014. The Applicant is seeking approval in patients with metastatic melanoma based on its pivotal Study CA209037 which was a multicenter international study, including U.S, study sites conducted under IND115195. The study enrolled patients with advanced melanoma who have progressed on or after anti-CTLA-4 therapy and/or subjects with BRAF V600 mutations, who have progressed on or after a BRAF inhibitor in addition to anti-CTLA-4 therapy. The dosing regimen was 3 mg/kg intravenously every two weeks.

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

The following pages contain the working version of the Opdivo labeling with my recommended edits and comments (identified as 'JC1' through 'JC53') and include the project manager's comments (initials 'ML'). Given that the scientific review of the labeling is ongoing, my labeling recommendations in this review should be considered preliminary and may not represent DOP2's final recommendations for the Opdivo labeling.

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

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/s/

JENNIE T CHANG
10/09/2014

RPM FILING REVIEW

(Including Memo of Filing Meeting)

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

Application Information		
BLA# 125554	BLA Supplement # N/A	Efficacy Supplement Type SE- N/A
Proprietary Name: Opdivo Injection for Intravenous Infusion (*Proposed*) Established/Proper Name: nivolumab Dosage Form: Injection for Intravenous Infusion Strengths: 40 mg/4 ml (10 mg/mL) vial, 100 mg/10 ml (10 mg/mL) vial		
Applicant: Bristol-Myers Squibb Company Agent for Applicant (if applicable): N/A		
Date of Application: July 30, 2014 Date of Receipt: July 30, 2014 Date clock started after UN: N/A		
PDUFA Goal Date: March 30, 2015	Action Goal Date (if different): Potential early action by December 19, 2014	
Filing Date: September 28, 2014	Date of Filing Meeting: September 12, 2014	
Chemical Classification: (1,2,3 etc.) (original NDAs only) N/A		
Proposed indication(s)/Proposed change(s): For the treatment of unresectable or metastatic melanoma in patients previously treated with ipilimumab, regardless of BRAF status		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.***		☐ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Type of BLA ***If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team***		☒ 351(a) ☐ 351(k)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher or pediatric rare disease priority review voucher was submitted, review classification is Priority.***		☐ Standard ☒ Priority ☐ Tropical Disease Priority Review Voucher submitted ☐ Pediatric Rare Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐	

Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)
☒ Fast Track Designation ☒ Breakthrough Therapy Designation ***(set the submission property in 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 [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ 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*): N/A	
List referenced IND Number(s): As listed on the FDA FORM 356h, INDs 100,052 (b) (4) 104,225 113,463 115,195 114,460 (b) (4) 117,607 (b) (4) 119,380 119,381 119,382 119,590 122,840; and Dako PMA #M13005, Dako IDE #G140020	

Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒	☐		Verified on 8/22/14
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	☒	☐		Verified on 8/22/14 Proprietary name is tentatively approved. Upon name approval, DARRTS will be updated
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? ***For NDAs/NDA supplements, 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.***	☒	☐	☐	Verified on 8/22/14

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***	☐	☒		Verified on 8/25/14
If yes, explain in comment column.				N/A
If affected by AIP, has OC/OMPQ been notified of the submission? **If yes,** date notified:	☐	☐		N/A
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	☒	☐		Verified on 8/6/14

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. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application: ☐ 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. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears

505(b)(2) (NDAs/NDA Efficacy Supplements only)	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☐	☒	N/A (BLA)
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)].**	☐	☐	☒	N/A (BLA)
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 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***	☐	☐	☒	N/A (BLA)
Is there unexpired exclusivity on any drug product containing the 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***	☐	☐	☒	N/A (BLA)

If yes, please list below:				

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

Exclusivity	**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*	☐	☒		Verified on 8/25/14
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☐	☐	☒	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☐	☒	N/A (BLA)
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?	☐	☐	☒	N/A (BLA)
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).***	☐	☐	☒	N/A (BLA)
For BLAs: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? ***If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM*** ***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.*	☐	☒	☐	Original BLA

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).	☒	☐	☐	Verified on 8/6/14
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) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.	☒	☐		Verified on 8/6/14
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐	☒	☐	Verified on 8/6/14
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), 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.*				

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

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)].***	☒	☐		Verified on 8/6/14
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	Verified on 8/25/14
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)?	☐	☐	☒	N/A (BLA)
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.*	☒	☐		Verified on 8/25/14
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***	☒	☐		Verified on 8/25/14
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…"*	☒	☐	☐	Verified on 8/25/14

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.***	☐	☐	☒	N/A (BLA)
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
For NMEs: 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:* For non-NMEs: *Date of consult sent to Controlled Substance Staff*:	☐	☐	☒	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
PREA Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients, 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.*	☐	☒		Orphan Designation
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?	☐	☐	☒	Orphan Designation
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***	☐	☐	☒	Orphan Designation
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? ***If no, request in 74-day letter***	☐	☐	☒	Orphan Designation

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

BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]	☐	☐		N/A (BLA)
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."***	☒	☐	☐	
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***	☐	☒	☐	'Risk Management Plan' is included
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☒ Medication Guide (MedGuide) ☒ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	☒	☐		Verified on 8/25/14
Is the PI submitted in PLR format?[4]	☒	☐		Verified 8/20/14
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.***	☐	☐	☒	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	☒	☐	☐	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	☒	☐	☐	

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

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

Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	☒	☐	☐	
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)			
	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, and current approved Rx PI (if switch) 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:***	☒	☐	☐	QT-IRT
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** July 17, 2012 ***If yes, distribute minutes before filing meeting***	☒	☐		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** July 9, 2014 ***If yes, distribute minutes before filing meeting***	☒	☐		
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***	☐	☒		

ATTACHMENT

MEMO OF FILING MEETING

DATE: September 12, 2014

BLA/NDA/Supp #: 125554

PROPRIETARY NAME: Opdivo Injection for Intravenous Infusion

ESTABLISHED/PROPER NAME: nivolumab

DOSAGE FORM/STRENGTH: 40 mg/4 ml (10 mg/mL) vial, 100 mg/10 ml (10 mg/mL) vial

APPLICANT: Bristol-Myers Squibb Company

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Original BLA for the treatment of unresectable or metastatic melanoma in patients previously treated with ipilimumab, regardless of BRAF status

BACKGROUND: This biological license application (BLA) is for accelerated approval of Opdivo (nivolumab) for the "treatment of unresectable or metastatic melanoma in patients previously treated with ipilimumab, regardless of BRAF status." The BLA will be supported by efficacy and safety data from the following studies:

- Study CA209037: entitled "A Randomized, Open-Label, Phase 3 Trial of BMS-936558 (Nivolumab) Versus Investigator's Choice in Advanced (Unresectable or Metastatic) Melanoma Patients Progressing Post Anti-CTLA-4 Therapy."

- Study CA209066: entitled "A Phase III, Randomized, Double-Blind Study of Nivolumab vs. Dacarbazine in Subjects with Previously Untreated Unresectable or Metastatic Melanoma."

- Study MDX1106-03 (Also referred to as CA209003): entitled, "A Phase 1, Open-label, Multicenter, Multidose, Dose Escalation Study of BMS-936558 (MDX1106) in Subjects with Selected Advanced or Recurrent Malignancies."

A subsequent supplemental BLA application is planned to support potential conversion to regular approval based on the CA209037 co-primary endpoint of OS.

The regulatory history includes the following: initial development program for the treatment of metastatic melanoma begun under IND 100052; BMS filed a new Investigational New Drug Application (IND) for the treatment of metastatic melanoma (IND 115195) administratively split from IND 100052 on June 13, 2012; an EOP2 meeting was held on July 17, 2012, regarding the preliminary data from the dose-finding and tolerability study (CA209003) conducted under IND 100052 and seeking feedback on the proposed clinical development plan for treatment of advanced, unresectable, or metastatic melanoma; new registrational Protocol CA209037 submitted to IND 115195 on October 17, 2012, Advice/Information Letters relating to Protocol CA209037 were issued on March 27, 2013, January 16, 2014, March 17, 2014; a Pre-BLA CMC only meeting was held April 18, 2014, and a Pre-BLA multidiscipline meeting

was held July 9, 2014, to discuss the content and format of the BLA and obtain agreement on any late components of an application.

Finally, BMS was granted Fast Track Designation for patients with unresectable or metastatic melanoma to demonstrate a clinically important and statistically robust improvement in overall survival over available therapies on October 4, 2012; BMS was granted orphan drug designation for the treatment of Stage IIb to Stage IV melanoma in the U.S. on January 23, 2013.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Meredith Libeg	Y
	CPMS/TL:	Karen Jones	Y
Cross-Discipline Team Leader (CDTL)	Marc Theoret		Y
Clinical	Reviewer:	Meredith Chuk Maitreyee Hazarika	Y Y
	TL:	Marc Theoret	Y
Clinical Pharmacology	Reviewer:	Xianhua Cao Hongshan Li (Pharmacometrics reviewer)	Y Y
	TL:	Ruby Leong (Acting Team Lead) Liang Zhao (Acting – Pharmacometrics Team Lead)	Y Y
Biostatistics	Reviewer:	Sirisha Mushti	Y
	TL:	Kun He	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Shawna Weis	Y
	TL:	Whitney Helms	Y
Product Quality (CMC)	Reviewer:	Joel Welch	N
	TL:	Laurie Graham	Y

Quality Microbiology *(for sterile products)*	Reviewer:	Steven Fong Bo Chi	Y N
	TL:	Patricia Hughes	Y
Facility Review/Inspection	Reviewer:	Steven Fong Bo Chi	Y N
	TL:	Patricia Hughes	Y
OSE/DMEPA (proprietary name)	Reviewer:	Jibril Abdus-Samad	Y
	TL:	Todd Bridges	N
OSE/DRISK (REMS)	Reviewer:	Carolyn Yancey	Y
	TL:	Kendra Worthy	N
Bioresearch Monitoring (OSI)	Reviewer:	Lauren Iacono-Connor	Y
	TL:	Jan Pohlman	N
Other reviewers	Patricia Keegan Jennie Chang		Y Y
Other attendees	Dow-Chung Chi		

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues: o Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? o Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., BA/BE studies):	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO

• Electronic Submission comments **List comments**:	☒ Not Applicable
CLINICAL **Comments**: All requests for information sent to BMS as of today, as of this review have been issued and addressed by the BMS.	☐ 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:*** ○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety or efficacy issues*** ○ ***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 drug/biologic is not the first in its class ○ the clinical study design was acceptable ○ the application did not raise significant safety or efficacy issues ○ 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
• Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• 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

CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ 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
IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	 ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO

Quality Microbiology (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☒ Not Applicable ☐ YES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO
Facility/Microbiology Review (BLAs only) **Comments**: 1. Please provide Rabbit Pyrogen data from three drug product lots tested in accordance with 21CFR610.13(b). 2. Regarding the sterilizing filter for the bulk drug product, submit the bacterial retention validation report. This report should include details on the filter integrity testing of the sterilizing filters pre- and post- filtration.	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
CMC Labeling Review **Comments**:	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days?	☐ N/A ☒ YES ☐ NO ☒ YES ☐ NO

• What late submission components, if any, arrived after 30 days?	None
• 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, M.D.

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in "the Program" PDUFA V):
October 30, 2014

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments:

Filing Meeting Summary Notes
The review team confirmed the application is sufficiently complete to permit a substantive review; therefore, is acceptable to be considered filed 60 days after the date we received the application.
The review team reconfirmed that the application will be priority review.
The review team determined to include initial potential review issues in the Day 60 letter to the sponsor, which would include any information requests that BMS had not responded to yet.
The review team determined that a consult for SGE(s) will be obtained, as appropriate. If SGE(s) are not able to be obtained, this will be documented in the clinical review
Application Orientation Presentation wil be held on Monday September 22, 2014 from 10:45 to 11:34 AM EDT.
The review team determined ODAC was not required for this application.
The review team requested the RPM to schedule a sponsor call to discuss the drug product facilities, specifically, to discuss the Lonza, Porrino, Spain facility site.
The review team requested the RPM to schedule an internal discuss with DRISK regarding the sponsor's proposed "Risk Management Plan."

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. List (optional): 74-Day comments will be provided in the Day 60 Filing Letter. Review Classification: ☐ Standard Review ☒ Priority Review
ACTIONS ITEMS	
☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug). – ***Completed by RPM.***
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	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.
☒	BLA/BLA supplements: If filed, send 60-day filing letter
☒	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
☐	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 NME NDAs in the Program) - ***Completed by RPM.***
☐	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [*These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f*]
☐	Other

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

/s/

MEREDITH LIBEG
09/26/2014

MONICA L HUGHES
09/26/2014

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

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

Application: BLA 125554

Application Type: New BLA

Name of Drug/Dosage Form: Opdivo (nivolumab) Injection for Intravenous Infusion, 40 mg/4 ml (10 mg/mL) vial, 100 mg/10 ml (10 mg/mL) vial

Applicant: Bristol-Myers Squibb Company

Receipt Date: July 30, 2014

Goal Date: March 30, 2015

1. Regulatory History and Applicant's Main Proposals

Bristol-Myers Squibb Company (BMS) is seeking an accelerated approval biological license application (BLA) for Opdivo (nivolumab) for the treatment of unresectable or metastatic melanoma in patients previously treated with ipilimumab, regardless of BRAF status.

BMS stated that the BLA will be supported by efficacy and safety data from the following studies:

- Study CA209037: entitled "A Randomized, Open-Label, Phase 3 Trial of BMS-936558 (Nivolumab) Versus Investigator's Choice in Advanced (Unresectable or Metastatic) Melanoma Patients Progressing Post Anti-CTLA-4 Therapy."

- Study CA209066: entitled "A Phase III, Randomized, Double-Blind Study of Nivolumab vs. Dacarbazine in Subjects with Previously Untreated Unresectable or Metastatic Melanoma."

- Study MDX1106-03 (Also referred to as CA209003): entitled, "A Phase 1, Open-label, Multicenter, Multidose, Dose Escalation Study of BMS-936558 (MDX1106) in Subjects with Selected Advanced or Recurrent Malignancies."

A subsequent supplemental BLA application is planned to support potential conversion to regular approval based on the CA209037 co-primary endpoint of OS.

The initial development program Opdivo (nivolumab) for the treatment of metastatic melanoma begun under IND 100052. On June 13, 2012, BMS filed a new Investigational New Drug Application (IND) for the monotherapy treatment of metastatic melanoma (IND 115195) administratively split from IND 100052. BMS was granted Fast Track Designation for patients with unresectable or metastatic melanoma to demonstrate a clinically important and statistically robust improvement in overall survival over available therapies on October 4, 2012. Lastly, BMS was granted orphan drug designation for the treatment of Stage IIb to Stage IV melanoma in the U.S. on January 23, 2013.

Under IND 100052, FDA and BMS conducted several meetings to discuss this development program and provide guidance to the sponsor. Specifically, a CMC only meeting was held on February 7, 2012, to discuss plans to support clinical trials supporting licensure and marketing approval under the cross-referenced IND 100052. Another CMC only meeting was held on December 13, 2012, to obtain FDA's feedback on the comparability of (b) (4) and assignment of the shelf life of a new 40 mg presentation. Finally, a pre-BLA CMC only meeting was held on April 18, 2014, to obtain feedback and agreement on the contents of the BLA application and acceptability of any late components to the application.

Following the administrative split from IND 100052, BMS requested a Type B meeting under IND 115195. On July 17, 2012, an End of Phase 1/Pre-Phase 3 meeting was held to provide the Agency with preliminary data from the dose-finding and tolerability study (CA209003); to seek FDA's feedback on the proposed clinical development plan for treatment of advanced, unresectable, or metastatic melanoma; and to discuss the potential to obtain accelerated approval based on this development plan.

On October 17, 2012, BMS submitted a new Protocol CA209037 entitled, "A Randomized, Open-Label Phase 3 Trial of BMS-936558 Versus Investigator's Choice in Advanced (Unresectable or Metastatic) Melanoma Patients Progressing Post Anti-CTLA-4 Therapy" To IND 115195. Based on the submission, FDA issued an Advice/Information Letter providing comments relating to Protocol CA209037 to BMS on March 27, 2013.

During a meeting conducted with FDA for another cross-referenced IND 104225, BMS sought FDA's advice on a proposal to "decouple" the timing of the analysis of the co-primary endpoints of ORR and OS in Study CA209037. In this cross-referenced IND meeting, FDA agreed to review a proposal for an alternate timing of the final objective response rate (ORR) analysis in Study CA209037 should the sponsor elect to submit the information to IND 115195.

Following receipt of the October 25, 2013, submission to IND 115195 requesting feedback on, FDA issued an Advice/Information Letter providing comments relating to BMS' proposal to "decouple" the timing of the analysis of the co-primary endpoints of ORR and OS in Study on January 16, 2014. FDA agreed with the proposal to perform an earlier analysis of ORR, but did not agree on the modification for alpha adjustment and recommended that the two-sided, alpha allocation ratio remain 0.01:0.04 for ORR and OS, respectively, as proposed in the original statistical analysis plan. FDA did not agree to accept investigator-assessed response rate for the primary analysis of ORR and recommended that BMS include investigator-determined ORR as a secondary endpoint with proper allocation of Type I error to include investigator-assessed ORR in the label. FDA did not agree that unconfirmed responses can be included when evaluating ORR.

Based on an Advice/Information Letter dated January 16, 2014 under IND 115195 BMS submitted a proposal on February 12, 2014, for modification to the primary analysis of ORR in CA209037 study under IND 115195 to incorporate an analysis of the independent review committee (IRC) assessed ORR in the first 120 patients treated with nivolumab in order to seek accelerated approval.
OS remains a co-primary endpoint and will serve as confirmation of clinical benefit (full approval). FDA provided a response to BMS on March 17, 2014, in an Advice/Information Letter agreeing with the proposal to analyze confirmed ORR based on an independent review in 120 nivolumab-treated patients based on a minimum of 6 months follow-up for all patients to seek accelerated

approval. FDA agreed with the proposed plan of using an alpha of 0.04 for the analysis of OS as a co-primary endpoint which would serve as confirmation of clinical benefit (full approval).

2. Review of the Prescribing Information

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

3. Conclusions/Recommendations

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

All SRPI format deficiencies of the PI and other labeling issues identified above will be conveyed to the applicant in the advice letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by **October 17, 2014**. The resubmitted PI will be used for further labeling review.

Appendix

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

Highlights

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

HIGHLIGHTS GENERAL FORMAT

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

Comment: *No comments.*

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: *Waiver requested was not present in the initial application. If HL extend beyond the requested length, team will discuss the need for the waiver at that time.*

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

Comment: *No comments.*

NO 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment: *"DOSAGE FORMS AND STRENGTHS" and "USE IN SPECIFIC POPULATIONS" don't appear centered.*

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

Comment: *No comments.*

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: *No comments.*

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

Section	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 the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment: *Boxed Warning, Drug Interactions, and Use in Specific Populations are not present in the sponosr submitted labeling. Additionally, Recent Major Changes is not present in the sponosr submitted labeling as this is a NME.*

HIGHLIGHTS DETAILS

Highlights Heading

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

Comment: *No comments.*

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: *No comments.*

Selected Requirements of Prescribing Information

Product Title in Highlights

NO 10. Product title must be **bolded**.

Comment: *No comments.*

Initial U.S. Approval in Highlights

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

Comment: *No comments.*

Boxed Warning (BW) in Highlights

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

Comment: *Not present in the sponosr submitted labeling*

N/A 13. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**"). The BW heading should be centered.

Comment: *Not present in the sponosr submitted labeling*

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

Comment: *Not present in the sponosr submitted labeling*

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

Comment: *Not present in the sponosr submitted labeling*

Recent Major Changes (RMC) in Highlights

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

Comment: *Not present in the sponosr submitted labeling as this is a NME*

Selected Requirements of Prescribing Information

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

Comment: *Not present in the sponosr submitted labeling as this is a NME*

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

Comment: *Not present in the sponosr submitted labeling as this is a NME*

Indications and Usage in Highlights

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

Comment: *Product is "programmed death-1 (PD-1) immune checkpoint inhibitor." Official confirmation of established pharmacologic class will be reviewed by the team during labeling meetings*

Dosage Forms and Strengths in Highlights

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

Comment: *No comments.*

Contraindications in Highlights

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

Comment: *Sponsor noted that no contraindications are present in the sponosr submitted labeling*

Adverse Reactions in Highlights

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

Comment: *No comments.*

Selected Requirements of Prescribing Information

Patient Counseling Information Statement in Highlights

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

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

- **"See 17 for PATIENT COUNSELING INFORMATION"**

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

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

Comment: *Sponosr submitted labeling noting the verbatim statement in the last bullet above.*

Revision Date in Highlights

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

Comment: *No comments.*

Contents: Table of Contents (TOC)

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

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

Comment: *No comments.*

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

Comment: *No comments.*

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

Comment: *Not present in the sponosr submitted labeling*

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

Comment: *No comments.*

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

Comment: *No comments.*

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

Comment: *No comments.*

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

Comment: *No comments.*

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

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

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

Comment: *No comments.*

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

Comment: *No comments.*

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

Comment: *Not present in the sponosr submitted labeling as this is a NME*

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

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

Comment: *No comments.*

BOXED WARNING Section in the FPI

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

Comment: *Not present in the sponosr submitted labeling*

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

Comment: *No comments.*

CONTRAINDICATIONS Section in the FPI

YES 38. If no Contraindications are known, this section must state "None."

Comment: *Sponsor noted that no contraindications are present in the sponosr submitted labeling.*

ADVERSE REACTIONS Section in the FPI

NO 39. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

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

Comment: *Statement is not verbatim. Sponsor will need to update the label to reflect this verbatim statement.*

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

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

Comment: *Not present in the sponosr submitted labeling as this is a NME*

PATIENT COUNSELING INFORMATION Section in the FPI

YES 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment: *References Medication Guide*

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

Comment: *No comments.*

Appendix A: Format of the Highlights and Table of Contents

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

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

WARNING: [SUBJECT OF WARNING]
See full prescribing information for complete boxed warning.

- [text]
- [text]

----------RECENT MAJOR CHANGES----------
[section (X.X)] [m/year]
[section (X.X)] [m/year]

----------INDICATIONS AND USAGE----------
[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

----------DOSAGE AND ADMINISTRATION----------
- [text]
- [text]

----------DOSAGE FORMS AND STRENGTHS----------
[text]

----------CONTRAINDICATIONS----------
- [text]
- [text]

----------WARNINGS AND PRECAUTIONS----------
- [text]
- [text]

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

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

----------DRUG INTERACTIONS----------
- [text]
- [text]

----------USE IN SPECIFIC POPULATIONS----------
- [text]
- [text]

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

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

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

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/s/

MEREDITH LIBEG
09/18/2014

MONICA L HUGHES
09/19/2014